Dissertation

Microstructural Changes detected with DTI in Bipolar Disorder

Submitted by

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Disclosure

The Dissertation was conducted in the Doctoral School ***"Life-Style related Medicine"*** at the **Medical University Graz**

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Zusammenfassung

Hintergrund/Ziele

Die bipolare affektive Störung ist eine schwerwiegende psychische Erkrankung, deren Erscheinungsform in vielfältiger Art und Weise charakterisiert ist. Im Rahmen der Erforschung der biologischen Grundlagen psychischer Erkrankungen nimmt sie in mehrfacher Hinsicht einen besonderen Stellenwert ein. Aufgrund ihrer meist sehr ausgeprägten Symptomatik besteht ein hoher Leidensdruck für die Betroffenen, da diese mit schwerwiegenden psychosozialen Konsequenzen konfrontiert sind, und die Symptome der Erkrankung zum Teil auch forensische Konsequenzen zeigen können. Die bipolare affektive Störung ist für die Forschung aufgrund ihrer umschriebenen diagnostischen Identität und dem somit klar definierbaren Kollektiv von großem Interesse. Es gibt gegenwärtig unzählige Forschungsbemühungen in unterschiedlichen Bereichen. Insbesondere Ergebnisse im Bereich der Genetik, des endokrinen Stoffwechsels, der funktionellen und strukturellen Bildgebung sowie des Entzündungssystems sind besonders hervorzuheben. In dieser Arbeit wende ich eine weiterführende Methode der strukturellen Bildgebung an um in Verbindung mit anderen Markern, die im Rahmen einer klinischen Studie erhoben wurden, tiefergehende Ergebnisse im Bereich der mikrostrukturellen Veränderungen des Marklagers zu erarbeiten. Wir haben hierzu eine Kohorte mit 107 Patienten und 57 Kontrollpersonen verwendet. A priori formulierte ich folgende Hypothesen:

(I) An der bipolaren affektiven Störung erkrankte Personen zeigen Bereiche im weißem Marklager, die eine signifikant geringere mikrostrukturelle Integrität aufweisen als gesunde Kontrollen.

(II) Die Konzentration von systemischen inflammatorischen Markern zeigt einen Zusammenhang mit dem Krankheitsverlauf der bipolaren affektiven Störung.

(III) Mikrostrukturelle Veränderungen im Gehirn erkrankter Personen weisen einen Zusammenhang mit Konzentrationen von systemischen inflammatorischen Markern im Blut auf.

Methoden

Die Erhebung der Daten erfolgte im Rahmen der BIPFAT-Studie (Bipolar disorder and fat metabolism). Im Rahmen dieser Studie werden bei den Proband*innen (Erkrankten wie auch gesunden Kontrollen) mehrere potentielle biologische Marker (Stoffwechsel, Inflammatorisches System, Genetik u. Epigenetik) bestimmt. Des weiteren werden umfassende demographische Daten erhoben und der individuelle Krankheitsverlauf so gut und objektiv wie möglich aufgezeichnet. Zusätzlich wird mittels eines 3 Tesla MRT-Scans, unter Anwendung mehrerer Bildgebungssequenzen, eine umfassende strukturelle Darstellung des Gehirns ermöglicht.

Zur Aufbereitung der Daten für die „diffusion-tensor“ Bildgebung (DTI) wurde die DTI-Fit Funktion des MR-Programms FSL verwendet. Danach wurde eine voxelbasierte Statistik auf Grundlage einer annähernden und summierenden Traktrekonstruktion mittels der „Tract based spatial statistics“ Funktion von FSL durchgeführt.

Ergebnisse

Die durchgeführte Analyse zeigte eine signifikante Reduktion der fraktionellen Anisotropie (FA) innerhalb eines ausgedehnten Clusters des Corpus Callosum (CC), die sowohl die anterioren als auch posterioren Regionen bei Personen mit bipolarer Störung (BD) im Vergleich zu gesunden Kontrollpersonen (HC) betraf. Die Ergebnisse wurden hinsichtlich Alter und Geschlecht korrigiert. Die Überlagerung der TBSS-Ergebnisse auf ein standardisiertes Gehirnmodell zeigte, dass die betroffenen Cluster überwiegend in den kommissuralen Fasern des Forceps major und minor lokalisiert waren. In Bezug auf Entzündungsmarker wurde eine statistisch signifikante positive Korrelation zwischen der Anzahl manischer und depressiver Episoden sowie den hsCRP- und IL-6-Werten bei weiblichen Patientinnen mit BD festgestellt ($p = .03*$, $n = 88$). Bei männlichen Patienten hingegen konnten keine signifikanten Korrelationen zwischen der Anzahl manischer und depressiver Episoden und den hsCRP- bzw. IL-6-Werten festgestellt werden. Auch die Korrelation zwischen Krankheitsdauer und hsCRP- bzw. IL-6-Werten erreichte weder bei männlichen noch bei weiblichen Patienten statistische Signifikanz. Einige Voxel-Cluster zeigten eine Korrelation zwischen niedrigerer FA und höheren IL-6- sowie hsCRP-Werten;

jedoch erreichten keine dieser Korrelationen statistische Signifikanz nach der angewandten Post-hoc-Analyse. Alle korrelierenden Voxel-Cluster befanden sich überwiegend in der linken Hemisphäre und waren über verschiedene weit verbreitete Regionen verteilt.

Diskussion

Die deutlichen Veränderungen innerhalb des Marklagers unterstützen die bereits bestehenden Hypothesen, dass mikrostrukturelle Defizite innerhalb der weißen Substanz eine wichtige Rolle in der Pathophysiologie und Neurobiologie der BD darstellen. Insbesondere die Lokalisation innerhalb der zentralen funktionellen Schaltstelle des Balkens (Corpus callosum) deckt sich mit Ergebnissen aus anderen Studien und spricht für die Qualität unserer Analysen. Die Untersuchung des potentiellen Zusammenhangs von inflammatorischen Markern mit dem Krankheitsverlauf erbrachte für die weibliche Subgruppe den Nachweis eines signifikanten Zusammenhangs und unterstrich die Bedeutung dieser Marker für die Verwendung in weiteren Analysen. Die Frage, warum diese Ergebnisse nur bei weiblichen Patientinnen das Signifikanzniveau erreichten, konnte nicht hinlänglich beantwortet werden. Diverse Unterschiede hinsichtlich inflammatorischer Einflüsse sind in Abhängigkeit des biologischen Geschlechtes vorbeschrieben. In unserem Sample konnte bzgl. des Zusammenhanges von Entzündungsmarkern und mikrostrukturellen Defiziten kein signifikantes Ergebnis erzielt werden. Die Daten wiesen jedoch einen starken Trend einer potentiell bedeutsamen Assoziation. Sie geben Anlass, diese Fragestellung weiter zu verfolgen.

Abstract

Background/Aims

Bipolar disorder (BD) is one of the major affective disorders in psychiatry. The study investigating microstructural deficits in BD is part of the ongoing "Bipolar Disorder and Fat Metabolism (BIPFAT) Study." All participants were drawn from the BIPFAT study sample, comprising 163 individuals, including 107 patients with BD and 56 healthy controls (HC).

Hypothesis (I) posited that there would be clusters exhibiting significantly lower fractional anisotropy (FA) in BD compared to the HC subgroup. To investigate this, a conventional group comparison using Tract-Based Spatial Statistics (TBSS) was conducted to test this assumption. The second working hypothesis (II) suggested that inflammatory markers are associated with the course of illness in BD. To address this, a standard statistical analysis incorporating inflammation, clinical data, and selected co-factors was performed. The third hypothesis (III) aimed to combine both factors, proposing that microstructural deficits have a significant association with inflammatory parameters. For this analysis, TBSS was also utilized to identify clusters with significant correlations.

Methods

Participants were scanned using a 3.0-Tesla MRI scanner (Siemens Trio). For the diffusion tensor imaging (DTI) data, a single-shot, diffusion-weighted spin echo echo-planar imaging sequence was employed. Diffusion tensor estimation was performed using the FMRIB Software Library (FSL) FDT tool. A total of 119 MRI scans underwent this procedure. Voxel-wise statistical analysis of the fractional anisotropy (FA) data was conducted using Tract-Based Spatial Statistics (TBSS), a component of FSL.

To localize voxels where FA was significantly lower in BD compared to HC, as well as those where FA was significantly associated with inflammatory parameters (hsCRP, IL-6), voxel-wise statistical analysis was performed using a generalized linear model. Age, sex, mood stabilizing treatment (lithium, atypical antipsychotics, anticonvulsants), and illness duration were included as covariates. A p-value < 0.05 was considered statistically significant.

For the general group difference analysis between statistical subgroups, Student's t-test was used for normally distributed variables. For non-normally distributed data, the Mann-Whitney U-test was applied. A p-value < 0.05 was deemed statistically significant.

Results

The applied analysis revealed a significant reduction in fractional anisotropy (FA) within a broad cluster of the corpus callosum (CC), affecting both the anterior and posterior regions in individuals with BD compared to healthy controls (HC). The results were corrected for age and sex. Overlaying the TBSS results onto a standardized brain model indicated that the affected clusters were predominantly located in the commissural fibers of the major and minor forceps.

Regarding inflammation, a statistically significant positive correlation was found between the number of manic and depressive episodes and hsCRP and IL-6 levels in female patients with BD *p=.03* (n = 88)*. No significant correlations were observed between the number of manic and depressive episodes and hsCRP or IL-6 levels in male patients. The correlation between illness duration and hsCRP or IL-6 levels did not reach statistical significance in either male or female patients.

Some voxel clusters demonstrated a correlation between lower FA and higher IL-6 and CRP levels; however, none of these correlations reached statistical significance following the applied post-hoc analysis. All correlating voxel clusters were predominantly located in the left hemisphere across various widespread locations.

Discussion

The significant changes within the white matter support the already existing hypotheses that microstructural deficits within the white matter play an important role in the pathophysiology and neurobiology of BD. In particular, the localization within the central functional hub of the corpus callosum aligns with findings from other studies, supporting the validity of our analyses. The investigation into the potential relationship between inflammatory markers and disease progression revealed a significant association in the female subgroup, emphasizing the importance of these markers for use in further analyses. However, the question of why these results reached statistical significance only in female patients could not be sufficiently answered. Various differences in inflammatory influences, depending on biological sex, have been previously described. In our sample, no significant result was obtained concerning the association between inflammatory markers and microstructural deficits. Nevertheless, the data indicated a strong trend toward a potentially meaningful association, warranting further exploration of this question.

Table of Content

Abbreviations

- *Bipolar Disorder BD*
- *Bipolar I disorder BD I*
- *Bipolar II disorder BD II*
- *International Cluster of Diagnosis ICD 10*
- *Diagnostic statistical manual DSM V*
- *Healthy controls HC*
- *Atypical antipsychotics AAP*
- *Random controlled trial RCT*
- *Central nervous system CNS*
- *Peripheral nervous system PNS*
- *Adenosinetriphosphate ATP*
- *Gamma-aminobyricacid GABA*
- *Corpus callosum CC*
- *Magnetic resonance imaging MRI*
- *Functional magnetic resonance imaging fMRI*
- *Spin-lattice relaxations time T1*
- *Spin-Spin relaxation time T2*
- *Fluid-attenuated inversion recovery FLAIR*
- *Diffusion weighted imaging DWI*
- *Diffusion tensor imaging DTI*
- *Mean diffusivity MD*

- *Fractional anisotropy FA*
- *Voxel based morphometry VBM*
- *Region of interest ROI*
- *Bipolar disorder and Fat Metabolism BIPFAT*
- *Interleukin 6 IL-6*
- *High sensitive C-reactive protein hsCRP*

Figures

Tables

Formula

1 Introduction

1.1 Bipolar disorder

Bipolar disorder (BD) is one of the major affective disorders recognized in psychiatry. It is defined by the International Classification of Diseases (ICD-11) as a disorder characterized by two or more episodes in which the patient's mood and activity levels are significantly disturbed. These disturbances consist of manic or hypomanic episodes, which are defined by elevated mood, increased energy, and heightened activity, as well as depressive episodes, which are marked by a lowered mood and decreased energy and activity (1).

Additionally, the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) differentiates between bipolar I disorder (BD I), which is defined by the occurrence of at least one manic and one depressive episode, and bipolar II disorder (BD II), which involves at least one hypomanic episode and one depressive episode, with the absence of mania (2).

1.1.1 Epidemiology

Epidemiological data on BD show considerable variation (1). It has been suggested that the lifetime prevalence of BD I is approximately 1% in the general population (2, 3). The overall lifetime prevalence of all bipolar spectrum disorders is estimated to be 2.4% (4). Evidence suggests that the prevalence varies to a lesser extent across different countries and regions (1, 5). The prevalence of BD in males and females is generally described as equal (5), although some studies report a higher prevalence of manic episodes and BD I in females (4).

The age of onset for BD typically ranges between 20 and 30 years, although there is often a significant delay in diagnosis in many cases (4). Because long periods of untreated and unrecognized illness episodes are common, especially at the onset of the disease, estimating the true age of onset is challenging. Symptoms that may have occurred during

adolescence are often undetected or overlooked, further complicating the identification of the disorder at its early stages (1).

1.1.1.1 Genetics and environment

There is strong evidence supporting the contribution of genetic factors to BD. Twin studies have shown a concordance rate of 40-70% in monozygotic twins (6). The lifetime risk in relatives of BD patients is estimated to be seven times higher than in the general population (1, 6). The genetic risk for BD appears to be very complex and based on multipole genetic mechanisms (6). However, it has not been identified that any individual genes are directly involved in the BD-associated pathomechanisms (7). Large genome-wide association studies (GWAS) have revealed multiple genetic loci, suggesting a polygenic risk for the disorder (8).

Additionally, epigenetic factors, such as the methylation of various genes, may play a role in BD. There is evidence indicating that the methylation of clock genes, which are associated with the activation of monoamine oxidase A, is significantly different in patients with BD compared to healthy controls (HC) (9, 10).

1.1.2 Psychological Factors

Psychological stress is believed to have a profound influence on the course of BD. Its impact appears to be particularly significant at the onset of the disorder (5), as well as in the periods preceding relapses into illness episodes (11). Severe life events, such as the suicide of relatives, disability, and unemployment, have been specifically linked to the first hospitalization for a manic episode (12).

1.1.3 Somatic comorbidities

BD, as a multisymptomatic and heterogeneous condition, is influenced by a wide range of somatic factors, including the genetic vulnerabilities mentioned earlier, as well as the consequences and side effects of long-term pharmacological treatment (1). BD is known to be comorbid with a variety of medical and psychiatric conditions (13). Particularly, disorders believed to have inflammatory and stress-related etiologies exhibit strong associations with BD, such as irritable bowel syndrome (13, 14). Other conditions, including asthma, obesity, and migraine, have also been reported to be associated with BD (1, 15).

1.1.3.1 Differential diagnosis

Additionally, somatic diseases and intoxication with various chemical substances can lead to clinical presentations similar to the symptoms commonly observed in BD. The charts below present common somatic differential diagnoses of BD (16, 17).

1.1.3.1.1 Organic mania

Organic-induced manic episodes appear to be relatively rare in occurrence, and detailed data on this phenomenon are limited. Their incidence is generally linked to the prevalence of the underlying disease (18). Some data indicate a high prevalence of manic symptoms and episodes in patients with multiple sclerosis following treatment with adrenocorticotropic hormone (ACTH) and prednisolone (19). In patients with Parkinson's disease, approximately 1% develop a manic episode after receiving medication, with 10% of these patients reporting an euphoric mood state (20).

Table 1: Somatic disorders leading to manic symptoms (16-18)

Somatic differential diagnosis of mania
• **Hyperthyroidism**
• **Systemic lupus erythematodes**
• **Morbus Cushing**
• **Multiple sclerosis**
• **Chorea Huntington**
• **Craniocerebral trauma**
• **Space-occupying intracerebral lesions**
• **Cerebrovascular diseases**
• **HIV- Encephalopathia**
• **Neurosyphilis**
• **Epilepsy**
• **Morbus Parkinson**

Table 2: Substances inducing manic symptoms (16-18)

Substances inducing manic symptoms
• **Glucocorticoids**
• **Antidepressants**
• **Didanosine**
• **Zidovudim**
• **Ganciclovir**
• **Penicilline**
• **Levetiracetam**
• **Cocaine**
• **Hallucinogens**
• **Alcohol**

1.1.3.1.2 Organic depression

A wide range of somatic disorders are thought to contribute to depressive symptoms. However, clinical data on organic depression remain scarce (21). The duration of somatically induced depressive episodes appears to be shorter than typical depressive episodes, which often leads to these states going unrecognized (21). Additionally, certain drugs and medications, particularly when taken continuously, can trigger depression (21).

Table 3: Somatic disorders leading to depressive symptoms (21)

Somatic differential diagnosis of depression
• **Morbus Alzheimer** • **Morbus Parkinson** • **Vascular dementia** • **Craniocerebral trauma** • **Epilepsy** • **Borreliosis** • **Viral infectious diseases (e.g. Hepatitis C)** • **Cushing Syndrome** • **Addison Syndrome** • **Multiple sclerosis**

Table 4: Substances inducing manic symptoms(21)

Substances inducing depressive symptoms
• **Clonidine** • **Beta-blocker** • **Antiepileptics** • **Oestrogene** • **Gestagenes** • **Cimetidine**

1.1.4 Treatment

The clinical treatment of BD typically involves both biological/pharmacological approaches as first-line therapy and psychotherapeutic and psychoeducational strategies. Pharmacological treatment is generally based on three main strategies, tailored to the clinical symptoms of BD: acute antimanic and antidepressive treatment, as well as mood stabilizing treatment aimed at preventing illness episodes (22). Psychotherapeutic and psychoeducational interventions are used in combination with pharmacological treatment to enhance treatment compliance and efficacy (22).

1.1.4.1 Acute illness episodes

1.1.4.1.1 Manic and hypomanic episodes

There are several treatment options available for acute manic episodes. The choice of medication is determined by the patient's clinical history and their individual risk profile for various side effects. Each treatment option presents a distinct balance of advantages and disadvantages, which must be carefully considered in the formulation of the individualized treatment strategy.

Although lithium is recommended as the first-line pharmacological therapy for mood stabilisation, there is also strong evidence supporting its effectiveness in the acute treatment of manic episodes (22,23). In acute manic states, the combination of lithium with an antipsychotic agent might enhance treatment efficacy (22).

The role of atypical antipsychotics in the treatment of BD has significantly expanded in recent years. Recent guidelines, such as the S3 guideline from the German Society for Psychiatry and Psychotherapy, recommend the use of atypical antipsychotic agents (AAPs) over conventional mood stabilizers in the management of acute manic episodes (24). In particular, aripiprazole, olanzapine, and quetiapine have been identified as the most effective agents for this indication (22).

Typical antipsychotics have been used for the treatment of acute manic episodes for decades, leading to a substantial body of clinical experience. However, due to their significantly higher risk of severe side effects compared to atypical antipsychotic agents (AAPs), they are currently classified as second-line treatment options in the most recent guidelines (22,24).

Valproate is approved for the treatment of severe acute manic episodes in patients who are intolerant to lithium, although randomized controlled trials (RCTs) have demonstrated its inferior efficacy compared to haloperidol and lithium (22). All other known antiepileptic drugs have not shown evidence for efficacy in the treatment of acute manic episodes (22).

1.1.4.1.2 Mixed episodes

A mixed episode is defined as an emotional state in which manic or hypomanic and depressive symptoms occur simultaneously or in rapid succession (25). These states are believed to have a high prevalence among patients with BD, and as such, they are increasingly receiving attention in clinical research (22).

Atypical antipsychotics (AAPs) have demonstrated good efficacy in the treatment of mixed episodes, with aripiprazole and olanzapine showing superiority over other AAPs (22). Lamotrigine has only shown evidence of effectiveness in cases where depressive symptoms are prominent during a mixed episode (22). Valproate is recommended solely for episodes with predominantly manic symptoms (22).

When antidepressants are prescribed, close monitoring of the patient and mood stabilizing treatment is essential. If the patient has a history of manic or hypomanic episodes, the use of antidepressants should be discontinued upon the onset of a mixed episode (22).

1.1.4.1.2.1 Rapid cycling

Rapid cycling is diagnosed when a patient experiences more than four episodes (manic or depressive) within a twelve-month period (25). In this context, distinguishing between acute treatment and mood stabilisation becomes challenging (22).
Mood stabilizing therapy

After addressing the acute symptoms, the primary therapeutic goal is the prevention of subsequent episodes. According to current literature, maintenance therapy following an episode should last for at least 12 months (22). Mood-stabilizing treatment should be initiated following the first manic episode due to the high risk of relapse (22).

1.1.4.1.3 Lithium

Lithium has demonstrated particularly good clinical efficacy in the treatment of euphoric mania and is therefore considered the first-line therapy in this context. Its use requires careful monitoring to ensure therapeutic plasma levels are maintained. Lithium is also recommended for long-term maintenance therapy, provided that potential side effects are appropriately managed (26). However, in terms of preventing depressive episodes, lithium does not show any clear advantage over other substances (22).

Dosage reduction should be performed gradually. After discontinuation of lithium treatment, the risk of a new manic episode is higher compared to untreated patients (22). Evidence suggests that the effectiveness of reinitiating lithium therapy is lower than when it is initially started (22).

1.1.4.1.4 Antiepileptics

Valproate is indicated for long-term treatment in BD. Current evidence suggests that it has better tolerability than lithium, although the treatment response is more favorable with lithium (22). Due to its potential teratogenic effects, it is not recommended for use in women of childbearing potential (22).

Lamotrigine has demonstrated efficacy in preventing depressive episodes in BD. However, its effectiveness in preventing manic episodes appears to be significantly weaker compared to other substances (22).

1.1.4.1.5 Atypical Antipsychotics

There is strong evidence, particularly for aripiprazole, asenapine, olanzapine, and quetiapine, in preventing manic episodes in BD. For other antipsychotic agents, the potential mood-stabilizing effect appears to be weaker. The most pronounced effect has been observed with combined treatment using antipsychotics and other phase-prophylactic agents, such as lithium and quetiapine (22).

1.2 Neurobiological principals

The human brain exhibits the highest histological, anatomical, and functional complexity of any organ in the body. Consequently, understanding the biological underpinnings of its pathological processes and diseases remains one of the greatest challenges in modern biological and medical sciences.

1.2.1 Cellular anatomy of the brain

Human brain tissue is composed of two distinct types of cells: the functionally active neurons and glial cells, which are thought to support neuronal function and indirectly influence functional processes in the brain (27)

1.2.1.1 Neurons

Neurons are highly specialized cells that exhibit considerable variation in size, number of synapses, and interactions with glial cells, depending on their specific functions. Neurons in the central nervous system (CNS) differ from those in the peripheral nervous system (PNS), and there are also numerous variations within the CNS itself. For instance, spinal cord neurons have axons that can exceed one meter in length, whereas certain neuronal cells in the cerebellum are among the smallest in the body (27).

The functions of a neuron can be categorized as receiving, processing, and transmitting information. Based on these primary functions, distinct topographic regions can be identified (27). Dendrites are small cellular protrusions that receive signals from other neurons via synapses. Following molecular processes of modification and transformation, the signal is transmitted to the cell body (27). The axon is a long extension that propagates the signal over long distances. In addition, neurotransmitters required for presynaptic transmission are transported through the axon along cytoskeletal structures known as microtubules. To ensure proper signal transmission, the axon is encased by specialized glial cells that form the myelin sheath (27). Neurofilaments are long, stable protein chains that constitute the main component of the axonal cytoskeleton (27). The structural integrity of neurofilaments is essential for various intracellular transport pathways. Pathological alterations in their state are implicated in the pathophysiological processes underlying neurodegenerative diseases (27).

1.2.1.2 Glia

Glial cells are non-neuronal cells that are integral to the structure and function of neuronal tissue within both the peripheral and central nervous systems (28). These cells surround and stabilize neurons, and are also involved in neurotransmission through the formation of the myelin sheath around axons (28). Additionally, glial cells participate in immune responses and contribute to the provision of nutrients to neuronal cells (28).

1.2.1.2.1 Oligodendrocytes

Oligodendrocytes are structurally and functionally closely interconnected. Within the central nervous system (CNS) of vertebrates, they form the myelin sheath, which consists of lipid and protein components (29). Oligodendrocytes perform a function analogous to that of Schwann cells in the peripheral nervous system (PNS) (29). One oligodendrocyte can extend its processes to myelinate up to 50 different axons (29). The myelin sheath of an axon is constructed by multiple oligodendrocytes, with each one contributing a segment to the sheath (29).

Oligodendrocytes develop during embryogenesis in the periventricular regions of the brain. Their precursor cells, known as oligodendrocyte progenitor cells (OPCs), migrate from the germinal zones into various regions of both gray and white matter, where they differentiate into oligodendrocytes and form myelin (30). However, not all oligodendrocytes are believed to follow this developmental pathway. At birth, three distinct stages of oligodendrocyte differentiation can be identified: mature oligodendrocytes (myelinating), immature oligodendrocytes (non-myelinating), and progenitor cells (31). It has been proposed that during subsequent stages of brain development, such as the second neurogenesis and general brain maturation, some oligodendrocytes undergo apoptosis, fail to differentiate, or persist as progenitor cells (31).

1.2.1.2.2 Astrocytes

Astrocytes constitute one of the most abundant cell types in the brain, outnumbering neurons by more than fivefold (32). Functionally, they are believed to play a critical role in the supply of nutrients to neural tissue and in the maintenance of ion homeostasis (32). Additionally, astrocytes are involved in the repair processes following traumatic injuries (32). Characterized by their star-shaped morphology, they envelop the synapses of neurons (32). Astrocytes also contribute to the maintenance of the blood-brain barrier and are responsible for the uptake and release of neurotransmitters at neuronal synapses (33).

1.2.1.2.3 Ependyma

The ependyma refers to a thin layer of cells that line the ventricular system of the brain, serving to separate brain tissue from the cerebrospinal fluid (CSF) and playing a role in the regulation of CSF composition (34). It has been proposed that these cells may act as a potential reservoir for reparative processes following brain tissue damage (34).

1.2.2 Molecular and cellular physiology of the brain

Neurons can be electrically and chemically excitable through ion channels in the cell membrane. The various types of ion channels are regulated by distinct mechanisms.

1.2.2.1 Intracellular signal-transmission

Neurotransmitters, released from the presynaptic axon terminal, bind to receptors on the postsynaptic membrane, thereby activating ligand-gated ion channels. This results in the flux of ions across the cell membrane. The induced electrical signal then passively propagates along a distance toward the cell body (27). The cell body receives multiple inputs from the various dendrites, and if the combined signals are sufficient to depolarize the axon hillock, an action potential is initiated (27).

1.2.2.1.1 Action potential

The action potential is an electrical spike that propagates along the axon as a wave. This electrical phenomenon arises from the differential concentrations of Na+, Cl-, and K+ ions inside and outside the axonal membrane (27). This concentration gradient is maintained by the activity of ion pumps that hydrolyze adenosine triphosphate (ATP).

1.2.2.1.2 Functional issues of the myelin sheath

As previously discussed, the myelin sheath in the central nervous system (CNS) is formed by oligodendrocytes. This sheath wraps around the entire axon, except for small gaps known as the nodes of Ranvier, which occur between the ends of adjacent myelinating oligodendrocytes (27). The myelin sheath acts to prevent the leakage of electrical current generated by the action potential. As a result, the action potential does not need to propagate along the entire length of the axon during transmission. Instead, between the nodes of Ranvier, where the action potential is actively generated, the signal is transmitted via conventional current (27). The action potential appears to "jump" from one node to the next, a process known as saltatory conduction (27).

1.2.2.1.3 Intrinsic information processing

In addition to signals transmitted through dendritic excitation, neurons generate their own intrinsic patterns of activity, independent of synaptic input (27). This endogenous activity is driven by specialized ion channels, which are regulated by intracellular second messenger pathways (27).

Neurons in the central nervous system (CNS) do not always respond to sudden synaptic stimuli in a uniform manner. The response to an incoming stimulus can vary depending on the current levels of second messengers and the membrane potential of the neuron (27). Furthermore, incoming stimuli not only affect postsynaptic neurons but can also influence the function of the presynaptic neuron (27).

1.2.2.2 Interneuronal signal-transmission

The communication between two or more neurons within the central nervous system (CNS) is organized through an electrochemical pathway. The transmitted electrical signal is converted into a chemical stimulus at the axonal terminal. This electrical signal triggers the release of various neurotransmitters into the synapse, where they bind to receptors on the postsynaptic membrane of an adjacent neuron. There are several types of synapses, each contributing in a highly sophisticated manner to the microarchitecture of the CNS.

1.2.2.2.1 Synapses

A typical type of synapse in the central nervous system (CNS) is the axodendritic synapse, which connects a presynaptic axon terminal with a postsynaptic dendrite. This type is characteristic of connecting interneurons (27).

Dendrodendritic synapses are commonly found in cortical areas with a high density of neuronal cells. These synapses establish a direct connection between dendrites (27).

Electrical synapses are formed by channels composed of protein subunits. The cytoplasms of the connected cells are directly linked through these channels, allowing ions to move directly from one cell to another, thus transmitting the electrical signal. Small molecules involved in intracellular signal transmission can also pass through these junctions (27).

The majority of synaptic connections in the CNS are chemical synapses. While they are not as rapid in signal transmission as electrical synapses, they offer a broader capacity for signal amplification and modulation (27).

1.2.2.2.2 Neurotransmitters

In general, there is a complex interplay of various types of neurotransmitters within the human neuronal system, notably including glutamate, gamma-aminobutyric acid (GABA), acetylcholine, serotonin, noradrenaline, dopamine, histamine, and glycine. Additionally, neuropeptides, which are larger molecules than classical neurotransmitters, are not released as rapidly as neurotransmitters (27).

These small molecules are stored within synaptic vesicles located in the presynaptic neuron. Highly specialized neurons synthesize and store only one type of neurotransmitter. When an action potential reaches the terminal zone of the axon, the release of neurotransmitters from the synaptic vesicles is triggered by a significant influx of calcium ions (Ca^{2+}) (27). The

released neurotransmitter diffuses across the synaptic cleft and binds to the corresponding postsynaptic receptors on the adjacent neuron, thereby initiating a new action potential (27).

The activity of the neurotransmitter is regulated by various mechanisms. For instance, serotonin is re-uptaken into the presynaptic neuron by transporter proteins, effectively deactivating the serotonin (27).

1.2.2.3 Postsynaptic signal processing

The postsynaptic response to neurotransmitters depends on the activity of receptors located on the postsynaptic membrane (27). These receptors are classified into two main types: ionotropic and metabotropic receptors. Ionotropic receptors are directly coupled to ion channels, which undergo conformational changes upon receptor activation. This alteration in conformation leads to changes in ion flow across the membrane, resulting in either depolarization or hyperpolarization of the membrane. Depolarization activates the cell, while hyperpolarization functionally inhibits it (27).

In contrast, metabotropic receptors regulate cellular function through a G-protein-coupled pathway, which modulates intracellular second-messenger cascades (27).

1.2.3 Macroscopic anatomy of the brain

The brain exhibits a highly complex anatomical architecture, which is determined by its numerous functions as the central organ of the nervous system. A comprehensive description of all brain structures would exceed the scope of this work; therefore, subsequent chapters will focus solely on those structures that are relevant to the pathophysiology of BD.

1.2.3.1 Gross structure

The organization of the brain is divided into two hemispheres, with all major structures being represented twice, once in each hemisphere. The brain's substance is composed of both grey and white matter. The cell bodies of neurons are located within the grey matter, while the white matter primarily consists of axons and glial cells (35). The brain's structures are further categorized into the neocortex, the cerebellum, and the brainstem (35).

1.2.3.2 Limbic system (36)

The limbic system encompasses several anatomical structures of the brain. Although the precise definition of its compartments may vary, it is generally regarded as the functional system responsible for emotion and emotional regulation. The main components of the limbic system include the hippocampus, the cingulate cortex, the parahippocampal gyrus, the amygdala, and the mammillary bodies (37,38). These structures are closely interconnected through dense white matter tracts (37). Additionally, there are significant connections to other brain regions, particularly the frontal cortical areas and the thalamus (37).

1.2.3.2.1 Papez circuit (36)

This structure is a bundle of white matter fibers that originates from various limbic structures. It consists of efferent fibers from the hippocampus, which travel to the mammillary bodies via the fornix, and then continue through the tractus mammillothalamicus to the thalamus. The circuit is completed by fibers that connect the thalamus to the hippocampus through the cingulate cortex (37).

1.2.3.2.2 Limbic cortex (36)

The term limbic cortex refers to all cortical areas that are part of the limbic system. This includes the cingulate cortex and the parahippocampal gyrus (37). The cingulate gyrus appears to play a central role in this system due to its numerous connections with various other brain regions. Additionally, it is connected to the septal nuclei, as well as to frontal,

parietal, and temporal areas of the neocortex (37). The cingulate motor area is a distinct region where motor efferent tracts project to spinal motoneurons via the internal capsule, and it is considered a primary site of interaction between emotional and motor functions (38).

1.2.3.2.2.1 Hippocampus (36)

The hippocampus is primarily located in the temporal lobe, with the parahippocampal gyrus surrounding its rostral end. On the opposite side, its fibers terminate in the fornix and project to the mammillary bodies. The hippocampus also sends efferent fibers to the amygdala, the thalamus, and the cingulate gyrus (38).

1.2.3.2.2.2 Amygdala (36)

The amygdala is located beneath the caudate nucleus, within the temporal lobe. It is composed of several small neuronal nuclei that are organized into distinct groups (37). One group projects to the diencephalon, while another smaller group sends its fibers to the hypothalamus and the frontobasal cortex (37,38).

1.2.3.3 White matter

The white matter of the brain consists of neural fibers that connect various cortical and subcortical regions. Millions of fibers within the brain tissue form anatomically defined nerve tracts (39). Based on the regions they connect, these fibers are categorized into association fibers, commissural fibers, and projection fibers (35,39).

1.2.3.3.1 Association fibers

Association fibers connect brain areas within the same hemisphere. Depending on the distance between the structures they connect, these fibers are classified as either long or short fibers (35).

Long association fibers connect widely separated gyri and are organized into bundles (35). Notable large association bundles include the arcuate fasciculus, the occipitofrontal fasciculus, the inferior and superior longitudinal fasciculi, the cingulum, and the uncinate fasciculus (35).

Short association fibers are located close to the grey matter and connect adjacent gyri over short distances (35).

1.2.3.3.2 Commissural fibers

These fibers provide interhemispheric connections. Like other white matter structures, they are organized into bundles, forming distinct anatomical structures (35).

1.2.3.3.2.1 Corpus callosum

The corpus callosum (CC) is a thick and prominent structure located at the center of the neocortex. It is the largest white matter structure in the brain, containing up to 200 million axonal projections (35). The corpus callosum is divided into several parts: the genu, body, rostrum, and splenium (35,38).

The genu is the most anterior part of the corpus callosum, with fibers projecting to the frontal areas. It forms a curve over the septum pellucidum (35), connecting the prefrontal cortex of both hemispheres. The fibers in this region also form a fork-like structure known as the forceps minor (40).

The rostrum is a smaller portion located just below the genu, extending from the lamina terminalis to the optic stalk (35).

The splenium is the largest part of the corpus callosum and is closely connected to the wall of the third ventricle. It is also in close proximity to the midbrain (35). The strongest fibers in this region connect the occipital and parietal lobes and contribute to the structure of the forceps major (35).

1.2.4 Physiological function of emotion (36)

Modern neuroscience has made significant efforts to reconstruct the processes within the human brain that are involved in the multifaceted functions of emotions. The current literature does not identify a single brain region associated with discrete emotions and emotional functions; instead, it highlights the involvement of various regions and their specific functional interactions (41). Consequently, a particular emotional state appears to emerge from the functional activity of multiple regions and interconnected neural networks.

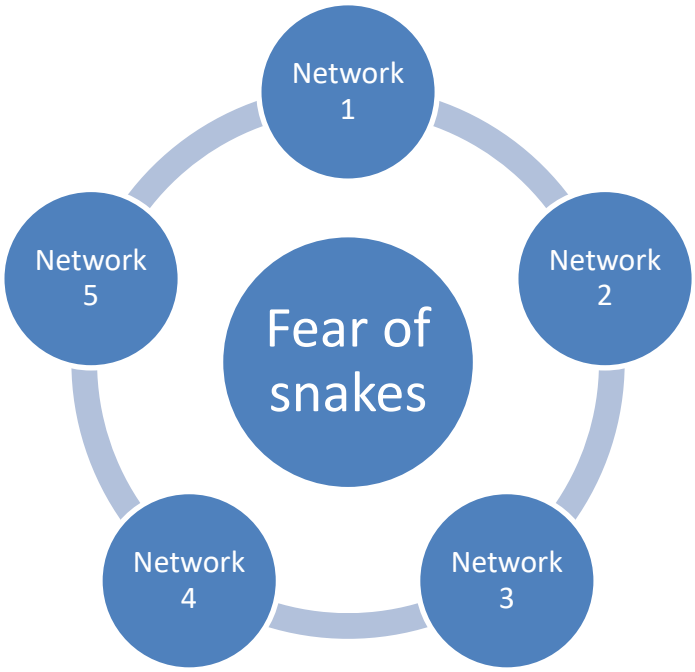

Figure 1: Concept of functional interactions of different networks at the example of fear according to Lindquist et al. (41)

1.2.4.1 Functional networks

The capacity to generate and process emotions is a major aspect of brain function, and it cannot be attributed to a single anatomical region. Contemporary neuroscience describes this function as arising from complex interactions among various brain structures, including the neocortex, subcortical regions, and the cerebellum (41). The specific interactions between these regions, in relation to distinct emotional functions, can be conceptualized within several functional networks.

1.2.4.1.1 Limbic network (36)

This network is believed to play a central role in generating the fundamental stimuli underlying emotional processes in the brain, referred to as the 'core affect' (41). It involves regions of the medial and lateral frontal cortex, as well as portions of the cingulate gyrus (42).

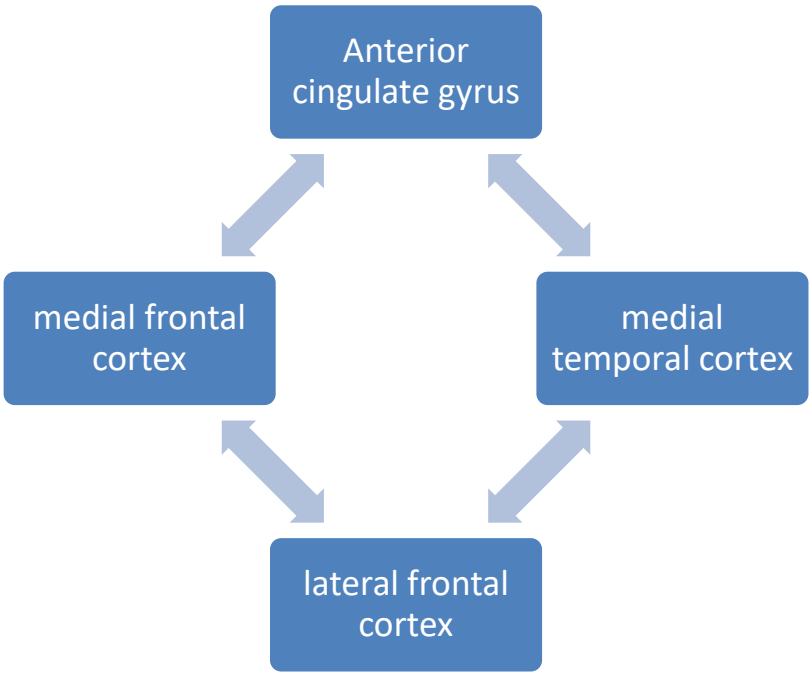

Figure 2 Schematic illustration of the limbic network (36)

1.2.4.1.2 Default network (36)

It is regarded as the second key contributor to the regulation of emotional states. This network is activated throughout emotional processing and functions in a manner similar to a switch, facilitating transitions between different emotional states. Additionally, it is involved in processes such as planning, making moral decisions, and recalling autobiographical memories (41). It encompasses regions of the temporal lobe, cingulate gyrus, frontal lobe, and portions of the hippocampus (42).

1.2.4.1.3 Frontoparietal network (36)

This network is implicated in the executive control of the emotional processing mechanism. Furthermore, it appears to be activated during tasks involving awareness and working memory (41). It is primarily located in the dorsolateral prefrontal cortex, the parietal cortex, and portions of the cingulate gyrus (42).

1.2.4.2 Hemispherical fragmentation (36)

Although all brain structures are bilaterally arranged, functional tasks are typically lateralized to one hemisphere. This principle also applies to the emotional system. Current literature suggests that emotional processes are predominantly localized in the right hemisphere. Furthermore, emotional functions are closely linked to movements and sensory processing, with activity in these functions corresponding to the activation of related motor and sensory brain regions (43, 44).

1.3 Brain imaging

Exploring the structure of the human brain through advanced imaging technologies has been a sustained effort within the field of imaging sciences. With the development of modern computer-based imaging techniques, detailed representations of human brain structure have become possible, particularly through the use of computed tomography (CT) and magnetic resonance imaging (MRI).

1.3.1 Magnetic resonance imaging (MRI)

Magnetic resonance imaging (MRI) is the most commonly employed technique for imaging brain structure. This technology utilizes magnetic field gradients to generate contrast in the resulting images.

1.3.1.1 Functional basics

The MRI signal is generated by stimulating the oscillating magnetic fields of hydrogen protons in water at their resonant frequency. The protons subsequently emit an electrical signal, which is detected by a magnetic coil. The duration required for the excited protons to return to their equilibrium state is referred to as the relaxation time. This parameter plays a crucial role in determining the contrast in the resulting images (45).

1.3.1.2 Conventional MRI

Conventional MRI images are generated using two primary relaxation times: the spin-lattice relaxation time (T1) and the spin-spin relaxation time (T2) (45). T1-weighted images are particularly useful for assessing changes in the cerebral cortex and fatty structures. These images are created by measuring the MR signal after the tissue has recovered from the magnetic stimulation (45).

T2-weighted images are the standard for detecting white matter lesions, edema, and inflammation. For these images, the MR signal is measured after allowing it to decay following stimulation (45).

A specialized T2 sequence, known as fluid-attenuated inversion recovery (FLAIR), suppresses the contrast of cerebrospinal fluid (CSF). This technique is commonly employed to evaluate white matter areas near CSF-containing regions, such as the subarachnoid space and ventricles (45).

1.3.1.3 Diffusion weighted imaging (DWI)

Diffusion-weighted imaging (DWI) is another variant of MRI. In DWI, the MRI signal is derived from the varying diffusion of protons within biological tissue. Diffusion is highly influenced by the cellular environment, and changes in water diffusion can indicate pathological abnormalities (46).

Due to Brownian motion, protons and water molecules move randomly in the absence of obstacles. In this case, protons are distributed isotropically, meaning equally in all directions. However, when movement is impeded by obstacles that restrict proton diffusion, the distribution becomes anisotropic, with a gradient developing on either side of the obstacle. This gradient, which can be described by Fick's law, generates a force that drives protons across the barrier to restore an equal distribution on both sides (47).

The diffusion signal is measured by stimulating the tissue with a pulse field gradient, causing protons to change their spin direction at different rates. A second pulse is then applied in the opposite direction to refocus the spins. Refocusing is imperfect for protons that have moved during the interval between the pulses, resulting in a reduction of the signal. This signal attenuation quantifies proton movement and the degree of diffusion.

1.3.1.3.1 Diffusion tensor imaging

Diffusion tensor imaging (DTI) is a method that enhances conventional diffusion information by providing additional data on the directional orientation of diffusion processes in three-dimensional space. In brain tissues, the microstructural anatomical conditions determine the constraints on diffusion, influencing the directionality and extent of molecular movement (47).

1.3.1.3.1.1 Diffusion tensor

The three-dimensional diffusion data are obtained using complex mathematical algorithms, which are processed through computerized procedures. The diffusion values for each voxel are mathematically integrated into a 3x3 matrix, known as the diffusion tensor (47).

$$\bar{D} = \begin{vmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{xy} & D_{yy} & D_{yz} \\ D_{xz} & D_{yz} & D_{zz} \end{vmatrix}$$

Formula 1: Matrix of the diffusion tensor (https://commons.wikimedia.org)

1.3.1.3.1.2 Diffusion ellipsoid

The diffusion ellipsoid is derived from the values of the diffusion tensor. It represents the direction and intensity of molecular diffusion. The ellipsoid's dimensions are described by three eigenvectors and their corresponding eigenvalues (λ_x). The eigenvalue along the principal axis of the ellipsoid is denoted as λ_1, while the two perpendicular eigenvalues are referred to as λ_2 and λ_3.

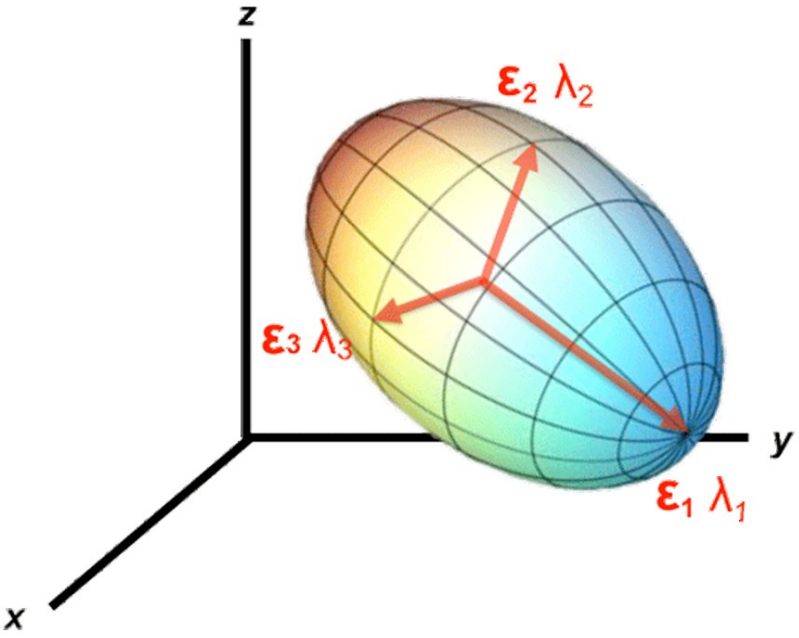

Figure 3: Diffusion ellipsoid with its eigenvectors and –values. (https://commons.wikimedia.org)

1.3.1.3.1.2.1 Axonal diffusivity

According to the microanatomy of axonal fibers, the cellular membrane acts as a barrier to diffusion. Therefore, in an intact axon, the greatest amount of diffusion occurs along the axis, as there are no restrictions in this direction. Consequently, the λ1 eigenvalue is referred to as axonal diffusivity (47).

1.3.1.3.1.2.2 Radial diffusivity

The cellular membrane restricts the movement of water molecules. Analogous to axonal diffusivity, the movement orthogonal to the principal diffusion direction is thought to occur through the membrane and is radial to the axon. The eigenvalues λ2 and λ3 associated with this movement are referred to as radial diffusivity (47).

1.3.1.3.1.2.3 Mean diffusivity (MD)

Mean diffusivity is a fundamental measure used to describe the diffusion within a single voxel. It is calculated by averaging all three eigenvalues.

$$\mathbf{MD} = (\lambda_1 + \lambda_2 + \lambda_3)/3$$

Formula 2: Mean diffusivity.

1.3.1.3.1.2.4 Fractional anisotropy (FA)

This value describes the relative distribution of diffusion within a single voxel. It is a scalar value ranging from 0 to 1, calculated as the square root of the sum of the squared diffusivities. The value indicates whether water movement is isotropic (equal in all directions, FA = 0), anisotropic (restricted to a single direction, FA = 1), or somewhere in between (0 < FA < 1). Since microanatomical structures create barriers to diffusion, changes in these structures can lead to a reduction in FA (47). The FA scalar is independent of local fiber orientation, making it a valuable and objective marker for comparing different subjects in cross-sectional studies (50, 51).

$$\mathbf{FA} = \frac{\sqrt{3((\lambda_1 - \mathbf{E}[\lambda])^2 + (\lambda_2 - \mathbf{E}[\lambda])^2 + (\lambda_3 - \mathbf{E}[\lambda])^2)}}{\sqrt{2(\lambda_1^2 + \lambda_2^2 + \lambda_3^2)}}$$

Formula 3: Fractional anisotropy

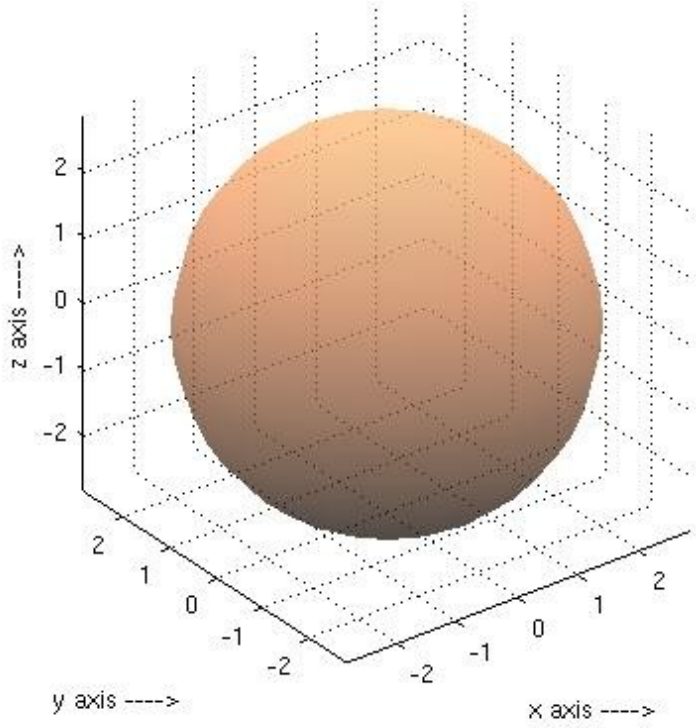

Figure 4 Spheroid with FA =0 (https://commons.wikimedia.org)

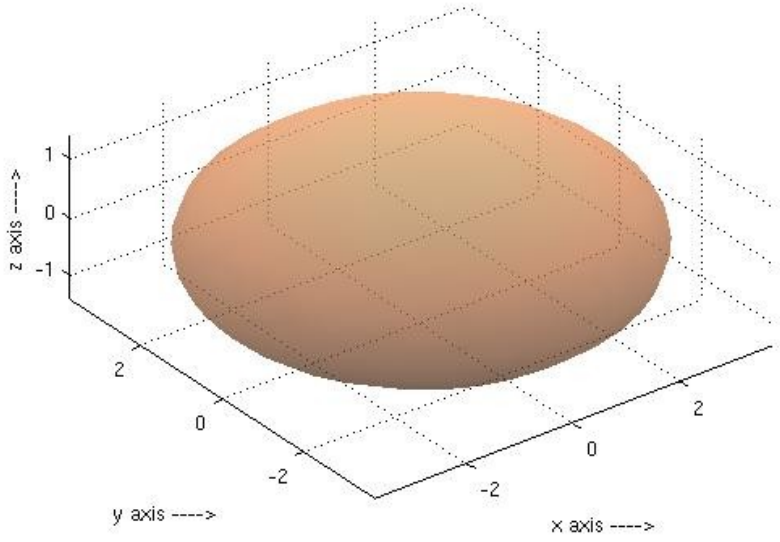

Figure 5 Spheroid with FA <1>0 (https://commons.wikimedia.org)

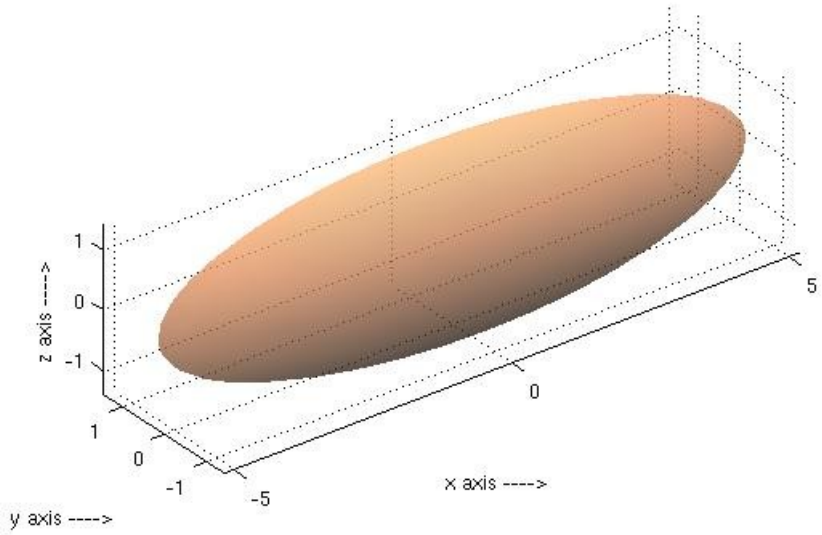

Figure 6 Spheroid with FA=1 (https://commons.wikimedia.org)

1.3.1.3.2 Diffusion data analysis

Various methods have been developed to use diffusion data in multi-subject analyses. Each method offers a unique set of advantages and disadvantages in terms of sensitivity and interpretability, particularly when identifying pathological changes in microstructure.

1.3.1.3.2.1 Voxel based morphometry (VBM)

This method was initially developed for analyzing changes in grey matter using T1-weighted structural images (52, 53). In this approach, the FA of each subject is registered into a common space, and subsequent correlations with covariates are assessed through voxel-wise statistics (50, 52). However, the registration into a common space presents a significant limitation for white matter analysis. The conventional method does not guarantee precise topographical alignment across subjects (50). For grey matter analysis, this issue can be mitigated by segmenting different structures, a technique that cannot be applied to white matter due to the indistinct boundaries and complex anatomy of fiber tracts (50).

1.3.1.3.2.2 Region of interest analysis (ROI)

This analysis enhances conventional voxel-based morphometry (VBM) results by incorporating additional complexity. FA values for each subject are extracted from a predefined region of interest (ROI), typically delineated manually. Cross-sectional comparisons are then conducted specifically for this region. This method is considered reliable for large white matter tracts, but for smaller tracts, manual ROI definition becomes impractical (50).

1.3.1.3.2.3 Tractography

The measured values of diffusion ellipsoids and tensors enable various computational methods for reconstructing white matter fiber tracts. Historically, this process required manual ROI definition, but modern techniques now utilize probabilistic fiber tracking, which allows for independent estimation without the need for manual tract definition (54, 55). Probabilistic algorithms identify fiber tracts based on the orientation of diffusion tensor and ellipsoid eigenvalues. Using this information and applying statistical methods, fiber tracts can be reconstructed with high precision, even in the absence of anatomical information (56).

1.3.1.3.2.4 Tract based spatial statistics (TBSS)

Tract-Based Spatial Statistics (TBSS) is a method designed to combine the advantages of both voxel-based morphometry (VBM) analyses and tractography. It offers an automated whole-brain analysis by addressing the alignment issue inherent in VBM, through the estimation of a 'group mean FA skeleton.' This model represents the central core of all fiber bundles common to all analyzed subjects. The FA data from each subject is projected onto this mean skeleton, with each voxel of the skeleton taking the FA value from the local center of the nearest relevant fiber tract (50).

1.3.1.3.2.4.1 Pre-processing

The first step involves pre-alignment to correct for head motion during the scan. Next, the diffusion tensor and eigenvalues are calculated, and brain tissue is separated from non-brain tissue using standard brain extraction software (50).

1.3.1.3.2.4.2 Nonlinear alignment

An important consideration during the alignment of different FA images is ensuring that the applied method does not alter the fundamental characteristics of the image, thereby preserving its information about the underlying conditions, such as white matter tract structure. To achieve this, a program called the 'Image Registration Toolkit' (57) is used, which employs complex interpolation algorithms (50).

1.3.1.3.2.4.3 Statistics

The statistical techniques employed in this method primarily focus on local FA differences between two groups (e.g., patients vs. controls). To assess these differences, univariate linear modeling is commonly applied. Additionally, a correction for multiple comparisons is performed. While Bonferroni correction is often considered overly conservative, a permutation-based approach is typically regarded as the most robust method for post-hoc analysis (50).

1.4 White matter changes in bipolar disorder

Biological research investigating the underlying mechanisms of severe psychiatric disorders, such as BD, targets a broad range of factors, including genetics, systemic inflammation, and both functional and structural changes within the brain (9, 58-62). These research efforts have provided substantial evidence suggesting that compromised white matter (WM) microstructure is a key factor in the pathophysiology of BD (63-68). Disruptions in white matter integrity are associated with various alterations in critical brain functions, including neurocognitive deficits, disease severity, and other related factors (69-72).

1.4.1 General white matter changes

Several studies have reported general changes in brain microstructure in individuals with BD. Multiple publications indicate lower FA across the entire brain in BD patients compared to HC (72, 73). These findings suggest that such changes have a significant impact on individuals with BD. However, these alterations appear to be nonspecific, making it difficult to derive functional consequences directly from these results. It may be hypothesized that widespread white matter damage leads to functional disconnections between various brain regions, including cortical and limbic structures (74, 75).

1.4.2 Particular white matter changes

Beyond the general changes noted, some studies have identified specific microstructural abnormalities in certain white matter regions.

1.4.2.1 Corpus callosum

The corpus callosum (CC), which contains the largest concentration of white matter fibers in the human brain, has shown significant changes, particularly in individuals with BD, according to recent studies (76-80). Several findings report decreased FA in the splenium and genu of the CC in BD patients (67, 81, 82). Similar results have been observed in adolescents whose parents suffer from BD (83). Overall, altered development of the CC has been identified as a potential marker of vulnerability to BD in youth from high-risk families, suggesting a possible onset of the disorder associated with degenerative changes within this structure (84).

In addition to diffusion tensor imaging (DTI) findings, morphometric data have also shown associations between BD diagnosis and structural changes in the CC, including reduced volume in both the anterior and posterior portions of the corpus callosum (85).

1.4.2.2 Association tracts

Several studies have reported a significant reduction in FA in both the superior and inferior tracts of the longitudinal fasciculus in comparison to HC. No significant differences have been found between the left and right hemispheres regarding the location of the microstructural deficit. However, some results suggest that changes are more pronounced in the inferior tract than in the superior fasciculus (72).

Tractography analyses have specifically shown that the widespread reduction in FA observed in the right temporal white matter primarily affects tracts within the fronto-occipital fasciculus (86).

Data on the uncinate fasciculus are limited, but some studies have reported reduced FA in the uncinate fasciculus and adjacent regions (72).

1.4.2.3 Projection tracts

1.4.2.3.1 Thalamic radiation

A significant number of studies have reported changes in the fiber tracts of the thalamus, primarily focusing on the anterior and superior regions of the thalamic radiation. These studies describe not only a reduction in FA, a common marker of microstructural damage, but also an increase in FA compared to HC (72).

1.4.2.3.2 Corona radiate

Some studies have reported differences in the posterior regions of the corona radiata and its large projection fibers between individuals with BD and HC. These findings were obtained through voxel-based analysis, but to date, they have not been replicated using methods such as TBSS analysis (72).

1.5 Associations between structural brain abnormalities and clinical co-factors of BD

BD manifests clinical symptoms across a wide range of variation in each affected individual. Consequently, studies investigating BD are confronted with the challenge of addressing a highly heterogeneous group of patients in terms of clinical symptoms. One potential approach to specify the analysis is to subcategorize the samples by focusing on more homogeneous clinical parameters (87).

1.5.1 Clinical subtype (BD I vs. BD II)

Studies comparing the BD-I and BD-II subtypes have employed various methodological approaches and have focused on different regions of the brain, including both grey and white matter structures.

1.5.1.1 Structural MRI

Structural MRI studies have consistently identified morphological brain abnormalities in BD, with the most robust findings localized to fronto-limbic circuits. Reductions in gray matter volume have been reported in the prefrontal cortex, particularly in orbitofrontal and dorsolateral regions, as well as in the anterior cingulate cortex—areas central to cognitive control and emotion regulation. Alterations in limbic structures, including the amygdala and hippocampus, further underscore dysfunction in networks that mediate affective processing and memory. While the specific patterns of change may vary across studies, converging evidence indicates that BD is characterized by structural disruptions in neural systems responsible for regulating mood, stress reactivity, and executive functions (89). In patients with BD I, grey matter volume appears to be reduced in the right orbitofrontal and left temporal regions when compared to BD II (79). Generally, both diagnostic domains are likely characterized by a focal loss of gray matter in regions functionally associated with executive functions (90). Additionally, in other regions such as the frontal, occipital, and cingulate areas, grey matter volume also appears to be lower in BD I than in BD II (90).

1.5.1.2 DTI

Diffusion tensor imaging studies in BD consistently show abnormalities in white matter pathways implicated in emotion regulation and cognitive control. Alterations in the uncinate

fasciculus and superior longitudinal fasciculus, which connect prefrontal regions with limbic and temporal areas, suggest impaired fronto-limbic connectivity that may underlie mood dysregulation in BD (91). Large-scale meta-analyses further demonstrate widespread and heterogeneous reductions in white matter integrity across multiple tracts, supporting a network-level pathology rather than isolated focal disruptions (92).In the temporal regions, white matter integrity, as measured by fractional anisotropy (FA), appears to be lower in BD II patients compared to BD I (79). However, there are also contradictory findings in this area of research, with some studies reporting higher FA values in temporal brain regions and lower diffusion coefficients in various brain regions, including the temporal and frontal areas (87).

1.5.1.3 fMRI

Functional analyses have shown that ventral striatal activity may be increased in BD-II compared to BD-I. Furthermore, the emotional reactivity of the amygdala appears to be downregulated to a greater extent in BD-I than in BD-II (63, 89).

1.5.2 Cognitive dysfunction

Cognitive dysfunctions or impairments are among the most prominent symptoms observed throughout the course of chronic psychiatric disorders. In BD, these conditions are present in several individuals, but not in all. The specific brain processes underlying this effect remain largely unknown. However, the presence of cognitive dysfunction can serve as a parameter to distinguish clinical subgroups with a more severe course of illness. From this perspective, several analyses have been conducted to explore potential differences in brain structure.

1.5.2.1 Structural MRI

Structural MRI analyses in this field employ various methodological approaches depending on the target of investigation. Some data have shown a negative correlation between functional cognitive domains and deep white matter hyperintensities (93). Left lateral ventricular volume was found to be associated with reduced motor speed performance and interference control, while temporal cortical surface volume was linked to processing speed performance (93). Deficits in executive functions appeared to be correlated with

lower grey matter volumes in the right inferior frontal, precentral, and postcentral regions (94).

1.5.2.2 DTI

Data have highlighted numerous associations between attention and information processing, executive functions, and working memory on the one hand, and various DTI parameters, particularly fractional anisotropy (FA) in the thalamic radiation, longitudinal fasciculus, and corpus callosum on the other (98). Connectome analyses have demonstrated correlations between cognitive parameters (e.g., processing speed) and interhemispheric connections (99). Microstructural abnormalities in the thalamic radiation and fornix appear to be linked to cognitive deficits (78, 100).

1.5.2.3 fMRI

Cognitive functions in BD patients related to interference task performance were associated with activation in the right temporal gyrus (98). A positive functional association between episodic memory performance and the superior and middle frontal gyrus was also reported (97).

1.5.3 Psychotic symptoms

1.5.3.1 Structural MRI

Patients with a history of psychotic symptoms exhibit differences in several brain areas that are generally thought to be involved in the pathogenesis of BD. The corpus callosum and right globus pallidus appear to be enlarged in patients with a history of psychotic symptoms compared to those without (99, 100). Additionally, ventricular volumes seem to differ, with left lateral and third ventricle volumes appearing larger in patients with psychotic symptoms (101, 102). Furthermore, grey matter volumes in the prefrontal cortex and insula are likely reduced in a subgroup of patients with psychotic symptoms (103).

There is one study that has analyzed differences in patients with BD using DTI. It demonstrated microstructural differences within the corpus callosum, although the effect was not particularly pronounced (99).

1.5.3.2 fMRI

Patients with a history of psychotic symptoms exhibited multiple functional differences across the brain. These changes were primarily observed in the parietal regions, including the angular gyrus and temporal gyrus, and were mainly associated with working memory tasks (87, 104).

1.5.4 Treatment response

Data suggest that non-response to lithium treatment is associated with smaller amygdala and left hippocampal volumes (105). In contrast, responders show an increased volume in the prefrontal cortex (105, 106).

One study reported differences in white matter microstructure in patients with BD depending on whether they were treated with lithium. In a general brain analysis, patients treated with lithium exhibited higher mean FA and lower mean mean diffusivity (MD) compared to those not receiving lithium treatment (107).

The amygdala appears to be a key region regarding treatment response. Increased amygdala activity prior to treatment seems to predict response (108). Additionally, altered connectivity between the prefrontal cortex and the amygdala is also likely to predict treatment response (87).

Table 5: Associations between structural brain abnormalities and clinical co-factors of BD; sMRI= structural magnetic resonance imaging; DTI= diffusion tensor imaging; fMRI= functional magnetic resonance imaging

	sMRI	**DTI**	**fMRI**
BD-I vs. BD-II	Volume reduced (BDI) in orbito-frontal right. temporal lobe left, frontal, occipital, cingulate	FA in BDII is lower in temporal area than BDI	Ventral striatal activity is increased in BDII. Emotional reagibilty of amygdala is downregulated in BDI
Cognitive dysfunction	Deep WMH are neg. correlated with functional cognitive domains. Left lateral ventricular volume is corr. with reduced motor speed performance/interference control. Reduced temporal cortical surface volume is neg. corr. with processing speed performance. Volume reduction in right frontal, pre- and postcentral areas correlate with deficits in executive functions.	FA in thalamic radiation, longitudinal fasciculus and corpus callosum correlates neg. with executive functions and working memory. Reduced microstructural integrity in fornix is related to reduced cognitive functions	Functional association episodic memory performance/frontal gyrus. Activation in right temporal gyrus in interference task functions.
Psychotic symptoms	Increased volumes of corpus callosum and right globus pallidus. Increased volume of right lateral and third ventricle. Lowered grey matter volume in prefrontal cortex and insula.	Inconsistent results. Microstructural changes in corpus callosum.	Changed activity focused in parietal regions concerning working-memory tasks.
Treatment response	Lithium non-response is related to reduced left amygdala and hippocampus volume. Increase of prefrontal cortex volume in lithium responders.	Patients with lithium treatment showed higher FA in whole-brain analysis than those without	Greater amygdala activity and altered connectivity between amygdala and prefrontal cortex prior treatment predicts treatment response.

1.6 Biological co-factors of BD

Various structural changes in BD can be identified in different ways. An important question in this context is which other biological factors may be involved in the pathological processes of BD and how they might influence brain microstructure.

1.6.1 Inflammation (16)

There is strong evidence of increased immune-inflammatory activity in BD (109-112). Reported differences vary between stage-dependent and trait-dependent changes (111-115). Recent studies have focused on identifying inflammatory parameters as potential biomarkers for illness progression and treatment strategies in BD (116, 117). However, the relationship between inflammatory markers and microstructural changes in the brain remains unclear.

The influence of various inflammatory pathways appears to be mutually reinforcing and affects a broad range of cells and systems (118). The connection between BD and the inflammatory system can be epidemiologically assessed through the higher rates of inflammatory comorbidities, such as autoimmune hypersensitivity reactions like asthma and allergies, in the BD population (119).

1.6.1.1 Acute phase proteins

Changes in inflammatory domains in patients with BD can be observed as elevations in proinflammatory elements such as cytokines, prostaglandins, acute-phase proteins, as well as in inflammatory gene expression (119-121). For example, a general elevation of IL-6 is observed in individuals with BD compared to HC (113, 122, 125). Elevated levels are particularly prominent in patients during acute manic and depressive states (110, 112, 113, 115).

C-reactive protein (CRP) plays a key role in the inflammatory cascades throughout the human body and is considered one of the most reliable markers of a general inflammatory state. CRP levels appear to be altered during all clinical states of BD (124). Additionally, elevated CRP levels during depressive episodes may increase the risk of transitioning into a manic state (125).

Evidence also suggests that specific patterns of cytokine expression depend on the duration of the illness and the phase (depression or mania) (126). Elevations in proinflammatory

cytokines, such as IL-6, during depressive phases increase the likelihood of a subsequent manic phase (121, 126).

Some parameters, such as TNF-α, seem to remain elevated throughout all stages of BD. TNF-α is primarily released by microglia to recruit peripheral monocytes into the central nervous system (CNS) and increases the permeability of the blood-brain barrier, creating a proinflammatory milieu thought to contribute to chronic neurodegeneration (121).

Furthermore, increased activation of T-cells has been observed in BD patients, as indicated by a higher Th1/Th2 ratio (a measure of proinflammatory cytokines) (127).

1.6.1.2 Treatment and inflammation

Overall, there are no consistent findings regarding the effect of anti-inflammatory treatments. However, evidence points to a moderate class effect (118). Several anti-inflammatory substances have been proposed as potentially having antidepressant effects, such as pioglitazone, minocycline, or TNF-α blockers like etanercept (121, 128). Data on their effects on manic episodes are limited (118). Preliminary findings suggest that substances like N-acetylcysteine, celecoxib, and L-tryptophan may be beneficial (121).

Currently, no concrete clinical applications of anti-inflammatory substances can be derived from these results. However, there are indications that anti-inflammatory agents may be most effective in patients with elevated baseline inflammatory markers (118).

1.6.1.3 Oxidative Stress

There is a functional link between cellular energy production, oxidative stress, and inflammatory cell activation. Most of these inflammatory processes are mediated by endogenous reactive oxygen species (ROS), which are produced and released by the mitochondria (129). It is suggested that BD may involve less efficient cellular energy production, as evidenced by structural alterations in mitochondria and impaired antioxidant capacity (118, 129). These hypotheses are supported by findings showing morphological differences in mitochondria in tissue samples from BD patients (129). Various reports indicate general differences in oxidative markers in both cellular and peripheral compounds, although a strict connection with clinical features of BD is rarely found (118). However, there is evidence suggesting that lithium treatment may increase mitochondrial activity and reduce oxidative stress markers (130).

1.6.1.4 Glutamate Signalling

Synaptic functioning is often impaired in most psychiatric disorders. Glutamate is described as a mediator of dendritic functioning through NMDA and AMPA receptors (131). The processes within the glutamate system are highly complex, and several studies suggest interactions with proinflammatory mediators, which lead to changes in glutamate release and reuptake (118). Altered glutamate levels result in the overactivation of extrasynaptic NMDA receptors, suppressing the synthesis of various neuronal growth factors and potentially leading to dendritic atrophy and neuronal loss (132).

Cytokine activity is a major trigger for glutamate metabolism. This effect arises from the fact that several promoter regions for glutamate reuptake receptors are responsive to immune signaling molecules such as TNF (132). The clinical impact of these interactions is primarily due to the CNS's high sensitivity to changes in its surrounding inflammatory environment.

Due to the high metabolic activity and complexity of metabolic and functional processes in CNS tissues, they are more susceptible to oxidative damage and inflammation compared to other tissues (133). In the CNS, interactions between neurons and glial cells can lead to increased oxidative stress and inflammation. The influence of oxidative stress impairs astrocytic glutamate reuptake, inducing microglial glutamate release and perpetuating a cycle of excitotoxicity (133). In this multifocal and multidirectional context of microinflammation, inflammatory cytokines may play a key role.

1.6.1.5 Connection between Major Psychiatric Disorders

Major depressive disorder, BD, and schizophrenia share some symptom similarities and overlap in several areas (118). These similarities may suggest a common underlying process in the pathogenesis of these disorders, potentially related to dysfunctions in various neurotransmitter systems. All of these mental disorders exhibit specific alterations in glutamate activity and changes in neurodendritic density (134). Furthermore, there are several parallels between these conditions, including the activity of glial cells, dopaminergic signal transduction, and mitochondrial function. While the precise cause of these connections cannot be determined causally, overlaps in candidate genes, such as DISC1, have been identified (135).

1.6.2 Age

In general, neurodegenerative processes in the brain are associated with aging (136). To some extent, changes in volume and microstructure are considered a symptom of physiological aging processes (59, 137). This fact is of significant importance in brain imaging studies when investigating disease-specific effects on the brain (137).

1.6.3 Sex

Although there are only limited data showing an association between sex and microstructure in BD, numerous studies demonstrate sex-related differences in various other aspects of BD. Findings report differences in the volumes of the amygdala, hippocampus, insula, and thalami between male and female individuals with BD (138-140). In light of these results, sex should be considered an important variable in neuroimaging studies (137).

1.6.4 Overweight and Life-Style

Severe mental illnesses such as BD do not only manifest with specific clinical symptoms; they also interfere with more general aspects of lifestyle and social behavior. One major area of research focuses on the generally reduced physical activity and unhealthy eating behaviors, which are common risk factors for obesity and metabolic syndrome in BD (58, 141, 142).

1.6.4.1 Brain-structure and obesity

Generally, there is strong evidence that elevated BMI is associated with changes in brain structure, particularly with volume loss in areas involved in emotion processing and higher cognitive functions (143, 144). The extent of brain volume loss over time, as a symptom of aging, is also greater in obese individuals (136). Additionally, specific findings for white matter show that structural disturbances and volume loss are associated with higher BMI following the first episode of mania (145, 146).

1.7 Aims and hypothesis

The foregoing summary of the current knowledge on the association between microstructural abnormalities and various aspects of BD provides strong evidence for the involvement of these changes in the pathophysiology of BD. However, the results published so far appear to be highly heterogeneous, and valid information with direct clinical implications is still lacking. This gap in knowledge motivated me to pursue research that may uncover potential associations between microstructure, clinical variables, and biological factors that could ultimately be considered as potential biomarkers in BD. Based on the current data, I focused on inflammation and its most relevant and commonly used markers in my analysis.

1.7.1 Hypothesis 1 (microstructural differences BD vs. HC)

There are clusters showing significantly lower FA in individuals with BD compared to our HC group. To verify this hypothesis, I conducted a statistical group comparison using TBSS .

1.7.2 Hypothesis 2 (impact of inflammation to BD)

In general, inflammatory markers are associated with the course of illness in BD. I applied a statistical correlation analysis to study associations between inflammation parameters, clinical data, and selected co-factors.

1.7.3 Hypothesis 3 (association of microstructure and inflammation)

By combining both factors, microstructure shows a significant association with inflammatory parameters. To study this more in detail, I also used TBSS to identify clusters with significant correlations.

2 Material and Methods

The investigation of microstructural deficits in BD is part of an ongoing research project, the 'Bipolar Disorder and Fat Metabolism (BIPFAT) Study.' All participants were recruited from the sample of the BIPFAT Study. A total of 163 individuals were included in our analysis, comprising 107 patients with BD and 56 healthy controls (HC).

It should be noted that statistical analysis of the inflammation parameters was not conducted concurrently with the Diffusion Tensor Imaging (DTI) studies. Furthermore, as not all parameters were collected for every participant, the number of individuals included in specific analyses may vary.

2.1 BIPFAT-Study

The BIPFAT Study is a single-center research project conducted at the Division of Psychiatry and Psychotherapeutic Medicine, Medical University of Graz. The aim of the study is to assess various aspects of the potential biological underpinnings and influences of BD. It focuses on anthropometric, metabolic, and inflammatory measurements, as well as genetic factors. Another key component involves neuropsychological testing, which is conducted using a wide range of assessments and psychometric instruments (e.g., HAMD, BDI, YMRC, D2, Stroop, etc.). The third aspect of the study includes functional and structural brain assessments, incorporating EEG and MRI. Some of the results from our MRI program have already been published (59).

All patients included in the study were former inpatients or outpatients of the Division of Psychiatry and Psychotherapeutic Medicine at the Medical University of Graz. The diagnosis of BD was made according to the DSM-V criteria, utilizing the SCID-I interview and medical history records. Exclusion criteria included the presence of any acute or chronic inflammatory or rheumatoid disease, as well as any neuroinflammatory or neurodegenerative disorders. For healthy controls (HC), exclusion criteria also included a history of any psychiatric disorder or having first- or second-degree relatives with a psychiatric disorder.

The study has been approved by the Ethics Committee of the Medical University of Graz (EK-number: 24-123 ex 11/12) and complies with the ICH guideline for Good Clinical Practice and the Declaration of Helsinki.

Further details of the study can be obtained from other recent publications by our research group, which address different aspects of the analysis (9,10,58,60-62,147).

2.2 MRI

Participants were scanned using a 3.0-Tesla MRI scanner (Siemens Trio). For DTI images, a single-shot, diffusion-weighted spin echo echo-planar imaging sequence was employed (TE/TR = 80/8400 ms; matrix size = 128x128x50; 80 axial slices, voxel size 1.9 x 1.9 x 2.5 mm^3) with 18 orientations for the diffusion-sensitizing gradients at a b-value of 1000 s/mm^2. To screen for brain pathology, T1, T2, and FLAIR sequences were acquired.

2.2.1 Image processing

The diffusion-weighted images were initially corrected for eddy current distortions and motion using the Eddy Correct utility in FSL FDT (55,148). A brain mask was extracted from the b0 image using automated skull stripping (148). Diffusion tensor estimation was performed on the voxels within the brain mask using FSL FDT (55), which resulted in a fractional anisotropy (FA) value for each voxel. Raw DTI and FA images underwent quality control through independent visual inspection by two researchers (RQ, SS). A total of 119 MRI scans underwent this procedure. T1, T2, and FLAIR images were reviewed for pathological changes by an experienced neurologist.

2.2.2 Tract based spatial statistics

Voxel-wise statistical analysis of the FA data was conducted using Tract-Based Spatial Statistics (TBSS) (50), a component of FSL (149). The FA data from all subjects were aligned into a common space using the nonlinear registration tool FNIRT (150), which employs a b-spline representation of the registration warp field (57). A mean FA image was generated and thinned to create a mean FA skeleton, which represents the centers of all tracts common to all participants (50,149).

To identify voxels where FA was significantly lower between the BD and HC subgroups, as well as those in which FA was significantly associated with inflammatory parameters (hsCRP), voxel-wise statistical analysis was performed using a generalized linear model. A non-parametric permutation test was conducted as a post-hoc analysis using the permutation-based statistical inference tool "RANDOMISE," part of FSL. Five thousand permutations were performed to construct the null distribution. Significant clusters were

identified using threshold-free cluster enhancement (TFCE) (151), with multiple comparisons corrected using the default values provided by the -T2 options of "Fsl-Randomise," which are optimized for TBSS (152).

Due to their known influence on brain structure from previous studies age, gender, sex, mood stabilizing treatment (lithium, atypical antipsychotics, antiepileptics), and illness duration were included as covariates. A p-value < 0.05 was considered statistically significant.

2.3 Statistics

For the statistical analysis, in addition to the methods included in the TBSS approach, SPSS was used.

2.3.1 General descriptive Data and group- differences

For the general group difference analysis between BD and HC, we used Student's t-test for normally distributed variables. For non-normally distributed data, the Mann-Whitney U-test was applied. A p-value < 0.05 was considered statistically significant.

2.3.2 Inflammation (16)

The analyses were conducted separately for men and women. Due to the absence of a normal distribution, the Mann-Whitney U-test was selected to compare differences between the male and female subgroups. Possible covariates were identified by detecting differences in IL-6 and hsCRP levels using the Mann-Whitney U-test for smoking, cardiovascular disease, and current medication intake, including atypical antipsychotics, lithium, antidepressants, and anticonvulsants (16). Associations between IL-6 and hsCRP levels and the number of depressive/manic episodes, illness duration, global assessment of function, affective symptoms (as measured by BDI, HAM-D, YMRS), and Body Mass Index (BMI) were determined through partial correlation. Error probabilities < 0.05 were considered statistically significant (16).

For the analysis of the relationship between hsCRP levels and the duration of lithium treatment over time, a Student's t-test was applied, given the normal distribution of the data.

3 Results

Based on my three main hypotheses, the analyses outlined in the following chapters were conducted.

3.1 Microstructural differences BD vs. HC

In the current investigation, 119 individuals with BD, with a mean age of 43.06 (SD 14.33), were included (45.4% females). The BD group had a mean illness duration of 18.65 years (SD 12.79). A total of 62 individuals were included in the HC group.

The applied analysis revealed a significant ($p < 0.05$) reduction in FA across a broad cluster of the corpus callosum (CC), encompassing both anterior and posterior parts, in individuals with BD compared to the HC group. The results were corrected for age and sex. The overlay of the TBSS results on a standardized brain model indicated that the affected clusters are primarily located in the commissural fibers of the major and minor forceps.

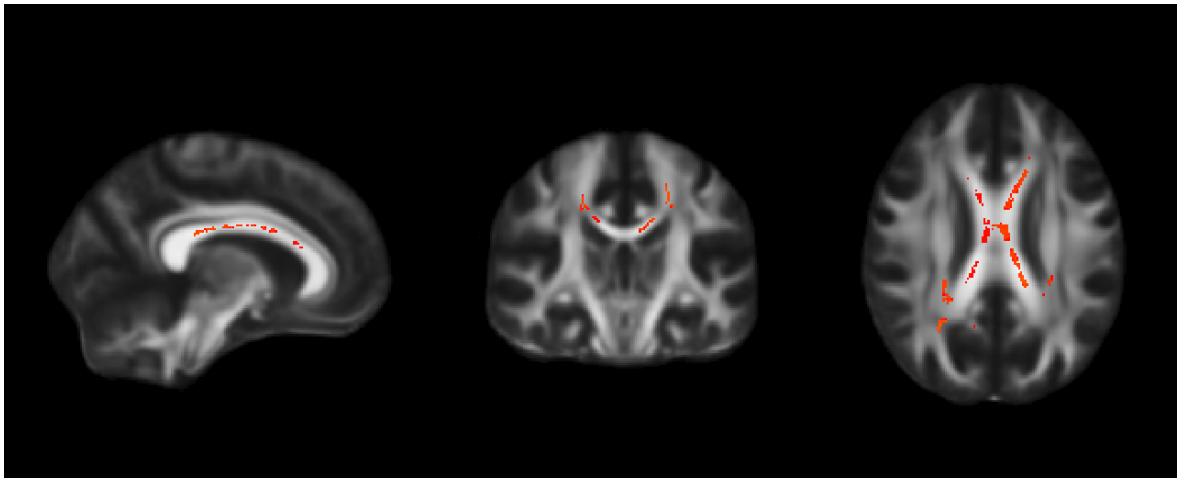

Figure 7 Clusters with significant lower FA in BD vs. HC shown in red and orange

3.2 Impact of inflammation to BD (16)

The general descriptive statistics for this analysis can be found in Table 6. Except for the YMRS, no significant differences were observed between the male and female subgroups for all variables analyzed. Clinically, the YMRS scores were sufficiently low to be demmed irrelevant for the present analysis.

Table 6: Descriptive statistics (16)

	Female		**male**		**Statistical significance[1]**
		92 (48,4 %)		*98 (51,6 %)*	
	M	***SD***	***M***	***SD***	
Age	43.09	12.61	44.89	14.71	n.s.
High-sensitive-CRP mg/dl	3.41	4.03	2.68	4.13	n.s.
Interleukin-6 mg/dl	3.22	4.84	3.10	2.64	n.s.
Number of depressive episodes	18.51	25.03	12.94	11.32	n.s.
Number of manic episodes	11.96	21.12	11.12	17.60	n.s.
BMI	27.59	6.00	25.59	5.78	n.s.
BDI	17.77	11.87	13.02	9.99	n.s.
HAMD	6.61	5.11	5.38	4.41	n.s.
YMRS	1.74	3.77	2.35	4.00	P < .05
Smoker	49%		48%		
Vascular disease	9%		15%		
Substance use	12%		13%		
Alcohol use	11%		18%		
Lithium	31%		40%		
Atypical antipsychotics	73%		57%		
Antidepressants	62%		63%		

***Note*. M= mean, SD= standard deviation, n.s. = not significant, BMI = Body Mass Index; BDI = Beck Depression Inventory; HAMD = Hamilton Depression Scale; YMRS = Young Mania Rating Scale; [1]Mann-Whitnney-U Test males versus females**

3.2.1 Covariates

3.2.1.1 Analyses of possible covariates (16)

3.2.1.1.1 Male

The male individuals with BD showed a significant correlation between BMI and hsCRP *(r = 0.380, p = 0.008, n = 98)* as well as IL-6 *(r = 0.381, p = 0.010, n = 96).* Among these male patients, smokers had significantly higher levels of hsCRP *(p = 0.012)* and IL-6 *(p = 0.017)* compared to non-smokers. IL-6 levels were significantly higher *(p = 0.002)* in men with BD and vascular diseases compared to those with BD without vascular disease. Treatment with atypical antipsychotics was associated with significantly lower levels of hsCRP in this subgroup *(p = 0.029)* (16).

3.2.1.1.2 Female

In the female subgroup, a significant correlation was found between hsCRP and *BMI (r = 0.470, p = 0.000)*. YMRS showed significant correlations with hsCRP *(r = 0.318, p = 0.006)* and IL-6 *(r = 0.288, p = 0.017)*. Lithium treatment was associated with higher hsCRP levels in female patients *(p = 0.031,)*(16).

3.2.1.2 *Correction of covariates* (16)

The covariates used for the different correlation analyses are presented in Table 7.6. Since no statistically significant differences were found in the levels of IL-6 or hsCRP between individuals currently treated with antidepressants and those not treated in this sample, we decided not to include this parameter as a covariate.

In addition to the parameters described above, age and illness duration were included as covariates in all analyses, as the number of episodes and illness duration can be assumed to be directly correlated. There was no significant difference in the number of manic or depressive episodes between men and women in our sample.

Table 7: Used covariates in correlation analysis

	Male	**Female**
Ilness episode vs. hsCRP	Smoking, BMI	YMRS, BMI,

Illness episode vs. IL-6	Smoking, BMI, Antipsychotics, Vascular diseases	YMRS, BMI, Lithium

3.2.2 Inflammatory markers and illness course (16)

There was a statistically significant positive correlation between the number of manic and depressive episodes and hsCRP and IL-6 levels in female patients with BD (see table). However, no significant correlations were found between the number of manic and depressive episodes and hsCRP or IL-6 in male patients (16).

The correlation between illness duration and hsCRP or IL-6 did not reach statistical significance in either male or female patients.

Due to potential outliers in the statistical analysis, we performed the same analysis on this sample, excluding individuals who had more than 60 lifetime manic or depressive episodes (16). The statistically significant correlation between manic episodes and IL-6 *(r = 0.402, p = 0.001)* as well as depressive episodes and IL-6 *(r = 0.301, p = 0.009)* in the female subgroup remained.

Table 8: Partial correlations between inflammation markers and the number of depressive and manic episodes respectively depending on sex. (16).

	Group	Number of depressive episodes	Number of manic episodes
High-sensitive-C-Reactive Protein	male	.27 (n = 77)	.25 (n = 78)
	female	.03* (n = 88)	.01* (n = 87)
Interleukin-6	male	.24 (n = 73)	.27 (n = 74)
	female	.04* (n = 78)	.01* (n = 78)
Note.* ***p* < .05;**			

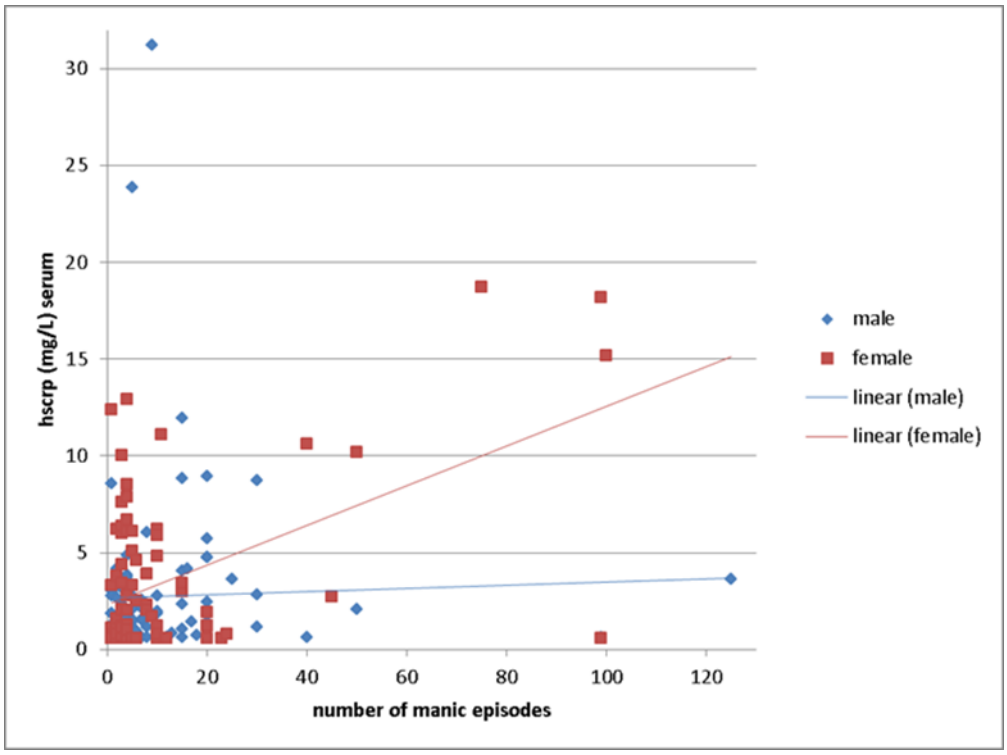

Figure 8 Correlations between number of manic episodes and hsCRP (16)

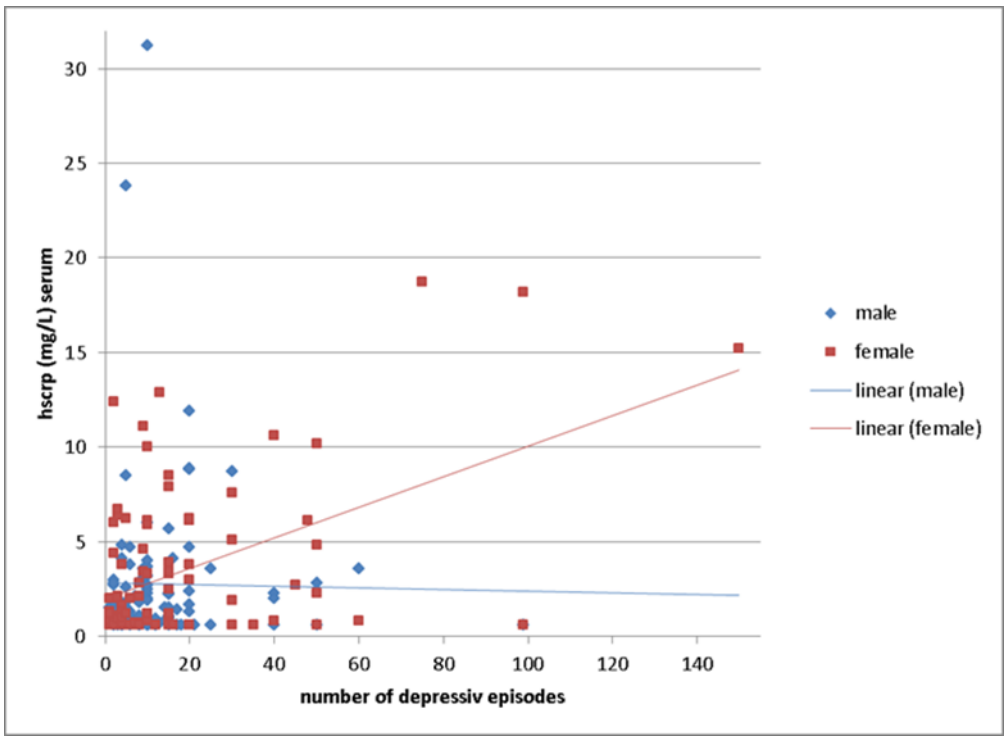

Figure 9 Correlations between number of depressive episodes and hscrp (16)

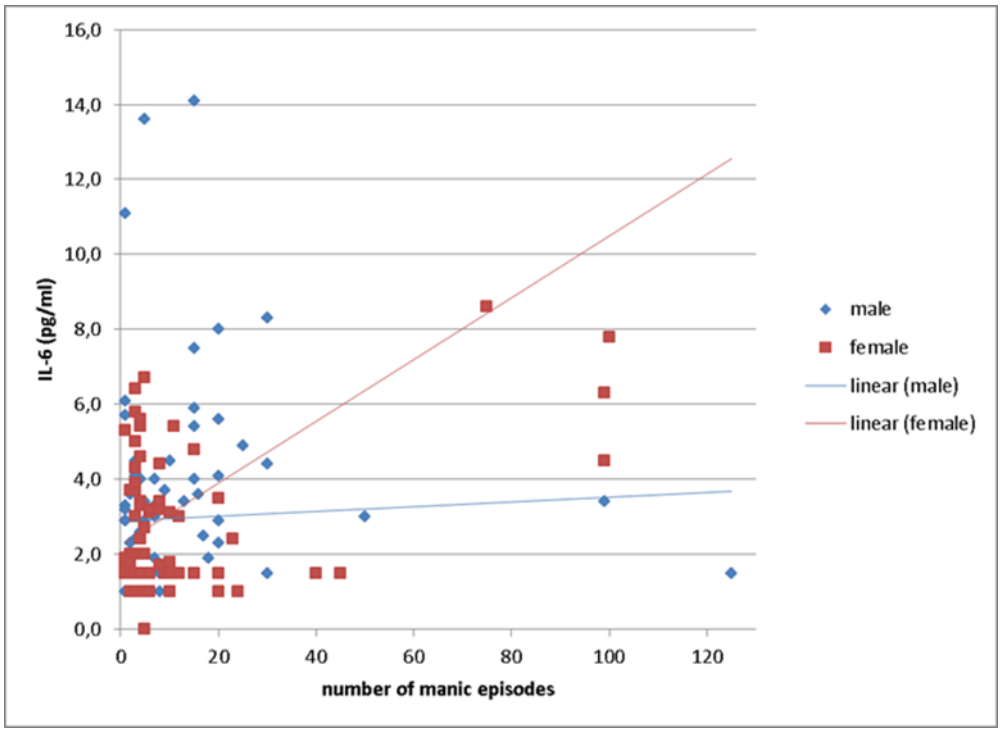

Figure 10: Correlations between number manic episodes and IL-6 (16)

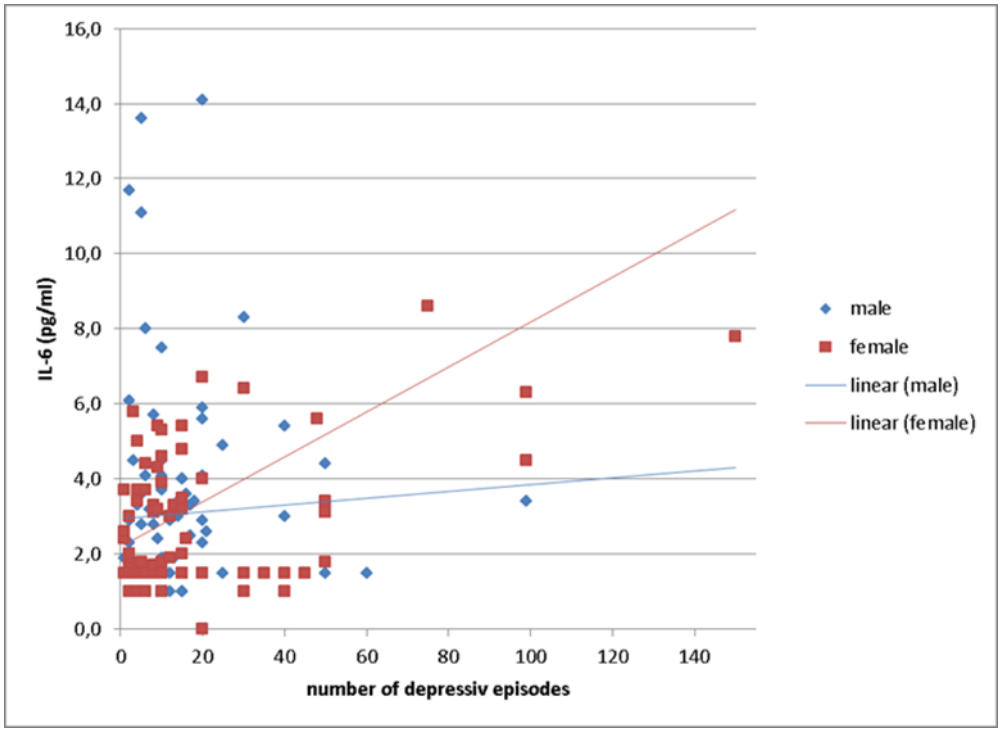

Figure 11 Correlations between number of depressive episodes and IL-6 (16)

3.2.3 Inflammation and duration of lithium treatment

In addition to the mentioned associations concerning inflammation, another analysis revealed a significant negative correlation *(r = -0.276, p < 0.05)* between the duration of lithium intake (*M = 5.7 years , SD = 7.8)* and hsCRP levels *(M = 3.0 years , SD = 4.0)*. Inflammatory parameters were significantly lower in individuals who had been treated with lithium for a longer period.

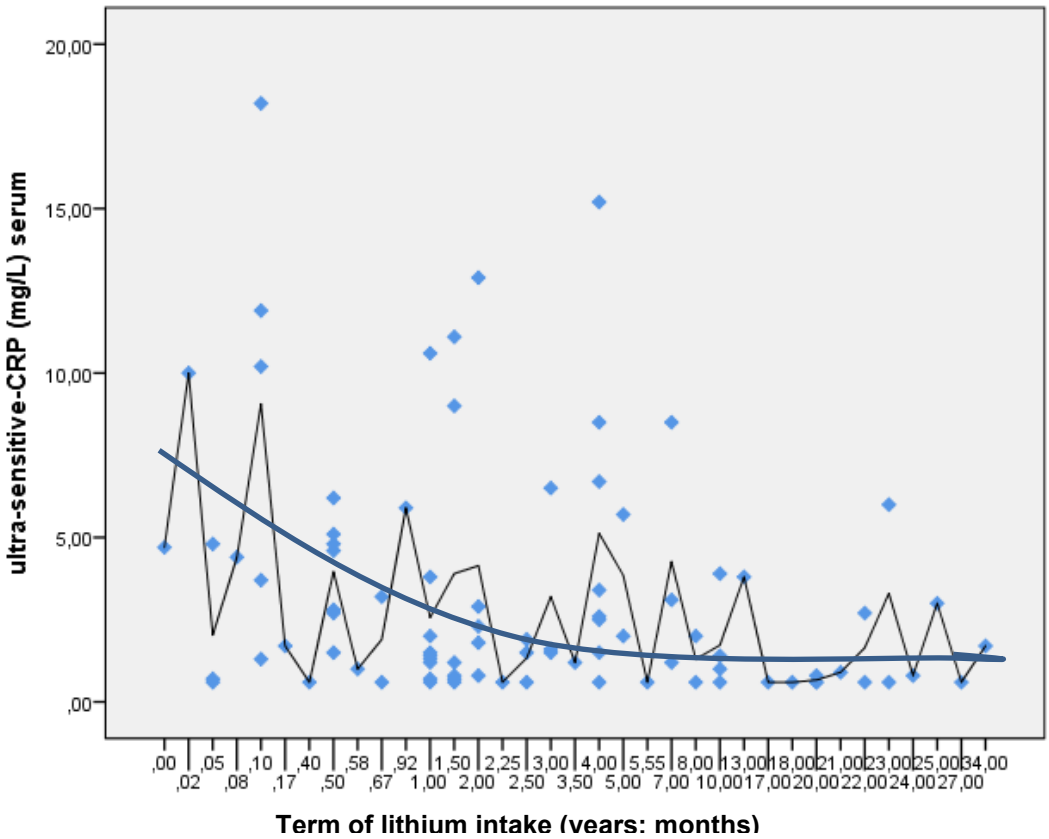

Figure 12 Correlation between duration of lithium-intake and hsCRP

3.3 Microstructure and inflammation

In a third step, we sought to find an association between inflammatory parameters and brain microstructure. We identified some voxel clusters that showed a correlation between lower FA and higher IL-6 and hsCRP levels. However, there were no voxels in which the correlation reached statistical significance after the applied post-hoc analysis (hsCRP p = 0.67; IL-6 p = 0.85). All the correlating voxel clusters were primarily located in the left hemisphere at various widespread locations.

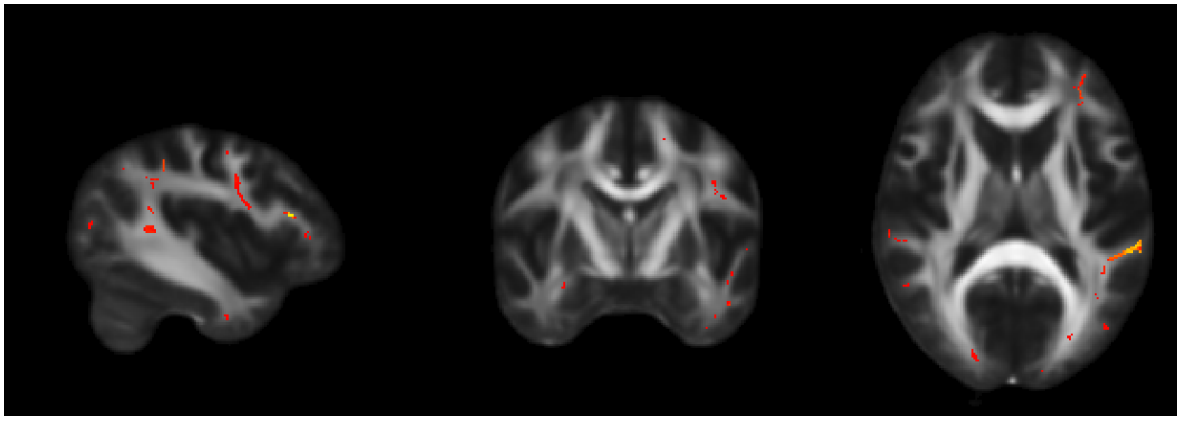

Figure 13 Correlating (statistical not significant after post-hoc test) clusters of reduced FA and altered hsCRP (threshold p=0,67) shown in red and orange

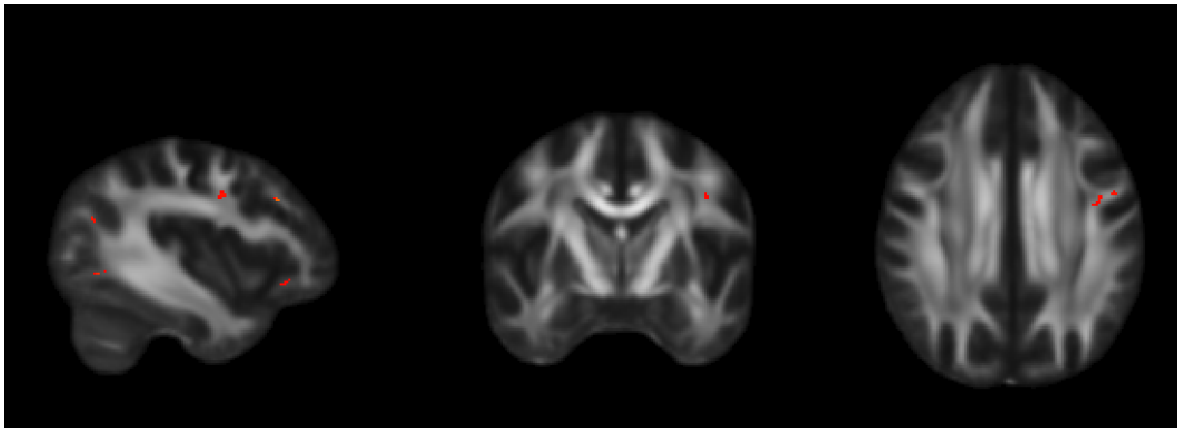

Figure 14 Correlating (statistical not significant after post-hoc test) clusters of reduced FA and altered IL6 (threshold p=0.85) shown in red and orange.

4 Discussion

4.1 Microstructural differences BD vs. HC

The objective of the present study was to analyze potential microstructural abnormalities in the brain's white matter in individuals with BD and to correlate these abnormalities with inflammatory parameters in comparison to healthy controls (HC). To address these issues, tract-based spatial statistics (TBSS) was utilized as a specific method. Our findings revealed significant differences in brain microstructure between individuals with BD and HC. Several clusters exhibited substantial reductions in fractional anisotropy (FA) throughout the entire corpus callosum (CC) in the BD group compared to HC. The results were corrected for multiple comparisons and adjusted for various relevant covariates.

The specific location of our findings aligns with previous research, suggesting microstructural changes in the CC in individuals with BD. A review of 18 publications identified the CC as the primary region showing reduced FA in individuals with BD (78-80, 99, 139). The literature indicates that particularly the frontal and dorsal parts of the CC (splenium and genu) are notably affected by FA reductions compared to other regions (67, 81).

The value of the present analysis lies not in the development of an entirely new investigative approach, but rather in reinforcing previous findings and confirming the CC as a likely hotspot for the pathophysiological processes underlying BD. In conclusion, these results support earlier research suggesting that interconnectivity deficits, arising from microstructural abnormalities, may serve as potential biomarkers for BD. This notion may establish crucial links to various clinical aspects of BD, as the corpus callosum plays a pivotal role in the brain's diverse functions, which are disrupted in line with the common symptoms observed in BD.

4.2 Impact of inflammation to BD (16)

A positive correlation was found between levels of hsCRP and IL-6, and the number of manic and depressive episodes in female patients. Additionally, hsCRP and IL-6 levels were positively correlated with current manic symptoms, as measured by YMRS. However, no statistically significant correlations were observed between hsCRP and IL-6 levels and manic or depressive symptoms in male patients with BD.

These findings suggest a probable association between the dysregulation of inflammatory systemic mediators and the impact of affective episodes over time. The chronic subclinical alteration of inflammatory mediators, referred to as low-grade inflammation, may represent a central pathophysiological mechanism in BD. Standard inflammatory markers, such as IL-6 and hsCRP, may serve as reliable indicators associated with these processes.

HsCRP is a non-specific acute-phase response protein (155, 156), whose production is induced by an increase in IL-6 concentration. IL-6 is produced in response to both acute and chronic inflammatory conditions by macrophages and adipocytes. In healthy young adults, the median concentration of CRP is 0.8 mg/l (157), but during inflammation, these values can increase to as high as 500 mg/l. In our sample, the mean concentration of hsCRP was 2.6 mg/l, with higher concentrations observed in the female group. Within the central nervous system (CNS), there exists a complex interaction between components of both the innate and adaptive immune systems (158).

It has been noted that the activity of CRP production is influenced by genetic polymorphisms in the genes encoding IL-1 and IL-6 (159). The baseline plasma level of CRP typically remains stable in an individual, with the main determinant being the synthesis rate, while the metabolism rate appears constant (160). Variations in baseline CRP concentration may also be influenced by a polymorphic GT repeat in the intron of the CRP gene (160). CRP levels generally increase with age due to the rising incidence of subclinical pathologies, but there is no significant seasonal variation (160). As evidenced by our data, elevated levels of hsCRP and IL-6 are associated with an increased number of affective episodes in BD, which may heighten susceptibility to further inflammatory responses and related consequences (16).

Several studies have shown that depressive patients with increased inflammatory markers at baseline are less likely to respond to antidepressant treatment (161). These findings have

led to the hypothesis that an altered inflammatory state may be linked to treatment resistance in depressive symptoms (161). As demonstrated by the results of the previous analysis, psychopharmacological treatments (e.g., lithium, atypical antipsychotics) may also have a relationship with inflammatory states (16).

In discussing the relationship of BD and inflammation the main question arises through which pathway an intracerebral process like BD may influence the systemic inflammatory system. The HPA-axis and cortisol-metabolism may be one potential mediator between inflammation and BD. Cortisol is an endogenous corticosteroid that is released in response to stress and regulated via feedback mechanisms in the HPA-axis (162). Cortisol levels of BD patients seem to be increased especially at the morning level (163). Further, the reaction of the cortisol level on psychological stress seems to be decreased (164,165). Evidence was found that certain clinical features of BD as illness chronicity, medication status or mood state, have a significant effect on HPA function (165). Furthermore, BD patients with longer illness duration seem to have lower levels of waking cortisol and differences in circadian cortisol rhythms (166).

A significant positive correlation between the number of affective symptoms/episodes, and inflammatory markers was found only in our female patients with BD. These findings support the results by former investigations that underline various differences concerning sex in different biological markers (59,60). Some recent investigations identified sex differences with respect to an association of the amount of white-matter lesions in the brain and the number of episodes in BD (59). Also in the peripheral markers of oxidative stress and antioxidative defence in a euthymic state of BD differences between a male and a female subgroup were described (60). However, in all results, there were no consistent trends regarding specific phenomena in relation to sex.

Several studies have suggested that sex differences in mood disorders may be attributed to variations in sex hormones (167-169). Inflammatory pathways and neurotrophic factors, which are likely implicated in BD, appear to be influenced by progesterone and estradiol (170). Neuroinflammation within the central nervous system (CNS) is accompanied by the activation of glial cells. Estrogen exerts a neuroprotective effect in the CNS (171,172) by inhibiting the release of pro-inflammatory cytokines from glial cells (173). Menopausal mood symptoms are generally associated with the reduction in circulating estrogen levels during menopause (174). The specific impact of hormonal fluctuations on BD remains insufficiently investigated. Some studies have shown that menopausal women with BD make more clinic visits due to depressive symptoms compared to similarly aged healthy men and pre-menopausal women (175). While the exact pathway linking hormones and inflammation in the CNS is still unclear, evidence supporting the existence of such a connection is provided by studies demonstrating that ovariectomized mice develop depressive-like symptoms alongside increased levels of inflammatory markers in the hippocampus (175).

Numerous studies have documented lithium-associated changes in brain tissue during long-term treatment of BD. The most compelling evidence points to volume reductions in various brain structures, particularly an increase in the volume of the amygdala and hippocampus, which are likely induced by the direct osmotic effects of lithium (177,178).

However, studies directly linking lithium treatment to inflammatory markers are scarce. Our findings suggest that lithium may exert a long-term effect on a chronic inflammatory process, as indicated by the acute-phase protein CRP. These results support previous studies that demonstrated significantly lower CRP levels in depressed BD patients undergoing lithium treatment (179). More recent research also reports associations between lithium response and reduced systemic inflammation, suggesting that CRP may serve as a potential biomarker of treatment efficacy (180). Similarly, CRP and cytokine alterations have been proposed as predictors of lithium responsiveness in BD patients (181). Nonetheless, the pharmacological mechanism of lithium remains incompletely understood. The potential influence of lithium on inflammatory processes represents a promising new avenue for pharmacological research.

4.3 Microstructure and inflammation

Our results did not reveal a significant association between decreased microstructural integrity and inflammation markers. While some clusters showed correlations, these did not reach statistical significance after post hoc tests. Notably, nearly all of the correlating areas were located in the left hemisphere, a finding that aligns with recent publications reporting isolated changes in this hemisphere.

Microstructural organization of white matter, measured using diffusional kurtosis imaging—a sophisticated neuroimaging technique for analyzing white matter microstructure (182)—was found to be reduced in the left dentate nucleus and left hippocampus in individuals with (BD) (183,184). A study conducted in the same region also reported decreased axonal density, assessed via neurite dispersion and density imaging (185). Additionally, several of the correlating clusters (FA and hsCRP) identified in our study were located within the left hippocampal region. This finding may underscore the left hippocampus as a potential hotspot for pathophysiological processes associated with inflammation. Since the voxels in these regions did not achieve statistical significance, we refrained from attempting to define their precise topographic location using an MRI atlas.

Previous studies have indicated corresponding volume reductions in the hippocampus (186) and disrupted connectivity within hippocampal circuits (187). It has been suggested that the observed alterations in hippocampal dendritic organization may be induced by the loss of connectivity (185).

In general, data providing comprehensive analyses of the relationship between systemic inflammation and white matter abnormalities remain scarce, and existing studies are rarely focused specifically on BD. However, findings from a large-scale study on atherosclerosis revealed multiple associations between inflammation—measured by CRP—and white matter alterations in a cohort of 1,495 individuals. In this study, elevated CRP levels were linked to increased volumes of white matter hyperintensities, particularly in individuals carrying the APOE ε4 allele (188).

Additionally, both reduced fractional anisotropy (FA) and mean diffusivity (MD) were associated with CRP concentrations, especially in deep white matter and periventricular regions (188). Notably, the extent of FA reduction related to elevated CRP levels was comparable to that observed for other well-established risk factors such as hypertension and diabetes mellitus (188).

4.4 Limitations

4.4.1 Microstructural differences BD vs. HC

Our findings align with previous studies that have reported similar reductions in FA in individuals with BD. TBSS offers a robust method for detecting such associations; however, it provides limited spatial resolution, making it difficult to precisely localize abnormal clusters within white matter regions due to the inherent resolution constraints of DTI. To achieve a more detailed understanding of which specific WM tracts are affected, tractographic approaches are necessary.

At present, there is insufficient evidence to clearly determine which pathophysiological alterations within WM tissue underlie the observed diffusion abnormalities. Consequently, the clinical and biological relevance of FA reductions as markers of pathological processes in WM remains uncertain. Furthermore, the role of potential confounding factors contributing to WM alterations has yet to be fully elucidated.

4.4.2 Impact of inflammation to BD (16)

One limitation of our data is that information on clinical episodes was gathered through personal reports rather than objective analysis, although it seems nearly impossible to achieve the latter in this field. We attempted to mitigate this issue by reviewing all available medical reports. Another challenge arises from the measurement of inflammatory markers at a single point in time, which prevents conclusions from being drawn regarding the longitudinal variation of these markers in patients with BD (16). Additionally, as inflammatory markers were measured in peripheral blood samples, these data do not provide direct insight into the levels of inflammatory markers in the brain (16). The directionality of the relationship between altered inflammatory states and the number of affective episodes cannot be inferred from these results.

4.4.3 Microstructure and Inflammation

Due to the uncertainty regarding how serological inflammatory markers accurately represent inflammatory processes within brain tissue, the peripheral approach can only be considered an experimental approximation in exploring the association between inflammation and microstructural deficits in BD. Given the lack of statistical significance, the observed correlation may be coincidental. To provide more valid insights, future research should incorporate neuron-specific markers, such as neurofilaments, or other CNS-specific biomarkers.

4.5 Conclusion

Our results appear to align with current findings regarding the multiple and largely unexplored pathophysiological pathways of the severe mental disorder, BD. In the BIPFAT sample, we employed a multi-methodological approach to investigate potential connections between various biological systems presumed to be involved in the pathophysiology of BD. Chronic mild inflammation and microstructural changes are currently prominent topics in BD research. Our study aimed to provide more precise insights into microstructural abnormalities by combining a specific neuroimaging method with the analysis of inflammatory markers. Our findings may offer a valuable framework for advancing future research in this area. Our cross-sectional analysis revealed significant differences in white matter between BD patients and HC, consistent with previous studies and underscoring the high quality of our sample and methods. Through our results, we identified meaningful and substantial correlations between chronic inflammation and BD, which provide a foundation for further investigation. These findings highlight the distinct impact of inflammation on the course of BD, as well as on sex-related differences. Although we were unable to establish a significant relationship between inflammatory markers and microstructural changes, our ambitious approach serves as an exemplary model for future research.

4.6 Future research

Although numerous neuroimaging studies in BD have been conducted, there is no consistent unifying thread that implicates a distinct pathogenesis of the disorder. Therefore, it seems appropriate to consider a variety of different pathological mechanisms contributing to the clinical and biological complexity of BD.

Future studies should focus on longitudinal approaches, which are better suited to detect differences in the course of the illness and to identify specific connections to underlying biological markers.

Scientific research should aim to position itself in a way that enables psychiatrists to provide validated information for both diagnosis and clinical treatment. To establish reliable 'biomarkers' for psychiatric practice, research must integrate immunological, imaging, genetic, and epidemiological data from large multicenter samples within a longitudinal framework.

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