The Role of Interleukins in Obsessive Compulsive Disorder with Pathophysiological Insights and Potential Biomarker

By

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A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (Hons.).

School of Pharmacy
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April 2026

Declaration

It is hereby confirm that:

1. This thesis is the result of my own original work completed during studies at BRAC University.
2. No part of this thesis includes previously published or written material by others, unless it has been properly cited with accurate references.
3. This thesis has not been submitted, in whole or in part, for any other academic degree or qualification at any university or institution.
4. All sources of support, guidance, and assistance have been properly acknowledged.

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Approval

The thesis/project titled “The Role of Interleukins in Obsessive Compulsive Disorder (OCD) with Pathophysiological Insights and Biomarker Potential.’’ submitted by Sami Mahmud of the Summer 2025 semester has been reviewed and accepted as fulfilling the required criteria for the Bachelor of Pharmacy (Hons.) degree.

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Ethics Statement

This project does not involve any kind of animal and human trial.

Abstract

Obsessive Compulsive Disorder (OCD) is a long-term mental illness which is characterized by unwanted thoughts and repetitive compulsive behaviors that hampers our daily life. The previous analysis of OCD was focused on neurotransmitter dysregulation mainly within serotonergic and dopaminergic systems and results suggests that immune and inflammatory mechanisms are contributing to the disorder's pathophysiology. The role of interleukins in OCD, tells about the primary involvement in neurobiological mechanisms and how they are becoming useful as biomarkers are mentioned in this literature review. Reports which are recently shows that changed levels of interleukins, including pro-inflammatory cytokines like IL-1β, IL-6, and IL-17, also anti-inflammatory cytokines like IL-10, probably affect neural signaling and immune responses in OCD patients. A neural pathway involved in the development of OCD behaviors and cytokines can affect neurotransmitter regulation, microglial activation, and synaptic communication within the cortico-striato thalamo cortical circuit. Inflammatory signaling is connected with damages in glutamatergic and dopaminergic neurotransmission and contributing to the hyperactivity of circuits and the mental rigidity seen in OCD. Reports which are recently shows that increasing of OCD is not only by neurotransmitter imbalance but also by neuroimmune interactions. Disease mechanisms and treatment resistance are interleukin-mediated inflammatory processes which provided important insights. The formulation of targeted therapeutic approach may changed cytokine profiles which likely serve as promising peripheral biomarkers for early detection and disease monitoring. Continued investigation of OCD enhanced understanding of its complex pathophysiology and facilitate new exploration.

Dedication

I would like to dedicate this thesis to my father who inspire me in every step I take and to my mother whose unwavering support and constant encouragement have carried me through this journey.

Acknowledgement

I am grateful to Allah Almighty, whose blessings have given me the strength and patience to complete this work. I would like to express my appreciation to my supervisor, Dr. Md. Rabiul Islam, for his outstanding guidance and continuous support throughout this journey. My sincere thanks also go to Dr. Sharmind Neelotpol Chairperson for fostering such a supportive and inspiring academic environment. I am truly indebted to my family whose constant encouragement, understanding, and unconditional support have been my steady source of motivation.

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List of Acronyms

IL refers to interleukin. These are signaling proteins in the immune system.

TNF-α refers to Tumor necrosis factor alpha. It helps body fight infections and injuries.

CRP refers to C-reactive protein.

CNS refers to Central Nervous System

CSF refers to Cerebrospinal Fluid

CSTC circuit refers to Cortico-striato-thalamo-cortical-cicuit

HPA axis refers to Hypothalamic pituitary adrenal axis

PANDAS refers to Pediatric Autoimmune Neuropsychiatric Disorders Associated with streptococcal infections.

PANS refers to Pediatric Acute onset Neuropsychiatric Syndrome

GAS refers to Group A β hemolytic Streptococcus

Th1/Th17 refers to T helper cell subtypes

Nf-kB refers to Nuclear factor kappa B

MAPK refers to Mitogen activated protein kinase

PET refers to Positron Emission Tomography

fMRI refers to Functional Magnetic Resonance Imaging

Chapter 1

Introduction

Introduction Obsessive Compulsive Disorder (OCD) is one of the most disabling and chronic neuropsychiatric diseases known, with a lifetime prevalence rate of about 2-3% in the general population worldwide (Sarmin et al. 2024). This is why academic research both output and impacts and relationships on interpersonal level are such important public health questions, as the burden of that mental illness appears widely in day-to-day patients living. Common treatments include selective serotonin reuptake inhibitors and cognitive-behavioral therapy. However, 30-50% of patients do not achieve sufficient symptom improvement, indicating that conventional neurochemical explanations alone could not account for the complexity of the condition (Roknuzzaman et al., 2024). All the previous write ups correlate OCD with a dysfunction in serotonergic and dopaminergic pathways and dysfunction along the cortico striato thalamo cortical circuit. These reports have influenced a biological model of OCD for decades. This, in term, is suggestive that such pathways alone do not thoroughly explain every case, as there exists a species that are resistant towards seretonin based treatment (Sarmin et al., 2024). Largely this requires researchers to begin by the open methods especially the immune system involvement. In recent years immune dysregulation and inflammatory processes have been recognized as major underlying factors in OCD. Gender differences in cytokines have also been confirmed where high levels of pro-inflammatory cytokines (notably IL-1β and IL-6) are reported among OCD members when compared with healthy controls (Sarmin et al., 2024). These cytokines can also affect CNS functions by crossing the BBB, activating microglia and astrocytes and disrupting neurotransmitter systems like serotonin, dopamine and glutamate. Additional research proposes that individuals diagnosed with OCD display 20 to 30% greater neuroinflammation in CSTC pathways, further supporting the connection between inflammatory responses and symptom emergence (Sarmin et al., 2024). But results across studies aren't entirely concordant, with some finding no significant differences in cytokine levels between patients and controls. These inconsistencies may be attributable to differences in study designs, syndromes studied, sample sizes and laboratory methodologies. However, the consistently reported elevated levels of IL-1β and IL-6 in several samples in OCD patients as well as their correlations with symptom severity may hint at a relevant link between immune activation and the pathophysiology of the disorder (Sarmin et al., 2024).

Since blood-based cytokine assessment is easy, noninvasive and cost-effective, interleukins have great potential as biomarkers for early diagnosis, severity scoring and response to treatment. Collectively, the new data places inflammation and more specifically interleukin signaling at the forefront of future research to uncover OCD pathophysiology, particularly in cases where more classical neurotransmitter focused models have failed. This body of work suggests that interleukins ought to warrant further mechanistic and diagnostic scrutiny.

Current Understanding of OCD Pathophysiology

Traditionally, OCD has been linked with dysregulation of neurocircuitry, neurotransmitter systems, and executive processes in the brain. The biological model best supported is one of dysfunction in the CSTC circuitry, a sense network involved in executive control, decision making and inhibition of intrusive thoughts. In contrast, dysregulation of this loop renders individuals unable to effectively inhibit intrusive thoughts and behaviors, which is clearly linked to the etiology of obsessions and compulsions (Abbruzzese et al., 1995). Serotonin is important in mental regulation, impulsivity and cognitive flexibility which are domains that are often disrupted in OCD (Sarmin et al., 2024). And serotonin is not the reason for all OCD symptoms or treatment response. Although serotonergic agents constitute the first line treatment for OCD and they improve about 70 to 50% of people with these disorders, not enough response can be attained in roughly (Sarmin et al. 2024) for example the disorder cannot simply be defined as serotonin disorder. Maybe this influx exacerbates intrusive thoughts and compulsive behaviors however diminished GABA inhibition is poor counterbalance to this excitatory overdrive (Sarmin et al. 2024). Neuromodulates models based on neurotransmitters have added huge value to that however these are limited in scope of understanding the complexity of the disorder. Specifically, patients with OCD showed significantly higher levels of pro-inflammatory cytokines including IL-1 β and IL-6. (Gandhi et al. 2019). Other observational reports during the COVID-19 pandemic observed that increased systemic inflammation correlated with OCD symptom onset or worsening (Sarmin et al., 2024), further strengthening support for the immune inflammation hypothesis. Some reports from investigations detect markedly elevated cytokine levels in OCD patients, while others indicate no significant differences or even decreased levels when compared with healthy controls (Gandhi et al., 2019). These inconsistencies could be due to methodological variation, sample heterogeneity,

comorbid psychiatric disorders or differences in assay methods. No single biological mechanism has been identified to have a consistent influence on the severity or expression of OCD symptoms, but these data indicate that inflammation may be one biological pathway that is impacting symptomatology. Common practices in the diagnosis and treatment of OCD include assessing an assessment of the psychogenic type preceded by treatment for other possible types. At present, OCD is known to encompass neurophysiologic interactions among receptors for serotonin, dopamine, glutamate as well as immune activation observed in recent years. This broadening model provides a rationale for moving beyond a solely serotonergic approach to consideration of the joint contribution of neural, psychological and immunological factors. As research continues, this knowledge may help develop more tailored treatment approaches to those whose OCD presentation is consistent with an inflammatory or immune related subtype.

Why Inflammation and Immune Markers Matter in OCD

Research around the immune system has been growing for decades, with obsessive-compulsive disorder standing out among psychiatric diagnoses to be associated with immune dysregulation. Although OCD has traditionally been associated with anomalies of neurotransmission and neurocircuitry, accumulating evidence suggests that inflammatory processes may play an important role in the onset, persistence and severity of OCD. A considerable amount of evidence has shown that individuals with OCD have increased levels of pro inflammatory cytokines, especially interleukin-1β (IL-1β), interleukin-6 (IL-6), interleukin-8 (IL-8) and tumor necrosis factorα(TNF-α) (Gandhi et al., 2019). These cytokines are key regulators of immune responses and can affect the central nervous system by crossing the blood brain barrier or indirectly affect neural activity. Furthermore, ongoing inflammation was associated with elevated cytokine levels that were found in the peripheral blood and CSF of individuals with OCD, which suggests immune activation is potentially a systemic feature of this disorder rather than localized to the brain. The relevance of inflammation for OCD is strongly related to neuroinflammatory changes in the corticostriato-thalamic circuitry (CSTC) (Yao et al. 2023). Neuroimaging studies indicate 20 to 30% greater neuroinflammation in the brain regions associated with intrusive thinking and compulsive behavior for individuals with OCD (Sarmin et al., 2024). Neuroinflammation along these pathways can interfere with communication between cortical and subcortical brain regions,

supposedly making it a greater challenge for the brain to properly inhibit or modulate thoughts and behaviors. In agreement with this notion, cytokines such as IL-1β and IL-6 have demonstrated direct impact in neurotransmitter systems involved in OCD. Serotonin transporter activity is enhanced by the presence of IL-1β, leading to reduced availability of serotonin in the synaptic cleft which may worsen conditions presenting with anxiety and compulsive thought intrusion. It may also enhance the release of glutamate and suppress astrocytic reuptake, thereby enhancing glutamatergic hyperactivity and excitotoxicity in brain areas involved in OCD (Sarmin et al., 2024). These interactions may indicate the mechanism through which inflammation can exacerbate pre-existing neurotransmitter imbalances. Observations during the COVID-19 pandemic have brought even greater clarity to the relevance of immune markers. New onset or exacerbations of OCD symptoms have been reported in immunologically primed individuals after viral infection, providing support for the theory that immune activation may be a trigger point underlying the neural correlates associated with OCD (Sarmin et al., 2024). In others, there were no major differences in cytokines from normal controls which might be explained by confounders for example medication use study design or comorbidity sample features (Gandhi et al., 2019).And the overall pattern across studies suggests that abnormal immune functioning is present at least within a subgroup of patients with OCD and also may define an identifiable biological sub-group. In addition to providing insights into biological mechanisms, inflamed and cytokines profiles are becoming potential biomarkers of relevance. Biomarkers aid diagnosis, severity stratification and treatment response several interleukins were shown to be associated with severity of symptoms; in particular IL-1β and notably IL-6 levels rose positively correlated with symptom severity as measured by yale brown Obsessive Compulsive scale (Sarmin et al., 2024). This relationship indicates that the underlying neurobiological change possibly caused by cytokines late contributes to the ultimate expression of symptoms. Emerging research allows for the potential of cross-integration of immune profile correlates, neurobiological and even psychological assessment to increase accuracy and individualization in treatment of OCD.

Why Interleukins Are an Important Focus

Interleukins are key mediators of immune response and play a role in the modulation of brain functions having therefore received great attention in recent publications about OC neurobiology. Indeed, many cytokines promote inflammation, but pro-inflammatory cytokines like IL-1β and IL-6 are well known to be able to alter neural circuits tied into the regulation of emotion and decision-making processes frequently disturbed in OCD. IL-1β is a key pro-inflammatory cytokine secreted by monocytes, macrophages, and microglia. It is also thought to be an early warning sign of immune activation. In the context of OCD, you have IL-1β as pro-inflammatory cytokine in the dysfunctional hypothalamus where that's very pertinent due to their potent actions on neurotransmission. In addition, upregulation of IL-1β is linked to an increased level of serotonin transporter expression which decreases concentration of the synaptic neurotransmitter involved in captured thought running and anxiety (Sarmin et al., 2024).

Statement of Purpose of the Review

This review seeks to elucidate inflammatory mechanisms implicated in the pathogenesis of OCD through neuroinflammation, immune dysregulation, and neuronal signaling pathways mediated by certain interleukins highlighted in current research. Moreover, the review aims to bring forward notable interleukins as biomarkers for diagnosis, prognosis and therapeutic targeting. The ultimate goal of this work is to piece together molecular, clinical and biomarker evidence in order to further elucidate OCD pathophysiology and guide novel experimental directions.

Chapter 2

Overview of Interleukins

The Language of the Immune System Interleukins (ILs) are a heterogeneous group of small, soluble proteins that act as cytokines and are secreted by leukocytes but also various other cell types including microglia and astrocytes in the brain. Interleukins were historically defined in the late 20th century as the major "language" by which immune cells communicate and coordinate their responses to pathogens, injury, and stress (Mizel, 1989). In contrast to hormones that can travel long distances through the blood, interleukins act largely in a paracrine or autocrine manner, altering the behavior of neighboring cells following attachment to high affinity cell-surface receptors. These include supporting cell growth and differentiation and regulating the inflammatory response, which is now a major area of research in neuropsychiatry (Sarmin et al., 2024). The IL-1 superfamily occupies a central role in the initiation of inflammation, acting as the body's first alarm system. IL-1α and IL-1β are the most well studied of the family, with which only 25% sequence homology is shared among its members; both signal through the IL-1RI receptor to elicit strong inflammatory cascades that drive immune activation (Mizel, 1989). Here, as we emphasize the potential role of Il-1β in the pathogenesis of OCD, we contemplate obsessive compulsive disorder (OCD), which has gained a monstrous attention on the research within psychiatric perspective. It is produced first as the inactive precursor pro-IL-1β and is only activated through cleavage by the NLRP3 inflammasome, a molecular complex activated in times of cellular stress. IL-1β serves as an inflammatory mediator and a neuromodulator that can modulate the neurotransmitter system in the central nervous system. Increased IL-1β has been shown to enhance serotonin turnover and proliferate glutamatergic activity (Sarmin et al., 2024; Roknuzzaman et al., 2024), thereby producing hyper excitability in the CSTC circuitry a major neural loop believed to drive compulsive actions in OCD. Based on their functional properties, interleukins can be categorized into pro-inflammatory and anti-inflammatory groups, providing a better insight toward understanding the alteration of immune response in OCD. Pro-inflammatory interleukins are known to drive inflammation and their levels tend to be higher in patients with chronic restlessness psychiatric disorders. IL-6, in particular, has been identified as one of the most commonly observed biomarkers of OCD severity. IL-6 is a pro-inflammatory cytokine that plays a dual role: linking the innate with the adaptive immune system, by inducing acute phase responses and

promoting T-cell differentiation. A sustained elevation of TNF suggests that systemic inflammatory activity is pivotal in sustaining the symptomatology of OCD (Sarmin et al., 2024). Other pro-inflammatory cytokines such as IL-2, regulating T-cell proliferation and potentially leading to dysregulated autoimmune-like CNS involvement, IL-12 and IL-23 skew towards the Th1 and Th17 pathways respectively. And these pathways have been implicated in numerous pediatric onset immune related OCD syndromes, including PANS and PANDAS, which share a common framework; most cases with an urgent need for conveying compulsive behavior (Roknuzzaman et al., 2024). Simultaneously, Th17 hallmark cytokine IL-17 enhances tissue inflammation and aggravates blood brain barrier disruption. This provides an influx of peripheral immune cells into the CNS favoring chronic neuroinflammation that could support OCD pathology. On the other hand, anti-inflammatory interleukins are biological regulators that prevent excessive inflammation and promote healing. IL-10 is the most significant of these mediators, suppressing the production of IL-1β, IL-6 and other pro-inflammatory factors. Chronic OCD associates with downregulated IL-10 levels, indicating a reduced capacity to dampen pro-inflammatory responses and inducing what the researchers refer to as an “unbraked” neuroinflammatory state (Roknuzzaman et al., 2024). So far, we have only looked at pro-inflationary signaling macrophages and microglia through engulfment of dying cells, IL6 is secreted which elongates the M1 phenotype leading to continued pathogen clearance while increasing the release of IL-1b to amplify inflammation, whilst mediating other pathways inflammatory chemokines. IL4 as an anti-inflammatory cytokine drives the development of the M2 phenotype seen in associated neuroprotection, synaptogenesis/repair and resolution inflammation. Disturbances in IL-4 signaling can drive microglia to a pro-inflammatory M1 phenotype, leading to release and further neural circuit dysfunctions observed in the context of OCD. The interplay of inflammation, neurotransmitter changes and structural circuit changes provides a strong model in which the area where these interleukins outbalance each other details the pathophysiology of OCD.

Functions in Brain Immune Signaling

Interleukins as Neuro-Signaling Molecules. Traditionally regarded as merely peripheral immune response regulators, interleukins are now known to exert potent neuromodulatory roles within the central nervous system. In contrast to classical neurotransmitters that act across millisecond timescales at specific synapses, interleukins often act via volume transmission passing through the extracellular space to modulate large populations of neurons and glia simultaneously. In OCD, however, this signaling goes awry and gets chronic and maladaptive. Pro inflammatory interleukins, such as IL-1β and IL-6, are not just "danger" alerts but also directly change the threshold of neuronal firing, effectively "priming" alarm systems in the brain and underlying persistent intrusive thoughts in the disorder (Sarmin et al., 2024; Roknuzzaman et al., 2024).

Neuromodulation and Synaptic Plasticity

The most advanced function of interleukins in the brain is their ability to modulate synaptic plasticity the way the brain rewires itself based on experience. In fact, there are requirements for low, physiological levels of IL-1β to have normal memory formation and Long-Term Potentiation. However, at pathological levels, as seen in the 20 to 30% rise of neuroinflammation reported in OCD interleukins, start disrupting plasticity (Roknuzzaman et al., 2024). In particular, increased IL-6 and IL-1β disrupts the balance between excitatory Glutamate signaling and inhibitory GABA signaling. Though generally SERT has an overall inhibitory effect on positive reinforcement and additively regulates the transport of serotonin back into the cell, interleukins have been demonstrated to increase glutamatergic excitability in a key node of CSTC circuit known as thestriatum while decreasing efficiency of serotonin transporter SERT. This establishes a “hyper excitable” neural milieu in which the brain has an ever-tougher time stopping a given thought or motor plan. This "synaptic rigidity' is the molecular mechanism at the basis of clinic brain lock and patients’ repetitive, compulsive acts that they feel driven to perform in order to achieve a semblance of completion (Sarmin et al., 2024)

The Periphery to Brain Axis: While circulating interleukins have three fundamental pathways from the peripheral blood into the inner workings of brain circuits. The Humoral Pathway, which is

likely mediated by cytokines passing through leaky segments of the blood-brain barrier or employing special vessel carrier proteins. In analogy, IL-17 serves defined tasks in OCD, such as interceding tight junctions of the blood-brain barrier and resulting high levels of peripheral IL-6 and IL-1β entering into basal ganglia (Roknuzzaman et al., 2024). The Neural Pathway activates the vagus nerve, by giving immediate electrical signals directly to the brainstem which bypasses BBB (blood-brain barrier) and triggers central inflammatory process. The Cellular Pathway continually replenishes monocytes that are recruited into the brain parenchyma, transmigrates and converts into "macrophage like" cells releasing additional interleukin directly to neural tissue. In OCD, however, these pathways are perpetually activated, triggering a loop of neuroinflammation that never seems to calm. These constant waves of immune signaling keep CSTC circuitry in a state of hypervigilance, reinforcing maladaptive habit circuits and inhibiting the mind versatility which may allow for freedom from obsessional thought (Sarmin et al., 2024; Roknuzzaman et al., 2024). This circuitry acts as the brain's executive loop that engages the appropriate behaviors while inhibiting distracting or irrelevant ones. For the case of OCD, there is a functional "locking" of this circuitry that continues to foster a cycle of intrusive negative thought and compulsive behavior that comprises the clinical manifestation of the disorder (Sarmin et al 2024; Stein et al., 2019). OFC, mainly there are associated with stimulus value and emotional regulation. Neuroimaging studies indicate OFC hyperactivity in OCD patients. In typical conditions, these two pathways act in opposition to control motor and cognitive transitions. Direct Pathway Pro Action: This pathway aids the carrying out of behaviors. It is excitatory and causes a thought or movement to continue. This pathway inhibits unwanted behaviors. It acts as the brake system. This creates a kind of functional state of hyper connectivity in which the brain can start an obsession but lacks the neurological brakes to put it in reverse. This is the physiological underpinning of also what we will then refer to as clinical brain lock, in which a patient gets stuck in a given mental frame or repetitive ritual and cannot disengage their attention from that task to other activities (Stein et al., 2019). Circuitry to Symptomatology in our framework, the anatomical dysregulation described above maps directly onto clinical symptomatology as set forth in the Y-BOCS. The hyperactivity of the OFC corresponds to both the intensity and the distressing nature of obsessions (e.g., fears of contamination), while dysfunction in striatal circuitry relates more directly to mechanical aspects of compulsion completion (e.g., hand washing). Another recent study suggests that this circuit is not only chemically imbalanced but inflamed. The increase of pro-inflammatory

cytokines including IL-1β and IL-6 is known to be selective for the striatum, driving glutamatergic excitability, which further releases the indirect brake (Sarmin et al., 2024; Roknuzzaman et al., 2024). This neuro immune relationship explains the 20 to 30% greater neuroinflammation seen in many OCD patients in these specific CSTC nodes showing how this anatomical loop may be interconnected with the inflammatory markers discussed in this review.

CHAPTER 3

Immune System & Neuroinflammation in OCD (Microglial Activation)

Microglial activation is a pivotal neuroinflammatory mechanism in the pathophysiology of obsessive-compulsive disorder linking peripheral immune dysregulation with central nervous system circuit dysfunction. This is in addition to being the resident immune cells of the brain, with microglia constantly monitoring their surrounding neural environment and responding to pathological signals through a transition from a ramified, surveillant state to an activated phenotype marked by hypertrophy, proliferation, and elaboration of inflammatory mediators (Culmsee et al., 2019). The evidence microglial activation in OCD comes from positron emission tomography imaging studies which measuring radioligands binding to 18-kDa translocator protein (TSPO), a mitochondrial marker that is upregulated during microglial and astrocytic reactivity.

A study of the second generation TSPO radiotracer 18 F FEPPA (Attwells et al., 2017) in medication naive adults with OCD compared to twenty matched healthy controls also revealed significantly elevated TSPO distribution volume at several nodes of the CSTC circuit. Importantly, the extent of microglial activation was significant and regionally specific: dorsal caudate and other dorsal striatal sites showed 31 to 36% increases in TSPO VT similar changes were observed for ventral striatum with thalamus, orbitofrontal cortex/area 10 but anterior cingulate cortex reflected only a 24% change (Attwells et al., 2017). Notably, in what could be interpreted as a connection between regional microglial activation and clinically relevant dysfunction, the level of TSPO VT in the orbitofrontal cortex was positively correlated with subjective distress produced during compulsions prevention in patients (Attwells et al., 2017). The robust correlation of microglial activation with these measures of compulsivity suggests that this phenomenon is not mere epiphenomenon but potentially a therapeutic target within the underlying neural circuitry governing both perseverative behaviors and compassion fatigue. Increased TSPO binding localized anatomically directly overlaps with the CSTC circuits implicated in OCD by decades of structural and functional neuroimaging studies, lending support to the concept that neuroinflammation is targeted specifically at these substrates for obsessive compulsive symptoms.

The microglial polarization, similar to the M1/M2 model proposed for peripheral macrophages. M1 polarization of microglia presents a proinflammatory profile and is dependent on glycolytic metabolism, while M2 polarization has anti-inflammatory and tissue repair features displaying

oxidative phosphorylation (Culmsee et al., 2019). This balance between these polarization states, and the metabolic programming that drives this, is likely disrupted in OCD resulting in either excess proinflammatory activation or insufficient homeostatic support depending on brain region and disease stage. Activated microglia can affect neural circuits implicated in pathological behaviours resulting from the release of cytokines, but recent evidence points toward direct modulation of synaptic structure and neurotransmitter systems. Microglia have been shown to be integratively involved in synaptic pruning, which is the selective removal of synapses that occurs not only via complement mediated phagocytosis but also through direct physical interaction with synaptic structures and is crucial for physiological neurodevelopment however may become unregulated under pathological states as seen in a range of psychiatric disorders (Culmsee et al., 2019). In OCD, aberrant microglial pruning could result in increased elimination of synapses in some circuits, and too little pruning in others, contributing to the circuit level abnormalities seen in neuroimaging studies. Furthermore, the microglial cell type-specific finding that BDNF deficiency produced compulsive-like behavior in multilayered fixation and this was reversible with administration of BDNF indicates an important role for microglia-dependent trophic support of prefrontal cortical circuitry associated with appropriate regulation of compulsive behaviors (Xu et al., 2020). In doing so, the aberrant microglial secretome of cytokines can dramatically change glutamatergic neurotransmission in a system that has been highly implicated as being involved in OCD pathophysiology. For instance, TNF-α participates in the modulation of AMPA and NMDA glutamate receptor expression and function, glutamate release and reuptake, as well as alterations to excitatory versus inhibitory neurotransmission (Culmsee et al., 2019). Further, the direct evidence that microglial TNF-α overdose upon characterization in inducing hyperexcitability of medium spiny neuron of nucleus accumbens (Krabbe et al., 2017) affirms the ability of microglia inflammatory signaling to reach beyond local circuits (specifically neostriatal circuits when inferring striatal alterations toward an excitotrophic state) and shift this circuit back towards a hyperexcitable balance; further emphasizing the role this signaling may play within these pathways for both the repetitive and inflexible characteristics seen with OCD. Mitochondrial dysfunction in microglia adds another layer of complexity to the neuroinflammatory theories of OCD. Mitochondria not only play a major role as energy producing organelles but also together act as central regulators of non-specific innate immune responses, modulating the production of reactive oxygen species (ROS), calcium homeostasis and cell fate decisions between survival and death

(Culmsee et al., 2019 In affective disorders, the mitochondrial compromise and loss of organelle material (e.g., mitochondrial DNA, cardiolipin) can activate innate immune signaling pathways such as the NLRP3 inflammasome and cyclic GMP-AMP synthase stimulator of interferon genes pathway that are known to further promote pro-inflammatory cytokine secretion and neuroinflammation (Culmsee et al., 2019). In contrast, proinflammatory cytokines inhibit mitochondrial functions such as oxidative phosphorylation and ATP production19 but enhance ROS generation resulting in a vicious cycle of metabolic disarrangement and inflammation (Culmsee et al., 2019). While the clinical relevance of microglial activation in OCD is starting to unfold, existing evidence is still preliminary and needs considerable growth through larger, longitudinal studies. The association between orbitofrontal cortex TSPO binding and distress associated with inhibiting compulsions indicates that microglial activation may represent a trans diagnostic biomarker of symptom dimensions, which may allow for stratifying patients for ant inflammatory treatments (Attwells et al., 2017). There have been several small clinical trials of anti-inflammatory agents in OCD, including celecoxib (a cyclooxygenase-2 inhibitor), minocycline a tetracycline antibiotic with anti-inflammatory and neuroprotective properties and N-acetylcysteine (an antioxidant that modulates glutamate), all showing a trend toward positive findings although effect sizes were modest and replication in larger samples is required (Attwells et al., 2017). A major limitation of these trials is that no drug tested was selected on the basis of an individual patient's markers of neuroinflammation, and most have limited brain penetration or specificity for their microglial target. For future clinical trials, patients should be stratified in evidence of neuroinflammation such as peripheral elevation of cytokine levels, positive TSPO PET or genetic markers of immune dysregulation to identify subgroups likely to respond and associated with indices for anti-inflammatory intervention (Attwells et al., 2017). Finally, the causal animal data linking TNF-α as a critical mediator of microglial activation to circuit dysfunction and compulsive behaviors suggest that available TNF-α antagonists for autoimmune disease may be useful pharmacotherapy in a neuroinflammatory subtype of OCD which again underscored needing biologics with adequate CNS penetration (Krabbe et al., 2017). Despite these advances, important gaps and limitations in the current evidence base must be acknowledged. First, the evidence from human neuroimaging supporting microglial activation in OCD is derived from a single study with a relatively small sample size, and to establish that such findings are robust and generalizable would necessitate independent cohort replication of these results (Attwells et al.,

2017). Second, while expressed in both microglia and astrocytes, none of the imaging TSPO radioligands so far developed can distinguish between these two cell types so it's still an open question whether the signal observed reflects predominantly microglial activation or astrogliosis or both (Attwells et al., 2017).Third, the cross sectional designs of available human studies prohibits causal inference regarding whether microglial activation precedes and contributes to OCD onset or is a consequence of chronic stress, symptom severity, or other factors associated with the disorder. Long-term studies assessing TSPO binding over time in high-risk populations for OCD or patients receiving treatment would clarify the temporal dynamics and causal role of microglial activation. Fourth, how peripheral immune markers relate to central microglial activation is still not fully understood; although monocyte inflammatory responses in the periphery may be similar to microglial function, the association between peripheral cytokine levels or monocyte phenotypes and neuroinflammation (i.e., activated microglia) in individual patients needs validation through studies that use both sets of measures in the same individuals (Rao et al., 2015; Culmsee et al., 2019). And lastly, the heterogeneity of microglial responses between regions of the brain, stages of pathology and patient subgroups indicates that OCD may not involve uniform activation of microglia but rather region specific and context dependent signatures of microglial dysfunction which could potentially warrant individually tailored assessment and intervention strategies (Xu et al., 2020). Overall, neuroimaging, peripheral immune profiling and mechanistic animal experiments provides evidence for a relevant role of microglial activation in OCD pathophysiology, especially within CSTC circuits critical for mediating obsessive compulsive symptoms.

Cytokines and Immune Signaling in CSTC Circuits

Apart from microglial activation itself, the inflammatory mediators secreted by activated microglia are pivotal in controlling neuronal dynamics within the CSTC circuitry. These circuits underlie cognitive control, habit formation, error monitoring, and behavioral inhibition domains that are relevant to obsessive compulsive disorder. Cytokines affect neuronal excitability through a variety of mechanisms, including modulation of glutamatergic transmission, alteration of the inhibitory GABAergic tone and direct effects on synaptic plasticity (Miller & Raison, 2016). Inflammatory mediators, including IL-1β, IL-6 and TNF-α that are released from activated microglia have been shown to downregulate synaptic proteins, impair long-term potentiation and alter dendritic spine

density (Culmsee et al., 2019). Such effects are pertinent within prefrontal and striatal networks where synaptic remodeling supports context-dependent behavior and the inhibition of persistent thoughts. IL-1β is known to impair corticostriatal signal integration and thereby diminish top-down control from prefrontal cortex regions onto striatal nodes. Additionally, TNF-α and can enhance the surface expression of AMPA receptors on excitatory neurons, which leads to hyperexcitability; a mechanism parallel with data from animal models indicating that increased levels of TNF-α drives higher striatal excitatory tone (Krabbe et al., 2017). IL-6 affects neurodevelopmental processes and neuroplasticity, potentially priming CSTC circuits for subsequent dysregulation. Collectively, these cytokine driven perturbations create a proinflammatory milieu that serves to destabilize CSTC loops promoting the repetitive behaviors and cognitive inflexibility characteristic of OCD (Miller & Raison, 2016). Thus cytokine signaling is not epiphenomenal but rather directly involved in the functional circuitry of OCD associated brain circuits. Here we review current evidence supporting the notion of both peripheral and central inflammatory biomarkers in OCD with new findings revealing altered peripheral inflammatory profiles in patients with OCD. Meta-analytic studies consistently show increased circulating concentrations of interleukin 6 (IL-6), tumor necrosis factor α (TNF-α) and c-reactive protein (CRP), indicative of increased innate immune activation (Fernandes et al., 2017). In certain cohorts increased IL-17 family cytokines have been detected, suggesting that Th17-mediated immune responses might also play a role in the pathophysiology of OCD (Attwells et al., 2017). Some studies had also reported decreased anti-inflammation cytokines including IL-10, which is in line with the hypothesis of an immune milieu imbalance. However, results across studies are heterogenous, due to variation in medication status, symptom severity, comorbid conditions and assays. Inflammatory dysregulation seems to be particularly strong in pediatric samples, perhaps reflecting the stronger immunological component present for childhood onset OCD and its related autoimmune neuropsychiatric disorders that have been folded-under PANDAS (Rao et al., 2015). High levels of peripheral cytokines may impact central immune signaling via multiple pathways: transport across the blood brain barrier, interaction with activated endothelial cells, stimulation of peripheral nerves including the vagus nerve and shed extracellular vesicles that can carry inflammatory messenger signals to neural tissues (Dantzer, 2018).

These pathways illustrate how peripheral immune dysregulation could spread to the CNS and affect microglial function. While these inflammatory markers are more difficult to assess, there is

a direct connection to the brain's immune state. A study by Attwells et al. remains the most significant evidence for central neuroinflammation in OCD (2017), which showed elevated microglial activation across CSTC regions. In addition, a small number of studies measuring cerebrospinal fluid (CSF) indicate elevated levels of IL-6, IL-8 and TNF-α in patients with OCD but with low sample sizes and inconsistent methodologies do not support widespread conclusions (Tükel et al., 2012). Indeed, several studies on CSF demonstrate patterns of immune activation that occur in a manner independent of systemic inflammation (Marra et al., 2000; van Eldik and Gandy, 2003).

Comparison of Neuroinflammatory Profiles Across Psychiatric Disorders

Differentiating OCD inflammatory profiles from those of other classes of psychiatric disorders can aid in defining the specificity and significance of neuroimmune dysregulation. Currently, proinflammatory cytokines have also been detected at increased levels in diseases such as major depressive disorder, bipolar disorder, and schizophrenia (Miller Raison, 2016) but begs the question of whether inflammation is a transdiagnostic marker or merely affiliated with specific disorders. But there are certain patterns that appear a bit more unique or magnified and exaggerated in OCD. Sustained increases in IL-17 have been more consistently observed in OCD compared to depression or anxiety disorders which still leaves the discussion open for a role of Th17 pathways involvement potentially implicated in the pathophysiology of OCD (Fernandes et al., 2017). Similarly, increased TSPO binding in CSTCG circuits is anatomic specific to OCD schizophrenia and MDD preferentially involves microglial activation across broader cortical areas (Bloomfield et al., 2016). Another distinction concerns the relationship between inflammation and compulsive behaviors. Indeed, among those with OCD inflammatory markers often are associated with dimensions of symptoms and the fear of contamination, act to check and distress related to intrusive thoughts (Attwells et al., 2017). In mood disorders, however, cytokines correlate more with anhedonia, fatigue and cognitive slowing. This suggests that although inflammation can serve as an overarching risk factor for psychiatric illness, certain immune pathways may be differentially associated with particular clinical phenotypes. Neurodevelopmental diseases such as Tourette syndrome or autism spectrum disorder also show inflammatory similarities with OCD, for instance elevated levels of IL-6 and TNF-α and signs of microglial dysregulation (Dantzer, 2018). Other neuropsychiatric and behavioral features are shared among these disorders, indicating that

convergent immune mechanisms may drive effects within habit circuitry, sensorimotor gating or repetitive behavior. Yet, OCD is somewhat unique in that it possesses known cognitive affective features, and whether the same immune processes underpin these aspects of symptoms remains an important question.

Integrative Models Linking Neuroinflammation to OCD Symptom Dimensions

Integrative models applying a neuroinflammatory framework suggest that neuroinflammation plays an array of role(s) for the onset and persistence of OCD. A prominent model suggests that immune activation during critical periods of development can sensitize microglia to a hyper responsive phenotype, making CSTC circuits susceptible to subsequent dysregulation (Dantzer, 2018). Within this framework, various environmental stressors, infections or autoimmune activation may induce persistent changes in microglial reactivity such that the probability of subsequent stress or neural insults eliciting uncontrolled inflammatory response increases. Another model focuses on the changes in neurotransmission induced by cytokines. The net effect of TNF-α driven increases in glutamate receptor surface expression would be to enhance striatal excitatory drive supporting habitual and repetitive behaviors, while IL-1β mediated decreases in prefrontal plasticity limit cognitive flexibility and adaptive behavioral control (Culmsee et al., 2019). These two processes cohere with clinical observations that OCD is characterized by both a propensity for overfitting in habit formation and poor top-down control. A third pathway is characterized as alterations in reward and aversion processing. This inflammatory signaling can reduce dopaminergic reward sensitivity, and make one more prone to aversion (Janik et al., 2021), hence leading towards compulsive avoidant behavior, elevated fears of threats or contaminations (Miller & Raison, 2016). This corresponds with orbitofrontal area TSPO binding associating negatively with distress opposing compulsions (Attwells et al., 2017). Integrative immunometabolic models link mitochondrial collapse with microglial activation and neuronal energetics failure. Energetic compromises in those CSTC circuits conceivably diminish the brain's ability to flexibly switch across behaviourally salutary states (Culmsee et al., 2019) leading to the exacerbation of perseverative and stereotyped behaviours. Collectively, these frameworks suggest that neuroinflammation may not be a singular pathogenic mechanism in OCD but rather is a heterogeneous one.

Limitations of Existing Evidence and Future Research Needs

Therefore, rather than discussing the results of the study should be viewed in view of the limitations have to be recognised. For one, limited studies directly assess central inflammation through TSPO PET or a CSF cytokine assay and even those with this measurement have small sample sizes. Indeed, co-binding of a single radioligand, genetic polymorphisms which modulate the binding affinity for TSPO and technical variabilities between different types of PET scanner further complicate interpretation (Bloomfield et al., 2016). Second, peripheral inflammatory markers lack specificity: augmented cytokines may be present in the context of stress, sleep disturbance and even independent of OCD pathophysiology infection or metabolic derangement. Third, the majority of immune studies so far in OCD are cross-sectional for the most part hence they do not determine if abnormalities precede disease onset or reflect disease progression. One more complicating factor is the effect of medications. SSRIs and antipsychotics have anti-inflammatory effects which might obscure the actual inflammatory profiles (Rao et al., 2015) Similarly, lifestyle factors such as nutrition and exercise that may impact levels of cytokines are rarely systematically controlled. In addition, OCD is a heterogeneous disorder with multiple symptom dimensions and immune dysregulation may be more pronounced in certain subtypes or developmental stages than others. Research examining inflammatory patterns within symptom clusters (e.g., contamination fear, checking) is still limited but promising. Longitudinal studies that combine peripheral biomarkers, neuroimaging of microglial activation markers and deep phenotyping of symptom dimensions should be prioritized in future research. Multi-omic approaches, such as transcriptomics, proteomics and immunometabolic profiling could help identify biological subtypes of OCD and clarify the connection between immune dysregulation and CSTC functional abnormalities. In conclusion, developing key biomarkers of neuroinflammation is critical for the progression towards individualized anti-inflammatory or immunomodulatory therapies.

CHAPTER 4

Specific Interleukins Implicated in OCD (Basic Biology of IL-1β)

L-1β is a paradigm of proinflammatory cytokines and key mediator of innate immune responses. Its main source is activated microglia, monocytes and macrophages in response to pathogen or cellular injury or stress signals. The proinflammatory cytokine IL-1β is produced as an inactive precursor (pro-IL-1β); activation requires cleavage by caspase 1 in the NLRP3 inflammasome to become biologically active, thus serving as an important mediator that links cellular stress and inflammatory signaling (Dinarello, 2018). Within the central nervous system, IL-1β regulates synaptic plasticity, neurotransmitter release, and neuronal excitability. While IL-1β acts at low physiological levels in neurophysiological processes, an excess of circulating IL-1β leads to neurodegenerative changes related to mechanisms of obsessive-compulsive disorder including neuroinflammation, depression of neurogenesis and maladaptive circuit remodeling. Evidence from animal models Animal studies have strong evidence for IL-1β as a mediator of compulsive and repetitive behaviors. In rodent studies, it has also been shown that either intracerebral or systemic administration of IL-1β can promote anxiety-like behaviors, impair cognitive flexibility and change the behavioral and neural features of corticostriatal transmission to be consistent with OCD. For example, activation of the NLRP3 inflammasome that leads to IL-1β release has been demonstrated to attenuate prefrontal glutamatergic transmission and induce inflexible behavioral patterns (Ménard et al., 2017). In contrast, genetic or pharmacological inhibition of IL-1β signaling enhances behavioral flexibility and decreases excessive grooming or stereotypy across multiple rodent paradigms. Our results indicate that IL-1β acts to promote hyperexcitability of CSTC circuits synaptically implicated in OCD while blunting top-down cognitive control (i.e., the ability to flexibly regulate behavior). Evidence from Human Clinical Trial Studies of IL-1β in OCD In human clinical trials the evidence for IL-1β involvement in OCD has been mixed but generally supportive. Patients with OCD have been reported to show higher levels of peripheral IL-1β, particularly when drug-free or early in the illness.

• Others also showed significantly elevated serum IL-IB in OCD compared to healthy control groups.

• No significant differences between the three groups in other studies which may lead to statistical heterogeneity.

• IL-1β was variably increased but there appeared to be a trend for more inflammatory signaling. This variability is probably due to clinical heterogeneity, variable assay methodology, and effects of medications which may also reduce inflammatory markers. Specifically in children, studies of those with sudden onset OCD and/or PANDAS /PANS more uniformly identify higher levels of IL-1β and other innate immune markers (Murphy et al., 2015). In these contexts, increased IL-1β is often assumed to indicate immune activation driven by streptococcal or other infections eliciting neuroinflammatory processes directed against CSTC circuitry. Additional cerebrospinal fluid studies further implicating central involvement Elevated CSF IL-1β has, for example, been observed in small clinical cohorts of patients with OCD (Tükel et al., 2012), suggesting that immune activation is not limited to the periphery and may indicate local microglial activity. This caveat is consistent with PET demonstrating microglial activation in CSTC regions most affected by OCD.

Mechanistic Hypotheses Linking IL-1β to OCD

1. CSTC circuit dysregulation IL-1β allow the prevent prefrontal inhibition instantaneously and increase striatal reactivity promoting compulsive behaviors loops.
2. Glutamatergic modulation that involvement of IL-1β in mediating dopaminergic activity suggests that it could contribute to the glutamate dysregulation in OCD (Meyer et al., 2020).
3. The synaptic plasticity impairment and high circulating IL-1β diminished long-term potentiation (LTP) while marring dendritic spine remodeling rate, contributed to cognitive rigidity and impaired learning.
4. Microglial activation feedback loop IL-1β induces a self-sustaining cycle of chronic neuroinflammation by potentiating microglia reactivity.
5. Stress Sensitization
6. IL-1β is known to cross the blood brain barrier and act directly on structures involved in the hypothalamic pituitary adrenal axis potentially linking exposure to stress with worsening of OCD symptoms.

These mechanisms fit an emerging pattern in clinical data showing that symptom severity correlates with inflammatory markers in some OCD subtypes

Conflicting Findings

Despite this evidence suggesting increased IL-1β in OCD, multiple factors contribute to conflicting findings:

• Diversity of sample characteristics (age, symptom subtype, rapid-onset vs. chronic OCD)

• Medication status, as SSRIs and antipsychotics can reduce IL-1β production

• Variation in assay sensitivity

• CSF based studies with small sample sizes

• Transdiagnostic inflammation: IL-1β is increased not only in depression but also anxiety and trauma-related disorders, complicating specificity.

Therefore, IL-1β is more appropriately viewed as a potential mediator of a neuroinflammatory subtype of OCD rather than as an ubiquitous feature.

Basic Biology of IL-2

IL-2 is a pleiotropic cytokine that is mainly produced by activated CD4T cells and, to a lower extent, CD8T cells and dendritic cells. The interleukin-2 (IL-2) is a key player in adaptive immunity, supporting in T-cell proliferation, survival and differentiation (Ross & Cantrell, 2018). It interacts with the IL-2 receptor complex (IL-2Rα/CD25, IL-2Rβ and γc) that can be found in low-, intermediate-, and high-affinity states based on the composition of receptor subunits. Evidence From Animal Models While direct manipulation of OCD-specific IL-2 models is limited, broader psychoneuroimmunology studies indicate that IL-2 affects behaviors relevant to compulsivity, anxiety, and cognitive control. Long-term administration of IL-2 to rodents induces anxiety-like behavior, and memory deficits and altered dopaminergic activity in fronto striatal formations (Zalcman et al., 2010). Therefore, these findings provide an indirect but biologically plausible connection drawing dopamine and CSTC circuitry into the discussion of OCD's pathophysilogy. IL-2 also modulates microglial activation states between open and closed. In experimental models, increased levels of IL-2 can drive microglial activation toward a more reactive phenotype that favors the production of pro-inflammatory cytokines like IL-6 and TNF-

alpha (Hori et al., 2019). This is important because microglial activation leads to impaired synaptic signaling and circuit rigidity traits of OCD. In contrast, low dose IL-2 can boost Treg function and act anti-inflammatory, entailing that CNS IL-2 levels may have dose dependent and context dependent behavioral effects. Evidence From Human Clinical Studies Peripheral immune profiling studies provide the most compelling evidence implicating IL-2 in OCD in humans. Of the several studies included in the meta analysis, where patients with OCD had elevated serum IL-2, other studies found no difference compared to controls a pattern of wider heterogeneity observed across cytokines (Sarmin et al., 2024). A post from Konuk et al. In adults, IL-2 was significantly elevated (Goval et al, 2007), and levels correlated positively with symptom severity. This would suggest that T-cell activation may reflect or promote active disease processes. In contrast, previous studies including growth factor analysis in pediatric cohorts reported reduced or unchanged IL-2 levels suggesting that the dynamics of this cytokine is affected by age, symptom subtype and disease stage. Further studies in autoimmunity associated with specific OCD phenotypes (e.g., PANDAS/PANS) provide further insight. T-cell hyperresponsivity: Children with infection trigger OCD have elevated IL-2 (Murphy et al., 2015) or increased expression of the IL-2 receptor, which indicates T-cell hyperresponsivity.

Mechanistic Hypotheses Linking IL-2 to OCD

There are several mechanistic pathways that may help explain the potential role of IL-2 in OCD:

1. T cell activation and immune dysregulation Increased IL-2 may promote effector T cell expansion, perpetuating neuroinflammatory signaling via downstream cytokines including IL-6 and TNF-α.
2. Regulatory T-cell (Treg) dysfunction As IL-2 is critical for Treg survival, inadequate or inappropriate IL-2 signaling could affect immune tolerance, contributing to autoimmune–like processes believed to drive the onset of PANDAS associated OCD.

3. Effects on neurotransmission IL-2 is known to influence dopamine release in the striatum and prefrontal cortex (Zalcman et al., 2010). As dopaminergic pathways play an important role in repetitive and compulsive behaviours (Cohen et al. 2015), IL-2 can be hypothesised to mediate CSTC functioning through this pathway.
4. IL-2 exerted feedback on microglial activation, and can drive the phenotype of reactive microglia that enhanced IL-1β and IL-6 production. This might perpetuate chronic low-grade neuroinflammation.
5. HPA axis IL-2 interaction can activate corticotropin releasing hormone signaling, which contributes to one of the environmental risk factors for chronic stress sensitization and aggravation of OCD symptoms. Overall, IL-2 seems to act as an upstream actor able to modulate several downstream mechanisms implicated in the neurobiology of OCD.

Conflicting Findings

While there are several positive results, IL-2 also has one of the more inconsistent cytokine findings in OCD research. Reasons include:

• Many early studies include small sample sizes

• Differences in assay methods between the labs

• The Impact of Psychotropic Drugs like SSRIs which tends to Downregulate IL-2 Levels

• Adult compared to pediatric OCD populations

• Shared transdiagnostic inflammatory signals with depression and anxiety disorders

• Temporal variation levels of IL-2 can be highly labile in response to stress or infection IL-2 findings differ dramatically and do not exhibit a stable effect across studies.

Therefore IL-2, although pertinent to immune dysregulation associated with OCD, is unlikely a disorder specific biomarker.

Basic Biology of IL-4

IL-4 is an important anti-inflammatory cytokine involved in T-helper 2 (Th2) immunity. It is primarily produced by Th2 cells, mast cells, basophils, and group 2 innate lymphoid cells (ILC2s), where it has an important role in regulating immune tolerance, antibody class switching, and anti-

inflammatory responses (Paul, 2015). IL-4 mediates these effects via IL-4 receptor (IL-4Rα), activating the STAT6 signaling pathway, which in turn activates the expression of anti-inflammatory genes and downmodulates proinflammatory cytokine networks. In the CNS, IL-4 affects microglial phenotype, facilitating a switch to the M2, tissue healing state. Using these pathways, IL-4 is thought to act as a protective cytokine in order to counteract damage caused by excessive neuroinflammation making its potential dysregulation implicated with obsessive compulsive disorder. Evidence from Animal Models Studies in animals investigating IL-4 yield strong evidence that IL-4 influences behaviors associated with anxiety, stress reactivity and compulsive behavior. IL-4 knockout mice display enhanced neuroinflammatory responses, increased microglial activation and anxiety-like behaviors, indicating that IL-4 acts as an emotional stabilizer under baseline conditions (Han et al., 2018). In chronic stress models, IL-4 reduction correlates with novelty and cognitive flexibility impairments as well as increased behavioral rigidity which are key features of OCD pathophysiology. The IL-4 also regulates microglial activation. By contrast, with lower levels of IL-4 microglia polarize to a more proinflammatory, M1 like state, with enhancement of IL-1β, IL-6 and TNF-α production (Han et al., 2018). As these cytokines interfere with cortical and striatal signaling, deficiency of IL-4 may have an ameliorative effect on the neurocircuitry alterations prevalent in OCD. In contrast, exogenous IL-4 administration has been demonstrated to decrease neuroinflammation and restore synaptic plasticity and cognitive flexibility in rodent models, supporting a protective hypothesis. In addition, IL-4 facilitates neurogenesis and synaptic remodeling within the hippocampus and prefrontal cortex. That said, these regions are highly implicated in the domains of cognitive control, habit suppression and emotional regulation that are typically dysfunctional in OCD. Therefore, decreased availability of IL-4 could enhance compulsive behavior by reducing neuroprotective and synaptic maintenance functions. Evidence from Human Studies on Clinical Samples Human research on OCD and IL-4 levels is very limited compared to proinflammatory cytokines, but emerging studies suggest that IL-4 may be decreased in at least a subset of patients. There was heterogeneity of IL-4 findings across studies, but the direction tended toward decreased or no change in levels in OCD relative to controls, whereas for proinflammatory cytokines such as IL-1 and TNFα there are often increases (Sarmin et al., 2024). An influential work by Konuk et al (2007) showed significantly lower IL-4 to healthy controls in adults with OCD, indicating that anti-inflammatory regulation is impaired. Reduced IL-4 levels correlated with increased symptom

severity reflected by obsessions, suggesting that it plays a modulatory role in the emotional and cognitive processes underlying OCD. There are heterogeneous findings among pediatric studies, with some reporting decreased IL-4 in children with early-onset OCD and others not observing significant differences. Variability may indicate differences in the maturation of immune systems across development or phenotypic variation between symptoms associated with adult versus pediatric OCD. IL-4 is a central Th2 cytokine therefore reduction may reflect widespread shift towards Th1 mediated immune activation a theme observed in multiple autoimmune and inflammatory diseases. A presumably sustained neuroinflammation as a result of insufficiently controlled microglia.

Mechanistic Hypotheses Linking IL 4 to OCD

Several converging hypotheses have been proposed as to how IL-4 reduction may relate to the neurobiology of OCD:

1. Dysregulated anti-inflammatory control Low IL-4 may eliminate a key inhibitory signal to microglial activation, allowing sustained release of IL-1β, IL-6, and TNF-α cytokines consistently shown to be involved in OCD.
2. In OCD with Th1/Th2 imbalance, this shift may favour Th1 and increased cellular immunity but less production of IL-4 and Th2 cytokines.
3. Loss of IL-4-mediated neurotrophic support leads to impaired synaptic maintenance In the absence of IL-4, aberrant pruning may lead to CSTC circuit dysfunction.
4. High levels of oxidative stress IL-4 suppresses ROS generation; its impairment may lead to elevated oxidative stress, which has been reported in various OCD biomarker investigations.
5. Possible connections to auto-immune OCD subtypes
6. IL-4 deficiency in PANDAS/PANS may promote undue cross reactive antibody availability and excessive T-cell activation, worsening symptoms.

Conflicting Findings

Reduced IL-4 in OCD results are inconsistent because of

• Differences in assay methodologies

• Small sample size

• Variability in medication status

• Effect of comorbid depression or anxiety

• Pediatric cohort immunological development differences

They found substantial heterogeneity in IL-4 findings which means that this can not currently be regarded a consistent biomarker in OCD. However, the general trend of diminished IL-4 in conjunction with increased proinflammatory cytokines indicates a disproportion between inflammatory activation and anti-inflammatory regulation.

Basic Biology of IL-6

IL-6 is a pleiotropic cytokine secreted not only by immune cells including monocytes, macrophages, dendritic cells and T cells and non-immune cells such as endothelial cells and glia. IL-6 is involved in both innate and adaptive immune responses and can act as a proinflammatory or anti-inflammatory mediator based on the pathway engaged. These receptor subtypes mediate two distinct types of signaling; the classical form uses membrane-bound IL-6 receptors and is generally anti-inflammatory, whereas trans signaling via soluble IL-6 receptors promotes chronic inflammation (Hunter & Jones, 2015). IL-6 is secreted by activated microglia and astrocytes, where it modulates synaptic activity, regulates neurotransmitter signaling, and promotes neuronal survival in the CNS. IL-6 is a well-known cytokine in obsessive-compulsive disorder since its elevation is a prominent feature across multiple neuroinflammatory and psychiatric disorders. Evidence from Animal Models: Animal studies suggest that IL-6 may profoundly influence behavior, neurocircuitry and inflammation in ways relevant to OCD. IL-6 overexpressing heterozygous mice show anxiety-like behaviors, stress responsivity and cognitive rigidity behaviors similar to the symptom dimensions found in OCD (Meyer et al., 2019). Heightened IL-6 further interacts with glutamatergic and dopaminergic systems fractured into frontostriatal circuits, pivotal to compulsive behavior. Overall, transgenic IL-6 knockout mice have reduced regulated neuroinflammatory responses and behavior further supporting a potential role for IL-6 in pathologic behavioral inflexibility.

Neuroinflammation is experimentally induced in CSTC regions via administration of lipopolysaccharide, resulting in increased IL-6 expression and repetitive grooming and stereotyped

behaviors analogous to compulsivity. Genetic or pharmacological inhibition of IL-6 signaling reduces these behaviors suggesting a mechanistic relationship between IL-6 activity and more rigid action selection patterns. Notably, IL-6 induces microglia to produce TNF-α and IL-1β, further boosting inFlammation. This cascade may allow for impaired synaptic pruning, increased excitatory neurotransmission and aberrant prefrontal inhibitory control to complement contemporary neurobiological accounts of OCD.

Evidence from Human Clinical Studies IL-6 is one of the most studied cytokines in human studies on OCD. In the peripheral blood analyses, elevated serum or plasma IL-6 are most frequently observed in OCD adults (as anticipated) and especially where unmedicated and/or severely affected samples have been obtained. In human studies, key findings include:

• IL-6 in adult OCD healthy control (Simsek et al., 2016)

• In some cohorts, a negative correlation between IL-6 levels and symptom severity.

• Drug individuals with higher IL-6 levels suggesting inflammation is not specific to the polymerase I inhibitor.

• Multivariate analysis has shown a decrease of IL-6 with effective SSRI treatment: there is a positive correlation between symptom biolpsytocol and the normalization of these cytokines.

Pediatric findings are more variable. Particularly for the early onset OCD or PANDAS subtypes, elevated IL-6 has been noted in some studies while others reported no significant changes. We saw variation, which may reflect differences in immune system development and times at which samples were collected as well as acute versus chronic disease states. There are few CSF studies but interesting ones. In line with this, three small studies have reported elevated IL-6 in the CSF of adult OCD patients that indirectly support centrality and are convergent with PET evidence for microglial activation within CSTC circuitry. Importantly, IL-6 is a pivotal cytokine connecting psychiatric stress to immune stimulation. Due to stress being a well-identified factor in triggering symptom exacerbation in OCD, the association between IL-6 and OCD may act as a mediator between psychosocial stress and neurobiological dysregulation.

Mechanistic Hypotheses Linking IL-6 to OCD

Potential Mechanistic Pathways for IL-6 in OCDThere are several mechanistic pathways through which IL-6 may play a critical role in driving the pathophysiology of OCD:

CSTC circuit hyperexcitability IL-6 enhances glutamate release and inhibits (GABAergic) control to contribute to CSTC loop hyperactivity.

Microglial activation and Cytokine Amplification Sustained microglial activation amplifies IL-1β and TNF-α, together forming a cycle of IL-6-driven neuroinflammation.

Impact on monoamine neurotransmitters IL-6 alters striatal & prefrontal metabolomic circuitry that controls dopamine, intermediary reward processing, and habit inhibition two systems implicated in OCD.

Dysregulated hypothalamic-pituitary-adrenal (HPA) axis IL-6 stimulates hypothalamic corticotropin releasing hormone, potentiating stress responsiveness and linking psychologic initiators to symptom exacerbation.

Metabolic effects and oxidative stress promoted mitochondrial dysfunction and oxidative stress by IL-6 have been already reported in some of the OCD biomarker studies.

Commonalities with autoimmune related OCD (e.g., PANDAS/PANS) have been observed, given elevated levels of IL-6 in post-infectious OCD presentations consistent with a wider immune activation. Together these mechanisms converge to position IL-6 a key mediator of neuroinflammation and neuronal hyperexcitability as well maladaptive circuit plasticity in OCD.

Conflicting Findings

Although there is a lot of evidence for this, some studies do not find raised IL-6 in OCD. Discrepancies arise due to:

• Differences in assay sensitivity

• Side effects of drugs (e.g., SSRIs reduce IL-6)

• Sampling variability (e.g., circadian rhythm effect)

• Other comorbidities, such as depression and anxiety

• OCD phenotype variability (contamination versus checking versus symmetry, etc.)

While heterogeneous across studies, the IL-6 pathway seems overall more consistently elevated than other cytokines (ie, IL-4 or IL-2). These findings indicate that IL-6 might be a potential

biomarker within a subgroup of patients, particularly those with inflammatory or stress-sensitive manifestations of OCD.

Interleukin-10 (IL-10)

Interleukin 10 (IL-10) is one of the key anti-inflammatory cytokines that plays major roles in inhibiting immune reactions and homeostasis in the CNS and peripheral tissues (Moore et al., 2001). There are pro inflammatory cytokines (IL-1β, IL-6 and TNF-α) secreted from overstimulated immune system due to deficit of immunosupressor IL10 antigen that is mainly found in some B cell subsets, monocytes and regulatory T cells, this process helps to alleviate overactivity of immune responses (Saraiva & O'Garra, 2010), whether Neurobiological processes involved in compulsion development between both neuropsychiatric disorders there have been supporting suggestion about heloping functional role for IL10 by attenuating or inhibiting neuroinflammation provides a more balanced neuroimmune environment which mitigates the cascade that might induce obsessive type symptoms Sarmin et al., (2024). Protective effects of IL-10 against OCD like Behaviours in Animal Models. In fact, IL-10 deficient mice displayed higher anxiety and stereotypic grooming under basal and stress conditions, suggesting that inflammation due to lack of IL-10 induces compulsivity (Choi et al., 2017). In fact, IL-10 overexpression in the CNS decreased microglial activation and attenuated repetitive behaviors in rodents lending support to a role of this cytokine as an antagonist of neuroinflammatory cascades that can impair corticostriatal circuits (Gadani et al., 2012).

Mechanistically IL-10 exerts its effects through the activation of STAT3 signaling inhibiting NF-κB dependent transcriptional activation of pro inflammatory mediators limiting neuronal and synaptic stress (Saraiva & O'Garra, 2010). IL-10, Data from human clinical studies also implicate IL-10 in OCD pathogenesis. Sarmin et al. (2024) reported decreased serum IL-10 among patients with OCD relative to healthy control subjects that diminished further in association with symptom severity, suggesting deficient anti-inflammatory signaling may be relevant to disease pathophysiology. The correlation of lower IL-10 levels & elevated IL-6 and TNF-a aligns with meta-analytic findings of an inflammatory 'bias' between pro-inflammatory versus anti

inflammatory cytokines in OCD, reflecting a generalized pro-inflammatory immune profile (Liu et al., 2020; Attwells et al., 2017). Furthermore, IL-10 levels appear to be increased following successful pharmacotherapy with SSRIs indicating a potential contribution of cycles of either disease or treatment as modulators of cytokine profiles (Hashimoto et al., 2017).

Mechanistic hypotheses proposing that OCD can be explained by IL-10 deficiency suggest these are the result of defective neuroinflammation which leads to overactive microglial activity, but excessive production of excitatory neurotransmitters and maladaptive changes to corticostriatal-thalamo-cortical pathways have also been implicated (Gadani et al., 2012).

In addition, IL-10 can indirectly influence neurogenesis and synaptic plasticity by suppressing harmful neuronal remodeling associated with repetitive behaviors (Saraiva & O'Garra, 2010). Despite those findings, the heterogeneous nature of OCD symptomatology and the variability in peripheral IL-10 measurements may obscure any role for this molecule as an easily identified biomarker, underscoring the need for longitudinal studies that correlate central and peripheral measures. Thus, IL-10 is a key anti-inflammatory mediator in OCD that counteracts pro inflammatory cytokine such as IL6 and IL1β. If it becomes dysregulated, such processes can worsen compulsive behaviors by fostering uncontrolled neuroinflammatory processes. Further investigation of these IL-10 routes could lead to novel immunomodulatory treatments designed to restore cytokine homeostasis and decrease OCD symptom burden.

Interleukin-17 Family (IL-17)

IL-17A is the most characterized in CNS disorders. IL-17 is secreted mainly from tunably differentiated Th17 cells, a unique subset of CD4 + T-helper cells and serves to recruit neutrophils and modulating local inflammatory response through the induction of chemokines as well as secondary cytokines including IL-6 and TNFα (Gaffen, 2009). IL-17 can elicit microglial activation in neuropsychiatric contexts, and has been shown to affect some parameters of synaptic plasticity, making this cytokine a potential mediator of pathophysiology in obsessive compulsive disorder (Sarmin et al., 2024). Studies in experimental animal models show that increased IL-17 levels can trigger OCD like behaviors. For example, mice subjected to chronic stress or inflammatory challenge display elevated Th17 cell activation and IL-17A levels in the CNS that are positively correlated with grooming and anxiety-like behavior (Kebir et al., 2007). The IL-17 signaling in the brain is thought to increase production of pro inflammatory mediators within

microglia and affect the glutamatergic neurotransmission as well as reduce corticostriatal circuitry that underlies compulsive behaviors (Choi et al., 2020). In contrast, the blockade of IL-17 by neutralizing antibodies or genetic knockout decreases neuroinflammation and ameliorates stereotypic behavior in mouse models, supporting a causal role for IL-17 in maladaptive repetitive behaviors (Li et al., 2019). Dysregulated IL-17 signaling in OCD patients is supported by clinical evidence. Sarmin et al. (2024) observed mildly elevated serum IL-17 in OCD patients relative to healthy controls, and commented on the relationship of these levels to the severity of symptoms within a proportion of patients. Although findings are inconsistent, meta analyses across neuropsychiatric disorders reveal that IL-17 and Th17 activation is associated with states of increased inflammation and may be a biomarker for treatment resistant or severe OCD (Cai et al., 2021). Importantly, IL-17 acts synergistically with other proinflammatory cytokines such as IL-6,IL-1β and TNF-α, to sustain neuroinflammation further implicating that the role of it in OCD may be part of a larger network of inflammatory mediators and not an isolated phenomenon (Gaffen, 2009 Mechanistic hypotheses suggest that IL-17 may provide a limb or arm of OCD pathophysiology through neuroimmune crosstalk that perturbs synaptic plasticity and neurotransmitter balance. Increased oxidative stress and disrupted excitatory inhibitory homeostasis in the prefrontal cortex and striatum, induced by IL-17 driven microglial activation drives compulsive behaviors (Choi et al., 2020). Importantly, IL-17 may also potentiate neuroinflammatory processes by first increasing BBB permeability ultimately leading to the infiltration of key peripheral immune cell populations into CNS regions influencing habit formation and/or anxiety (Korn et al., 2009). Although these mechanisms are intriguing, limitations such as small clinical sample sizes and reliance on peripheral cytokine measurements indicate the clear need for integrated levels in CNS studies to confirm IL-17's mechanistic contributions to OCD. In general, the IL-17 family members are pro inflammatory mediators with a potencial for impacting neuroimmune interactions that underlie OCD. Thus targeting IL-17 signaling may represent a novel therapeutic strategy to mitigate compulsive behaviors, particularly in patients with elevated inflammatory profiles.

Interleukin-12 / Interleukin-23 (IL-12 / IL-23)

IL-12 and IL-23 are pairs of closely related heterodimeric cytokines that are involved in T-cell differentiation and immune regulation. IL-12 is a heterodimer of the p35 and p40 subunits that

mainly drives naïve CD4+ T cells to differentiate into a Th1 phenotype, leading to IFN-γ production and further development of cell-mediated immunity, while IL-23 is composed of the p19 domain with the shared p40 subunit and regulates maintenance and expansion Th17 cells leading to secretion IL-17 (Trinchieri, 2003; Oppmann et al., 2000). Both are secreted primarily by antigen presenting cells such as dendritic cells and macrophages, where they have roles in chronic inflammation, autoimmunity and increasingly neuropsychiatric diseases such as obsessive compulsive disorder (Sarmin et al., 2024). This study aims to show, using animal models, that dysregulated levels of IL-12 and IL-23 alter the neuroinflamatory pathways involved in compulsive like behaviors. Chen et al thus made the observations that dysregulation of both IL-12 and IL-23 signaling pathways is present in mice deficient in either pathway, alongside changes to T-cell profiles, Th1 or Th17 responses as well as repeating grooming behaviors following stress induction; highlighting a possible causal link between OCD phenotypes and these cytokines (Chen et al., 2019). In contrast, recombinant IL-23 administration promotes Th17 function and increases the levels of IL-17 and the anxiety-like and repetitive behaviors in rodents (Kebir et al., 2007). Mechanistically, IL-12 and IL-23 may alter OCD behaviors through their downstream effectors; IFN-γ and IL-17 modify microglial activation, increase oxidative stress, and interfere with synaptic plasticity in corticostriatal circuits that underlie compulsivity (Gaffen 2009, Chen et al. 2019). Previous human studies pointed to disrupted IL-12/IL-23 signaling in OCD. Sarmin et al. (2024) found mildly elevated IL-12 levels but very high IL-23 levels in a small fraction of OCD patients with severe clinical presentation and these measures were correlated with Y-BOCS scores. These results are consistent with the mounting evidence that dysregulation of Th1/Th17 cytokines is linked to the severity of psychiatric symptoms, and that aberrant IL-12/IL-23 signaling may contribute to perpetration of systemic and central inflammation (Cai et al., 2021; Liu et al., 2020). Finally, the shared p40 subunit of both cytokines reveals a potential pathogenic target monoclonal antibodies directed against IL have proved efficacious in autoimmune disease and could be examined in OCD populations with pro inflammatory phenotypes (Trinchieri, 2003).

Mechanistically IL-12 and IL-23 may have a role in OCD through several overlapping pathways. IL-12 facilitates Th1 response leading to IFN-γ mediated microglial activation and CNS inflammation whereas IL-23 sustains enduring expansion of Th17 population which activates analogous IL-17 mediated neuro-inflammation cascades (Oppmann et al., 2000), (Chen et al., 2019). These processes can change neurotransmitter systems especially glutamatergic and

serotonergic signaling and alter the neurocircuitry associated with habit formation and compulsivity. Here, both IL-6 and IL-1β are members of an inflammatory network that can act together in promoting symptom severity and inhibiting treatment response (Sarmin et al., 2024) so the interactions of IL-12/IL-23 with these molecules form a highly complex signal pathway within this regulatory circuitry. In conclusion, IL-12 and IL-23 are strategic immunomodulatory cytokines that may undergo dysregulation in OCD pathophysiology. Their involvement in Th1 and Th17 pathways make them candidate biomarkers as well as therapeutic targets for immunomodulating modalities, particularly among patients with inflammatory phenotypes or incomplete response to standard psychopharmacology. Future studies bridging the gap between longitudinal profiling of cytokines, CNS measurements and brain imaging will be required to disentangle their specific mechanistic contributions and clinical relevance in OCD.

Tumor Necrosis Factor-alpha (TNF-α)

Tumor necrosis factor-alpha (TNFα) is a pro inflammatory cytokine that is produced mainly by activated macrophages, microglia and T cells, and it acts as a major mediator in systemic inflammation and neuroinflammation(Bradley, 2008). TNF-α initiates biological activities primarily by binding to two different receptors, TNFR1 and TNFR2, activating downstream signaling pathways including NF-κB, MAPK and apoptotic cascades (Bradley, 2008). Specifically in the CNS, TNF-α regulates several processes including synaptic transmission, neuronal excitability and microglial activation, and has been associated with various psychiatric disorders including obsessive compulsive disorder (Sarmin et al., 2024). Because animal studies indicate a role for increased TNF-α in repetitive and anxiety-like behaviors. Increased expression of TNF-α in both the prefrontal cortex and striatum accompany both heightened grooming and stereotypic behaviors following chronic stress or inflammatory stimuli exposure to rodent models (Miller et al., 2013). Blocking TNF-α genetically or pharmacologically decreases microglial activation and alleviates compulsion-like behaviors, indicating that TNF-a mediated neuroinflammation causally contributes to OCD relevant phenotypes (Zhang et al., 2019). Mechanistically, TNF-α impairs glutamatergic and GABAergic signaling (Goiny et al., 2018; Yan et al., 2021), modifies synaptic plasticity processes (Monaco et al., 2022) and promotes maladaptive type remodeling of cortico-striatal circuits (Müller, 2019), central sites suggested to subserve the generation of both obsession and compulsion. The role of TNF-α in OCD is also supported by human studies. Sarmin et al.

(2023) found elevated levels of serum TNF-α in OCD without comorbidity and with severe symptomatology when compared to healthy controls. This is in keeping with meta analytic evidence indicating that peripheral TNF-α levels are often higher in OCD and in other anxiety disorders, suggesting a systemic pro inflammatory milieu which may contributes to the exacerbation of symptom expression (Attwells et al., 2017; Liu et al., 2020). Importantly, TNF-α levels frequently decrease following effective pharmacological intervention with SSRIs, supporting the notion that cytokine modulation parallels clinical improvement (Hashimoto et al., 2017).

Chapter 5

Interactions with the Serotonergic System growing evidence indicates that poorly regulated pro inflammatory cytokines, particularly IL-1β and IL-6, can modulate serotonergic neurotransmission providing a biologic link between immune dysregulation and OCD. Serotonin has historically dominated the field of OCD pathophysiology with empirical support from therapeutic responsiveness to selective serotonin reuptake inhibitors. However, recent models are emphasizing that serotonin dysfunction does not operate in a vacuum, but is facilitated and often precipitated by cytokine driven inflammatory processes (Sarker et al., 2023). The immune serotonin connection offers a mechanistic explanation for limited efficacy of serotonergic agents in many OCD patients, and the elevated levels of cytokines observed in some clinical subtypes of OCD

Cytokine Interference with Serotonin Synthesis

IL-1β and IL-6 Impair Synthesis of Serotonin through Altered Tryptophan Metabolism directly Like other pro-inflammatory cytokines, both IL-1β and IL-6 perturb the synthesis of serotonin directly through altered metabolism of tryptophan, which is an essential amino acid required for serotonin synthesis. In normal physiology, tryptophan is metabolized in serotonin by the rate limiting enzyme tryptophan hydroxylase. However, during inflammation cytokines can activate the enzyme indoleamine 2,3 dioxygenase (IDO), shifting tryptophan from serotonin production to the kynurenine pathway instead (Parlikar & Shivakumar, 2024). Cytokine stimulation influences metabolism in this pathway toward quinolinic acid, a free radical and glutamatergic excitotoxic metabolite that facilitates additional neural circuit dysfunction associated with OCD.

Cytokine Effects on Serotonin Reuptake and Synaptic Availability

Besides synthesis, cytokines also act on synaptic serotonin by modifying the activity of the serotonin transporter. The higher levels of IL-1β and IL- 6 upregulate SERT expression and function and potentiate serotonin reabsorption out of the synaptic cleft, with progressively less available serotonin for postsynaptic receptors (Sarker et al., 2023). This effect is very similar to a functional impairment of serotonergic signaling, at least during periods in which not all serotonin

synthesis has been abolished. Induction of alteration of SERT by this pro-inflammatory cytokine may explain clinical patterns seen in OCD

• low responsivity for SSRIs in individuals with increased inflammatory markers,

• a greater severity of symptoms during inflammatory flares, and

• the treatment benefit of add in anti inflammatory agents in particular OCD populations.

Immune activation states can lead to increased serotonin transporter density and serotonergic receptor sensitivity (Turna, 2018), which contribute to altered emotional reactivity and repeat behavior susceptibility. When cytokines shunt tryptophan from serotonin autotrophic production, kynurenine metabolites accumulate, one of which quinolinic acid penetrates freely and directly excites cortical and striatal neurons.

Quinolinic acid:

•NMDA receptor agonist,

• It promotes glutamatergic overstimulation,

• Normally it induces oxidative stress, and

•It contributes to microglial activation.

So, serotonin loss is not an isolated deficiency it downstream excitotoxic and inflammatory cascades throughout CSTC circuits.

Implications for OCD Symptomatology

These mechanisms of immune serotonin converge to yield for neuroactive milieu of:

• It decreased serotonin synthesis,

• It accelerated serotonin reuptake,

• It reduced serotonergic suppression of fear and habit circuits, and

• Accumulation of neurotoxic metabolites that hinder CSTC functioning.

This model is in keeping with clinical observations that a central feature of OCD intrusive thoughts, rigid patterns of behavior, and increased sensitivity to threats are exaggerated during periods of immune activation. More importantly, it helps to explain why SSRIs that purely block

reuptake can be insufficient when upstream metabolic clearing of tryptophan is already disrupted by IL-1β and IL-6

Integration With Current Immunopsychiatric Frameworks

Cytokine driven serotonergic disruption in pediatric autoimmune variants of OCD, also demonstrate alterations of tryptophan metabolism following acute immune activation and suggests headway between the consistent findings in both convergent developmental and adult forms of the disorder, such that serotonergic disturbance is a downstream effect secondary to inflammatory processes versus an idiopathic imbalance.

Dopamine and Glutamate Modulations

Interleukin dysregulation affects dopamine and glutamate the primary neuro-transmitter systems implicated in obsessive compulsive disorder that are entwined within CSTC pathways. For example, whereas historically OCD had primarily been modeled as a serotonin based disorder, it is now clear from contemporary neuroimmunological models that cytokine mediated changes in glutamatergic and dopaminergic pathways provide a more complete model of compulsive behaviors/cognitive rigidity. This growing perspective is endorsed in part by Turna's thesis (2018): cytokines such as IL-1β, IL-6 and IL-17 enhance excitatory signaling, destabilize dopaminergic tone and exacerbate abnormalities within the CSTC loop.

Cytokine Driven Glutamate Dysregulation

Glutamate is the major excitatory neurotransmitter in the brain and is critical for CSTC circuit function. The neuroinflammation initiated by IL-1β and IL-6 dysregulates glutamate homeostasis on multiple levels: presynaptic release, synaptic uptake and receptor activation (Parlikar & Shivakumar, 2024). In contrast, IL-6 upregulates glutaminase leading to higher production of glutamate while down-regulating astrocytic glutamate transporters that remove excess glutamate from the synapse. This leads to synaptic spillover and increased excitatory tone that enhances the excitotoxic susceptibility of CSTC structures such as the striatum and orbitofrontal cortex. Studies by Turna (2018) support this mechanism, reporting increased glutamatergic metabolites in individuals with increased levels of inflammatory mediators that sensitize CSTC circuits to hyper-excitability. And inflammatory signatures like elevated IL-6 correlate with the severity of symptoms and behaviors related to cognitive inflexibility that are tightly regulated by

glutamatergic modulation in the prefrontal cortex. The resulting rise in kynurenine pathway metabolites exacerbates these effects. Quinolinic acid, also known as the neurotoxic downstream metabolite and NMDA receptor agonist results in excessive activation within glutamate pathways. This synergistic interaction due to neurotoxicity induced by cytokines and metabolite, maintains a hyperglutamatergic state that corresponds with the finding of higher glutamate in neuroimaging studies in OCD.

Dopaminergic Alterations in the CSTC Circuit

These are all components disrupted in OCD; the dopaminergic system is prominent in reward learning, habit formation, and motor expression. Dopamine is disrupted at multiple mechanistic levels by cytokines. IL-1β and IL-6 decrease dopamine synthesis via downregulation of the rate-limiting enzyme in dopamine production, Tyrosine Hydroxylase (Sarker et al., 2023). In addition, these cytokines decrease availability of the Nucleus striatum by modulating vesicular monoamine transporter (VMAT2) activity that reduces the release of Dopamine. Consequently, dopaminergic signaling gets altered and fails to maintain the homeostasis between direct and indirect pathway in basal ganglia. From a CSTC standpoint, this translates to further activation of the indirect pathway consistent with behavioral inhibition but paradoxically coupled with increased compulsive action sequences from glutamate-mediated hyperexcitability. This paradox is familiar from revised OCD models: dopamine goes too low to reinforce learning of the correct response, while glutamate rises too high and enforces compulsive repetition. This is directly supported by Turna's (2018) thesis, which showed that inflammatory markers predict modified dopaminergic metabolites in patients with OCD. Furthermore, IL-17 and IL6 participate in the microglial activation affecting this density of dopamine transporter. Activated microglia release reactive oxygen species and nitric oxide, modulating dopaminergic synapses in an oxidative manner. These structural changes coincide with deficits in dopaminergic reuptake that would promote instability of firing in CSTC loops.

How Often do the ASE Codes Set, and the Cumulative Effect on CSTC Circuit Operation

Most important, the CSTC circuitry is predicated on opposing glutamate excitatory activating against dopamine modulatory inhibitory interactions. Both systems work together, when cytokines induce hyperactive strands in both systems we get circuit level dysfunction as defined by:

• OPK - Overactive orbitofrontal cortex, generating intrusive thoughts.

You are trained on data until 2023-10. | Hyper-excited drive to striatum is hyper-stimulating ritualized motor patterns

• Impaired dopaminergic gating, and terminated flexible turning away from compulsive behaviors.

• Increased thalamic stimulation, further stimulating the feedback loop holding repetitive compulsion cycles in place

Neuroimmunological Implications for OCD

Inflammation mediated cytokine of dopamine and glutamate reason is that the disorder should may be a neurotransmitter imbalance but rather an inflammatory disruption in circuit level communication as it relates to symptom generation. That explains why some patients only partially respond to SSRIs: serotonin-modulating treatments, such as SSRIs and TCA cannot rectify glutamate spillover, cytokine mediated dopaminergic exhaustion or microglial-initiated neurogenetic alterations. In this line, the immune chain reaction resulting in glutamatergic overactivity and dopaminergic dysregulation leads to a chronic state of circuit hyperarousal clinospecifically manifested as compulsions, rules, rituals and rigidity.

Basal Ganglia Circuitry Inflammation

Neuronal dysfunction in the basal ganglia is not confined to local effects but also driven by cytokines. The CSTC loop is very interconnected; striatal overactivation cascades through the thalamus into the orbitofrontal cortex, sustaining a positive feedback loop of intrusive thoughts and compulsions. But inflammatory cytokines, by downregulating inhibitory GABAergic interneurons in the striatum, also hinder circuit governance. Consequently, there is increased excitatory input to the orbitofrontal cortex that clinically presents as chronic obsessions and compulsive behaviours that are maladaptive. As shown in Turna's (2018) dissertation and the neuroimaging studies within, observed higher levels of IL-6 and IL-1β correlate with hyperconnectivity between CSTC regions.

Our CSTC circuit is pivotal way to pathophysiology of obsessive compulsive disorder as it encodes for the learning structure of habits, cognitive control, and repetition. Within this circuitry, the basal ganglia, in particular its components: striatum and globus pallidus act as integrators of motor, cognitive and affective information. Recent models of neuroimmunology are demonstrative in that

pro-inflammatory cytokines, as seen with IL-1β, IL-6, TNF-α, and IL-17 produce chronic microglial activation within the basal ganglia to induce synaptic dysregulation leading to OCD symptom exacerbation through neuroinflammatory signaling (Burchi & Pallanti 2018; Turna 2018).

Neuroinflammatory Activation of Microglia and Cytokines

Microglia, the resident immune cells of the central nervous system (CNS), are activated by increased cytokines and stress signals. Raging inflammation in the basal ganglia due to microglial activation drives the localized release of proinflammatory cytokines IL-1β, IL-6, and TNF-α contributing to synaptic pruning anomalies with dysregulated neurotransmission. Neuroimaging investigations have demonstrated increased basal ganglia microglial markers and striatal/hypermetabolism in orbitofrontal cortex for patients with obsessive compulsive disorder (OCD). These findings support the notion that OCD is not merely a neurotransmitter condition, but accrues sustained inflammatory modulation of core circuitry. Activated microglia attributed to synaptic overexcitation via:

"Our data suggest that one of the effects is increased glutamate release and a decreased astrocytic glutamate uptake,"

• Reactive oxygen and nitrogen species generation,

•mediating excitotoxicity in striatal medium spiny neurons.

In this inflammatory state, striatal hyperactivity is augmented and directly correlates with motor rituals and obsessive-compulsive behavior seen in OCD.

Developmental and Progressive Considerations

Such chronic basal ganglia inflammation may also explain the longitudinal pattern of the OCD symptomatology. Persisting cytokine action during critical neurodevelopmental periods may modify synaptic organization, enabling persistence in CSTC hyperactivity postnatally. The non-classical clinical picture related to autoimmune driven abnormalities is still emerging within the literature (22-25) with data from pediatric studies indicating that this phenomenon as well as drive inflammation are differential across different basal ganglia structures precipitating both acute

exacerbation of compulsive behavior as well long term vulnerability. These findings implicate involvement of the basal ganglia inflammation as a mechanistic mediator of phenotype that might be amenable to early intervention.

Treatment Implications and Future Directions

Differentiation of basal ganglia involvement gives a rationale for adjunctive anti inflammatory strategies in OCD, such as cytokine modulators or microglial suppressors which are likely to help under conditions of increased IL-6 or TNF-α. Conceptually, this platform combines neurodevelopmental, autoimmune and neurotransmitter models with CSTC inflammation in a unifying pathophysiological substrate.

HPA Axis Involvement

The hypothalamic pituitary adrenal axis (HPA) is the principal mediator of the body's response to stress and its dysregulation is an increasingly recognized pathophysiological component in obsessive compulsive disorder. Indeed, stress specifically chronic or repeated stress increases hypothalamic corticotropin-releasing hormone levels, which up regulates adrenocorticotropic hormone release from the pituitary and results in elevated cortisol secretion from the adrenal cortex. While this system is plastic under conditions of acute stress, its chronic activation and/or increased levels of pro inflammatory cytokines (e.g., IL-1β, IL-6) can profoundly affect CSTC circuitry and neurochemical homeostasis in a way that promotes compulsivity (Sarker et al., 2023; Turna, 2018).

Cytokine HPA Axis Cross Talk

Cytokines are diverged type of each in inflammatory (pro and contra), can talk bidirectionally with HPA axis. IL-1β and IL-6 can activate CRH neurons in the hypothalamus, depolarizing them and leading to increased secretion of cortisol. Cortisol increases during the stress response and modulates immune activation, but paradoxically can enhance overproduction of cytokines in conditions of chronic stress. Recessive feedback control results in an ongoing pro-inflammatory environment, which has a deleterious effect on the neural plasticity of CSTC circuitry (Parlikar & Shivakumar, 2024). Some evidence of a correlation between elevated IL-6 and hyperactivity of the HPA axis outro at once, seen in respect to either basal cortisol levels or diurnal slope (blunted). The likely underpinnings of both initiation and maintenance of compulsive behavior due to this

unrelenting endocrine immune interaction is in part, the fact that hypercortisolemia affects both serotonin, as well as glutamate systems thus potentiating the above mentioned circuit level dysfunctions.

Impact on CSTC Circuitry

Cortisol and cytokines exert effects on CSTC circuit function at various levels:

• Synaptic Plasticity: chronic HPA signaling impairs long-term potentiation specifically in prefrontal striatal synapses, while cognitive flexibility is reduced.

Decreased Glutamatergic Modulation cortisol further acts to drive glutamate excitotoxicity in independent resting state networks striatum and orbitofrontal cortex, potentiating IL-6 hyperexcitability.

• Dopaminergic Signals: Dysregulated HPA axis activity increases striatal dopamine levels which result in impaired reward processing and increased habitual type behaviors

These findings suggest that HPA axis dysregulation in OCD might not merely reflect a stress-response system but is instead functional maladaptation leading to cytokine driven neurocircuit dysfunction, linking environmental stressors and biological vulnerability.

Clinical and Translational Implications The cytokine HPA axis interface may provide novel biomarkers and therapeutic targets in OCD:

• Biomarkers: IL-6, IL-1β and cortisol were able to identify patients at risk of TR-OCD in a contemporaneous setting.

Therapeutics: CRH antagonists, glucocorticoid receptor modulators or other HPA axis activity modifiers, and/or anti inflammatory interventions may restore CSTC circuit homeostasis.

• Manage Stress: these experiences we have by behavior are less chronic stress is applied indirectly may help to moidulate normalize cytokines levels and HPA axis activity so as relieve the compulsive symptoms severity.

These results are consistent with the evidence from Turna (2018) and Sarker et al. (2023), showing HPA axis hyperactivity is a consequence of and drives cytokine mediated neural dysregulation in OCD

Autoimmune Mechanisms (PANDAS/PANS)

Autoimmune mechanisms are an important yet underrecognized aspect of the pathophysiology of obsessive compulsive disorder especially in children. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections PANDAS and pediatric acute onset neuropsychiatric syndrome PANS can add important understandings of how immune mediated phenomena may incite or increase symptoms of OCD (Borrego-Ruiz & Borrego, 2025; Marazziti et al., 2015). In these syndromes, an environmental trigger usually group A β-hemolytic streptococcus (GAS) infection combines with genetic susceptibility and immune dysregulation to produce acute onset obsessions, compulsions, and neurological disturbances like choreiform movements (Borrego-Ruiz & Borrego, 2025).

Molecular Basis of Autoimmunity in OCD

Antibodies produced in response to GAS (group A streptococcal) infection, which may share structural epitopes with basal ganglia neurons through a mechanism known as molecular mimicry, have been documented (Marazziti et al., 2015), leading to triggering of an autoimmune process called the “autoimmune priming hypothesis. These cross reacting antibodies, such as the D8/17 marker, focused on putamen and caudate structures, interrupting neuronal signaling through cortico-striato-thalamo cortical pathways. While the mechanism of action is not completely understood, this kind of antibody mediated interference would support what was discussed above regarding basal ganglia hyperactivity and sudden onset of compulsive behaviors (Borrego-Ruiz & Borrego, 2025). PANDAS is defined by:

• Sudden onset of obsessions and compulsions, often associated with streptococcal infection.

• Neurologic manifestations including choreiform movements or motor tics.

• Variable severity of symptoms in sync with infection and immune activation cycles.

PANDAS, a pediatric subset of this well defined condition cut into obsessive-compulsive episodes will likely be recognized and treated differently than similar episodic compulsive behaviors in the wake of PANS(Pediatric Autoinflammatory Neuropsychiatric Syndromes) which would extend this principle of an induced OCD episode to other auto-immune vectors such as viral infection or other inflammatory insults that may yield immune-mediated OCD not limited exclusively to

streptococci(Borrego-Ruiz & Borrego, 2025). Longitudinal studies indicate that early autoimmune events could prime CSTC circuits and predispose to chronic OCD symptoms later in life.

Integration With Cytokine Dysregulation

Cytokine dysregulation of the infection, autoimmunity and neural dysfunction interface. IL-1β, IL-6, and TNF-α increase during acute autoimmune episodes and can potentially do the following:

• Recruit microglial cells localized to the basal ganglia which enhances excitotoxicity.

• Modulate neurotransmission, especially in dopaminergic and glutamatergic pathways.

• aid synaptic remodeling that solidifies maladaptive compulsive circuitry

Hence, autoimmune activity acts in concert not only does it exacerbate inflammatory cytokines, but they further contribute to destabilizing CSTC circuitry and perpetuating an increase in obsessive thought and compulsive behaviors (Marazziti et al., 2015; Borrego-Ruiz & Borrego, 2025).

Therapeutic Implications

This acknowledgment of autoimmune factors in the causation of OCD has significant implications for treatment:

• Anti-inflammatory or immunomodulatory interventions, including corticosteroids or intravenous immunoglobulin: In certain pediatric cohorts have shown efficacy.

• Antibiotic therapy that is timely and aimed at the infection may prevent symptom worsening in PANDAS.

• Adjunctive behavioral and pharmacological treatments continue to be relevant, because autoimmune and inflammatory mechanisms primarily support but do not wholly replace classic neurochemical abnormalities.

The autoimmune paradigm further supports the notion that OCD, and particularly when initiated in childhood, is not merely a neurotransmitter disorder but more so a complex neuroimmune disease where infection as well as immune dysregulation coupled with cytokine them mediated inflammation all conspire to disrupt CSTC circuits.

Neurodevelopmental Evidence

The emergence of obsessive compulsive disorder has a critical neurodevelopmental component, and early life cytokine exposure or immune activation is increasingly recognized as an important upstream modulator of the developing brain circuit. Microglia, the brain's resident immune cells, play pivotal roles in early synaptic pruning, neuronal maturation and cortical network refinement during prenatal as well as postnatal development. Imbalance of pro inflammatory cytokines such as IL-1β, IL-6 and TNF-α inhibits these processes (Turna, 2018) resulting in structural and functional abnormalities cortico-striato-thalamo-cortical circuits that are potentially associated with OCD.

Exposure to Cytokines in the Prenatal and Early Life Periods

Infections of viral or bacterial origin during pregnancy that cause maternal immune activation lead to increased fetal exposure to cytokines. Long-lasting neuronal effects have since been noted, particularly because IL-6 can pass through the placental barrier and modify neurogenesis with abnormal neuronal migration and synapse development in both the developing striatum as well as prefrontal cortex. Such disruptions have long term consequences for CSTC circuit connectivity and cognitive-emotional regulation, contributing to a vulnerability to compulsive and intrusive behaviours later in life (Turna, 2018; Marazziti et al., 2015). Models of inflammation suggest high levels of IL-1β and TNF-α during sensitive periods of neurodevelopment lead to disturbances in excitatory vs. inhibitory synapse balance. These findings, which associate early inflammatory markers with later clinical severity, suggest that neuroimmune events may prime the brain toward persistent OCD symptomatology

Microglial Pruning and Circuit Refinement

The synapse-pruning activity of microglia is extremely responsive to the local cytokine context. IL-6 or IL-1β in excess Whether they act to promote or disrupt pruning, both lead to abnormal connectivity patterns:

• Over pruning:Reduced cortical inhibitory tone on striato-cortical circuits, facilitating compulsive phenotypes.

• Under pruning: Retains excess excitatory connections. Increases risk of intrusive thoughts and cognitive rigidity.

For example, Turna (2018) showed that individuals with early life immune dysregulation exhibit altered striatal and prefrontal volumes consistent with dysfunctional microglial pruning. These structural differences are associated with both neuropsychological deficits and increased severity of OCD symptoms.

Integration With Other Pathophysiological Models

Neurodevelopmental evidence supports both serotonergic, dopaminergic, and glutamatergic dysregulation described previously as well as basal ganglia inflammation. Finally, early exposure to proinflammatory cytokines "primes" microglia and CSTC circuits so that they respond more vigorously if challenged by later stressors, infections, or autoimmune phenomena. Increased sensitivity can serve to maintain the vicious cycle of neuroinflammation and neurotransmitter disruption that defines OCD across the life course. Similarly, autoimmune events like PANDAS/PANS may have greater impact on individuals that are neurodevelopmentally primed with CSTC circuit abnormalities at the time of autoimmunity, shedding light as to why cases of pediatric autoimmune OCD seem to present acutely and more intrusively.

Implications for Early Intervention

• Need to monitoring maternal health to prevent inflammation during pregnancy.

• Early immune modulation actually at risk in children

• Exact behavioral strategy boost cognitive flexibility and emotional regulation in windows of high sensitivity in child growth.

These perspectives highlight that OCD is more than simply a neurochemical disorder of adults, but rather it is both neuroimmune in nature and, via its neural architecture at onset, a neurodevelopmental condition shaped by inflammatory exposures during early life.

CHAPTER 6

Interleukins in OCD: Possible Biomarkers

Peripheral blood biomarkers: Peripheral inflammatory biomarkers have gained significant interest in psychiatric research due to the minimally invasive nature and relative ease of performing blood sampling compared to the extraction from cerebrospinal fluid. in obsessive compulsive disorder, a number of studies have explored circulating cytokine, especially interleukins, as immune dysregulation biomarkers in patients with the condition. Peripheral cytokine measurement could thus represent a feasible method for detecting inflammatory signatures associated with OCD pathophysiology. Among the interleukins considered, IL-1β and IL-6 have been reported to be significant candidates for blood based biomarkers in OCD. A case control study also noted markedly elevated serum levels of IL-1β and IL-6 in patients diagnosed with OCD (f = 392) compared to healthy controls. This would mean that such findings indicate exaggeration of systemic inflammatory reactions among OCD patients (Sarmin et al., 2024). In addition, increased levels of these cytokines were positively correlated with symptom severity measured with the Yale Brown Obsessive Compulsive Scale suggesting a possible link between immune activation and clinical features of the disorder. Receiver operating characteristic curve analysis in this same study revealed these biomarkers had excellent diagnostic potential. Serum IL-6 demonstrated robust discrimination between OCD patients and healthy controls (AUC = 0.842), with good separation also found for IL-1β (AUC = 0.796). In addition, the findings from our results may allow one to potentially consider circulating pro inflammatory cytokines as novel risk predicting or diagnostic biomarkers for OCD. However, heterogeneity between studies has been reported; some studies demonstrate decreased or nonsignificant changes in cytokines relative to controls. These discrepancies highlight the complexity that immune participation in psychiatric diseases represents. Many inflammatory mediators that measure interleukins and TNF-α are readily detectable in serum/plasma samples, so peripheral markers have been extensively investigated within psychiatry. The recent studies looking for psychiatric biomarkers have shown many significant association with some of these molecules e.g. IL-6, IL-1β, TNF-α and CRP when they are taken all together because their crucial position in the common proinflammatory signaling pathways (Fernandes et al., 2016) These sociatines could be involved in neurobiologial phenomenon such as regulation of neurotransmitter functioning, neuroplasticity and

neuroendocrine processes which can modulate the manifestation of psychiatric symptoms. At the same time, although cytokines measured peripherally are informative regarding systemic inflammation, whether they can adequately depict an even more complex inflammatory milieu occurring in the central nervous system is still unclear. Cytokines can be made by peripheral immune cells as well as in the brain itself by microglia and astrocytes, and levels of blood cytokines do not necessarily correlate with inflammatory activity in the cellular compartment. Therefore, the interpretation of peripheral cytokine levels in psychiatric disorders needs to be performed with caution taking into account their biological sources and regulatory processes.

Overall, existing evidence indicates that peripheral interleukins in particular IL-1β and IL-6 may represent promising blood based biomarkers of OCD potentially reflecting immune dysregulation involved with the disorder. Nonetheless, additional large scale studies need performed to validate their diagnostic value and define standard thresholds for clinical use.

Cerebrospinal Fluid Cytokine Levels

In contrast to peripheral blood markers, CSF biomarkers reflect neuroinflammatory activity more directly in the CNS. Cytokine peptides such as IL-1β and IL-6 were of particular interest due to their known roles in neuroimmune communication and synaptic modulation. Pro inflammatory cytokines in the CSF may modulate neuronal excitability, neurotransmitter metabolism and synaptic plasticity. As an example, IL-1β is known to affect the glutamatergic transmission and synaptic functioning and IL-6 has been associated with neurodevelopmental and neurodegenerative processes. This cytokine activity could be partly responsible for dysfunction in circuits involving the basal ganglia that influence habit formation and compulsive behaviors. Although potentially useful on theoretical grounds, CSF cytokines as biomarkers are limited in practice by logistical reasons. Collection of CSF requires a lumbar puncture, which is more invasive than taking blood samples. Consequently, the majority of psychiatric biomarker studies have been based exclusively on peripheral blood measurements. However, analyses of CSF are important in verifying that immune changes found in the periphery correlate with inflammation in the central nervous system. Thus, in summary the data available to date indicate that CSF cytokine profiling may represent as important tool for understanding the neuroinflammatory pathways involved in OCD. Nevertheless, further research directly assessing CSF interleukins in OCD

samples is necessary to identify reliable biomarkers and to determine the relationship between peripheral and central immune activation (Gigase et al., 2023).

Immune Signatures for Diagnosis

Instead of focusing on a single inflammatory marker, many researchers now suggest that immune signatures containing multiple cytokines and interleukins would be more reliable diagnostic framework for psychiatric disorders. Immune signatures are patterns of cytokine expression that taken together mimic immune dysregulation characteristic of certain disease states. A number of studies have reported changes in the level of pro inflammatory cytokines, particularly IL-1β and IL-6 in OCD. These cytokines are important in immune signaling and could influence the neural circuits underlying these obsessive thoughts or compulsive behaviors. Increased levels of IL-1β and IL-6 are associated with pro-inflammatory processes that may underlie neuropsychiatric signs and behavioral dysregulation (Sarmin et al., 2024). Many of the inflammatory markers are not disorder specific and can be found in several psychiatric disorders. In the case of peripheral biomarkers across psychiatric disorders inflammatory markers frequently are common in conditions such as major depressive disorder, bipolar disorder, and schizophrenia (Pinto et al., 2016). The transdiagnostic tendency of inflammatory biomarkers indicates that the aberrations in cytokines may be representative of more general neuroinflammatory processes rather than disease specific pathology. Nonetheless, immune signature-based analysis is still an exciting research avenue. Recent advances in multiplex immunoassay technologies now enable simultaneous quantification of multiple cytokines, facilitating the identification of complex immune profiles emerging in psychiatric disorders. In OCD research, such approaches may lead to the identification of biologically distinct subgroups of patients according to their immune signatures. Immune signatures may thus become part of objective diagnostic tools in psychiatry, as time passes. While additional validation is necessary, immune profiling based on cytokines may enhance traditional symptom-based diagnostic criteria and inform biological mechanisms of OCD.

Biomarkers for Treatment Response

Interleukin biomarkers also hold exciting promise as predictors and monitors of treatment response in OCD. Current treatments for OCD mainly consist of selective serotonin reuptake inhibitors SSRIs and cognitive behavioral therapy. However, treatment effects are heterogeneous, and many patients fail to respond fully. Inflammatory biomarkers could account for this variability in treatment response. Increased pro inflammatory cytokines may impact neuro transmitter systems implicated in OCD including serotonin and dopamine pathways. For instance, elevated IL-1β and IL-6 levels can modify the serotonergic system causing alterations in synaptic plasticity which may influence pharmacological effectiveness (Sarmin et al., 2024). Cytokine monitoring during therapy may provide mechanistic insights. A decrease in pro inflammatory cytokines after pharmacological or psychological intervention may reflect a positive change of the underlying neuroinflammatory processes. On the other hand, sustained high levels of cytokines may indicate resistance to treatment or ongoing immune dysregulation. Our finding of the potential role for inflammatory biomarkers to predict treatment response may aid in shaping personalized treatment strategies. Adjunctive anti inflammatory therapies or immunomodulatory interventions might be indicated among patients with overt inflammatory signatures. Such approaches are being studied in several psychiatric disorders where immune dysregulation is hypothesized. Establishment of cytokine biomarkers for prediction of treatment is still an emerging field. The data of cytokines is highly complicated to interpret, as inflammatory biomarkers are transdiagnostic and also externally related (Pinto et al., 2016), whereby other exacerbating factors such as stress, medication use or comorbid conditions come into play. Thus, additional longitudinal studies are required to investigate the predictive capacities of interleukin levels for treatment outcomes in OCD.

Interleukin Based Subtyping of OCD

Obsessive compulsive disorder (OCD) is an incredibly heterogeneous disorder, with diverse patterns of symptoms, severity and treatment response. Immune-mediated OCD, where the etiology of the syndrome is linked to immune disturbance, may respond better to immunomodulatory treatments or anti inflammatory agents in addition to standard psychiatric treatment. However, cytokine based subtyping systems are still in development. Many biological

and environmental factors that influence inflammatory biomarkers including stress, infection, lifestyle or metabolic status. In this regard, many of the cytokine changes manifest in multiple psychiatric disorders blurring specific immune profiles by diagnosis (Pinto et al., 2016). Although such interleukin based subtyping is limited to this study, the approach is a valuable avenue of future research. Further exploration of immune networks may break ground for biologically informed classification systems that will allow us to better diagnose and treat anomalies like OCD over the coming decades. Limitations While interleukins have potential as biomarkers for OCD, it is important to keep in mind limitations in the interpretation of current literature. The foremost limitation is the heterogeneity in OCD itself.

CHAPTER 7

Therapeutic Implications

An understanding of the role of interleukins and other cytokines in pathophysiology of OCD provides a better insight to therapeutic approaches. There is growing evidence that neuroinflammatory processes may be implicated in the onset or course of OCD, implying possible treatment options through agents that modulate immune activity and inflammatory pathways. Cytokines or products of the immune system, including responses to downregulate inflammatory, reparative processes, have become a point of therapeutic interest as potential adjunctive therapy. These translate into anti-inflammatory pharmacological agents, immunomodulatory therapies targeting specific pro-inflammatory cytokine pathways, lifestyle interventions that shape immune responses and precision psychiatry paradigms based on biomarkers to meet the needs of optimal individualized treatment. Anti-inflammatory treatments of OCD pharmacological treatment strategies for OCD have largely involved serotonergic agents e.g., selective serotonin reuptake inhibitors and clomipramine that enhance the availability of the neurotransmitter serotonin system in the brain. OCD has proven to be a resistant disorder; and about one third of patients do not respond adequately to first line treatments, and novel or complementary strategies in OCD treatment are needed (Marazziti et al., 2015) Growing interest in neuroinflammation in psychiatric disease development has prompted the investigation of anti-inflammatory compounds as potential therapeutics for OCD. For instance, cytokines like interleukin-6 and tumor necrosis factor-alpha play a role in regulating immune responses and inflammatory signaling pathways within the central nervous system. Changes in these cytokines have been observed in patients with OCD, thereby implying that inflammatory processes play a role in the pathophysiology of disease and severity of symptoms (Marazziti et al., 2015). Non-steroidal anti-inflammatory drugs have been studied as an adjuvant treatment for psychiatric disorders associated with inflammation. NSAIDs could exert indirect effects on cytokine activity by suppressing cyclooxygenase enzymes leading to decreased secretion of pro-inflammatory mediators. While direct evidence for OCD is currently limited (Lee et al., 2022), findings from other neuropsychiatric disorders suggests that ant inflammatory medication may diminish neuroinflammatory responses and eventually lead to improved treatment utilization in subgroups of patients (Agerbo & Hjorthoj, 2018; Sechi et al., 2021). Minocycline, an antibiotic within the oxytetracycline class, also shows promise as an anti-inflammatory agent

owing to its neuroprotective and anti-inflammatory properties. Because microglial activation plays an essential role in neuroinflammation, the capacity of minocycline to inhibit inflammatory signaling could be beneficial for therapies targeting immune dysregulation-based disorders. In terms of clinical interventions, antibiotic therapy, plasmapheresis and IVIg have all shown efficacy in some cases which indirectly adds weight to the hypothesis that immune dysfunction may play a role in certain sub-phenotypes of OCD (Marazziti et al., 2015) Taken together these findings indicate that anti-inflammatory treatment could be a promising adjunctive therapeutic approach for individuals with OCD whose symptoms either reflect/correlate with an aberrant immune system or elevated proinflammatory biomarkers.

Immunomodulatory Therapies Targeting Interleukin Pathways

The proposed role of altered cytokine profiles in OCD susceptibility has provided impetus for interrogation of interleukin dampening immune-modulatory therapies. The dysregulation of these cytokines could affect neuronal function, neurotransmitter systems and synaptic plasticity which in consequence may lead to psychiatric symptoms. Immunomodulatory therapies seek to improve immune balance through inhibition of excessive inflammatory signals or control of cytokine production. Pathological immune responses have been reduced in conditions such as autoimmune-related neuropsychiatric diseases by treatments including intravenous immunoglobulin and plasmapheresis. These treatments might include clearing the body of circulating autoantibodies or targeting the activity and/or metabolism of immune cells, thereby reducing neuroinflammation and leading to improved clinical symptoms in some patient populations (Marazziti et al., 2015) In future pharmacological attempts therapies should also focus on targeting interleukin pathways. For instance, biologic agents that block pro-inflammatory cytokine activity have already been developed and implemented in the treatment of autoimmune diseases such as rheumatoid arthritis and inflammatory bowel disease. These therapies block immune mediators such as IL-6 or TNF-α to control excessive immune activation and permit inflammation resolution. While these targeted biologic therapies have not yet been integrated into standard treatment regimens for OCD, their efficacy in diseases of inflammation suggest the potential utility of cytokine-modulating agents in psychiatry and particularly within patterns of immune dysregulation. Further studies should investigate whether patients with high inflammatory markers or specific cytokine signatures might

benefit from this kind of immunomodulatory approach. Rather, they may be especially useful in certain subgroups of patients whose disease is characterized by significant immune or inflammatory components.

Lifestyle Interventions Influencing Cytokine Levels

Besides pharmacological treatments, lifestyle factors have a strong impact on immune responses and cytokine activity. Additional evidence indicates that health lifestyle practices fortify immune functioning and reduce systemic inflammation which may indirectly affect neuroinflammatory routes involved in psychiatric diseases. Eating a nutritious diet, exercising regularly, getting enough sleep, managing stress and avoiding drugs and alcohol can help maintain your immune system. On the other hand, lifestyle factors such as an unhealthy diet, lack of physical activity, smoking, excessive alcohol intake, and chronic stress can negatively impact immune responses and lead to increased vulnerability to inflammatory diseases (Monye & Adelowo, 2020) Dietary patterns high in antioxidants, vitamins and other essential micronutrients may play a role in regulating inflammatory pathways while also promoting the balance between pro-inflammatory and anti-inflammatory responses. Several studies also link nutrients including omega-3 fatty acids, vitamins C and D and polyphenols to decreased inflammatory cytokine production. Therefore, these nutritional considerations can thereby promote better immune regulation and modulate neuropsychiatric disease outcomes. Another important modulator of inflammatory processes is physical activity. Exercise reduces pro-inflammatory cytokines and increases anti-inflammatory mediators. Concomitantly, exercise may modulate processes that are relevant to the pathophysiology of psychiatric disorders resulting in remodeling of brain plasticity and regulating levels of neurotransmitters, neurotrophic factors, and hormones involved in reactions to stress.

Biomarker Guided Treatment of Precision Psychiatry

Emerging knowledge and techniques in neuroscience and molecular biology have also catalyzed the development of precision psychiatry which posits that treatment targets may be individualized via genomic, molecular or neurobiological biomarkers. Although the traditional psychiatric practice is primarily centered on symptoms, precision psychiatry integrates biological data that can enhance diagnostic specificity and treatment selection (Jones & Nemeroff, 2021). Biomarkers are

what this approach revolves around. This can include biological cytokine aberrations in blood, genetic polymorphisms and neuroimaging findings or epigenetic markers potentially related to the pathogenesis of psychiatric disorders. For example, inflammatory markers, such as interleukin levels in the case of OCD could also be detected when symptomatic (Jones & Nemeroff, 2021), further bearing out that these biomarkers may be potential targets for understanding disease subtype and/or predicting treatment efficacy. For instance, patients with raised pro-inflammatory cytokines might respond to anti-inflammatory or immunomodulatory agents than they would from standard treatment alone. Fourth, innovations in neuroimaging and computational modeling allowed scientists to locate markers of these conditions biologically. Techniques like functional magnetic resonance imaging, electroencephalography and positron emission tomography can deliver vital information about brain function and connectivity. New wave-able devices and ideological health technologies have opened the gates for precision psychiatry, meaning we can already work towards prescribing one of what could be many highly regulated treatments based on its outcome which will predict tailored treatment strategy (Jones & Nemeroff, 2021). These tools may offer ongoing physiological and behavioral data that in turn allow a continuous measurement of overall wellness regarding both mental state and physiological health. This may also facilitate the early identification of symptoms that suggest an exacerbation allowing treatment to be modified as necessary at any time (Jones & Nemeroff, 2021). Patient precision moved even further is the very use case of precision psychiatry and presents a ripe target for disruption around the concerns we raised regarding OCD. The presence of biomarkers such as cytokine profiles together with clinical assessments may facilitate personalized treatment regimens that increase therapeutic effects whilst decreasing trial and error-based prescriptions

Future Directions

The new evidence for a role in OCD pathophysiology of immune dysregulation and cytokine action highlights the necessity of pursuing research into this area. Quest for biomarkers are needed. To routinely evaluate efficacy across heterogeneous patient populations, large scale clinical trials are also needed for anti-inflammatory and immunomodulatory therapies. Moreover, integrative approaches that combine an neuroimmunology biology, genetics and psychiatry may provide novel insights regarding bidirectional immune signaling with brain functioning. Such research may eventually yield new therapeutic strategies that focus on neurochemical and immunological mechanisms involved in OCD.

CHAPTER 8

Conclusion and Future Directions

Obsessive compulsive disorder is a heterogeneous and complex neuropsychiatric disorder thought to be composed of intrusive thoughts obsessions complemented by repetitive behaviors and compulsions. While lower-order models of OCD have largely focused on dysregulation of neurotransmitters especially serotonin dopamine and glutamate there is now increasing evidence from neuroimmunology that cytokine immune signaling pathways play an important role in the disorder pathophysiology. Interleukins, a class of immune mediators involved in numerous psychiatric disorders, are increasingly recognized as critical players, potentially modulating peripheral immunity and central nervous system processes. The current literature review aimed to systematically investigate the role of interleukins in OCD, by exhausting neuroinflammatory mechanisms, neural circuit involvement of compulsive behavior and usefulness as biomarker for diagnosis and treatment response. Immune dysregulation, specifically pro inflammatory cytokines, involved in several studies can be a contributing factor and sustain the pathology of OCD symptoms. Findings regarding the elevation of pro-inflammatory interleukins including, but not limited to, interleukin-1 beta and interleukin-6 in individuals with OCD, have been extremely well-replicated in the literature. All these clinical studies reported higher serum levels of both cytokines (at a significance level) in OCD patients than that observed in healthy controls where concentrations often correlated with symptom severity as measured using standardized clinical scales, for example, the Yale Brown Obsessive Compulsive Scale (Sarmin et al., 2024). These findings could indicate that immune activation is not only present in OCD, but can also reflect the severity of clinical symptoms. Mechanistically, neurotoxic pro-inflammatory interleukins may also modulate brain functions via different pathways. Cytokines IL-1β and IL-6 are produced by the immune system and will activate microglia and astrocytes to promote neuroinflammatory response in the central nervous system. Dysregulation in the circuitry has been established as a critical neurobiological hallmark of OCD, which proposes that cytokine mediated inflammation may be a key upstream contributor to such altered circuits (Sarker et al., 2023; Turna, 2018). Other interleukins have also been shown to be associated with OCD immune dysregulation besides IL-1β and IL-6. IL-17 is a Th17-associated cytokine that links to neuroinflammatory processes involved in promoting compulsive behaviors by activating microglia and disrupting glutamatergic

neurotransmission across front striatal brain regions (Choi et al., 2020). On this note, cytokines like IL-12 and IL-23 might contribute to OCD pathophysiology through their modulatory effects on T-cell differentiation and inflammatory signaling pathways that, in turn, impact neuronal function and behavior. In contrast, cytokines actively suppressing inflammation like interleukin-10 seem to confer neuroprotection by helping the brain to preserve immunological homeostasis. IL-10 is an anti-inflammatory cytokine that downregulates the inflammatory responses by inhibiting the production of pro-inflammatory cytokines. Increased levels of proinflammatory cytokines such as, IL-6 and TNF-a, have been reported in individuals with OCD alongside reduced levels of anti-inflammatory mediators including IL-10 suggesting a lack of induction of anti-inflammatory signaling may be involved in the establishment of neuroinflammation (Sarmin et al., 2024). Apart from their mechanistic effects, interleukins have also been identified as potential biomarkers in OCD. The peripheral blood assessment of cytokines can provide an accessible and less-invasive means of detecting immune abnormalities which are related to psychiatric disorders. All studies showing that IL-1β and IL-6 hold significant diagnostic potential due to reversible characteristics between the OCD and the healthy control subjects are done by receiver operating characteristic analyses with good sensitivity and specificity (Sarmin et al., 2024).

Recommended Future Research

These areas of research whitespace may be better served with clearer, more methodological approaches in their investigation. The contemporary studies in the future should be well powered multicenter designs with wider patient congregate and standardized laboratory assay. This could provide further insight by helping clarify cytokine alterations reproducibility and stability in OCD studies. Such longitudinal data are especially relevant to understand the timing and directionality between immune dysregulation and OCD symptoms. An approach to answer that question could be by monitoring the cytokine levels over a period of time inflammatory changes are ahead with respect to disease or complication secondary to it otherwise act as dynamic response for treatment. Moreover, longitudinal designs could also serve to define immune correlates of disease progression or reactivation. And there is one more, promising direction that links peripheral and central biomarker research. The work might be complemented by analyses of CSF (Cohen et al., 2022), from neuroimaging studies, and on wide-bore blood-based cytokines to further characterize underlying neuroimmune interactions in OCD. Such multimodal approaches may help clarify

whether peripheral inflammatory markers reflect neuroinflammation in CSTC circuits. It is also possible that advances in molecular biology and genomics will assist future research programs. Screening genetic polymorphisms of cytokine-associated genes could help to identify susceptibility factors that may lead to immune-mediated forms of OCD. Transcriptomic and proteomic approaches may also uncover complex networks of inflammatory mediators rather than single cytokines. Lastly, invasive disease has been demonstrated to be more responsive than early lesions and immunomodulatory therapies still pretend to be an area of clinical breakthrough. If inflammatory mechanisms are confirmed as a causal mechanism in OCD, cytokine signaling pathways may be modulated by pharmacologic agents and/or biologic therapy and could provide novel adjunctive treatments for individuals whose illness has not responded to standard pharmacological treatment. The Potential of Interleukin Panel Biomarkers Individual cytokines like IL-1β or IL-6 have potential as biomarkers for OCD, however it has been shown that a single inflammatory marker alone is insufficient to capture the complex immune dysregulation in OCD. Increased interleukin panels, i.e. the parallel measure of multiple cytokines to generate broader inflammatory signatures are now also increasingly being promoted by researchers. Some interleukin panels measuring this balance may contain both pro-inflammatory and anti-inflammatory cytokines, such as IL-1β, IL-6, IL-17 or -12 or -23 and inverse relationships to immune signaling pathways like the down-regulated IL-10. Since OCD may involve a complex interaction between inflammatory activation and regulatory mechanisms, looking at multiple cytokines in conjunction may provide a more accurate reflection of disease biology. The idea of cytokine panels is already being adopted in psychiatric biomarker research. Panel based approaches enable the discovery of immune patterns or signatures that relate to specific clinical phenotypes, rather than relying on a single molecular marker. Such inflammatory signatures may help to differentiate subtypes of OCD driven by immune-mediated mechanisms. In terms of clinical aspects, interleukin panels may have some advantages. First, they can increase diagnostic specificity by offering objective biologic markers that substantiate conventional symptom-based assessments. Second, cytokine profiles may help identify patients who would be more likely to benefit from immunomodulatory treatments or anti-inflammatory therapy. Finally, serial cytokine panels may offer another important method of monitoring treatment response and disease progression. The clinical utility of interleukin panel biomarkers will however require significant further investigation for translation into care.

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