Clinical findings from PSSD community members

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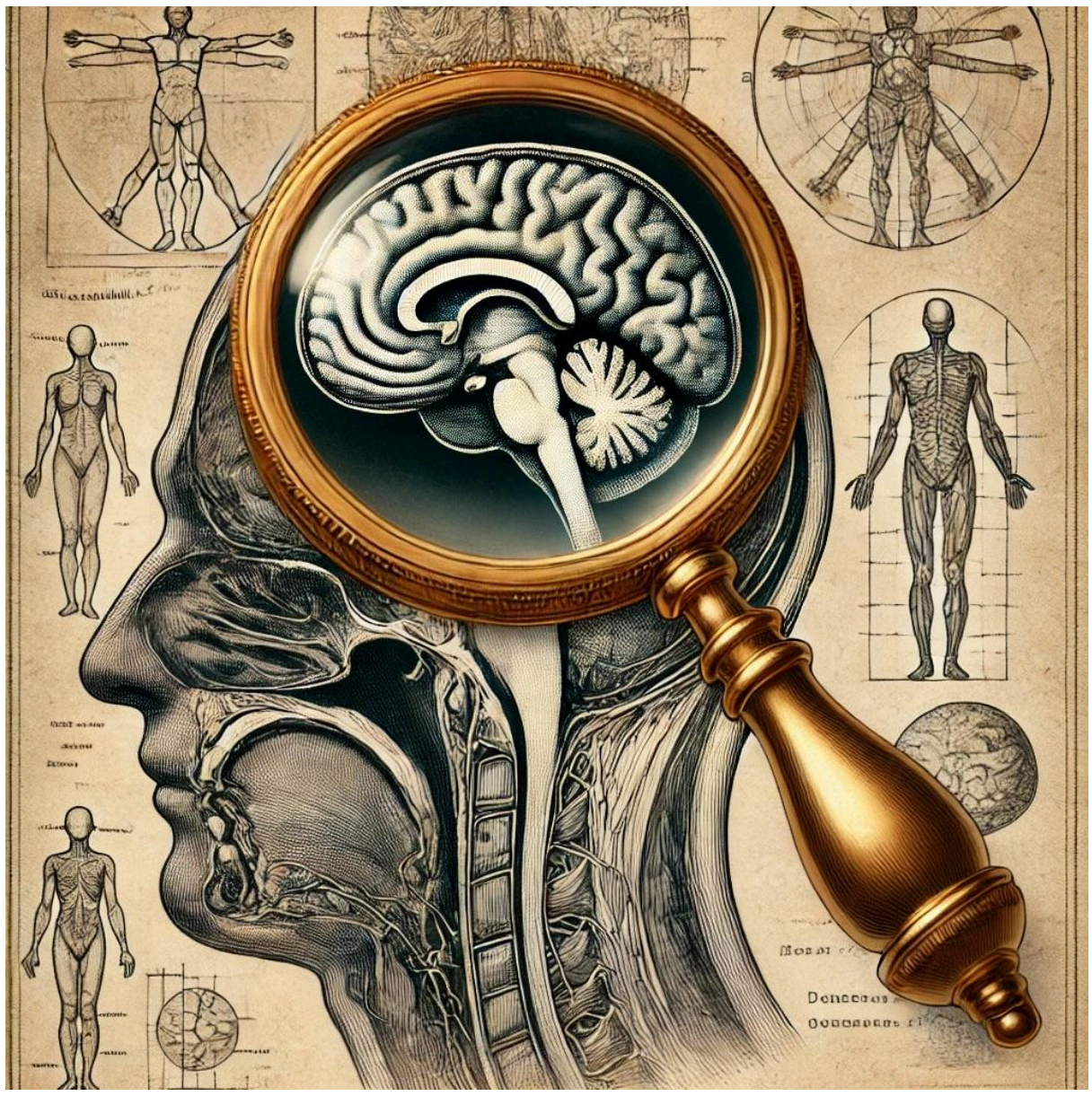

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The goal of this document is to provide a comprehensive overview of potential mechanisms surrounding Post-SSRI Sexual Dysfunction (PSSD). By integrating community-reported data, established research and emerging insights from our layman research and interpretations, we aim to raise awareness, inspire future research, and support both patients and clinicians alike in trying to understand and uncover the mechanisms behind this complex condition.

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Abstract

Post-SSRI Sexual Dysfunction (PSSD) is a poorly understood and understudied condition, often characterized by persistent symptoms of sexual dysfunction, genital numbness, anhedonia, emotional blunting and/or cognitive impairment, following the discontinuation of antidepressants such as (but not limited to) selective serotonin reuptake inhibitors (SSRIs) and selective serotonin-norepinephrine reuptake inhibitors (SNRI's).
This document provides a comprehensive exploration of potential mechanisms, clinical findings, and hypotheses underlying PSSD, integrating community-reported data and survey results, layman research and established scientific literature.

The investigation begins by exploring related conditions that share striking overlaps with PSSD, such as Post Finasteride syndrome, Long Covid, Multiple sclerosis and Schizophrenia (negative symptoms), to identify potential shared underlying mechanisms.
Subsequent chapters examine autonomic nervous system (ANS) dysfunction, which may contribute to sexual dysfunction and cognitive deficits in PSSD, highlighting findings such as G-protein coupled receptors (GPCR) autoantibodies linked to dysautonomia, showing a high prevalence of **97% of 39 patients being positive for at least one biomarker.**
Small fiber neuropathy (SFN) is examined as a potential contributor to sensory and autonomic symptoms, supported by skin biopsy and quanti-sensory testing data (QST), **which shows a high incidence rate of 70% based on 56 patients.**
The central nervous system (CNS) is explored through brain imagings such as MRI and PET scans, lumbar punctures, cytokine panels, and a neuronal autoantibody panel (Cunningham), focusing on the roles of neuroinflammation, immune dysregulation and potential downstream consequences like neurotransmitter dysregulation and deficits in neuroplasticity as potential explanations for cognitive, hedonic and emotional symptoms in PSSD. Additionally, gut dysbiosis is considered, with data suggesting the involvement of the gut-brain axis in systemic and central inflammation (neuroinflammation).
Community-reported treatment anecdotes are discussed alongside **detailed case reports of four PSSD patients' extensive neurological workups with official statements from medical professionals, pointing towards a neuroimmune pathology.**

Building on these findings, interconnected pathological processes are explored and proposed to collectively contribute to the persistence of symptoms, including; autonomic dysfunction (with downstream endothelial dysfunction and thromboinflammation), immune-mediated SFN, central neuroinflammation (including a potential autoimmune encephalitis and dysregulation of neurosteroids), as well as gut dysbiosis (including alteration of gut-derived neurosteroid).
Potential predispositions and triggering mechanisms for disease initiation are discussed, including molecular mimicry, covalent receptor interactions, latent infection reactivation, and mitochondrial impairment. Persistent epigenetic changes are considered as potential contributors to the maintenance and perpetuation of symptoms. Alternative hypotheses are briefly discussed, such as ion channel dysfunction and hyponatremia.

By integrating these diverse findings, this document proposes that PSSD may represent a multi-systemic immune-mediated neurological (neuroimmune) disorder.

The goal of this work is to raise awareness, inspire future research and support patients and clinicians alike in understanding and addressing this complex condition.

Highlights

- **Community data indicates neuroimmune processes and related downstream mechanisms may contribute to post-SSRI sexual dysfunction (PSSD) pathology**

- Autonomic GPCR Autoantibody test results (Celltrend, Ganzimmun) show a **97% incidence rate** for at least one biomarker among 39 test subjects. Furthermore, a large portion were positive for several biomarkers, such as;
    - 86% (24/28) were positive for anti-ACE-2 which is linked to Long Covid
    - 75% were positive for anti-CHRM3 & 4
    - 70% were positive for anti-beta1-adrenergic receptors
    - 68% were positive for anti-beta2-adrenergic receptors

  The results indicate a possible immune-mediated dysautonomia

- **70% of 56 patients tested positive for small fiber neuropathy (SFN)** through diagnostics such as skin biopsy and quanti-sensory testing (QST). Combined with other test results and the clinical presentation the **results indicate an immune-mediated SFN** (non-length dependent (NLD) subtype)

- Diagnostics such as lumbar punctures, PET-scans, and the Cunningham panel suggest a **potential neuroinflammatory component** in PSSD.

- **Gut microbiome test results indicates potential gut dysbiosis** based on 67% of 16 samples showing low levels of Faecalibacterium Prausnitzii, consistent with previous research showcasing gut dysbiosis in animal models by Prof. Melcangi and his research group (Giatti et al. 2024b)

1. Introduction

As many parts of the world are struggling with a mental health crisis, antidepressant usage is skyrocketing. In Europe alone, antidepressant consumption has more than doubled in the past 20 years, in many countries, consumption is estimated to be between 60-120 per 1000 people in 2021 (OECD 2022, "Europe's mental health in data" 2023). There is a wide off-label use of antidepressants today, where physicians can prescribe them for all kinds of non-psychiatric issues, including migraines, sleep disorders, premature ejaculation and even menopause (Jannini et al. 2022, Stubbs et al. 2017). Many psychiatric medications, including Selective Serotonin Reuptake Inhibitors (SSRI) and Serotonin-Norepinephrine reuptake inhibitors (SNRI), are generally considered as safe and effective and thus prescribed widely by not only psychiatrists but also general practitioners. However, both publication bias and reporting bias have been shown to take place in clinical studies on antidepressants, especially in 1986-2004 which can be assumed to have led to overestimation of efficacy and underestimation of risks (Turner et al. 2022).
Unfortunately a common experience among patients is that when the prescribed medicine is causing unexpected side effects, the symptoms are often attributed to a psychiatric or psychosomatic cause. In many instances, the symptoms are considered to be part of a previously acquired psychiatric diagnosis, such as depression or anxiety, even if the patient never experienced these symptoms prior to using the medication. This leaves the patient understandably feeling unheard and neglected, where the new symptoms can be even more debilitating than the original condition on which the medication was prescribed for. Sometimes use of psychotropics such as antidepressants can lead to long lasting changes that end up staying after the drug has been discontinued, culminating in what is known as a post-drug syndrome (Healy et al. 2022). The suffering that these syndromes inflict upon patients is often life changing, heavily impacting their function and quality of life. In many instances, drug related syndromes have even led to **suicides.**

One of these post drug syndromes is Post-SSRI sexual dysfunction (PSSD), which is a poorly understood and understudied medical condition that involves persistent symptoms of genital numbness and sexual dysfunction following an exposure to, and withdrawal from, a psychiatric medication such as (but not limited to) SSRIs or SNRIs (Bala et al. 2018). In addition, PSSD patients frequently report experiencing additional symptoms such as emotional blunting, cognitive impairment and anhedonia. Reports indicate that the syndrome may be seen as a spectrum where patients' symptoms vary in presentation and can range from mild to severely debilitating.
While PSSD was first reported in the medical literature in 2006 (Reisman 2020), its underlying causal mechanisms remain largely unknown.
Most studies up to this point have focused on investigations into neurosteroid, gut microbiome and gut steroid related changes following SSRI exposure in animal models, such as seen in Professor Melcangi's work (Giatti et al. 2018, Giatti et al. 2021, Diviccaro et al. 2022, Giatti et al. 2024b).
Outside of this, most research has evolved around epigenetic changes (Csoka and zsyf, 2009), (Kanherkar et al. 2018), exploring the PNMT enzyme inhibition as a proposed explanation for sexual dysfunction (Giatti et al. 2022), and a paper showcasing gene expression changes in the hypothalamus and nucleus accumbens of male rats following SSRI exposure (Giatti et al. 2024).

Due to lack of research, aside from an old post-market research study from 2006 (Bala et al. 2018) and a more recent low quality retrospective cohort analysis (Ben-Sheetrit et al. 2023) (where prevalence was estimated to be 5-15% and 0.46%, respectively), an accurate incidence rate for PSSD has not been established yet. Recently however, a paper that looked at frequency of self-reported persistent post-treatment genital hypoesthesia among past antidepressant users, showed that **13.2%** of the participants reported persistent genital hypoesthesia after discontinuing antidepressant treatment, compared to 0.9% among past users of other psychiatric drugs who had not taken antidepressants (Yassie Pirani et al.). Given that genital anesthesia is perhaps the most distinct symptom of PSSD, this may provide a clue towards the possible incident rate for PSSD. Additionally, (99, Montejo et al. 1999) discovered that 55% of people who had used an SSRI and were switched to a different antidepressant that successfully addressed their depressive symptoms; still had not recovered from the initial SSRI-induced sexual dysfunction 6 months after having discontinued the medication that caused it. Furthermore, David Healy and Dee Mangin recently published a paper discussing barriers to quantifying incidence and prevalence of PSSD (Healy and Mangin, 2024), citing a master's thesis from the Utrecht University (Lüning, 2019) where 76 former antidepressant users were screened for persistent sexual dysfunction. **The study reported that 52.6% (*n* = 40) of participants suffered from persistent sexual dysfunction, while 26.3% (*n* = 20) of participants suffered from genital anesthesia and/or nipple insensitivity, which could be suggestive of PSSD**. This could indicate that the prevalence could be much higher than previously thought. Considering the growing number of people that are prescribed antidepressants worldwide, the number of people suffering with this condition will likely continue to grow as long as there is no real progress on knowledge and research in the area. More research is needed to uncover not only the prevalence of PSSD, but more importantly to understand the condition so effective treatments may be established.

As a consequence of the overall lack of research, community members have made numerous attempts over the years to gain insight into the nature of the condition in hopes of finding a way to treat it. Aside from a few anecdotal reports of various spontaneous recoveries and treatment trials with varying levels of success, only a small number of people are known to have ultimately recovered from the syndrome. However, in the past few years, the rise in awareness and recognition by the European Medicines Agency in 2019 (Reisman 2020) have drastically increased the size of the community, and

thus various theories and findings have surfaced over time. For instance, several community members have, during the past year and a half, reported having been diagnosed with small fiber neuropathy (SFN) and specifically SFN secondary to an autoimmune reaction (known as Immune-mediated SFN). This is noteworthy considering Zimelidine, the first commercially available SSRI released in the early 1980's, was taken off the market in Sweden shortly after it turned out to trigger Guillain-Barré syndrome in a select number of patients (Fagius et al. 1985), which is a serious form of autoimmune neuropathy that usually affects large (and sometimes small) nerve fibers (Nguyen and Taylor 2024).
Community interest in immune-mediated neuropathies first emerged in late 2022 when a PSSD patient, nicknamed "Patient zero", experienced unusually severe symptoms following SSRI use and cessation. The patient reported that he had been taken to a university hospital where he was diagnosed with a novel autoimmune condition affecting the central and peripheral nervous systems, a part of which included a diagnosis of SFN confirmed with a punch skin biopsy. He subsequently shared his experience and test results with the community and urged other patients to seek out the same testing. First, a group of PSSD patients in Finland sought out the same testing and several of them had positive SFN biopsies. These test results were later reported in an article about PSSD in the Finnish newspaper Helsingin Sanomat (Saaritsa, 2023). Since then, multiple PSSD patients have followed suit and ultimately been diagnosed with and treated for immune-mediated SFN.

In response to these recent developments, we began investigating neuropathy and autoimmunity in particular while gathering extensive lab results from the community ranging from skin biopsies and autonomic autoantibody panels, to magnetic resonance imagings, lumbar punctures and more.
All of this data has been compiled into separate tables, which we have termed «trackers», and all of them are presented here in this document.
Additionally, around the time we started gathering community data we began looking into and researching various established neurological, autoimmune, psychiatric, iatrogenic and neuropathic conditions that shared symptomatic similarities with PSSD. We wanted to see if they could possibly steer us in a direction that could lead to further discoveries and provide clues from potential shared mechanisms.
After extensive research and discussions we created a list of these conditions, which will be discussed and referenced throughout this document (see chapter 3).

Before discussing the potential etiological components of PSSD, we have written comprehensive introductions to each topic in order to provide some context to the clinical findings and their interpretations:

- The first chapter (**2**) will define the condition, its name, triggers and symptomatology.
- Then we will investigate disease states with similarities to PSSD (**3**).
- This will then be followed by 4 sections investigating:
    - **The autonomic nervous system and dysautonomia (4)**
    - **The somatosensory nervous system and small fiber neuropathy (5)**
    - **The central nervous system and neuroinflammation (6)**
    - **Gut microbiome and gut dysbiosis (7)**

  These will provide background information to the data we will be presenting in the following section.
- The order of presentation will be guided by the largest sample sizes combined with the highest incidence rates, and thus, we will be putting most emphasis on dysautonomia and its autonomic GPCR autoantibody panel "Celltrend", as well as SFN and skin biopsies.
- The relevant data compilation tables will then be presented in a separate section called «Clinical findings» (**8**), which includes tables 1-9 termed "trackers" in the following order:
    - **Celltrend, Celltrend stats & info, SFN skin biopsy, MRI, PET-Scans, lumbar puncture, cytokine results, Cunningham panel** and lastly **F. Prausnitzii**. Each table will include a statistical breakdown and discussion around the findings.
- There will then be a section exploring various anecdotal treatment reports from the community (**9**), including 6 case reports with patient profiles and diagnostics. 4 of the profiles will include additional case reports written by their neurologist, with the other two in the appendix.
- Lastly there will be a summarizing of the data and research, with our own interpretation, elaboration and speculation on potential etiology based on data and research correlations (**10**), followed by a section exploring susceptibilities, triggering mechanisms and alternative hypotheses (**11**). Lastly we will provide a brief conclusion (**12**) and closing words (**13**) at the end.

Based on what we have seen from the community data and our research so far, we have reasons to suspect that PSSD may involve immune-mediated mechanisms that contribute to it's pathology in a multisystemic fashion, leading to certain downstream consequences such as dysautonomia and SFN, and thus, we will be focusing on the most relevant aspects in the introductory sections in order to make it easier to highlight the correlations that may point to the underlying etiology, which will be summarized and discussed near the end.

2. PSSD: Definition, triggers & symptomatology

PSSD, which, as mentioned, stands for post-SSRI sexual dysfunction, refers to a condition where persistent symptoms of sexual dysfunction occur after the discontinuation of a selective serotonin reuptake inhibitor (SSRI) (Bala et al. 2018, Reisman, 2020, Ben-Sheetrit et al. 2023), is a term we don't think accurately convey the possible triggers (medication type), spectrum of symptomatology, nor the severity of the condition itself. In this chapter we will discuss these aspects, go in depth on symptomatology and present a community survey that will be incorporated in the rest of the document.

2.1 Triggers

Despite the name referring to SSRIs only, patients have reported getting PSSD from all kinds of pharmaceuticals, ranging from SSRIs like Escitalopram (Lexapro), SNRIs like Venlafaxine (Effexor), NDRIs like Bupropion (Wellbutrin), TCAs (tricyclic antidepressants like Amitriptyline) and even atypical antidepressants such as Mirtazapine (Remeron). Additionally, many have also reported acquiring identical syndromes after having used other psychotropic drug classes, such as antipsychotics like Olanzapine. A Community survey conducted on Reddit identified many of these medications as triggering factors. A recent study by (E. Rice et al. 2025) further supports these observations, suggesting that different classes of psychotropics can induce PSSD. Other drug classes such as benzodiazepines like Clonazepam (Klonopin) are more commonly associated with withdrawal syndromes, but have also been reported to have caused PSSD-like symptoms in some individuals.

2.2 Symptomatology

While most patients share certain core symptoms, there is considerable variation in symptomatology and severity among patients.
The official criteria from the existing literature state that PSSD is characterized primarily by a range of persistent sexual side effects that endure after the discontinuation of SSRI (Selective Serotonin Reuptake Inhibitor) treatment (Bala et al. 2018). These symptoms can include decreased libido, erectile dysfunction, genital anesthesia, anorgasmia, and overall sexual anhedonia.
We think the omission of non-sexual symptoms from the diagnostic criteria is problematic because it overlooks critical aspects of PSSD that can significantly affect a patient's quality of life (Studt et al. 2021). There is a general consensus among the community that the name PSSD does not quite adequately describe the full clinical picture and spectrum of the syndrome, as many have symptoms outside of sexual dysfunction, such as cognitive impairment, emotional blunting and anhedonia, which, according to community members, can be even more debilitating and disabling than the sexual dysfunction alone. In addition, in some cases, cognitive symptoms can even take place where there are only minimal symptoms of sexual dysfunction. Thus, the focus on only sexual symptoms might hinder the medical field and support network from fully grasping and understanding the severity and extent of this condition. Many have also reported that the name brings a lot of stigma and shame due to its focus on the sexual aspect of the syndrome which is considered intimate, leaving patients often feeling hesitant to bring it up and discuss their symptoms with their doctors and loved ones. It is vital that the medical community begins to place greater emphasis on the non-sexual symptoms. There are several reasons for why this might be beneficial; First, these symptoms may offer insights into the underlying mechanisms of PSSD, which are not yet understood. Second, recognizing the full spectrum of symptoms can lead to more comprehensive treatment approaches, rather than focusing solely on sexual dysfunction. Lastly, bringing the non-sexual symptoms to the forefront can improve patient outcomes by validating their experiences and guiding more effective management strategies.

Due to the issues related to the official criteria, we have decided to categorize the main symptoms based on what's been most consistently reported in the community. This will be further supported by the results from a community survey (see 2.3).

Up next we will present the 5 core symptoms of PSSD most often reported in the community.

Core symptoms:

Genital Numbness

Genital numbness refers to a reduced or absent sensation in the genital area, which can impact sexual pleasure and function. A person may have difficulty feeling sexual arousal or pleasure during intimate activities. Even direct stimulation may feel significantly less intense or not pleasurable at all. Some report full numbness of the genitalia, while others report reduced or absent erogenous sensation.

Emotional Blunting

Emotional blunting is characterized by a diminished ability to experience emotions, both positive and negative. Patients often describe feeling detached or indifferent and might find it hard to feel excitement, joy, sadness, or anger. This can lead to difficulties in forming and maintaining emotional connections with others. Additionally, some patients report blunted affect, which is a decrease in emotional expression and reactivity (Guessoum et al. 2020).

Sexual Dysfunction

Sexual dysfunction encompasses a range of issues that inhibit sexual desire, performance, and/or satisfaction. This can affect both physical and psychological aspects of sexuality. Common manifestations include decreased libido (sex drive), erectile dysfunction/lack of lubrication, and difficulty achieving orgasm, or experiencing muted or absent orgasmic sensations (anorgasmia). Additionally, individuals may experience loss of arousal and a general decrease in sexual satisfaction.

Cognitive Impairment

Cognitive impairment involves difficulties with cognitive processes, including memory, attention, and executive functions. Individuals may struggle with memory recall, concentration, problem-solving tasks and what is referred to as «brain fog». This can manifest as forgetting important appointments, losing train of thought easily, problems retaining information, finding it challenging to make decisions and the inability to think clearly.

Anhedonia

Anhedonia is the inability to experience pleasure from activities usually found enjoyable, such as eating, socializing and hobbies.
It can be further divided into anticipatory and consummatory anhedonia (Guessoum et al. 2020). **Anticipatory Anhedonia** refers to decreased motivation, which is a reduced ability to look forward to future pleasurable activities. For example, someone might no longer feel excited about planning a vacation or looking forward to a favorite meal. **Consummatory Anhedonia** refers to a reduced ability to experience pleasure in the moment of the activity. It is the actual reward (feeling of pleasure and satisfaction) of the activity. For instance, a person might not feel good after exercising (endorphins) or joy while eating their favorite food or during a social gathering, or even watching their favorite movie, even though they used to enjoy these activities in the past. Many patients with PSSD report also not feeling pleasure from substances like alcohol, cannabis, and other recreational substances, which also falls under consummatory anhedonia.

These symptoms collectively contribute to the significant impact PSSD can have on an individual's function and quality of life, affecting both their personal and social well-being. Most patients fall somewhere on a spectrum in severity with variable presentations. Milder cases might for example ‘only’ have some form of sexual dysfunction like loss of libido and muted orgasms, while more severe cases will usually have most if not all of the core symptoms listed above, and in many instances may have additional symptoms such as fatigue, gastrointestinal disturbances and sleep issues, which will be discussed down below.

Additional symptoms

Besides the core symptoms, the community has reported a wide range of additional symptoms as well. These include symptoms such as insomnia and sleep issues, gastrointestinal disturbances like gastroparesis, IBS, bloating and constipation, chronic fatigue, fasciculations, agitation, akathisia, tremor, genital shrinkage, heart rate variability, loss of hunger, lack of sweating, cold extremities and poor temperature regulation, loss of physical strength or muscle weakness, loss of balance, speech impairment and word retrieval difficulties, difficulty learning new things, information retention issues, depersonalization and derealization, hair loss and thinning (facial and body hair), head pressure, aphantasia, visual snow, tinnitus and neuropathic symptoms such as burning, pain and numbness of the skin. Another often reported symptom are so-called «brain zaps» where the patient may experience sensations such as «jolts and bolts» in their head. Additionally, many patients report getting sick less frequently than before, where some even experience temporary improvements in symptoms during sickness. Many members also report hypersensitivity to substances (medication, supplements, food etc) with either temporary worsening or longer term «crashes». Some members also mention transient improvements from fasting.

*For more see **“Ancillary symptoms reported by Yassie Pirani (RSW RCC - PSSD clinical counsellor and researcher) with conversations with over 100 PSSD sufferers”** in the appendix.*

2.3 Community survey

During the summer of 2023, community member Goldenhour created a survey to explore symptoms suggestive of autoimmunity and neuropathy in the PSSD community. 115 members participated in the survey, and the results showed a high prevalence for PSSD symptoms such as loss of genital sensitivity (90%), loss of sexual desire (90%) and changes in orgasmic sensation (77%), with 84% reporting some degree of anhedonia and emotional blunting (which was grouped together in the survey). Additionally, it showed a high prevalence of many other symptoms as well, such as memory problems (67%), brain fog (66%), fatigue (63%), Sleep issues (52%) and vision abnormalities (44%). Based on this survey we created a list of some of the symptoms in the survey to use as a reference point going forward:

Symptoms associated with PSSD

(excerpt based on community survey):

Sexual dysfunction

- Loss of genital sensitivity: 103 (90%)
- Loss of sexual desire: 103 (90%)
- Loss of erotic sensation: 98 (85%)
- Erectile dysfunction (males): 66 (84% of males)
- Changes in sensation of orgasm: 88 (77%)
- Loss of feeling during intercourse: 81 (70%)
- Difficulties in reaching orgasm: 71 (62%)
- Size of genitals changed: 46 (40%) (additionally, 40% reported changes in color of their genitals)

Cognitive Symptoms (including hedonic and emotional disturbances):

- Reduced memory ability: 77 (67%)
- Brain fog/forgetfulness/can't focus: 76 (66%)
- Issues with speech, communication, or word-finding: 70 (61%)
- Lost ability for visual thinking and creativity: 70 (61%)
- Cognitive issues impacting daily life: 69 (60%)
- Emotional blunting/anhedonia of both positive and negative emotions: 67 (58%)
- Blank mind: 56 (49%)

Miscellaneous:

- Fatigue: 73 (63%)
- Sleeping problems: 60 (52%)
- Weakness: 56 (49%)
- Increased/decreased sweating: 51 (44%)
- Vision problems (blurred vision, vision loss, tunnel vision): 48 (42%)
- Feeling of dullness in skin anywhere in the body: 44 (38%)
- Frequent urination/incontinence: 42 (37%)
- Urinary symptoms (hesitancy, incomplete emptying): 42 (37%)
- Cannot feel the effects of alcohol: 42 (37%)
- Ringing in ears (tinnitus): 40 (35%)
- Mood swings: 40 (35%)
- Abnormally fast or slow heart rate: 38 (33%)
- Symptoms of constipation, diarrhea, abdominal distension, food intolerance: 38 (33%)
- Feeling short of breath (especially during exercise): 37 (32%)
- Dizziness, lightheadedness, vertigo: 37 (32%)
- Exercise intolerance (heart rate doesn't adjust to changes in activity level): 36 (31%)
- Sensation of coldness: 35 (30%)

Note: *Due to some differences of opinion regarding some of the categorization of symptoms in the survey we have decided to categorize these based on our own interpretations. The full survey can be found in the Appendix of this document*

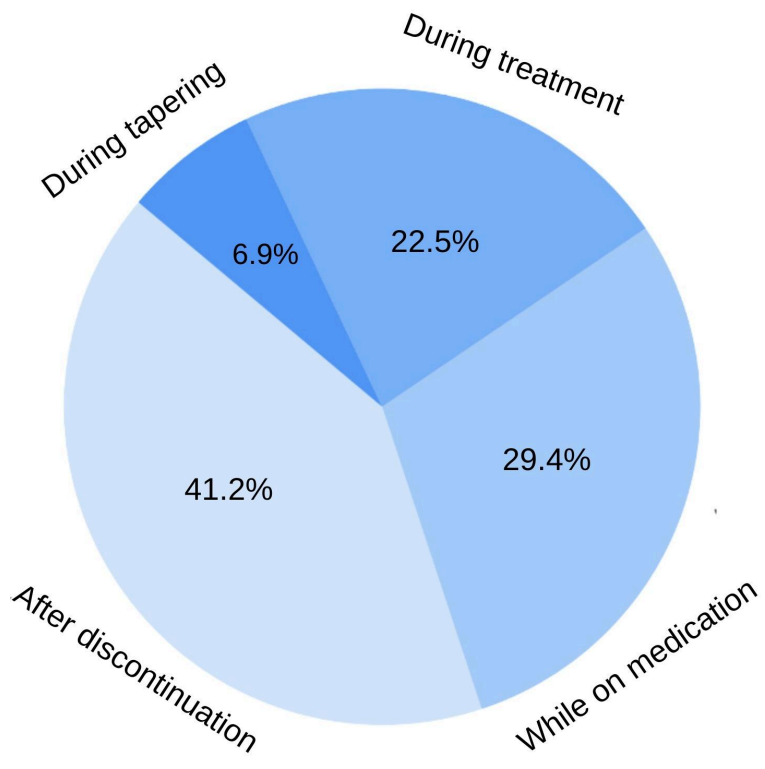
2.4 Symptom onset & length of time with PSSD

“Pssd came overnight 4 months after quitting in horrible withdrawal (Akathisia, insomnia, terror, anxiety). Woke up with numb and shrunk genitals” - Anonymous patient (community survey)

PSSD, as the name suggests, refers to persistent symptoms that remain after discontinuing the medication. Most patients report that symptoms, or the majority of them, appear after discontinuation. However, symptom onset can vary widely. In some cases, symptoms arise while still on the medication, during tapering, or even during reinstatement or a second medication trial. Remarkably, there are reports of PSSD occurring after as little as one pill. The community survey highlights this variability in symptom onset:

- 42% reported that PSSD symptoms presented after discontinuation.
- 30% experienced symptoms while actively on medication.
- 23% reported symptom onset at some point during treatment.
- 7% noted symptoms developing during tapering.

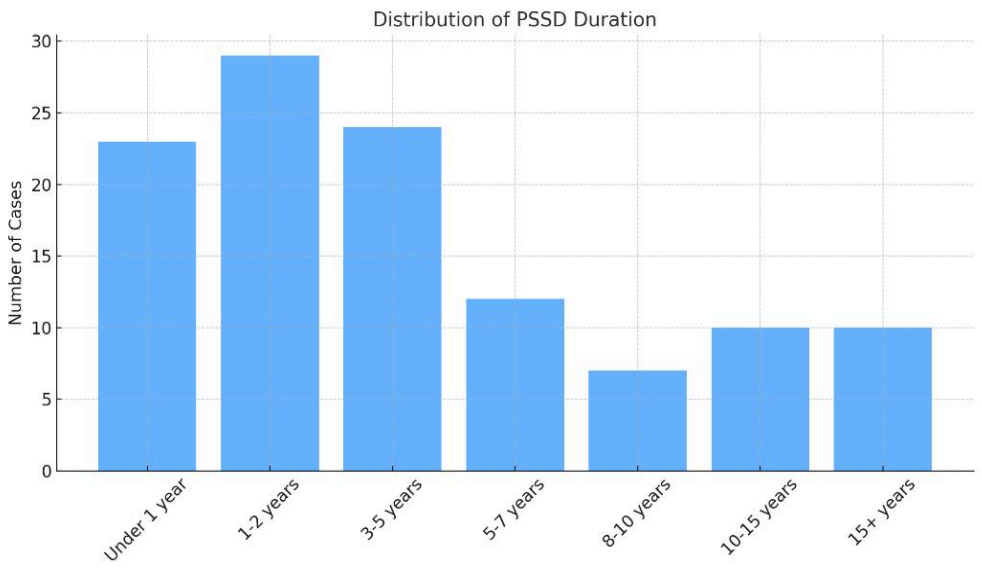
This variability in onset patterns is puzzling and points to the complexity of the syndrome’s underlying mechanisms.



“I have tremors in my hand and occasional dropping things or loss of balance. It started while on SSRIs and I was told it would go away after withdrawal. It has not gone away and has been with me for around 24 years.” - Anonymous patient

Although anecdotal reports exist of cases achieving remission or partial remission within months or even years after symptom onset, PSSD is often chronic in nature. The community survey further underscores this:

- PSSD for under 1 year: 23 (20%)
- PSSD for 1-2 years: 29 (25%)
- PSSD for 3-5 years: 24 (21%)
- PSSD for 5-7 years: 12 (10%)
- PSSD for 8-10 years: 7 (6%)
- PSSD for 10-15 years: 10 (9%)
- PSSD for 15+ years: 10 (9%)



The results emphasize the long term and often chronic nature of this condition with 55% of participants reporting a length of time of at least 5 years or more, with as many as 18% reporting over 10 years.

2.5 The patient experience

"Antidepressant Lexapro has ruined my sex life. I only took it for 3 weeks when all my symptoms started and have persisted for over a year. It has done damage to both my body and my mind. These drugs are so much more powerful and dangerous than doctors think. Please help those who are suffering."
- Anonymous patient

As previously discussed, the symptoms of PSSD can profoundly affect all aspects of life. These range from the inability to fulfill basic needs, such as eating and drinking, getting restful sleep, and participating in sexual activities, to losing general motivation for everyday tasks. Beyond the physical symptoms, patients often find themselves incapable of enjoying even the simplest pleasures, such as watching a movie, reading, socializing, or engaging in hobbies. The heavy toll of these limitations is further compounded by the syndrome's severe impact on academic and professional performance, often stunting career progression and overall diminishing quality of life. Many patients report ending up on disability, unable to work or leave their homes due to debilitating symptoms.

The cognitive symptoms, in particular, are a significant barrier to functioning in work and academic spaces. Survey data highlights this impact, with **60% of 69 participants reporting cognitive issues that severely affected their daily lives**. Among these, 48% noted confusion in everyday tasks, 33% of 38 respondents reported being unable to work due to cognitive symptoms, and **32% of 37 stated they were entirely unable to function.** Alarmingly, **48% of 55 respondents indicated that cognitive impairments prevented them from pursuing their previous or desired career paths**. These statistics underscore the devastating impact PSSD has on patients' function and quality of life.

The wide-ranging symptoms that impact patients with PSSD, as detailed in this chapter, raise questions about its underlying mechanisms, and while PSSD presents a unique constellation of symptoms, it shares striking overlaps and parallels with other neurological and systemic conditions. Investigating these parallels may offer valuable insights into PSSD's potential pathophysiology. In the next chapter, we will explore these related conditions and their parallels to PSSD.

3. Conditions with similarities to PSSD

After extensive research and discussions we have compiled a list of the conditions we believe share the most similarities with PSSD to use as reference points for later discussions throughout the document.

Similar syndromes to PSSD

- Post Finasteride syndrome (PFS)
- Post Accutane syndrome (PAS)
- Neuroleptic induced deficit syndrome
- Fluoroquinolone antibiotic toxicity (“floxies”)

Psychiatric disorders with similarities to PSSD

- Negative symptoms of schizophrenia (formerly known as Schizophrenia simplex).

Neuropathies with similar symptoms to PSSD

- Guillain-Barré syndrome (GBS)
- Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)
- Chronic Immune-sensory polyneuropathy (CISP)
- Autonomic neuropathy

Diseases with variable similarities to PSSD:

- Multiple Sclerosis (MS) and Clinically isolated syndrome (CIS)
- Myalgic encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS
- Long covid
- Parkinson's Disease
- Limbic Encephalitis
- Myelitis (transverse myelitis)
- Sjögren's Syndrome
- Lupus (CNS)
- Postural Orthostatic Tachycardia Syndrome (POTS)
- Cauda Equina Syndrome
- Neurosarcoidosis
- Mitochondrial Encephalomyopathies
- Frontotemporal Dementia
- Acute Disseminated Encephalomyelitis
- Multiple system atrophy

To keep the scope of this document focused, we decided to highlight 13 disease states from the list across 3 different primary categories (neurological, immunological and psychiatric) to discuss symptomatic similarities, investigate potential shared pathophysiological components and point out other interesting observations. We believe this may complement the clinical findings presented later on. Other conditions from the list will be referenced throughout later chapters.

3.1 Iatrogenic conditions

Post-finasteride syndrome (PFS)

Iatrogenic disorders may arise from various psychotropics, statins, antibiotics, vaccines and other types of substances. The most relevant is perhaps **Post-finasteride syndrome (PFS)**, a condition that arises after use of the 5-alpha reductase-inhibitor Finasteride (commonly prescribed for hair loss and enlarged prostate), comprising of symptoms such as **persistent sexual dysfunction**, **genital numbness**, **cognitive impairment**, depression and fatigue (Borgo et al. 2021). Sexual dysfunction symptoms often reported are erectile dysfunction, loss of libido, ejaculatory disorders and reductions in penis size. PFS also causes gynecomastia, muscle atrophy, fatigue and dry skin. Additionally, PFS is highly associated with **anhedonia** (Traish 2020), as well as **peripheral neuropathy.** The condition is considered by many as more or less identical to PSSD, as demonstrated in this study by prof. Melcangi’s research group (Giatti et al. 2024b), where they propose that PSSD and PFS may share similar mechanisms such as neurosteroid disruption and gut dysbiosis (see more in chapter 10.3.2). PFS has also been linked to epigenetic changes and androgen receptor upregulation (Traish 2020).

Post-Accutane Syndrome (PAS)

Post-Accutane Syndrome (PAS) refers to a collection of persistent, long-term side effects experienced by some individuals after discontinuing isotretinoin (Accutane), a medication used to treat severe acne. Symptoms may include chronic fatigue, **sexual dysfunction**, dryness of skin and mucous membranes, gastrointestinal issues, depression, and **cognitive difficulties**. While the exact cause is not understood, it is thought to involve lingering effects on the endocrine system, nervous system, or lipid metabolism. PAS remains a poorly defined and controversial condition, with limited research and no standardized treatment, making it a topic of ongoing concern among patients and medical professionals (Healy et al. 2022).

Accutane has been observed to trigger Guillain Barrè syndrome (**neuropathy**) in some individuals (Pritchard et al. 2004), as well as a case report where a patient developed demyelinating polyneuropathy and sacroiliitis after six-months of isotretinoin use (Cakir et al. 2014). Additionally, several case reports and observational studies have shown that PAS can trigger axial spondyloarthropathy (Elnady et al. 2020), which is an inflammatory condition causing chronic low back pain (Margrey et al. 2020). Lastly, Isotretinoin may have triggered Optic neuritis, an inflammatory disease of the optic nerve associated with acute or subacute loss of vision, in a case report involving a 16 year old girl (Perèz-Perèz et al. 2012).

Neuroleptic-induced deficit syndrome

It is well known that neuroleptics (antipsychotics) can induce physical adverse effects such as extrapyramidal symptoms and oversedation, but they can also induce mental adverse effects, which involve deficit status in thought, affect, cognition, and behavior, the typical phenomena of which are **apathy**, lack of initiative, **anhedonia**, indifference, **blunted affect**, and reduced insight into disease. They very much resemble negative symptoms of schizophrenia (see Schizophrenia in 3.3). Such effects are known as **neuroleptic-induced deficit syndrome (NIDS)**, which was a concept proposed more than 20 years ago with the aim of differentiating it from negative symptoms in schizophrenia. While NIDS is not specifically mentioned in association with sexual dysfunction in the literature, antipsychotics are generally highly associated with sexual dysfunction (Knegtering et al. 2003), and thus it can be assumed that this symptom could be part of NIDS as well. Numerous community members have also reported sexual dysfunction after antipsychotic use. Therefore it is reasonable to suggest that the lack of research on NIDS may explain the absence of this symptom association in the literature. NIDS has been considered to be pharmacologically caused by the inhibition of the central dopaminergic reward system where D2 receptor antagonism of antipsychotics may reduce activation of the system. However, even atypical antipsychotics with weak affinity for D2 antagonism can cause NIDS (Ueda et al. 2016) which may suggest that a more complex causative mechanism might be at play. Another syndrome that may arise from antipsychotic use is **Neuroleptic malignant syndrome (NMS)**, defined by a**utonomic dysfunction**, rigidity, fever, and altered mental status, has been associated with the occurrence of **severe peripheral neuropathies** in some patients (Anderson and Weinschenk 1987).

Fluoroquinolone Toxicity Syndrome

Fluoroquinolone Toxicity Syndrome, commonly referred to as **"Floxies"**, revolves around individuals who experience adverse reactions to fluoroquinolone antibiotics (e.g., ciprofloxacin, levofloxacin). These reactions can include tendon damage, **peripheral neuropathy**, muscle weakness, fatigue, insomnia, **cognitive dysfunction**, agitation, hallucinations, depression, anxiety, vision problems, hearing issues, gastrointestinal symptoms, cardiovascular disturbances and various skin reactions. Symptoms can persist for months or years and cause severe disability in affected individuals. Fluoroquinolones have also been shown to cause **dysautonomia** in some individuals, such as seen in this case series (Golomb et al. 2015). Potential mechanisms proposed involve oxidative stress and mitochondrial toxicity (Michalak et al. 2017).

3.2 Immune-mediated neuropathies

Guillain-Barré syndrome (GBS)

Guillain-Barré syndrome (GBS) is a rare immune-mediated neuropathy that causes weakness and **sensory disturbances** such as paresthesias. In severe cases patients can even end up with paralysis (more info about GBS here). **Autonomic dysfunction** is a common and serious complication of GBS, occurring in up to two-thirds of all patients and can present with various symptoms, including orthostatic hypotension, abnormal sweating, gastrointestinal dysfunction, and bowel abnormalities (Lehmann et al. 2010). Additionally, a study of 396 men surveyed more than three years after their acute illness with GBS showed a significant increase in the rate of **erectile dysfunction** compared to the general male population of the same age groups. The author added that the research strongly suggests that the **reported impotence is organic and related to the residual autonomic dysfunction** following GBS (Burk and Weiss 1998).

As mentioned in the introduction, one of the first commercially available SSRIs, Zimelidine, was withdrawn from the market after triggering GBS in several patients during 1980's (Fagius et al. 1985). Many PSSD patients experience symptoms of paresthesia, including burning sensations, tingling and numbness, which is noteworthy considering the history between GBS and Zimelidine, and thus, it is highly relevant seeing as SSRI's are one of the most common triggers for PSSD. To add to this point, the antipsychotic Risperidone has been seen to trigger GBS in a couple of case reports (Bektas et al. 2016, Kıcalı, 2022). Moreover, as mentioned earlier, PAS have been observed to trigger GBS in some individuals (Pritchard et al. 2004).

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

Chronic inflammatory demyelinating polyneuropathy (CIDP) is an immune-mediated neuropathy characterized by inflammation of peripheral nerves and nerve roots, leading to progressive damage to the myelin sheath (the protective covering of nerves) resulting in symptoms such as muscle weakness, sensory loss, and fatigue. CIDP is closely related to Acute inflammatory demyelinating polyradiculoneuropathy (AIDP) which is the demyelinating form and the most common variant of Guillain-Barré syndrome (GBS) (Dimachkie and Barohn 2013). CIDP can vary in its presentation, affecting motor, sensory, or both types of nerves, and can be progressive or have a relapsing-remitting pattern. The most common presentation seen involves a symmetric, motor-predominant weakness and **sensory impairment**, affecting vibration and position sense (proprioception) more than pain and temperature sense. Symptoms of **autonomic dysfunction** are also common but underreported in CIPD (Pasangulapati et al. 2017).

Areflexia (loss of reflexes) is also common. Cranial involvement is sometimes seen as well which can manifest in a type of diplopia or facial muscle paralysis (Gogia et al. 2024).

Cognitive impairment has been associated with CIDP. A preliminary report on 7 patients with CIDP showed that cognitive dysfunctions were seen in all patients. Executive function, the ability to focus on relevant stimuli (selectiveness) and to divide attention across tasks (divisibleness) were significantly lower compared to control subjects. The results suggested dysfunction of the prefrontal cortex in CIDP patients, where the authors considered it possible to be of immune-mediated cortex damage (Slotwinski et al. 2015).

There is a less common subtype of CIDP that primarily affects sensory nerves, that is referred to as **Chronic immune-sensory polyradiculopathy (CISP)** (Dziadkowiak et al. 2021). Unlike classic CIDP, which impacts both motor and sensory nerves, CISP predominantly affects sensory nerve roots and small nerve fibers, resulting in pain and temperature sensitivity changes without motor involvement. Since CIDP usually affects both large nerve fibers as well as small nerve fibers, electromyography (EMG) is the standard test used to detect myelin damage in peripheral nerves to diagnose CIDP (more information about diagnosis of CIPD Here). While some PSSD members in the community have had positive findings on EMGs and some have even been diagnosed with CIDP, several patients do not show any detectable anomalies on EMG's.
A specialist in neurology (name redacted) has proposed that PSSD could be a novel form of CISP (sensory subtype of CIDP), given some of the symptoms commonly seen in PSSD such as sensory loss and sexual dysfunction. In addition, some patients have been diagnosed with inflammatory polyneuropathy which is a general diagnostic code also including CIDP. See chapter 5 for more on immune-mediated neuropathies (SFN).

3.3 Various neurological and systemic conditions

Long Covid & Post Acute Covid Vaccination Syndrome

Long COVID (LC) (sometimes referred to as 'post-acute sequelae of COVID-19') is a multisystemic condition comprising often severe symptoms that follow a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. At least 65 million individuals around the world are estimated to have LC based on a conservative estimated incidence of 10% of infected people. Hundreds of biomedical findings have been documented, with many patients experiencing dozens of symptoms across multiple organ systems. Common new-onset conditions include cardiovascular, thrombotic and cerebrovascular disease, type 2 diabetes, myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and **dysautonomia**, especially postural orthostatic tachycardia syndrome (POTS) (Davis et al. 2023). LC has also been associated with **small fiber neuropathy (SFN)** (Azcue et al. 2023). Typical symptoms of LC include fatigue, shortness of breath, **brain fog**, sleep disturbances, chest pain, joint pain, muscle pain, headache, heart palpitations, gastrointestinal issues (such as diarrhea and nausea), loss of taste and/or smell, depression and anxiety, dizziness, rash and menstrual cycle irregularities. Additionally, LC has been linked to **sexual dysfunction** such as erectile dysfunction (Grutman et al. 2024, Yelin et al. 2023, Seehuus et al. 2024), **cognitive impairment** (Li et al. 2023), **anhedonia** (Liao et al. 2024, Lamontagne et al. 2021) and even anecdotal reports of **genital numbness** (reddit post 1, reddit post 2, reddit post 3).
On the topic of Long Covid, **Post-vaccine injuries** is another well known phenomena that describes adverse effects following vaccination. While most vaccines are considered safe and effective, rare adverse reactions can occur, one of which is a novel condition known as **Post-acute Covid-19 vaccination syndrome (PCVAS)**, which occurs in some individuals following the Covid-19 vaccine (SARS-Cov2). Similar to LC, the condition encompasses a wide range of symptoms, including chronic fatigue, **cognitive deficits** such as brain fog, cardiovascular disturbances (POTS), sensory abnormalities (**neuropathy**), muscular dysfunction, sleep disturbances and various gastrointestinal issues consistent with other **dysautonomia** syndromes (Semmler et al. 2023). Additionally, psychosis and even **anhedonia** have been reported to occur (Balasubramanian et al. 2022).

Myalgic encephalomyelitis (ME/CFS)

Myalgic encephalomyelitis or chronic fatigue syndrome (ME/CFS) is a frequent, complex and often severe disease triggered by various, mostly viral infections. It affects millions of people worldwide and can have debilitating impacts on those affected. It is part of a spectrum of post-infectious diseases with core symptoms that include; post-exertional malaise, neurocognitive challenges such as **cognitive impairment**, pain and sleep issues. Additionally, a significant majority of patients experience **autonomic symptoms**, including orthostatic intolerance, gastrointestinal disturbances, and circulation issues (Steiner et al. 2023, Kemp et al. 2019). Additionally, some individuals with ME/CFS are diagnosed with **small fiber neuropathy (SFN)** (Azcue et al. 2023). ME/CFS has been associated with an increased risk of developing **erectile dysfunction** and some limited research that suggests a link between ME/CFS and **sexual dysfunction** (Blazquez et al. 2009). ME/CFS has also been loosely associated with **anhedonia**, although literature exploring this connection is limited. A mixed-method study exploring anhedonia in adolescents with ME/CFS suggested that the anhedonia was due to depression as a consequence of the impact of the condition (Smith et al. 2021). However, anhedonia and depressive symptoms are linked to many neurological disorders affecting the brain, outside of primary depression. Some anecdotal reports from ME/CFS patients mention both anhedonia and emotional blunting (Pheonix rising forum thread), consistent with what's seen in PSSD. A subset of PSSD patients, especially those with a more severe disease state, have reported comorbid diagnosis of ME/CFS. Interestingly, high-dose SSRI treatments have been shown to induce intra-and extracellular serotonin spillover in the dorsal raphe nuclei of mice (Lee et al. 2024a), which resulted in severe fatigue and ME/CFS-associated symptoms. The conclusions noted that the findings support the involvement of 5-HTergic hyperactivity in the pathophysiology of ME/CFS.

Multiple Sclerosis (MS)

Multiple sclerosis (MS) is a chronic autoimmune disease affecting the central nervous system (CNS) and is characterized by inflammation, demyelination, gliosis, and neuronal loss. MS is the most common immune-mediated inflammatory demyelinating disease of the CNS and affects approximately 2.5 million individuals worldwide. This condition manifests with a wide range of neurological symptoms, such as vision impairment, **numbness** and tingling, focal weakness, bladder and bowel dysfunction, and **cognitive impairment**. MS has various disease courses, including relapsing-remitting, primary progressive, and secondary progressive. Additionally, the following 3 categories are sometimes considered within the spectrum of MS: 1; Clinically isolated syndrome (CIS) (classified as a single episode of inflammatory CNS demyelination), 2; fulminant (severe MS with multiple relapses and rapid progression toward disability) and 3; benign (an overall mild disability course with rare relapses).

Typical clinical manifestations in MS include: vision loss, double vision, pain with eye movement, vertigo and gait imbalance, dysarthria and dysphagia, weakness, facial muscle weakness, tremors, spasticity, fatigue, **loss of sensation, paresthesias, dysesthesias**, and a band-like sensation around the chest or abdomen. Additionally, patients frequently experience **cognitive deficits** such as memory impairment, executive dysfunction and difficulty concentrating, Psychiatric symptoms such as depression and anxiety are also common (Tafti et al. 2024). **Autonomic nervous system disturbances** including sweating abnormalities, urinary dysfunction, orthostatic dysregulation, gastrointestinal symptoms and **sexual dysfunction** are frequent complications that reduce the quality of life of affected patients (Pintér et al. 2015). Furthermore, **small fiber neuropathy (SFN)** can occur in a subset of patients (Rizvi et al. 2021). Symptoms of sexual dysfunction may present as **erectile dysfunction**, **vaginal dryness, reduced libido, anorgasmia** and **reduction in tactile sensitivity of the genital regions** (Guo et al. 2012), all of which coincide with certain hallmark symptoms of sexual dysfunction in PSSD.

Parkinson's disease

Parkinson's disease (PD) is a neurodegenerative disease that causes the death of dopaminergic neurons in the substantia nigra. The resulting dopamine deficiency in the basal ganglia leads to a movement disorder that is characterized by classical parkinsonian motor symptoms, such as bradykinesia, muscular rigidity and resting tremor. The non-motor features include olfactory dysfunction, **cognitive impairment**, psychiatric symptoms and **autonomic dysfunction** (De Virgilio et al. 2016). Interestingly, **small fiber neuropathy** is a common comorbidity in PD (Novak et al. 2012). Parkinson's patients also frequently experience **sexual dysfunction** including symptoms such as **erectile dysfunction, loss of lubrication, decreased desire and inability to achieve orgasm** (Bronner and Vodušek 2011). Additionally, symptoms like apathy and **anhedonia** frequently occur in Parkinson's disease. In a study on anhedonia and apathy in PD from 2011, the authors noted the following when assessing PD patients for treatment options: ***«Generally, antidepressants are not effective for the treatment of depression in which remarkable decrease in willingness*** **(symptom of apathy and anhedonia)** ***is observed. On rare occasions, antidepressants worsened the decreased willingness. Thus, antidepressants should not be imprudently used for cases where apathy or anhedonia is independently observed»*** (Kaji and Hirata 2011). In alignment with this, some literature has linked antidepressants to an increased risk of developing Parkinson's disease (Guo et al. 2018a).Furthermore, a case report noted that a patient developed irreversible parkinsonism after the use of an SSRI (Dixit et al. 2015).
PD shows many similarities with PSSD and the negative links to antidepressants is an additional interesting observation.

Limbic encephalitis

Limbic encephalitis (LE) is an autoimmune subtype of encephalitis, where antibodies target brain cells triggering neuroinflammation. Possible manifestations of encephalitis, regardless of etiology, include fever, headache, seizures, lethargy, irritability, personality change, nuchal rigidity, focal neurology, coma, gastrointestinal symptoms, respiratory symptoms, rash, photophobia, and urinary symptoms. The clinical hallmark of LE includes acute and subacute onset of **memory and cognitive deficits**. Other symptoms include confusion, psychiatric symptoms (such as anxiety, depression, or psychosis), behavioral changes, seizures, movement disorders (such as ataxia, dystonia, or myoclonus), **autonomic disturbances**, and sleep disturbances (Kao et al. 2020). A case report of a patient with atypical LE noted **anhedonia** as one of the symptoms (Vengadavaradan et al. 2019). Another case report stated that the patient in question had lingering symptoms of **emotional blunting** and **absence of motivation** even after treatment with immunotherapy (Gerace et al. 2013). Due to the heterogeneity of the symptoms of limbic encephalitis and the challenge of differentiating it from other conditions, diagnosis can be challenging. **A 2019 retrospective study of 50 patients diagnosed with autoimmune encephalitis revealed that two out of three patients were originally suspected of having a different condition such as a primary psychiatric illness, a neurodegenerative disease, or epilepsy** (Ding et al. 2020). While there is little existing literature on psychotropic induced AE, a case report from 2023 showed a patient with a previous diagnosis of schizophrenia presenting with agitation and diffuse muscle stiffness after recently having changed medications from the antipsychotics Olanzapine and Risperidone to Haldol. The medication was discontinued before admission. The patient ended up with a diagnosis of serotonin syndrome and comorbid features of encephalitis after testing positive for SOX1 antibody. SOX1 has been associated with a variety of CNS diseases such as MS, GBS and neuromyelitis optica. The patient improved with treatment of the serotonin antagonist Cyproheptadine in addition to IVIG (Hoffer et al. 2023). For more on AE see chapter 10.3.

Negative symptoms of Schizophrenia

Schizophrenia (SCZ) is a chronic and disabling psychiatric illness characterized by two main symptom domains; positive and negative symptoms. Positive symptoms refers to an excess or distortion of normal function (e.g, delusions, hallucinations, and disorganized behavior), while negative symptoms refer to a reduction or absence of normal behaviors related to motivation and interest (e.g, **avolition, anhedonia, asociality**) or expression (e.g, blunted affect, alogia). Negative symptoms are a core component of schizophrenia and account for a large part of the long-term morbidity and poor functional outcome in patients with the disorder (Correll and Schooler 2020). In addition, cognitive impairments are also common in SCZ.

In the context of PSSD, we wish to draw attention to the negative and cognitive symptoms of SCZ due to the striking similarities between the conditions. Besides **Anhedonia**, a hallmark symptom of both SCZ and PSSD, **cognitive impairments** such as lack of concentration, executive dysfunction and memory issues are also common in both conditions. **Avolition** (apathy), which refers to a lack of motivation to initiate, complete tasks, and sustain goal-directed behavior, is another symptom cluster reported by some PSSD patients. **Loss of motivation and apathy** are common presentations among many individuals with PSSD, and can in some ways be seen as an extension of anhedonia (anticipatory). **Blunted affect**, which manifests as a reduced expression of emotions through facial expressions, tone of voice, and gestures, often accompanied by **difficulty feeling or showing emotions**, even in emotionally charged situations, is frequently reported by individuals with PSSD. Furthermore, **Asociality** which is marked by withdrawal from social interactions and a lack of interest in forming or maintaining close relationships, is frequently reported by PSSD patients and may be seen as an consequence of blunted affect and emotional deficits. Emotional withdrawal involves difficulty **connecting emotionally with others** and detachment from personal relationships, which is a phenomenon frequently reported by PSSD patients when discussing the social challenges of anhedonia and emotional blunting (Correll and Schooler 2020).

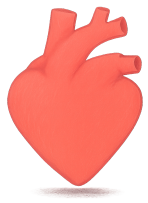
Outside of the typical negative symptoms mentioned, schizophrenic patients frequently report **sexual dysfunction** such as **decreased libido**, **erectile dysfunction** and **orgasmic disturbances**. While most studies in this context have focused on sexual dysfunction in relation to treatment with antipsychotic drugs, one study by (Aizenberg et al. 1995) assessed patients at baseline prior to any medication, and the results showed that **37% of the patients reported sexual dysfunction**, including more frequent reduction of sexual desire vs unaffected controls. It is suggested that the reduced sexual desire in patients with SCZ may be linked to the general reduction of initiative they experience as a consequence of the negative symptoms (de Boer et al. 2015). Lastly, **autonomic dysfunction** has been associated with multiple aspects of Schizophrenia pathophysiology, including symptom severity, cognitive impairment, and the development of cardiometabolic comorbidities, such as metabolic syndrome and high BMI. Research has demonstrated, through the use of heart rate variability (HRV) testing, that decreased parasympathetic activity (the part of the autonomic nervous system that helps the body relax), is correlated with increased severity of negative symptoms (Stogios et al. 2021). The underlying mechanisms behind schizophrenia are not fully understood but one of the main hypotheses involves dopaminergic dysfunction (Correll and Schooler 2020).

Despite differences in established or proposed etiologies, the abovementioned disorders show many similar symptoms which may suggest potential shared mechanisms. We aim to further explore these commonalities in the following chapters.
When assessing the clinical features of PSSD after investigating the similarities above, there are clear indications of problems occurring within the peripheral nervous system, particularly the autonomic nervous system (autonomic dysfunction/dysautonomia), as well as peripheral nerves (neuropathy). This is further backed up by clinical findings and diagnostic reports from the community consistent with dysautonomia and small fiber neuropathy. In addition, there are strong indications of a potential central nervous system (CNS) involvement (neuroinflammation) and immune dysregulation as well. To explore these connections, we will now systematically investigate each relevant section of the nervous system in 4 different chapters (4-7) to provide background information for context, while incorporating the community data with our own interpretation and discussion around the results in the subsequent sections (chapter 8).

We begin with an investigation into the autonomic nervous system.

4. Investigating the autonomic nervous system

Focus: Dysautonomia



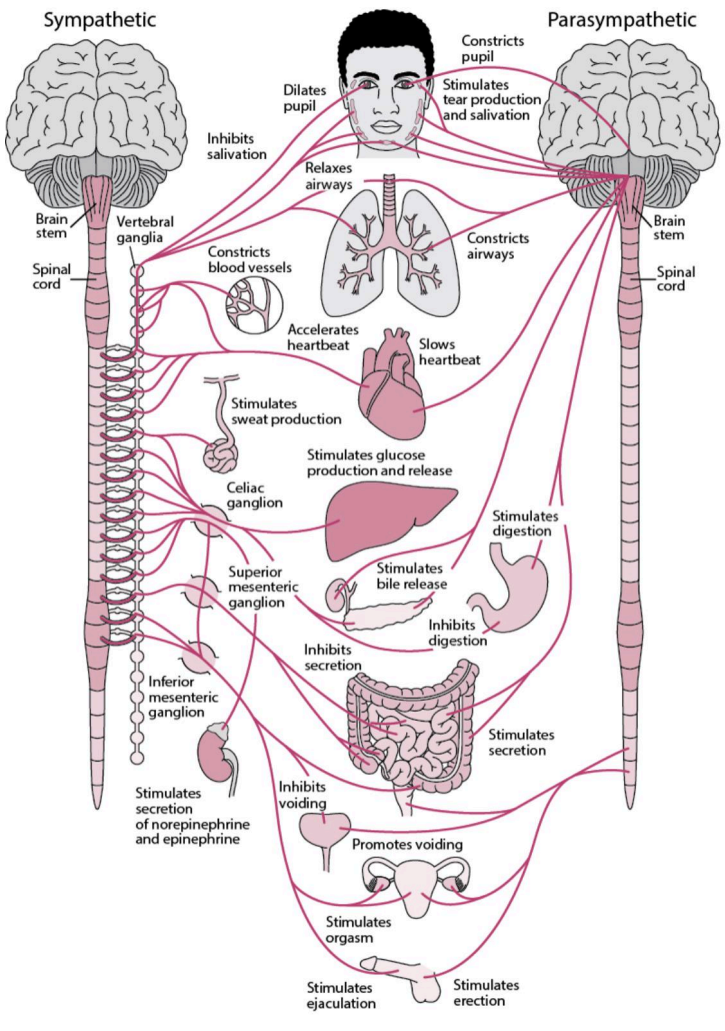
Approximately two years after the beginning of the COVID pandemic, a German lab named Celltrend began offering a G-protein coupled receptor (GPCR) autoantibody panel specifically designed for the investigation of Long Covid, ME/CFS and dysautonomia. During this time “Patient zero”, who had never had COVID-19 nor the COVID-19 vaccine, noticed that Long Covid and ME/CFS shared notable symptoms with PSSD. Thus, he decided to order the panel to see if he would be positive for any markers. After testing and receiving his results, he turned out to be positive for several autoantibodies (see patient 6 on the Celltrend tracker, Table 1). The patient decided to share his results with the community, which prompted other members to start pursuing the same testing. A group of patients in Finland were among the first to begin seeking out these tests, and eventually a professor in neurology, who had been meeting several of them, stated that he believed the condition to be autoimmune in an article about PSSD in the Finnish magazine Voima (Vistilä, 2024). Further positive results emerged, suggesting that autoantibodies might be disrupting the autonomic nervous system, causing dysautonomia in PSSD patients.

This chapter will explore the role of the autonomic nervous system in PSSD and connect with the clinical findings that support a link between dysautonomia and the condition.

4.1 The autonomic nervous system

The autonomic nervous system (ANS) is the part of the peripheral nervous system that controls the internal organs, including the blood vessels, stomach, intestine, liver, kidneys, bladder, genitals, lungs, pupils, heart, and sweat, salivary, and digestive glands. The ANS acts by stimulating body processes after receiving information from the external environment, as may be done through the sympathetic division, or by inhibiting them, as may be done through the parasympathetic division. Generally, **the sympathetic division** prepares the body for stressful or emergency situations—fight or flight. Thus, the sympathetic division increases heart rate and the force of heart contractions and dilates the airways to make breathing easier, causing palms to sweat, pupils to dilate, and hair to stand on end. It makes the body release stored energy and slows body processes that are less important in emergencies, such as digestion, defecation and urination. **The parasympathetic division** controls body processes during ordinary situations, conserving and restoring. It slows the heart rate and decreases blood pressure. It also stimulates the digestive tract to process food and eliminate waste. Sometimes the two divisions have opposite effects on the same organ. For example, the sympathetic division increases blood pressure, and the parasympathetic division decreases it.

Two main chemical messengers (neurotransmitters) are used to communicate within the autonomic nervous system: **Acetylcholine** and **Norepinephrine**.
Generally, acetylcholine has parasympathetic effects and norepinephrine has sympathetic effects. However, acetylcholine also has a role in the function of the sympathetic nervous system. For example, it sometimes stimulates sweating or makes the hair stand on end.



The autonomic nervous system controls internal body processes such as:

- Blood pressure
- Heart and breathing rates
- Body temperature
- Digestion
- Metabolism (thus affecting body weight)
- The balance of water and electrolytes (such as sodium and calcium)
- The production of body fluids (saliva, sweat, and tears)
- Urination
- Defecation
- Sexual response (arousal, erection/lubrication and ejaculation)

For more information visit Merck manuals overview of the ANS.

4.2 Dysautonomia

When there is a dysfunction or failure of the autonomic nervous system, the result is a disorder classified as a type of **dysautonomia**. Dysautonomia is not a diagnosis but an umbrella term that describes autonomic disorders. It is sometimes referred to as autonomic dysfunction or autonomic neuropathy, although it may occasionally arise from non-neuropathic causes. The organ systems most commonly affected in dysautonomias are neurological, pulmonary, cardiovascular, urinary, gastrointestinal, secretomotor and pupillomotor. Because autonomic disorders affect multiple organ systems, the presentation of symptoms are heterogenous, and may vary widely between different individuals.

Symptoms associated with dysautonomia:

- Thermoregulation issues: Body being too cold or too hot unrelated to external factors
- Cold extremities (hands, feet etc)
- Secretomotor: Lack of sweating or sweating too much, dry mouth, dry eyes
- Bladder issues: Difficulty urinating, incontinence (neurogenic bladder)
- Gastrointestinal disturbances: Slow gut motility and poor peristalsis leading to constipation, diarrhea, swallowing problems, gastroparesis, acid reflux, neurogenic bowel and intestinal pseudo obstruction
- Sexual dysfunction: Erectile dysfunction, lack of lubrication, lack of arousal, difficulties reaching orgasm, ejaculation problems
- Cardiovascular issues: Exercise intolerance, tachycardia, dizziness/lightheadedness, orthostatic intolerance
- Sensory problems: Lack of hunger and thirst, difficulties with eyesight due to slow pupil reflexes
- Abnormal breathing (shortness of breath, hypoventilation)
- Cognitive difficulties: Brain fog, cognitive sluggishness (secondary to other symptoms such as postural hypotension)

Sources: AN clinical presentation, Gastrointestinal motility disorders).

There are two types of dysautonomia - primary and secondary. A primary dysautonomia is when the autonomic dysfunction is the main disease process. Examples of primary dysautonomias include familial dysautonomia, multiple system atrophy, pure autonomic failure, and some forms of syncope.
In contrast, secondary dysautonomias arise as a consequence of another underlying condition. For instance, **autonomic neuropathy** often develops in association with diabetes. Other causes include medications, vitamins B and E deficiencies, chemotherapy, radiation therapy, and injuries to the spinal cord or head. **In some cases, the body's immune system mistakenly attacks parts of the autonomic nervous system, leading to conditions such as autoimmune autonomic ganglionopathy** (Nakane et al. 2018), as well as acute sensory autonomic neuropathy (ASANN) (Gutierrez et al. 2020), Guillain-Barré syndrome, and Sjögren's syndrome (Dupond et al. 1999). As discussed in chapter 3, secondary dysautonomia can also occur in diseases such as Parkinson's disease, Multiple sclerosis, ME/CFS, Long Covid, PACVS and even Schizophrenia. (For more info click here).

Community survey symptoms on dysautonomia (see Appendix for full survey)

- Loss of sexual desire (90%)
- Erectile dysfunction (84% of males) & loss of lubrication (71% of women)
- Difficulties in reaching orgasm (62%)
- Ejaculatory disturbances (premature, delayed, absent, dribbling) (56% of males)
- Brain fog/ forgetfulness/lack of focus: 76 (66%)
- Fatigue: 73 (63%)
- Increased/decreased sweating (44%)
- Vision problems (blurred vision, vision loss, tunnel vision) (42%)
- Inability to feel hunger (39%)
- Hesitancy to urinate, incomplete emptying (37%) & frequent urination, incontinence (30%)
- Ringing in ears (35%)
- Abnormally fast or slow heart rate (33%) & large swings in heart rate and blood pressure (14%)
- Constipation, diarrhea, abdominal distension, food intolerance (33%) & bloating (32%)
- Dizziness, lightheadedness, vertigo (32%)
- Feeling short of breath (32%)
- Exercise intolerance (31%)
- Sensation of coldness (unable to feel warmth in body) (30%)
- Dry eyes and mouth: 32 (28%)

The stats are based on the SFN community survey from summer of 2023

By assessing symptoms occurring in dysautonomia, putting emphasis on sexual dysfunction and cognitive difficulties in particular, there are clear parallels with several of the symptoms reported by PSSD sufferers. Many patients also frequently report additional symptoms such as gastrointestinal disturbances, lack of sweating, problems regulating body temperature and loss of hunger, all of which are symptoms of dysautonomia as well, and commonly reported to occur acutely during SSRI use or as a part of a withdrawal syndrome. The symptoms in the community survey (see Appendix) show clear signs of dysregulation of several autonomic functions (cardiovascular dysfunction, temperature dysregulation, orthostatic intolerance, secretomotor abnormalities and enteric nervous system dysfunction), consistent with dysautonomia. 23% of patients in the survey reported a diagnosis of dysautonomia, with a further 10% reporting a diagnosis of POTS (2023).

Dysautonomia diagnostics

There are various tests designed to check for autonomic dysfunction. **The Tilt Table Test (TTT)** may be used to determine how the body reacts to changes in position, specifically if standing up provokes orthostatic hypotension, neurally mediated hypotension, an excessive increase in pulse rate, or autonomically mediated syncope (Zysko et al. 2023). **The Valsalva maneuver** is another diagnostic tool used to assess autonomic nervous system function by analyzing heart rate variability (HRV). It involves a forceful exhalation against a closed airway, typically achieved by closing one's mouth, pinching the nose, and exhaling forcefully. This action increases intrathoracic pressure, leading to specific cardiovascular responses that can be monitored to evaluate autonomic function (Srivastav et al. 2023). **Heart Rate Variability (HRV)** can be tested through other means as well, such as by using Electrocardiography (ECG), which is considered the gold standard and most accurate method, or by using photoplethysmography (PPG), which is used in wearable devices such as smart watches or Pulse oximeters (though less accurate than ECG). There Are different types of analysis to detect HRV, but generally speaking low HRV is indicative of autonomic abnormalities (Tiwari et al. 2021). Other tests include Quantitative Sudomotor Axon Reflex Test (QSART), thermoregulatory sweat tests, and gastrointestinal motility tests like colon transit time. In addition, various tests may be done in order to investigate the underlying cause, which can include ultrasound, **antibody Tests** and **skin biopsies.**

4.3 PSSD Community data on dysautonomia

Autoantibodies targeting the autonomic nervous system

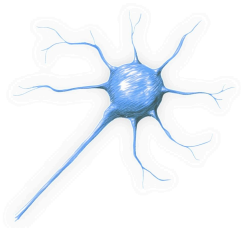
Related tables: 1 & 2

As briefly mentioned earlier, autoantibodies targeting receptors within the autonomic nervous system (ANS) have been implicated in various autoimmune and neuroimmune conditions. These antibodies can disrupt normal receptor function, leading to dysautonomia symptoms such as orthostatic intolerance, gastrointestinal dysmotility, and cardiovascular irregularities. In PSSD, our data suggests that these autoantibodies may interfere with neurotransmitter signaling, contributing to the condition's multisystemic features such as dysautonomia and cognitive deficits .
The identification of these autoantibodies not only supports the hypothesis of a potential neuroimmune etiology but also highlights potential diagnostic and therapeutic targets. 39 individual results are included. **This will be presented in table 1 and 2 (Celltrend tracking, chapter 8.1).**

Note: We have only tracked GPCR autonomic autoantibody results and do not have tables on other dysautonomia diagnostics outside of what is reported in the SFN tracker (table 3) for a select number of individuals.

5. Investigating the somatic nervous system

Focus: Small fiber neuropathy



Following the Celltrend autoantibody testing, the Finnish community compiled by Patient zero started acquiring skin biopsies of small nerve fibers to look for signs of peripheral neuropathy. It quickly turned out that several patients were positive for small fiber neuropathy (SFN), and Patient zero was subsequently diagnosed with an immune-mediated form of SFN. The emerging findings suggested that SFN may be a common occurrence in PSSD, and to investigate this further, we started tracking these results. As more and more patients reported positive diagnostics, SFN has now become a leading hypothesis within the community for contributing to some of the symptoms seen in PSSD. This chapter examines the role of the small nerve fibers in sensory and autonomic function, explores SFN as a mechanism underlying symptoms in PSSD, and discusses findings from community-gathered data.

5.1 The somatic nervous system & small nerve fibers

The somatic nervous system (SNS) connects the brain and spinal cord to the peripheral nerves, governing sensory and motor functions essential for movement and sensation. Generally this happens through two pathways; **Efferent** pathways which send information from the spinal cord to the muscles and regulate motor functions involved in movement of the body and limbs, and **Afferent** pathways which run toward the spinal cord and carry information from sensory organs. Within these pathways, **small nerve fibers** play a key role in transmitting sensory and autonomic signals through two main types of fibers; A-delta fibers, which are thin and myelinated, transmitting fast, sharp pain and temperature sensations, and C fibers; which are unmyelinated and conduct signals more slowly, carrying sensations of dull, aching pain, warmth, itch, and certain touch sensations. While primarily involved in sensory processing, C-fibers also play a role in the ANS, regulating functions like heart rate, digestion, and sweating (Glatte et al. 2019).
For more see osmosis.

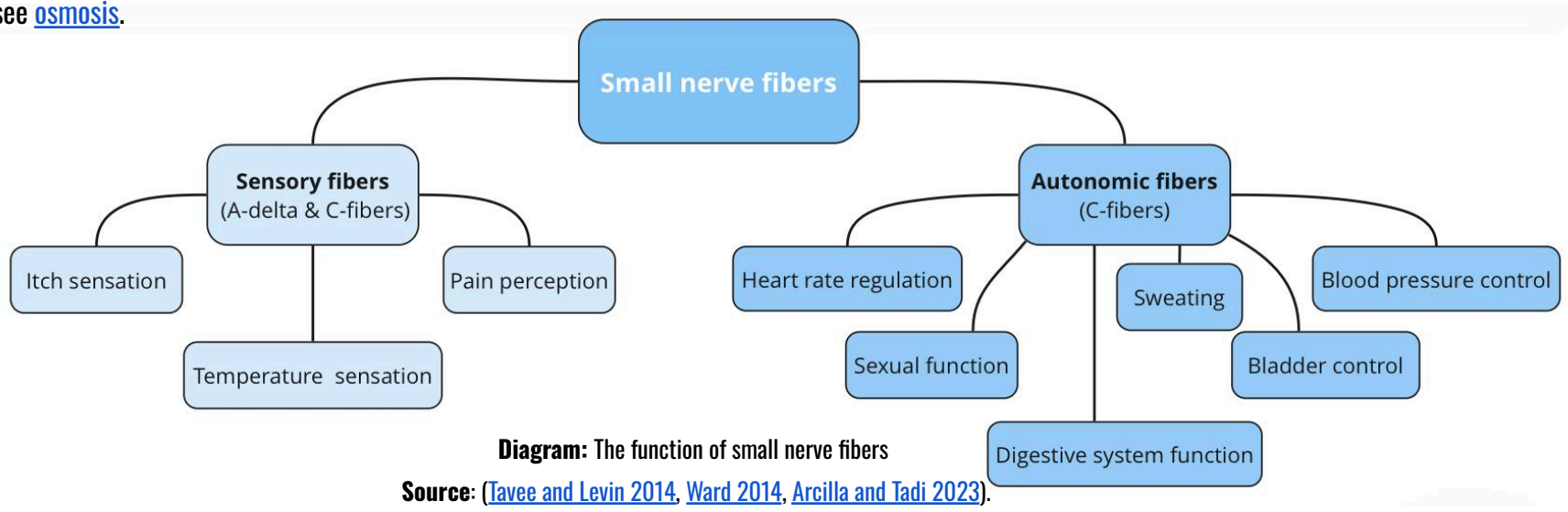
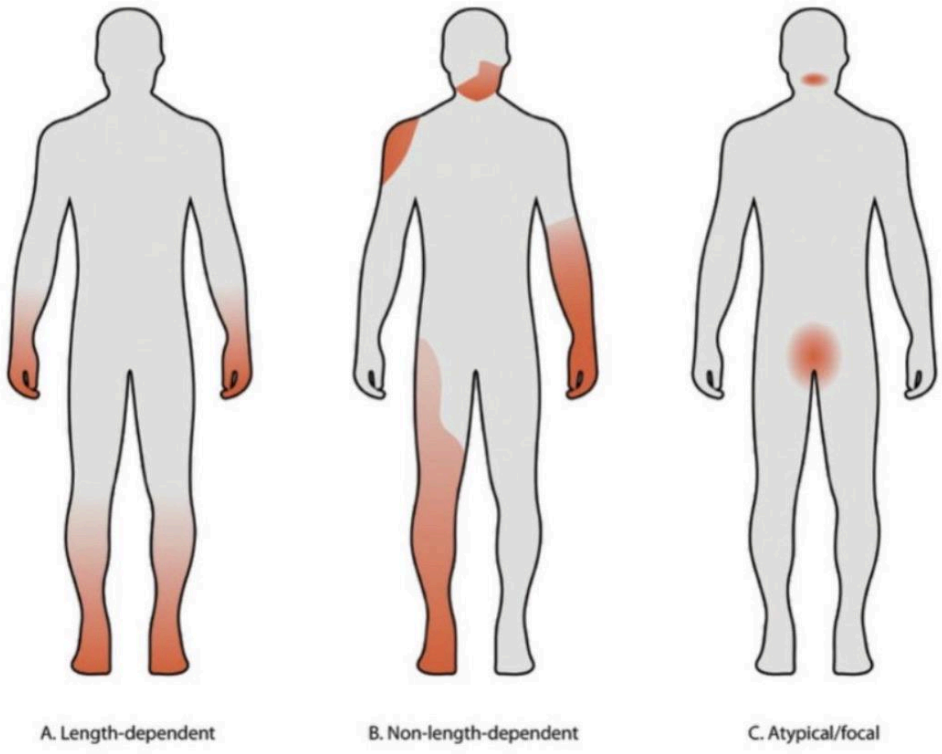


Diagram: The function of small nerve fibers
Source: (Tavee and Levin 2014, Ward 2014, Arcilla and Tadi 2023).

5.2 Small fiber neuropathy

Small fiber neuropathy (SFN) is a type of nerve dysfunction or damage that is specific to small nerve fibers, and affects the thinly myelinated and unmyelinated nerve fibers, leaving the larger myelinated fibers relatively unaffected. Since these nerves can be found in both the skin as well as in the autonomic nervous system (ANS), SFN can lead to a wide variety of sensory and autonomic symptoms. These can include sensory symptoms such as numbness, pain, burning and electric shocks, and/or autonomic ones (dysautonomia), such as sexual dysfunction, gastrointestinal issues and problems with regulating body temperature (Geerts et al. 2023). The extent of the damage as well as the capacity for recovery depend on the causative agent and will vary a lot with time relative to development as well as severity between affected individuals
There are three main types of SFN; Length dependent (LD), Non-length dependent (NLD) and Focal/atypical.
Length dependent SFN (LD) is the most common type of SFN and is characteristic of diabetic neuropathy, which is a type that affects both legs equally and starts at the furthest away point (feet) working its way upwards; in other words the longest nerves are the first to be affected.
Non-length dependent (NLD) is the other main type of SFN and has a more unusual and scattered pattern of areas affected. It is most commonly seen as a secondary downstream complication to another disease process, and is more likely to be of immune-mediated origin. It can affect all areas of the skin and the autonomic nervous system, which is referred to as autonomic neuropathy. Often patients will have both sensory (skin) and the autonomic system affected (Tavee 2018). Although no official criteria exist for this subtype (Terkelsen et al. 2017), **Focal/atypical** is another type of SFN and is a neuropathy that refers to a single point affected that is unusual to a typical clinical picture of SFN. Areas affected can be limited to the mouth or genitals for example, and resemble conditions such as burning mouth syndrome (Kouri et al. 2024) or vulvodynia (Bornstein and Palzur 2020).

Figure 1: Types of SFN



The different subtypes of small fiber neuropathy **Source:** (Devigli et al. 2020)

Symptoms of PSSD appear to have more in common with a mix of focal and non-length dependent neuropathies than length-dependent ones, which, as mentioned, are also more commonly seen in immune or inflammatory types. Toxic or metabolic neuropathies typically have a slower, less certain date of onset while immune or infectious ones tend to start more suddenly, which is again typical of PSSD. Additionally, the implications of autonomic neuropathy aligns well with the typical sexual dysfunction aspect of PSSD.

With numbness being a textbook symptom of nerve problems in general, PSSD has been openly suspected to involve SFN by some researchers such as professor David Healy since 2015 ("PSSD, Withdrawal & Small Fiber Neuropathy?" 2018). Besides numbness, sexual dysfunction itself is a textbook symptom of autonomic dysfunction, and although the European Medicines Agency (EMA) refuses to recognize other SSRI-induced symptoms as a part of PSSD, many patients do present with additional symptoms pointing to SFN or dysautonomia such as paresthesias, pain or dizziness. Furthermore, they are also known to be common symptoms in SSRI withdrawal syndrome, which is occasionally comorbid with PSSD itself.

On the other end of the SFN spectrum opposite of the typical numbness and sensory loss, is Persistent genital arousal disorder (PGAD), another condition that may arise after antidepressant use, consisting of unprovoked sexual arousal/orgasmic sensations. It has recently been hypothesized that many cases of PGAD are caused by unprovoked firing of C-fibers in the regional special sensory neurons that subserve sexual arousal, where some PGAD symptoms may share pathophysiologic mechanisms with neuropathic pain and itch (Oaklander et al. 2020). This is an important aspect to touch upon as this underscores how neuropathic symptoms exist on a spectrum of sensory abnormalities, and may help explain differences in symptoms experienced by PSSD sufferers, even if PGAD itself is its own distinct condition on the opposite extreme of the spectrum.

One of the most unique and seemingly paradoxical characteristics of PSSD has to do with its onset, because patients may become symptomatic while starting the medication, while on it, during tapering, or only develop them after cessation. However, this is another parallel with known forms of iatrogenic neuropathies such as chemotherapy-induced peripheral neuropathy (CIPN), where such a phenomenon is not only known, but common enough to have its own name "coasting" (Colvin 2019).

Another point worth mentioning is the fact that patients report getting PSSD from other types of psychotropics outside of the usual SSRI/SNRI class. A paper from 2004 showed that Amitriptyline, which is a tricyclic antidepressant, has significant toxic side effects in the central nervous system and cardiovascular system that are dose-related to its systemic administration, **leading to degeneration of peripheral nerve fibers** (Estebe and Myers 2004). This further illustrates the potential toxic side-effects of pharmaceuticals, as well as their ability to trigger peripheral neuropathy.

As discussed in chapter 3, neuropathy is often seen as a secondary complication in several disease pathologies, such as with ME/CFS, Long Covid (Azcue et al. 2023), Parkinson's Disease (Novak et al. 2012) and Multiple sclerosis (Rizvi et al. 2021). Additionally, SFN is highly associated with other chronic systemic conditions such as Sjögrens syndrome and Systemic Lupus Erythematosus (Sène et al. 2013, Tekatas et al. 2020). Given the striking similarities between PSSD and these conditions as discussed in chapter 3, this could be a clue of PSSD potentially having a systemic nature with SFN as a common downstream outcome.

Due to the reasons mentioned above, we believe that there is good reason to suspect that PSSD may be partially explained by a novel form of small fiber neuropathy, more specifically an immune-mediated type, and by now, several patients have already been formally diagnosed with it in clinical settings, even if formal research into the matter is still ongoing.

Symptoms associated with SFN

- Burning pain
- Tingling or prickling sensation (paresthesia)
- Numbness
- Electric shock-like pain
- Increased sensitivity to touch (allodynia)
- Temperature sensitivity
- Autonomic dysfunction
- Worse sexual function & decreased orgasm intensity
- Erectile dysfunction
- Decreased ejaculation or lubrication
- Gastroparesis and other gastrointestinal disturbances
- Genital sensory dysfunction

Sources: (Pollard et al. 2024), (Hong Hoo et al. 2019), (Hicks et al 2020), (AbdulRazek et al. 2017), (Geerts et al. 2023)

Community survey symptoms on SFN (excerpt)

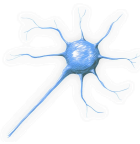
- Loss of genital sensitivity (90%)
- Numbness: 97 (84%)
- Loss of erotic sensation (85%)
- Changes in sensation of orgasm: 88 (77%)
- Loss of feeling during intercourse (70%)
- Numbness of other parts of the body besides genitals (55%)
- Pain (26%)
- Tingling (24%)
- Burning (18%)
- Unable to feel pain: 19 (17%)
- Shocks (10%)

The stats are based on the SFN community survey from summer of 2023

Cranial neuropathy and implications of the vagus nerve

Another complication of SFN and subsequent autonomic neuropathy, is damage and dysfunction to the vagus nerve (referred to as vagal neuropathy). The vagus nerve is one of the cranial nerves, and the longest nerve in the autonomic nervous system. It plays an important role in the regulation of the parasympathetic nervous system, regulating various physiological processes such as digestion, heart rate, immune response, anti-inflammatory response, and stress reactions. It communicates in a bidirectional way via the gut brain axis, sending and receiving signals from the brain and gut (Carabotti et al. 2015). When the vagus nerve is damaged, such as in the case of autonomic neuropathy, individuals may experience complications of dysautonomia such as tachycardia, gastroparesis, difficulties with swallowing or speaking, vasovagal syncope (fainting), respiratory issues and mood related issues. Inflammation of the vagus nerve has also been seen to contribute to dysautonomia in long covid (Woo et al. 2023). Moreover, damage to the vagus nerve can contribute to sexual dysfunction by impairing the autonomic regulation needed for arousal and orgasm. In women, research has shown that the vagus nerve can transmit sensory information from the cervix and uterus to the brain, suggesting its involvement in the experience of orgasm, even in cases of spinal cord injury (Whipple and Komisaruk 2002). Additionally, disruption of vagal tone has been associated with increased stress and anxiety, which can indirectly impact sexual performance and desire.

Dysfunction of the cranial nerves in general may be another potential explanation for some of the more puzzling symptoms related to SSRI use and discontinuation, such as vision problems, tinnitus, and peculiar electric shock sensations characteristic of SSRI withdrawal, often dubbed “brain zaps” by affected patients. They are responsible for delivering sensory input from the eyes and ears as well as from within the internal organs through the autonomic nervous system, and damage to them has been reported to occasionally give rise to peculiar symptoms that have not been known to occur in sensory loss secondary to dysfunction of the brain or the sensory organ itself. As an example, damage to the vestibulocochlear nerve as a result of surgery has been known to induce an unusual form of tinnitus that is dependent on eye movements. This rare, gaze-evoked tinnitus (GET) has been hypothesized to be caused by axonal sprouting during regeneration, as well as neuroplastic adaptations of the brainstem following damage to the nerve (Gendt et al. 2012). Notably, this pattern is analogous with what patients have observed with “brain zaps”, which are also often induced by certain eye movements. As GET appears to be unique to instances of impairment of cranial nerve function in particular, this suggests that “brain zaps” may not only have similarities in terms of presentation, but possibly in the underlying etiology as well. Furthermore, ototoxicity has recently been reported as a rare side effect of Mirtazapine following a case report (Zhang and Opler 2024). This is a frequent occurrence among patients of the Mirtazapine tapering community, where tinnitus is a rather common symptom that may persist after discontinuation of the medication. In this specific instance however, the patient was put on a 15-day steroid treatment following the discontinuation of Mirtazapine, and despite having to stop the treatment after 6 days due to side effects, initial and final audiograms showed that her hearing loss and associated symptoms largely resolved even with a partial treatment. This suggests that inflammation and immune dysregulation may have been a contributing factor behind her symptoms.



SFN Diagnostics

The inflammation and subsequent damage that occurs in neuropathy through the underlying disease process will result in a decrease in nerve fiber density over time, which can be detected with a test called **punch skin biopsy**. Due to the variable and patchy nature of the NLD subtype, along with the fact that some patients present with predominantly autonomic neuropathy symptoms, this test will not always be helpful in detecting it due to the fact that reference ranges are limited to a small number of specific areas of the body. Thus, additional diagnostic methods may occasionally be required for demonstrating evidence of nerve dysfunction, such as the autonomic testing mentioned in the section about dysautonomia. With that said, punch skin biopsies are a novel and promising way of detecting SFN in PSSD affected individuals. Besides this, other diagnostics such as **Quantitative sensory testing (QST)**, that measures vibrational and temperature abnormalities of the skin can also be used to determine the diagnosis of SFN (Fabry et al. 2020).

Corneal confocal microscopy (CCM) is another (fairly new) diagnostic method that measures small nerve fiber density in the cornea of the eye with a high precision microscope (Lukashenko et al. 2021). It has been proposed to be a reliable, effective and non-invasive method for diagnosing SFN, and has been used as such in one small scale study by Dr. Kenneth M. Peters (Stachelek et al. 2025).
With that said, some PSSD cases (5) have tested negative with this method and we suspect that it might not be the best tool to diagnose NLD SFN. For example, one patient that already had a positive skin biopsy of 1.8/mm had no decrease in nerve fiber density detected in his eyes when he was evaluated with CCM (although it did show an increase in dendritic cells which is a sign of inflammation). Thus, at the moment it seems that CCM could possibly be a good indicator for detecting systemic inflammation by looking at the dendritic cells, but as far as nerve fiber density goes, it seems to either not be sufficiently accurate or may fail to detect the loss of nerve fiber density due to the patchy nature of NLD SFN.

5.3 PSSD community data on small fiber neuropathy

Related table: 3

Data collected from the PSSD community has shed light on the potential involvement of small fiber neuropathy (SFN) in this condition. Diagnostic tests, such as skin biopsies and quantitative sensory testing, have been utilized by community members to investigate nerve fiber damage. Preliminary findings suggest abnormalities consistent with SFN, prompting further exploration into its role in the sensory and autonomic symptoms experienced by individuals with PSSD. We have received 56 reports in total of SFN diagnostics (50 skin biopsies and 6 QST's).
These are compiled in table 3 (SFN skin biopsy tracker, chapter 8.2) together with some additional info on a select number of patients, such as other diagnostics (EMG, CCM, TTT etc).

6. Investigating the central nervous system

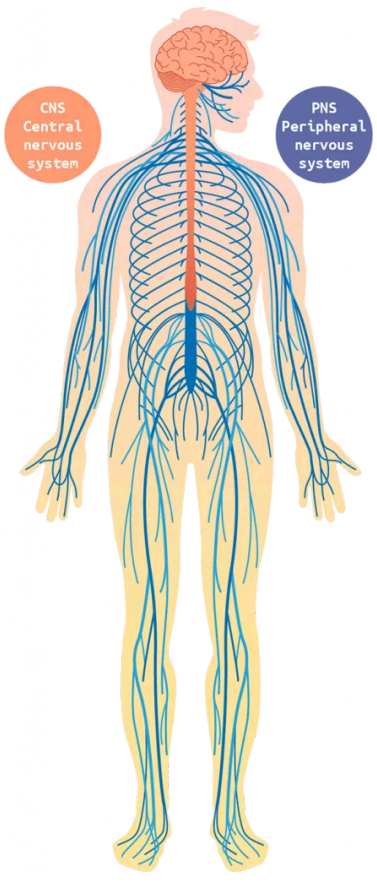
Focus: Neuroinflammation & immune dysregulation

In January 2023, “Patient zero” shared another update with the community on an online forum saying that he had received an extensive neurological examination and had acquired a diagnosis of immune-mediated small fiber neuropathy. The diagnostics that led to this were a combination of findings in his cerebrospinal fluid, positive skin biopsy and a holistic clinical assessment. In addition, the patient also had a PET-scan of his brain showing hypometabolism, suggestive of neuroinflammation. The patient showed all the classic signs of PSSD with severe dysfunction across the board, where the individual ended up totally incapacitated and bed-bound. He was quickly put on immunological treatment, and after a few months, he shared another update with the community, noting that his symptoms had slowly started improving. Due to the stubborn nature of his symptoms he was put on additional immunological treatments which further improved his state over the following year. Eventually more patients reported similar neurological diagnostics, and while not all acquired the findings to qualify for treatment, more patients started getting diagnosed with autoimmune SFN. We then corresponded with these patients around their diagnostics, and started tracking more community test results involving various diagnostics of the central nervous system (CNS), such as lumbar punctures, MRIs and cytokine panels. As more patients continued providing test results and getting diagnosed with autoimmune conditions, we eventually started noticing certain patterns and correlations. After over a year of tracking these labs, the results indicate that there may be a CNS involvement in PSSD.

This chapter delves into the CNS’s potential role in PSSD, focusing on the reward system and exploring neuroinflammation and immune dysregulation as potential contributors to pathology.

6.1 The central nervous system

The central nervous system (CNS) consists of the brain and spinal cord and is responsible for everything the body does — such as the creation of awareness, thoughts, feelings, speech, movement and the 5 senses (seeing, hearing, feeling, tasting and smelling). The CNS receives sensory input from the nerves, which it processes and responds to. It communicates by sending messages from the brain to the spinal cord, which is connected to the peripheral nervous system (PNS) and is thus able to transmit the message to complete the action. Signals travel to and from the CNS at all times to keep the body functioning (for more see the Cleveland clinic).



The brain serves as the control center of the CNS, orchestrating every aspect of bodily function and human experience. It processes sensory input, initiates movement, and regulates emotions, thoughts, and memories. Within this complex network of billions of neurons, specific systems govern key functions.
One such system is **the reward system**, also known as the mesolimbic system, which drives motivation, pleasure, and reinforcement of survival behaviors such as eating, socializing, and reproduction. It involves key brain regions within the basal ganglia, including the ventral tegmental area (VTA), which initiates dopamine signaling, and the nucleus accumbens, often called the “pleasure center”, where dopamine and opioid signaling interact to drive motivation and amplify pleasure during rewarding experiences. The prefrontal cortex, part of the limbic system, evaluates and regulates the value of rewards and guides decision-making and impulse control (as well as governing working memory, attention, and executive function). Other limbic structures, such as the amygdala and hippocampus, assign emotional significance to rewards and store memories of pleasurable experiences, ensuring these behaviors are reinforced.
The reward system depends on a balance of neurotransmitters. **Dopamine** plays a central role in motivation and reinforcement, while serotonin modulates dopamine activity (Lewis et al. 2021). **Endorphins** contribute to pleasure and relief, and under certain conditions can produce euphoria. These receptors, particularly the mu-opioid subtype, are essential for generating pleasurable “liking” responses and amplifying motivation to pursue rewarding stimuli.
Mu-opioid signaling interacts closely with the dopaminergic system in the mesolimbic pathway, shaping both hedonic experience and goal-directed behavior (Peciña & Berridge 2005, Nummenmaa & Tuominen, 2017). GABA, an inhibitory neurotransmitter, maintains balance by regulating dopamine release, and glutamate (excitatory) facilitates learning and memory of rewards. When disrupted by stress, inflammation, or substance use, dysfunction in the reward system can lead to conditions like anhedonia, addiction, or depression, underscoring its critical role in mental and emotional health (Lewis et al. 2021).

The spinal cord, which extends from the brainstem, serves as the primary communication pathway between the brain and the rest of the body, transmitting sensory information from the peripheral nervous system (PNS) to the brain and sending motor commands back to muscles and organs. This intricate network of nerve pathways not only enables voluntary movements and reflexes but also regulates essential functions like posture and coordination. Damage or dysfunction in the spinal cord can disrupt these processes, contributing to sensory loss, muscle weakness, or autonomic issues. Its role is closely integrated with the brain's functions, ensuring seamless communication for bodily operation (Grau et al. 2024).

6.2 CNS disease, neuroinflammation & immune dysregulation

Given the essential processes governed by the central nervous system such as movement, sensation, cognition, and emotion, diseases of the CNS can profoundly impact a patient's function and quality of life. Symptoms may vary widely depending on the type of condition, and may include cognitive difficulties (confusion, memory loss, attention deficits), sensory abnormalities (pain, numbness), muscle weakness, involuntary spasms, tremors, seizures, headaches, and loss of consciousness. In more severe cases, these conditions can lead to paralysis, speech and language difficulties, or significant cognitive decline. CNS disorders encompass a broad range of conditions, including neurodegenerative diseases like Parkinson's, Alzheimer's, MS, amyotrophic lateral sclerosis (ALS), and multiple system atrophy; autoimmune conditions like autoimmune encephalitis and neuromyelitis optica; infectious diseases like meningitis and encephalitis; cerebrovascular conditions such as stroke, traumatic brain injury (TBI), tumors, spinal cord injuries (SCI), and myelitis (inflammation of the spine). Each CNS disorder has unique mechanisms, but many share common features such as **neuroinflammation, neuronal degeneration, and disruption of communication pathways**.

Neuroinflammation refers to inflammation of nervous tissue, and is a complex reaction of the central nervous system (CNS) involving the activation of the brain's immune cells, primarily microglia and astrocytes, in response to various stimuli such as infections, toxins, trauma, or **autoimmune reactions**. The process of neuroinflammation is mediated by pro-inflammatory cytokines, chemokines, and other signaling molecules that can lead to neuronal dysfunction and cell death if not regulated properly (Adamu et al. 2024). Neuroinflammation is a central component of many CNS disorders, including neurological, neurodegenerative, certain autoimmune diseases and some psychiatric illnesses.
While acute neuroinflammation is a protective response to injury or infection, chronic neuroinflammation can be harmful and is a key area of interest in understanding the pathophysiology of various CNS diseases. Chronic neuroinflammation is thought to contribute to the progression of these conditions by causing sustained damage to neurons, disrupting normal brain function, and altering the brain's chemical environment (Adamu et al. 2024).

Symptoms associated with neuroinflammation

- Anhedonia
- Apathy
- Cognitive dysfunction
- Attention deficits
- Fatigue
- Sleep disruption
- Loss of appetite
- Anorexia
- Depression
- Anxiety
- Irritability
- Fever
- Lethargy
- Muscle pain

Based on established research on "sickness behaviour" (Dantzer & Kelley 2006), (O'Callaghan & Miller 2019).

Community survey symptoms on neuroinflammation (CNS) (excerpt)

- Emotional blunting/ anhedonia (81%)
- Impaired memory and understanding (66%)
- Brain "fog"/ forgetfulness/can't focus (66%)
- Fatigue (63%)
- Issues with speech, communication, word-finding (61%)
- Loss of ability for visual thinking and creativity (61%)
- Sleeping problems (52%) & Insomnia (38%)
- Blank mind (49%) & loss of inner dialogue (36%)
- Loss of appetite (40%)
- Anxiety (38%) & severe anxiety or panic attacks (26%)
- Muscle or joint pain (34%)

The stats are based on the SFN community survey from summer of 2023

Many PSSD patients report significant cognitive impairment, including difficulties with concentration, memory, and mental clarity, often described as "brain fog." These symptoms bear a resemblance to those experienced by patients with neuroimmune disorders such as Long COVID and MS, which are both proposed to involve neuroinflammation (Kavanagh 2022, (Al-Badri and Castorina, 2018). PSSD, which also commonly presents with emotional blunting and anhedonia, may further suggest neuroinflammation and subsequent dysfunction in brain regions responsible for emotional regulation and reward processing, such as the basal ganglia and the limbic system, including the amygdala, which has been observed to cause emotional numbness as a consequence of a lesion (Melzer et al. 2015). **In MS, studies have shown that neuroinflammation causes cytokine-induced disruption of monoaminergic neurotransmission.** This disruption leads to altered mesocorticolimbic function and connectivity, which **culminates in**

dysfunctional reward processing, causing symptoms such as anhedonia. Sustained neuroinflammation, driven by microglial activation as well as demyelinating lesions, might foster neurodegeneration of brain structures involved in valence and reward processing in more advanced disease stages (Heitmann et al. 2022). Additionally, a rapidly growing body of research suggests that immune-derived signaling factors, such as pro-inflammatory cytokines, play an important role in the pathogenesis of depression (which can have comorbid anhedonia). A paper discussing the impact of inflammation on behavior noted that depressed patients who fail to respond to antidepressant therapy show increased inflammatory markers, and that patients with increased inflammatory markers at baseline were less likely to show a response to treatment, suggesting a relationship between inflammation and treatment resistance. Additionally, higher plasma levels of inflammatory cytokines, most consistently interleukin IL-1B, IL-6, and TNF-A, are correlated with greater depressive symptomatology (Hassamal 2023). Polymorphisms in the cytokine IL-1B gene have also been associated with treatment response in depressed patients as well as alterations in emotional processing as measured by functional magnetic resonance imaging (fMRI) (Haroon et al. 2012). While the specific link between IL-1B polymorphisms and emotional blunting remains underexplored, these findings suggest a plausible connection, as IL-1B influences brain regions involved in emotional regulation and reward processing.

Anhedonia has been linked to inflammation and immunity, where higher levels of anhedonia were associated with higher circulating levels of T-cell-derived cytokines in adults diagnosed with major depressive disorder (Kudinova et al. 2020). Anhedonia and emotional blunting are also characteristic of the negative symptoms of schizophrenia, a condition increasingly understood to involve neuroinflammation (Vallée 2022).
A TSPO-PET study on LC patients showed neuroinflammation in the ventral striatum and dorsal putamen in the brain, and proposed that this could explain the symptoms of anhedonia reported by a patient (Braga et al. 2023). Neural circuitry dysfunction such as hypoactivation between the ventral striatum and the ventromedial prefrontal cortex underlies the melancholic phenotype of depression (Hassamal 2023). In Parkinson's disease (PD) neuroinflammation and subsequent dopamine depletion in regions such as ventral striatum contribute to both motor symptoms and non-motor symptoms such as cognitive dysfunction and apathy, which is reminiscent of cognitive impairments and anhedonia seen in PSSD. Interestingly, **the past decade has provided evidence for a significant role of the immune system in PD pathogenesis, either through inflammation or an autoimmune response**. Several autoantibodies directed at antigens associated with PD pathogenesis have been identified in PD patients.
This immune activation may be the cause of, rather than a response to, the observed neuronal loss (De Virgilio et al. 2016).

In ME/CFS neuroinflammation is proposed to be the most convincing hypothesis for the condition's pathophysiology, explaining its multifaceted symptoms (Lee et al. 2024b). ME/CFS has also been proposed to involve an autoimmune component (Morris et al. 2013) and interestingly, a recent study found demyelinating antibodies in about half of the test subjects in a group of patients with ME/CFS (Jensen et al. 2023). One of the authors of the paper, Ronald Davis, did a YouTube video around the study and when asked by a community member how it was different to MS, he said that «as far as i can tell it's the same thing», indicating the idea that ME/CFS could perhaps be seen as some sort of subcategory of Multiple Sclerosis (Youtube). This suggests that ME/CFS might share more commonalities than previously thought with other neuroinflammatory disorders.

A possible downstream complication of neuroinflammation which is also seen in ME/CFS, is **dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis** (Tomas et al. 2013), which is a central stress response system involving the hypothalamus, pituitary gland, and adrenal glands, which through a complex interplay stimulates the adrenal glands to secrete cortisol upon encountering stress.
This system operates through feedback loops to maintain physiological balance (Sheng et al. 2021). Microglial activation can exacerbate HPA axis dysregulation by releasing cytokines, chemokines, and reactive oxygen species, destabilizing neural circuitry and impairing plasticity (Hassamal 2023, Brites and Fernandes 2015). The interplay between neuroinflammation and HPA axis dysfunction forms a self-reinforcing loop, amplifying the stress response and driving chronic disease progression. Dysregulation of the HPA axis can lead to a variety of symptoms, like for example persistent fatigue, sleep disturbances, cognitive impairments (Tomas et al. 2013), which are common symptoms in many patients with PSSD.

Sexual dysfunction, which is considered one of the core aspects of PSSD (including genital numbness) is not unique to the condition, as seen in chapter 3. MS patients may even experience genital sensory loss or numbness, which is one of the hallmark symptoms of PSSD. While this symptom in particular could potentially be attributed to SFN in PSSD, it is not unreasonable to think that the etiology could involve a more complex combination of components, such as a central dysfunction or injury to the CNS in addition to PNS involvement. To highlight this we wish to draw attention to another example. A case report of a 47-year old man with a preceding viral illness and subacute encephalopathy and rapidly progressing myelopathy, presented at the ICU with symptoms of genital numbness, urinary retention and weakness in his legs (YouTube presentation on AE).

Systemic inflammation & the blood-brain-barrier

The blood-brain barrier (BBB) is a protective barrier in the brain that controls what substances can pass from the blood into the brain, ensuring that harmful substances, such as toxins and most pathogens, are kept out while allowing essential nutrients and oxygen to enter. However, under certain conditions, like inflammation or injury, the BBB can become compromised, allowing unwanted substances to cross into the brain, which can lead to issues such as neuroinflammation. BBB dysfunction is implicated in various CNS pathologies, and is directly linked to brain-related diseases such as Multiple Sclerosis (MS), acute disseminated encephalomyelitis (ADEM), encephalitis (infectious or immune-mediated), cerebral vasculitis and neurodegenerative diseases (such as Alzheimer's). In addition, it can also occur secondary to an extra neurological condition such as toxic-metabolic disturbances (including medications) (Le Guennec and Weiss 2023).

Systemic inflammation is an immune response to infections and injuries that occurs throughout the body rather than being localized to a specific area. It involves the release of inflammatory molecules like cytokines into the bloodstream, which can affect various organs and tissues. This type of inflammation is associated with chronic diseases, including cardiovascular diseases, diabetes and autoimmune disorders such as Systemic Lupus erythematosus (SLE), Sarcoidosis and Sjögrens syndrome (Pohl and Benseler 2013), as well as ME/CFS, MS and Long Covid (Komaroff 2017, Murta and Ferrari 2013, Tandon et al. 2024). Systemic inflammation can lead to a persistent, low-grade inflammatory state, which increases the risk of tissue damage and disease progression over time. Systemic inflammation can also reach the brain to cause central inflammation (neuroinflammation).
This can happen through several routes:

- The primary route where circulating cytokines communicate to the brain across the intact (or compromised) BBB
- Through regions of the brain that lack a BBB such as circumventricular organs (such as the postrema and pineal gland)
- When inflammation in the body activates the vagus nerve which then sends signals to the brainstem
- Or where cytokines enter the brain via specific transport mechanisms.

Once inside the CNS, the inflammatory signals cause alterations in the BBB, generate proinflammatory and anti-inflammatory cytokines, disrupts amino acid metabolism, causes oxidative damage, mitochondrial dysfunction, glial cell activation, brain ischemia, and **imbalance of neurotransmitters**; **all of which leads to neuroinflammation** and neurodegeneration. In addition, this crosstalk between systemic inflammation and central inflammation is known to induce behavioral alterations and cognitive dysfunction (Giridharan et al. 2023). As an example, a recent paper suggested that sustained systemic inflammation and localized blood-brain-barrier (BBB) dysfunction is a key feature of long Covid-associated cognitive impairment (Greene et al. 2024). Considering the multifaceted symptoms seen in PSSD, it could indicate a similar pathophysiology.
Many PSSD patients report additional symptoms such as fatigue, body aches and brain fog which are often associated with systemic inflammation and seen in diseases with similar symptomatic profiles such as LC and ME/CFS.
Additionally, the peripheral neuropathies observed in PSSD may be downstream from an active inflammatory insult. It is possible that the same inflammation could have other systemic effects, which may also be relevant in the mechanism of some of the cognitive symptoms such as emotional blunting and anhedonia. Previously published hypotheses about PSSD have suggested that a part of the etiology may be related to alteration of dopamine signaling due to serotonin-dopamine interactions based on the work of Bala et al. (2018), which showed that SSRIs cause inhibition of dopamine transmission in the ventral tegmental area. However, dopamine signaling can also be altered through other mechanisms as discussed earlier, and even mild systemic inflammation can affect substantia nigra reactivity, which is remarkable due to it being a major source of dopamine within the brain. In fact, inflammation such as that caused by infections has been observed to induce psychiatric symptoms such as psychomotor retardation, which has been proposed to be in part due to said dopamine effects. Therefore, persistent systemic inflammation from a chronic autoimmune condition could account for deficits in dopamine signaling that continue after the cessation of the triggering medication.

A recent rat study by Prof. Melcangi's research group on transcription profiles after cessation of Paroxetine (Giatti et al. 2024a) showed seven differentially expressed genes (DEGs) in the hypothalamus and 245 in the nucleus accumbens (NAc), a main component of the brain's reward system. Gene-Set Enrichment, Gene Ontology, and Reactome analyses also confirmed that inflammatory signature and immune system activation were present in both brain areas (Giatti et al. 2024a). This implies there is an innate immune dysregulation. Additionally DEGs related to neurotransmitters with a role in sexual behavior and the reward system, such as dopamine, glutamate and GABA associated with neurexin and neuroligin pathways and brain-derived neurotrophic factor (BDNF) signaling, were reported to be dysregulated in the NAc, further confirming dysfunction in this brain area.

One possible downstream mechanism of neuroinflammation is how pro-inflammatory cytokines may damage neuronal structure and function leading to deficits of neuroplasticity, the ability of the nervous system to perceive, respond and adapt to external or internal stimuli. One of the mechanisms underlying the negative impact of pro-inflammatory cytokines on neuroplasticity may be the reduction of Brain-derived-neurotrophic factor (BDNF) expression and function. BDNF is a crucial mediator of neuronal plasticity and neurogenesis, since it is abundant in brain regions particularly relevant for plasticity, and shows a remarkable activity-dependent regulation of expression and secretion, suggesting that it might bridge experience with enduring change in neuronal function.
The negative effects of neuroinflammation on neurogenesis could lead to impaired survival and proliferation of new neurons, and the consequences of inflammation on neurogenesis could also have functional implications for cognition. In fact, the impact of neuroinflammation could also affect the

correct integration of newborn neurons into pre-existing circuits, through changes in cellular morphology and in electrophysiological properties (Calabrese et al. 2014). This may indicate a possible route for why BDNF signaling was dysregulated in Prof. Melcangis recent paper.

The observations noted above paint a compelling picture of a potential neuroimmune process in PSSD, and suggest that neuroinflammatory mechanisms could be driving many etiological components and subsequent symptoms in the condition.

CNS diagnostics

When investigating disorders of the CNS, different diagnostic tools are applied depending on the symptoms and areas affected. Typical diagnostics include brain imaging such as computed tomography (CT scan), magnetic resonance imaging (MRI), electroencephalogram (EEG) and examination of the cerebrospinal fluid through a lumbar puncture (spinal tap). Additionally, supplementary diagnostics such as FDG-PET scans and antibody tests are sometimes needed in order to reach the correct diagnosis. In some cases, Cytokine panels may be used as well.

6.3 PSSD community data on CNS markers

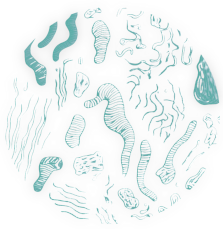
Related tables: 4, 5, 6, & 8

Community-reported data has provided valuable insight into potential central nervous system (CNS) involvement in PSSD. Neuroimaging techniques such as MRI and PET scans, along with cerebrospinal fluid analysis, have been used by some members of the community to investigate abnormalities. Early findings indicate structural and functional disruptions, including hypometabolism and neuroinflammatory markers, highlighting the need for further study into the CNS's role in PSSD pathology

Since we started gathering patient data on brain imagings and inflammatory markers (CNS), we have collected a total of 105 individual results across 5 different (CNS) tests over the past year and a half, comprising of the following diagnostics in the following order:
MRI and PET scans, Lumbar punctures, Cytokine panels and a neuronal autoantibody panel (the cunningham panel).
We will give short introductions to each test before interpreting and discussing the findings. **See tables 4-8 (chapter 8.3-8.8) for the results.**

7. Investigating the gut microbiome

Focus: Gut dysbiosis



The gut-brain axis is a critical communication network that links the gastrointestinal system to the brain. Disruptions in the gut microbiome, known as gut dysbiosis, can influence systemic and neuroinflammation, potentially contributing to PSSD symptoms. Community data and research suggests that microbial imbalances, including reduced levels of Faecalibacterium Prausnitzii, may play a role. This chapter explores the connection between the gut microbiome and PSSD, presenting findings from community data and discussing their implications.

7.1 The gut microbiome & The gut-brain axis

The gastrointestinal (GI) tract is home to trillions of microorganisms, including bacteria, archaea, fungi, and viruses. These microorganisms form networks of communities, collectively known as “the gut microbiome” (Belizário et al. 2018). The gut microbiome is responsible for food digestion, drug metabolism, the production of bioactive molecules and it's notably involved in regulating the immune system and maintaining overall health. A balanced gut microbiota is crucial for maintaining immune tolerance, the mechanism by which the immune system distinguishes between foreign and self-produced antigens. Disruption of immune tolerance can lead to the immune system mistakenly attacking the body's own tissues, triggering autoimmune diseases (Belizário et al. 2018, Wu and Wu 2012).

The gut microbiome plays a regulatory role in the physiology of the central nervous system (CNS) through the gut-brain axis, a bidirectional communication network between the gut and the brain which allows them to influence each other's function and health (Anand et al. 2022).

The gut-brain axis involves the following main components (Carabotti et al. 2015):

- **The enteric nervous system (ENS)** in the gut (often called the “second brain”) communicates with the CNS primarily through the vagus nerve and spinal pathways.
- **The gut-associated immune system** interacts with the brain via inflammatory signaling molecules (cytokines) that can influence systemic inflammation and brain function.
- The gut microbiome’s trillions of microorganisms play a crucial role by **producing signaling molecules including metabolites (e.g. short-chain fatty acids), neurotransmitters (e.g. serotonin), and neurosteroids (e.g. allopregnanolone)** that regulate the health and homeostasis of both the gut and the brain.
- **The vagus nerve serves as a direct communication highway between the gut and the brain**, transmitting sensory information and regulating autonomic responses.
- **The endocrine system** produces hormones such as cortisol during stress, and gut-derived peptides (e.g. ghrelin and leptin) to help regulate appetite, mood, and stress responses.

Disturbances in any of these systems, such as gut microbiome imbalances, vagus nerve dysfunction, or inflammatory conditions can disrupt the gut-brain axis influencing blood-brain barrier (BBB) integrity, potentially contributing to brain disorders (Khlevner et al. 2018).

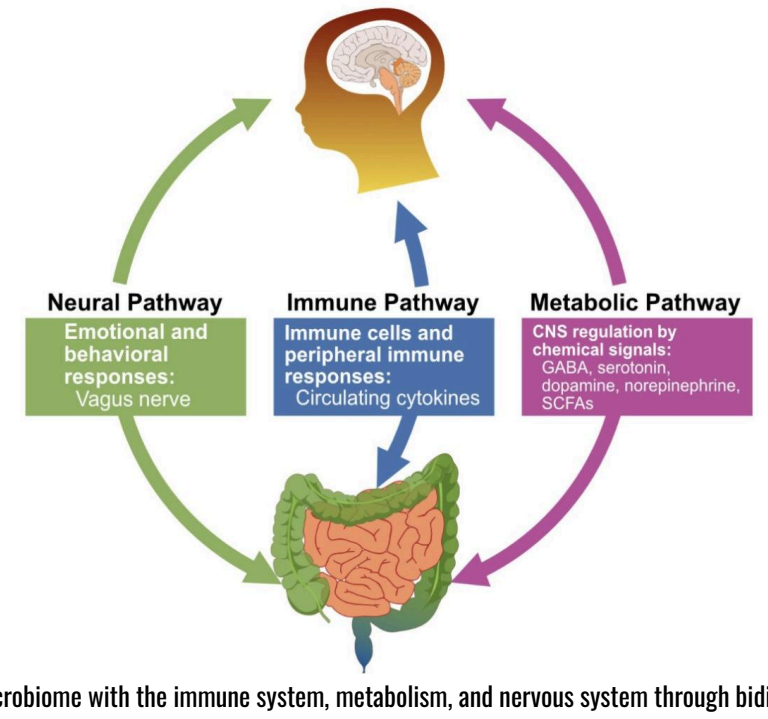


Image illustrates the interconnectedness of the gut microbiome with the immune system, metabolism, and nervous system through bidirectional communication via the vagus nerve.

Source: (Kwak et al. 2023)

7.2 Gut microbiome dysbiosis

Gut dysbiosis refers to an imbalance in the composition of the gut microbiome, characterized by a disruption in the ratio of beneficial to pathogenic bacteria. Experimental models in both PSSD & Post Finasteride Syndrome (PFS) have demonstrated alterations in gut microbiota composition (Diviccaro et al. 2022b, Diviccaro et al. 2019). A clinical study on PFS further confirmed these microbiota changes in human patients, revealing pathological changes of reduced diversity and richness of the gut microbiota (Borgo et al. 2021).

One of the main consequences of dysbiosis is the disruption of the intestinal barrier, often referred to as “leaky gut.” This condition allows larger molecules, toxins, and pathogens to enter the bloodstream, triggering systemic inflammation and over time, chronic inflammation can lead to the loss of immune tolerance (Belizário et al. 2018). As described prior, immune tolerance plays the central role in preventing autoimmune disease by ensuring that the immune system doesn’t mistakenly attack the body's own tissues. Similarly, immune tolerance also prevents the immune system from overreacting to harmless substances by not recognizing them as allergens. Mast Cell Activation Syndrome (MCAS) is a condition where mast cells, a type of immune cells involved in allergic reactions become abnormally activated. Anecdotal reports from some PSSD patients suggest symptoms aligning with MCAS, patients report newfound sensitivities to certain foods, medications and environmental allergens. MCAS has also been demonstrated as part of Long Covid with observation of abnormal granulation of mast cells and excessive inflammatory cytokine release (Sumantri and Rengganis 2023).

As discussed in chapter 4, autonomic disorders may involve the parasympathetic, sympathetic and enteric nervous systems, and can have multisystemic consequences where among these, gastrointestinal dysmotility is a common presentation (Kornum et al. 2021). Gut motility that’s controlled by the enteric part of the autonomic nervous system is crucial for essential functions of gastrointestinal health such as digestion, nutrient adsorption and detoxification. Autonomic dysfunction (dysautonomia) is thus associated with a predisposal and higher incidence rate of developing gastrointestinal pathologies like dysbiosis, SIBO & GERD all of which are associated with the PSSD patient group. Symptomatic disturbances of dysmotility may involve dysphagia, nausea, bloating, early satiety (feeling full early after eating), abdominal pain, constipation, diarrhea, weight loss, problems with bowel control as well as the absorption of nutrients and medications (Kornum et al. 2021).

Community survey symptoms on GI disturbances

- Enteric symptoms of constipation, diarrhea, abdominal distension, food intolerance (33%)
- Bloating (32%)
- Weight loss (24%)
- Stomach pain (23%)
- Nausea (23%)

GI diagnostics

Testing for gut dysbiosis primarily involves different types of GI-map panels, some more comprehensive than others. Their main function is analyzing stool samples to assess gut health by examining the microbiota composition, identifying pathogens, examining intestinal permeability and inflammation (Gingras and Maggiore 2020, Seethaler et al. 2021). Hydrogen and methane breath tests can be done to look for small intestinal bacterial overgrowth (SIBO) (Losurdo et al. 2020) and gastroscopy can be used to look for esophageal dysmotility and inflammation to diagnose gastroesophageal reflux disease (GERD) (Coleman 1988).

7.3 PSSD community data on gut dysbiosis

Related table: 9

A number of community members have reported various gut microbiome tests, screening for dysbiosis and other health indicators of the gut.
We received 16 samples of various **GI-map panels**, and after assessing the samples we quickly noticed not only a general pattern of gut dysbiosis, but also that a large number of the samples had low levels of a specific bacteria called *Faecalibacterium prausnitzii*. Upon further investigation, we discovered that this was a key bacterium in the gut with specific anti-inflammatory properties (Parsaei et al. 2021). Given the other indicators of inflammation possibly being a key component in PSSD, we found this discovery to be noteworthy. Low levels of F. Prausnitzii have been linked to various neuroinflammatory disorders such as MS and Parkinson's (Thirion et al. 2023a, Zhang et al. 2023c), further indicating its potential significance. See table 9 (chapter 8.8) for the results.

8. Clinical findings

Test results from PSSD community members

In this chapter, we delve into the clinical findings collected from the PSSD community. These findings provide quantitative data to further explore and validate the proposed mechanisms outlined in Chapters 4–7. By examining patterns in autonomic autoantibodies, small fiber neuropathy, neuroimaging, inflammatory markers and gut microbiome composition, we aim to highlight how mechanisms align with findings from other investigated systems, such as the autonomic and central nervous systems, and support the hypothesis of PSSD as a multi-systemic condition.

Background information on community data

This section provides the data compiled into tables (1-9) called «trackers» and discussions around each set of test results provided by community members so far, starting with the biggest sample sizes combined with the highest incidence rates.

All test results are based on PSSD patients, all of whom have consented for their test data to be used for research purposes. Most of the reports are verifiable by raw data (lab results), however, a number of results have been gathered from patients who have been unable to provide medical reports (exact numerical results) from their labs. Unfortunately, we have no way to verify the data the community members are giving, hence one limitation is the possibility that some data points could contain inaccurate information. It is worth noting that some of these tests are quite expensive and as public health care does not necessarily cover them, patients whose data is included in the trackers can be assumed to have higher probability of having more severe symptoms than on average and/or greater financial possibilities than on average to pay for such tests.

Numerical values of the trackers have been redacted to protect patient privacy, as well as for easier and simpler viewing for the reader. Assessing the results is complicated by variables such as the possibility of having been affected by COVID-19 infections, vaccine injuries, current use of other medications, and other potential health comorbidities not mentioned by patients prior to testing. Selection bias presents another problem for attempting to interpret results collected solely from reporting by patients outside of a controlled research setting. We aim to take these factors into consideration while gathering more extensive information on patients going forward for easier assessment of the results in the future.
This includes being able to hopefully provide more detailed information about each patient's symptoms in the trackers, as currently such information is not available.

We have observed and received a number of various test results from community members over the past year. Due to reasons such as time constraints, small sample sizes and/or lack of relevant literature supporting them as diagnostic tools, we have not been able to track all the tests provided by community members. This includes tests such as infection panels investigating various pathogens like Epstein-barr virus (EBV) and Lyme, various specific immune and antibody panels, hormone panels, standard blood samples including vitamin levels and so on. With that said, we think it might be useful to briefly elaborate on certain additional diagnostics reported in the community (not currently tracked), such as SPECT scans, QEEG (8.4) and SIBO (8.8) in related sections as it may potentially offer some additional valuable info.

Note: Due to differences in which tests patients have gotten as well as the times the data has been added, the patient numbers on each tracker is different - ie Patient 1 on the Celltrend tracker is not the same as Patient 1 on the Cunningham tracker. This is something we eventually aim to correct as much as possible where you can form a more comprehensive view of each patient's profiles.

8.1 Findings on autoantibodies targeting G-protein coupled receptors

The Celltrend Panel

The G-protein coupled receptor (GPCR) autoantibody panel by Celltrend is an enzyme-linked immunosorbent assay (ELISA) test for autoantibodies targeting specific GPCRs (https://www.celltrend.de/en/elisa/gpcr-antibodies/). These include adrenergic and muscarinic-acetylcholine receptors, other antibody markers such as ACE-2 (which is heavily linked to Covid-19), as well as SFN specific biomarkers like TSHDS and FGFR3. These autoantibodies are proposed to be 'functional', in other words they either agonize or antagonize the receptors they are attached to. Research on these antibodies is still preliminary, but those have been proposed to be linked to various disorders such as POTS, ME/CFS and Long Covid (Cabral-Marques et al. 2023, Bynke et al. 2020, Gunning et al. 2019, Wallukat et al. 2021). What is noteworthy is that these biomarkers may indicate when an autoimmune process is present. Some evidence has already been gathered showing that GPCR autoantibodies take place together with autoimmune SFN (Schelke et al. 2022). To our knowledge, this association does not currently seem to be robust enough to make these panels clinically validated in the diagnosis of SFN, but some doctors have been more open to taking them into consideration in clinical settings, especially if the patient had already tested positive with a skin biopsy and the pattern and clinical picture matched non-length dependent subtype, and probable immune-mediated onset in terms of presentation. While Celltrend offers a wide range of different antibody markers, these are the relevant ones that have been most tested in the community:

Celltrend panel biomarkers tested in PSSD

Anti-A1-adrenergic	Anti-CHRM1
Anti-A2-adrenergic	Anti-CHRM2
Anti-B1-adrenergic	Anti-CHRM3
Anti-B2-adrenergic	Anti-CHRM4
Anti-AT1R	Anti-CHRM5
Anti-ETAR	Anti-TSHDS
Anti-ACE-2	Anti-FGFR3

The specific panel is called «the long covid/CFS/POTS panel» due to the receptor's proposed role in the pathology of long covid, ME/CFS and POTS. For more information please visit Celltrends website: https://www.celltrend.de/en/pots-cfs-me-sfn/important-publications/.
You can read more about the various functions of these receptors and other clinical indications associated with them in the Celltrend Stats & info breakdown (table 2). We will present the patient results in the Celltrend tracker (table 1).

Note: The panel has been under some criticism for not having specific enough borderline values, and one research paper showed no difference between POTS individuals and healthy control subjects (Hall et al. 2022). It is also based on an enzyme immunoassay (ELISA) and thus does not involve functional assays. Only the presence and quantity of each antibody is measured, and as such, it can be difficult to know if they are actively interfering with the receptors at the moment of testing. In part due to these limitations, the panel is considered to be experimental for now, but may provide additional information in combination with other tests in order to assess their patients overall clinical picture.

It's been about 2.5 years since Patient zero shared his autoantibody results with the community, and the Celltrend test has become the most popular and comprehensive autoimmune panel in the community so far. See the results on the next page.

Info: We have received 39 test results on GPCR autoantibody panels (sample sizes differ per marker). All of the patients that tested for these antibodies have the iatrogenic condition known as PSSD. A majority of the results have been from the Celltrend panel, while a few come from another autoantibody panel targeting the same receptors known as Ganzimmun. The fact that many had Covid and/or the Covid vaccine in addition to PSSD prior to testing complicates the assessment of the results, as Covid would also affect levels of GPCR's.

Table 1. Celltrend tracking

Celltrend panel checks for autoantibodies targeting autonomic GPCRs

CELLTREND TRACKING PSSD																
	anti AT1R	anti ETAR	anti α-1 adrenergic	anti α-2 adrenergic	anti β-1 adrenergic	anti β-2 adrenergic	anti M1	anti M2	anti M3	anti M4	anti M5	FGFR3	TSHDS	ACE2	Covid b/f	Vax b/f
PT1	At risk	Neg	Neg	Neg	Pos	Neg	Neg	Neg	At risk	Neg	Neg	Pos	Pos	Pos	Y	Y
PT2	Pos	Pos	Pos	Pos	Pos	Pos	Pos	Pos	Pos	Pos	Pos	Neg	Neg	Pos	UNK	UNK
PT3	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Pos	Pos	Pos	N	UNK
PT4	Pos	Pos	Pos	Neg	Pos	Pos	Neg	Neg	Pos	Pos	Neg	Neg	Neg	Pos	UNK	UNK
PT5	N/A	N/A	N/A	N/A	Pos	Pos	N/A	N/A	Pos	Pos	N/A	N/A	N/A	N/A	UNK	UNK
PT6	Pos	Pos	Pos	Neg	Pos	Pos	Neg	Neg	Pos	Pos	Neg	Neg	Neg	Pos	N	N
PT7	Pos	Pos	Pos	Pos	Pos	Pos	Pos	Pos	Pos	Pos	Pos	Neg	Neg	Pos	UNK	UNK
PT8	Pos	N/A	N/A	N/A	Pos	Pos	Pos	Pos	Pos	Pos	Neg	Neg	Neg	Pos	Y	Y
PT9	Pos	Pos	Pos	Pos	Pos	Pos	Neg	Pos	Pos	Pos	Pos	Neg	Neg	Pos	UNK	UNK
PT10	Pos	Pos	Pos	Neg	Pos	Pos	Neg	Neg	Pos	Pos	Neg	Neg	Neg	Pos	UNK	UNK
PT11	At risk	Pos	Pos	Neg	Pos	Pos	Neg	Neg	Pos	Pos	Neg	Neg	N/A	Pos	N	Y
PT12	At risk	At risk	At risk	Neg	Neg	At risk	Neg	Neg	Pos	Neg	Neg	Neg	Pos	Pos	Y	N
PT13	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Pos	UNK	UNK
PT14	Pos	Pos	Pos	Pos	Neg	Pos	Pos	Pos	Pos	Pos	Neg	N/A	N/A	N/A	Y	Y
PT15	Pos	Pos	Pos	Pos	Pos	Pos	Pos	Pos	Pos	Pos	Neg	Pos	Neg	Pos	Y	Y
PT16	Neg	N/A	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	N/A	Neg	N/A	Pos	UNK	Y
PT17	Pos	Pos	N/A	N/A	Pos	Pos	N/A	N/A	Pos	Pos	N/A	N/A	N/A	N/A	UNK	UNK
PT18	Neg	Neg	Pos	Neg	Pos	Pos	Neg	Neg	Pos	Pos	Neg	Neg	N/A	Pos	Y	Y
PT19	Pos	Pos	Pos	Neg	Pos	Pos	Neg	Neg	Pos	Pos	Neg	Neg	N/A	Pos	Y	N
PT20	At risk	At risk	Pos	Neg	Neg	Pos	Neg	Neg	Pos	Pos	Neg	Neg	N/A	Pos	Y	Y
PT21	Pos	Pos	Pos	Neg	Pos	Pos	Neg	Neg	Pos	Neg	Neg	Neg	Pos	Neg	Y	UNK
PT22	Pos	Pos	N/A	N/A	Pos	Pos	N/A	N/A	Pos	Pos	N/A	N/A	N/A	N/A	N	Y
PT23	Pos	Pos	N/A	N/A	Pos	Pos	N/A	N/A	Pos	Pos	N/A	N/A	N/A	N/A	UNK	Y
PT24	Neg	At risk	At risk	Neg	Neg	At risk	Neg	Pos	Pos	Pos	Pos	Neg	Neg	Pos	Y	N
PT25	Pos	Pos	N/A	N/A	Pos	Pos	N/A	N/A	Pos	Pos	N/A	N/A	N/A	N/A	UNK	UNK
PT26	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	At risk	Neg	Neg	Neg	Neg	Neg	Y	Y
PT27	At risk	At risk	Pos	Neg	Pos	At risk	Neg	Neg	Pos	Pos	Neg	N/A	N/A	Pos	Y	Y
PT28	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Pos	Neg	Y	Y
PT29	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Pos	Y	Y
PT30	Pos	Pos	Pos	Neg	Pos	Pos	Neg	Neg	Pos	Pos	Neg	Pos	Pos	N/A	Y	Y
PT31	Pos	Pos	N/A	N/A	Pos	Pos	N/A	N/A	Pos	Pos	N/A	N/A	N/A	N/A	Y	Y
PT32	At risk	At risk	At risk	Pos	Neg	At risk	Neg	Pos	At risk	Pos	Pos	Neg	Neg	Pos	Y	Y
PT33	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Neg	Pos	Neg	UNK	UNK
PT34	Neg	Neg	Neg	Neg	Neg	Neg	N/A	N/A	N/A	N/A	N/A	Pos	Neg	Pos	Y	Y
PT35	At risk	At risk	At risk	Neg	Pos	Pos	Pos	Pos	At risk	Neg	Pos	Neg	Neg	Pos	UNK	UNK
PT36	At risk	At risk	At risk	Neg	Pos	At risk	Neg	Pos	At risk	Pos	Pos	Pos	Neg	Pos	UNK	UNK
PT37	Pos	Pos	N/A	N/A	Pos	Pos	N/A	N/A	Pos	Pos	N/A	N/A	N/A	N/A	Y	Y
PT38	Pos	Pos	N/A	N/A	Pos	Pos	N/A	N/A	Pos	Pos	N/A	N/A	N/A	N/A	UNK	UNK
PT39	Pos	Pos	N/A	N/A	Pos	Pos	N/A	N/A	Pos	Pos	N/A	N/A	N/A	N/A	N/A	N/A

Tracker created by: Goldenhour. **Abbreviations:** PT = Patient. Pos = Positive. Neg = Negative. N/A = Not applicable. UNK = Unknown. Y = Yes. N = No.

The results show a high incidence rate with 97% of 39 test subjects positive for at least one biomarker.

To date, only one test subject has been negative (with 1 biomarker at risk). The individual in question had a relatively mild symptomatic presentation according to their report (mainly lowered libido and emotional blunting, with the absence of genital numbness, erectile dysfunction and other autonomic symptoms). Interestingly, several of the patients in this table went on to test positive for small fiber neuropathy and other inflammatory markers where some individuals ended up acquiring a diagnosis such as immune-mediated SFN and «inflammatory polyneuropathy» (see 8.2).
Previous studies on anti-GPCR antibodies have identified them as natural components of human biology. However, their production is deregulated in COVID-19 and their level and pattern alterations might predict COVID-19 disease severity (Cabral-Marques et al. 2022).
We aim to add test result values and levels to each marker eventually to see if these results/levels generally deter from those seen in control groups. Additionally, we wish to see if higher levels of GPCR autoantibodies correlate with symptom severity. Due to time constraints however, this will need to be assessed at a later stage.

In an attempt to more easily understand and interpret the results from the Celltrend tracker, we created a table sorting the test markers by their incidence rates (Table 2), in addition to adding relevant info to each marker such as their main biological functions and their associated disease pathologies, to try to form a surface level understanding of the possible implications. This will be presented up next.

Table 2. GPCR Autoantibodies results stats & info

Breakdown of Celltrend tracking results and explanation of the biomarkers biological function and clinical significance

PSSD - Celltrend stats & info				
Biomarkers	**Total pos/tests**	**At risk**	**Positive ratio**	**Examples of biological function**
Anti-ACE-2	**24/28**	**0**	**86%**	**Angiotensin converting enzyme 2** is an integral part of the RAAS system that keeps the body's blood pressure in check. ACE-2 has opposing effects to ACE (lowering blood pressure). Other examples include regulation of vasoconstriction, cytokine production, inflammatory response and tryptophan transport. It also has some involvement in respiratory health. Clinical indication: Long Covid, Vasculopathy, Fibrosis
Anti-CHRM3	**27/36**	**5**	**75%**	**Muscarinic acetylcholine receptor 3** regulates insulin homeostasis (brain) and glucose homeostasis (pancreatic beta-cells). It also mediates glandular secretion (e.g saliva, sweat), smooth muscle contraction and vasoconstriction. Clinical indications: Sjögrens Syndrome, Post Ganglionic Cholinergic Dysautonomia.
Anti-CHRM4	**27/36**	**0**	**75%**	**Muscarinic acetylcholine receptor 4** are involved in regulation of locomotion, neurotransmission and signal transduction. Clinical indication: CFS/ME, POTS
Anti-b1-adrenergic	**26/37**	**0**	**70%**	**Beta-1 adrenergic receptors** are involved in fear response (fight or flight), temperature regulation and homeostasis. Clinical indications: Cardiomyopathy.
Anti-b2-adrenergic	**25/37**	**5**	**68%**	**Beta-2 adrenergic receptors** mediates smooth muscle relaxation (e.g gi tract, bladder, seminal tract) and bronchodilation. Other functions include facilitation of muscle contraction and motility, regulation of systemic arterial blood pressure, insulin and glucagon secretion as well as heat generation and response to cold temp. Clinical indication: Myasthenia Gravis.
Anti-a1-adrenergic	**15/27**	**5**	**56%**	**Alpha-1 adrenergic receptors** are involved in processes such as smooth muscle contraction (gi, bladder) and sweat gland secretion. Clinical indication: Vascular disease.
Anti-AT1R	**20/36**	**8**	**56%**	**Angiotensin II receptor 1** has vasopressin effects and regulates aldosterone secretion among other functions, such as;Regulation of vasoconstriction, inflammatory response and stimulation of drinking behaviour. Clinical indications: Linked to inflammation, fibrosis, systemic sclerosis, vasculitis(arteritis), decline in renal function and associated with elevated IL-8.
Anti-ETAR	**18/34**	**7**	**53%**	**Endothelin A receptors** function to promote vasoconstriction, smooth muscle contraction, growth and inflammation. Clinical indication: Linked to inflammation, fibrosis, systemic sclerosis, arthritis, decline in renal function and associated with elevated IL-8.
Anti-CHRM2	**10/27**	**0**	**37%**	**Muscarinic acetylcholine receptor 2** are involved in smooth muscle contraction, regulation of heart contraction, response to virus and choline. synaptic transmission. Clinical indication: CFS/ME, Cardiovascular disease.
Anti-THSDS	**7/23**	**0**	**30%**	**Trisulfated Heparin Disaccharide** is a kind of complex sugar found on cell surfaces (including on certain nerve cells). Clinical indication: Small fiber neuropathy.
Anti-CHRM5	**7/26**	**0**	**27%**	**Muscarinic acetylcholine receptor 5** are involved in gastric acid secretion, transmission of nerve impulse and dopamine transport. Clinical indication: Implicated in Schizophrenia and mood disorders (cholinergic dopamine regulation)
Anti-CHRM1	**6/27**	**0**	**22%**	**Muscarinic acetylcholine receptor 1** is involved in processes like cognition, regulation of locomotion and saliva secretion. Clinical indication: CFS/ME, Scizophrenia.
Anti-a2-adrenergic	**6/27**	**0**	**22%**	**Alpha-2 adrenergic receptors** are involved in vasoconstriction, decrease of smooth muscle in the gi tract and facilitation of cognitive function in the prefrontal cortex. Clinical indication: Adrenal issues.
Anti-FGFR3	**6/28**	**0**	**21%**	**Fibroblast growth factor 3** is a protein (part of a family of four) that play a role in several cellular processes, for example proliferation, formation of blood vessels and wound healing. Clinical indication: Small fiber neuropathy.
Notes				**Info**
General: This table is based on the GPCR 'Long covid/POTS/Cfs' panel made by the german company Celltrend gmbh and dissects the stats from the results shown on the «Celltrend tracker» by the community member "Goldenhour". **Definitions:** ACE-2 = Angiotensin converting enzyme 2 a1 & a2 = Alpha adrenergic receptors b1 & b2 = Beta adrenergic receptors CHRM1-5 = Muscarinic acetylcholine receptors AT1R = Angiotensin 2 receptor 1 ETAR = Endothelin A receptor FGFR3 = Fibroblast growth factor 3 TSHDS = Trisulfated Heparin Disaccharide **Test subjects:** The stats are based on 39 test subjects with "PSSD". A main suspected outcome among the test subjects (confirmed in some cases) is small fiber neuropathy. **Disclaimer:** The Celltrend panel (except FGFR3 and TSHDS) is regarded as a research panel in a majority of the healthcare industry at the moment and these stats are thus meant for research purposes only. A factor to keep in mind regarding the results is that most test subjects had covid, the covid vaccine or both prior to testing which complicates the assessments of the results.				**Autoantibodies and GPCR's:** Autoantibodies are misguided or pathogenic antibodies. Instead of antigens, they react to your own proteins. This can lead to immune system dysfunction where your own cells, tissues and organs are attacked. This can be the cause of many other dysfunctions and disease. G protein–coupled receptors (GPCRs) mediate the majority of cellular responses to external stimuli, including light, odors, hormones, and growth factors. GPCRs are integral membrane proteins that contain seven transmembrane. They are specific G Protein-Coupled Receptor Ligands Causing Unique Cellular Effects and Diseases. **The renin-angiotensin-aldosterone system:** The renin-angiotensin-aldosterone system (RAAS) is a hormone system that regulates blood pressure, fluid and electrolyte balance, and systemic vascular resistance. It consists of three major substances, including: the enzyme renin and the hormones angiotensin 2 and aldosterone (secreted by adrenal glands). Several organs, glands and tissues are involved in the RAAS system, including the kidney, liver, blood vessels, lungs, adrenal glands, the pituitary gland and the hypothalamus. **Chemical messengers:** Adrenergic receptors uses the neurotransmitter **norepinephrine** to send messages to the sympathetic system of the ANS. Muscarinic receptors uses the neurotransmitter **acetylcholine** to send messages mainly to the parasympathetic system of the ANS, but also has some effects on the sympathetic system.

The associated disease pathologies indicate potential significant complications of varying nature occurring in the test subjects. Overall, the proposed functional aspect of the autoantibodies in this panel could have large implications when targeting these receptors, with the potential to exert both agonistic and antagonistic effects, causing dysregulation of autonomic functions.

By assessing the incidence rates, sample sizes and information in Table 2, we are now going to evaluate and expand on each biomarker with regards to their function and role, as well as pathological implications. The results are (generally) presented in the order of highest to lowest incidence rate.

Anti-ACE-2

Angiotensin-converting enzyme 2 (ACE-2) has the highest incidence rate among all the test-markers, with 86% based on 28 test samples. This is a significant incidence rate and could potentially be seen as a biomarker for PSSD.

ACE-2 (Angiotensin-Converting Enzyme 2) is a crucial enzyme in the body that plays a significant role in the renin-angiotensin system (RAS), which regulates blood pressure, fluid balance, and systemic vascular resistance (Fountain et al. 2024, Nakagawa et al. 2020). It is widely spread in the body including lungs, cardiovascular system, gut, kidneys, central nervous system and adipose tissue. ACE-2 converts angiotensin II (a potent vasoconstrictor) into angiotensin 1-7, which has vasodilatory effects, thereby helping to lower blood pressure and exert anti-inflammatory, anti-fibrotic, and anti-proliferative effects (Kuriakose et al. 2021). The implications of functional autoantibodies targeting ACE-2 could potentially lead to significant disruptions in its normal function. This could happen by antagonizing (blocking or inhibiting) it, which could potentially lead to preventing the enzyme from converting angiotensin II into its less harmful counterpart, angiotensin 1-7. The inhibition (antagonizing) on this receptor could then result in an accumulation of angiotensin II, which can cause **increased blood pressure, inflammation, and fibrosis**. Autoantibodies targeting ACE-2 may also exacerbate inflammation, as the unchecked angiotensin II promotes a pro-inflammatory environment. This heightened inflammatory response can damage tissues and organs over time. Additionally, studies have shown that ACE-2 autoantibodies play a major role in long COVID, where individuals experience persistent symptoms after recovering from the acute phase of COVID-19 (Davis et al. 2023). Gut dysbiosis and altered gut permeability are also linked to ACE-2 in Covid-19 (Zhang et al. 2023b), as well as to vascular disease, lung disease and diabetes mellitus (Gheblawi et al. 2020). Interestingly, gut dysbiosis has been proposed to play a key role in PSSD (Diviccaro et al. 2022b, Giatti et al. 2024b).

Cholinergic-muscarinic receptors

Muscarinic acetylcholine receptors (CHRMs) are G-protein-coupled receptors (GPCRs) with five subtypes (M1-M5) that play a crucial role in the central nervous system (CNS). These receptors can be classified into two groups: the 'M1-like' receptors (M1, M3, M5), which typically have excitatory effects and are located postsynaptically, and the 'M2-like' receptors (M2, M4), which tend to be inhibitory and are found both pre- and post-synaptically. Acetylcholine, the neurotransmitter binding to these receptors, is integral to their activation and modulation of neuronal signaling. CHRMs are involved in a variety of functions, including cognitive processes such as learning and memory, and are implicated in several disease processes (Ryan et al. 2019).

Anti-CHRM3

The **Muscarinic-acetylcholine receptor 3 (anti-CHRM3)** or simply **M3** may be another promising candidate as a PSSD biomarker with its high incidence rate **of 75% based on 27 out of 36 samples.** M3 receptors are present in smooth muscle structures, such as the bronchi, gastrointestinal tract, pupils, and blood vessels. They are involved in bronchoconstriction, gastrointestinal and gallbladder smooth muscle contraction, pupil constriction, and vasodilation of the blood vessels (Kudlak and Tadi 2024). While there is comparatively less known about the function of these receptors within the CNS, M3 receptors are localized in brain regions that regulate insulin homeostasis, including the hypothalamus and dorsal vagal complex of the brainstem (Teal et al. 2019). M3 receptors have been suggested to regulate learning and memory, potentially being linked with Alzheimer's disease (Poulin et al. 2010). Autoantibodies targeting these receptors may lead to significant complications. Antagonistic effects are associated with inhibition of cholinergic transmission in the GI tract, inhibiting gastrointestinal motility as well as inhibition of fluid secretion by lacrimal and salivary glands (Kovács et al. 2005, Freitag et al. 2021).

M3 autoantibodies are also present in Sjögren's syndrome, causing symptoms such as dry eyes, mouth and sweat glands, due to impaired secretion from exocrine glands (Yu et al. 2018, Katayama et al. 1995). In systemic sclerosis, these autoantibodies are associated with gastrointestinal dysmotility (Kumar et al. 2016). Additionally, a study on a group of patients with ME/CFS showed a general pattern of increased antibody levels towards muscarinic and adrenergic receptors, specifically the M3 and M4 (Bynke et al. 2020). Lastly, M3 together with B2AR's functional disturbances is proposed to result in vasoconstriction and hypoxemia (Wirth and Scheibenbogen 2020).

Anti-CHRM4

The **Muscarinic-acetylcholine receptor 4 (anti-CHRM4)**, shows a high incidence rate of **75% based on 27 out of 36 samples.**

These receptors are highly expressed in the CNS (cortex, hippocampus and striatum), and function as inhibitory autoreceptors for acetylcholine and have regulatory effects on dopaminergic neurotransmission. M4 receptors are also found presynaptically on glutamatergic projections, where they play a modulatory role in cortico-striatal glutamatergic signaling. In addition, **M4 receptors are colocalized with D1 dopamine receptors on medium spiny GABAergic neurons within the striatum and act to regulate GABAergic signaling within the direct pathway of the basal ganglia circuitry.** Due to their role in modulating acetylcholine and dopamine, muscarinic receptors have long been viewed as possible drug targets for the treatment of various conditions such as Alzheimer's disease, schizophrenia, Parkinson's disease, and drug abuse (Teal et al. 2019). For example, a new drug that modulates the M4 and M1 receptors has shown promise in alleviating both positive and negative symptoms of schizophrenia (Hassan and Abid 2024).

Potential pathological effects of autoantibodies targeting M4 receptors are modulation of cholinergic neurotransmission (Valonen, 2022, Sudowe, 2024), which theoretically could cause disturbances leading to symptoms such as cognitive impairments and memory deficits.
A paper investigating the dynamics of M4's cholinergic and dopaminergic neurotransmission in relation to CNS pathologies, stated that loss of M4 control of cholinergic function effectuates a state of dopaminergic hyperexcitability, and could thus be responsible for pathological conditions in which appetitive motivation as well as affective and cognitive processing is impaired (Tzavara et al. 2004). This could suggest that the presence of autoantibodies targeting M4 receptors could have detrimental downstream effects on dopaminergic neurotransmission, resulting in cognitive and reward processing deficits. Lastly, elevated levels of autoantibodies targeting the M4 receptor are also associated with ME/CFS (Bynke et al. 2020) and Postural orthostatic tachycardia syndrome (POTS) (Gunning et al. 2019).

Adrenergic receptors

Adrenergic receptors are G-protein-coupled receptors (GPCRs) responsive to the neurotransmitters adrenaline (epinephrine) and noradrenaline (norepinephrine). They are classified into two main groups: alpha (A) and beta (B) receptors. These are subclassified as A1 and A2 as well as B1, B2, and B3, respectively. The organs that respond to norepinephrine or epinephrine have one or more of these receptor subtypes. Both norepinephrine and epinephrine can have excitatory or inhibitory effects, based on the subclass of the receptor that is most predominant in the target organ. Organs that respond to norepinephrine or epinephrine have one or more of these receptor subtypes. Alpha receptors are involved in vasoconstriction and inhibition of neurotransmitter release, whereas beta receptors primarily regulate heart rate and smooth muscle relaxation (Moini et al. 2024).

Anti-B1-adrenergic

Beta-1 adrenergic receptors (B1-AR) show a high incidence rate of 70% based on 37 samples. These receptors are primarily expressed on cardiomyocytes (specialized heart muscle cells). Autoimmunity against B1-AR are associated with significant cardiovascular complications due to their crucial role in regulating heart rate and overall cardiac function. A paper from 1999 found associations between B1-AR activating autoantibodies and reduced cardiac function in patients with Cardiomyopathy (chronic heart failure) (Jahns et al. 1999). Additionally, elevated levels of autoantibodies targeting B1-AR's are associated with «autoimmune» orthostatic hypotension (Yu et al. 2011), causing arrhythmias, such as tachycardia, by disrupting normal heart rhythm. B1-AR's are also associated with ME/CFS (Valonen, 2022, Sudowe, 2024) and Graves' disease (Stavrakis et al. 2009).

Anti-B2-adrenergic

Beta-2 adrenergic receptors (B2-AR) show an incidence rate of 68% based on 37 samples. These receptors are essential in regulating cardiovascular, pulmonary, metabolic, and immune functions. Furthermore, B-AR, which include B1-AR, B2-AR, and B3-AR are proposed to play important roles in inflammation. Of note, B2-AR is regarded to play a key role in the process of immunological imbalance (Wu et al. 2018). Antagonistic autoantibody activity could in theory result in decreased production of certain cytokines and trigger autoimmune disease. Impaired function of B2-AR in circulating T cells is proposed to induce immunological diseases such as Rheumatoid Arthritis (RA) by decreasing production of select cytokines (Wu et al. 2018). Impaired B2-AR signaling has also been shown to induce metabolic disorder in axons in MS, triggering inflammation, as well as glutamate excitotoxicity, which results in the progression of damage to the myelin sheath (Wu et al. 2018). Additionally, it's been observed that the B2-AR agonist fenoterol significantly improved outcomes associated with MS, and reduced the risk of MS by 51% (Wu et al. 2018). Circulating B2AR autoantibodies serve as vasodilators and may cause or exacerbate orthostatic hypotension (Li et al. 2012). Furthermore, the presence of B2-AR autoantibodies have also been associated with myasthenia gravis (Eng et al. 1992), which is an autoimmune neuromuscular condition affecting the skeletal muscles involved in breathing and movement.

Anti-A1-adrenergic

Alpha-1 adrenergic receptors show a 56% positive ratio. These receptors play key roles in the sympathetic nervous system. They are primarily activated by the neurotransmitters norepinephrine (noradrenaline) and epinephrine (adrenaline). These receptors mediate a variety of physiological responses, particularly those involving smooth muscle contraction and vascular regulation. Antibodies against A1 are shown to contribute to vascular damages in rats and might play particular roles in the pathological changes of hypertension (Zhou et al. 2008).
Release of high concentrations of norepinephrine acting on A1 adrenergic receptors in the prefrontal cortex have been shown to impair prefrontal cortex function. This could in theory suggest that strong agonistic effects of functional autoantibodies could negatively impact the prefrontal cortex, causing symptoms such as executive dysfunction. Additionally, blockade of A1 adrenergic receptors in the medial preoptic area elicits sedation, which could suggest symptoms of sedation and lethargy in the context of autoantibodies blocking this receptor (Gnegy 2012).

Ant-AT1R & ETAR

Anti-AT1R and Anti-ETAR are seen in just slightly more than half of patients **(56% and 53%**) that tested for these markers (19/35 and 17/33 respectively). The borderline results (at risk) which stands at 7 and 6 respectively, indicates that the receptors may be more commonly involved than the current incidence rate shows. Angiotensin-II is an eight amino acid peptide hormone that plays a key role in the renin-angiotensin-aldosterone system (RAAS). Angiotensin-II mediates its effects on, among others, endothelial cells and vascular smooth muscle cells as well as immune cells by binding to GPCR's such as the **angiotensin-II type 1 receptor (AT1R)**.
Potential pathological effects of autoantibodies targeting the AT1R are vasoconstriction and hypertension, as well as the release of proinflammatory cytokines (inflammation). Elevated levels of AT1R autoantibodies are associated with an increased risk of rejection after organ transplantation, pre-eclampsia, systemic sclerosis and ME/CFS (Valonen, 2022, Sudowe 2024) and Vascular disease (Schneider et al. 2007). In a study from 2015, increased levels of AT1R antibodies was found in patients with Alzheimer's Disease (Giil et al. 2015**).**

Endothelin Type A Receptor (ETAR) is one of the receptors for endothelin-1, a potent vasoconstrictor peptide that plays a critical role in regulating vascular tone, cell proliferation, and inflammatory responses. ETAR is primarily located on vascular smooth muscle cells and mediates vasoconstriction and cell proliferation (Motte et al. 2006). ETAR antibodies are associated with vasculitis (Rowaiye et al. 2022) and decline in renal function (ETAR) (Pearl et al. 2020). Research has shown that when functional autoantibodies target ETAR and AT1R, they can chronically activate these receptors, mimicking the effects of their natural ligands such as seen in Systemic sclerosis (Kill et al. 2014, Riemekasten et al. 2011), an autoimmune disease causing hardening and tightening of the skin and connective tissues. This continuous receptor activation leads to prolonged vasoconstriction, increased inflammation, vascular damage and fibrosis, contributing to disease progression. While functional autoantibodies could in theory antagonize (block) these receptors as well, most existing research in relation to ETAR and AT1R autoantibodies focuses on their agonistic properties.

Anti-CHRM 2, CHRM5 & CHRM1

The Muscarinic-acetylcholine receptor 2 (Anti-CHRM2) shows a 37% incidence rate based on 27 samples, with Anti-CHRM5 and CHRM1 showing 27% and 22% (6/26 and 6/27) respectively. The M1, M2 (and M4) receptors make up the majority of CHRMs found in the CNS, where the M1 receptor is highly expressed throughout all layers of the cerebral cortex, hippocampus and striatum, and the M2 receptor is the predominant CHRM in the thalamus and brainstem. The M5 receptor is the subtype with the lowest levels of expression but is detectable in the hippocampus, striatum and midbrain.
Both M5 and M1 have been associated with the modulation of dopamine. Studies have implicated M5 and M1 receptors on dopamine neurons in the modulation of dopamine transporter (DAT) function, and that this indicate that stimulation of cholinergic pathways can lead to modulation of dopamine through internalization of the DAT (Underhill and Amara, 2021). Additionally functional evidence has indicated that M5 may act within the striatum to modulate **DA release in the nucleus accumbens (the reward system)** (Teal et al. 2019).
Muscarinic receptors have been associated with symptom presentation in Schizophrenia which is highly associated with dopaminergic dysfunction. A study from 2019 that investigated the relationship between the availability of the M1 and M4 receptors, clinical symptoms and cognitive functioning in 12 patients with schizophrenia, concluded that decreased receptor availability in the dorsolateral prefrontal cortex was associated with increased severity and presence of negative symptoms measured by the PANSS. Since the M1 receptor is the predominant CHRM expressed in the prefrontal cortex, it was concluded that this relationship was due to decreased M1 receptor availability. Reductions in CHRM densities have been repeatedly observed in neuropathological post-mortem studies of brains from people with schizophrenia, where significant receptor density reductions of M1 receptors in the cortex have been observed. The authors hypothesized that one possible reason for this, could be due to antibody-mediated killing of cells expressing these receptors (Alexander E. Ryan et al. 2019).

A retrospective study that analyzed the autoimmune etiology of POTS found that gastrointestinal symptoms and disease severity showed a significant association with the serum level of anti-muscarinic acetylcholine receptor antibodies (gastrointestinal symptoms; **M1, M2, M5**; disease severity, **M1**, M3, M4, **M5**) (Sunami et al. 2022). Additionally, another study investigating muscarinic antibodies in relation to POTS, showed that a significantly higher number of **POTS patients had higher levels of M1 and M2 receptor antibodies** compared to controls (Dysautonomia international).
Lastly, serum anti-M2 levels have been shown to be higher in atrial fibrosis (AF) patients and are associated with the severity of AF **(**Ma et al. 2019).

Anti-TSHDS & FGFR3

Anti-TSHDS and **Anti-FGFR3** which are considered SFN specific biomarkers on the Celltrend panel **shows a positive ratio of 30% (7/22) and only 21% from 28 samples respectively.** The Celltrend tracker results are very reminiscent of the incident rates seen in a retrospective study from 2019-2020 (Trevino and Novak 2021) where associations between TSHDS/FGFR3, skin biopsies and dysautonomia were assessed. **The study showed that out of 322 patients; 28% had elevated anti-TS-HDS, 17% had elevated anti-FGFR3, 96% had autonomic dysfunction and 71% had abnormal nerve fiber density. This is very similar to the correlations seen in our data, where even the incident rate with skin biopsies being more or less the same (70%).** Interestingly this study showed that TSHDS and FGFR3 were evident in patients with dysautonomia irrespective of whether they had normal or abnormal skin biopsies.

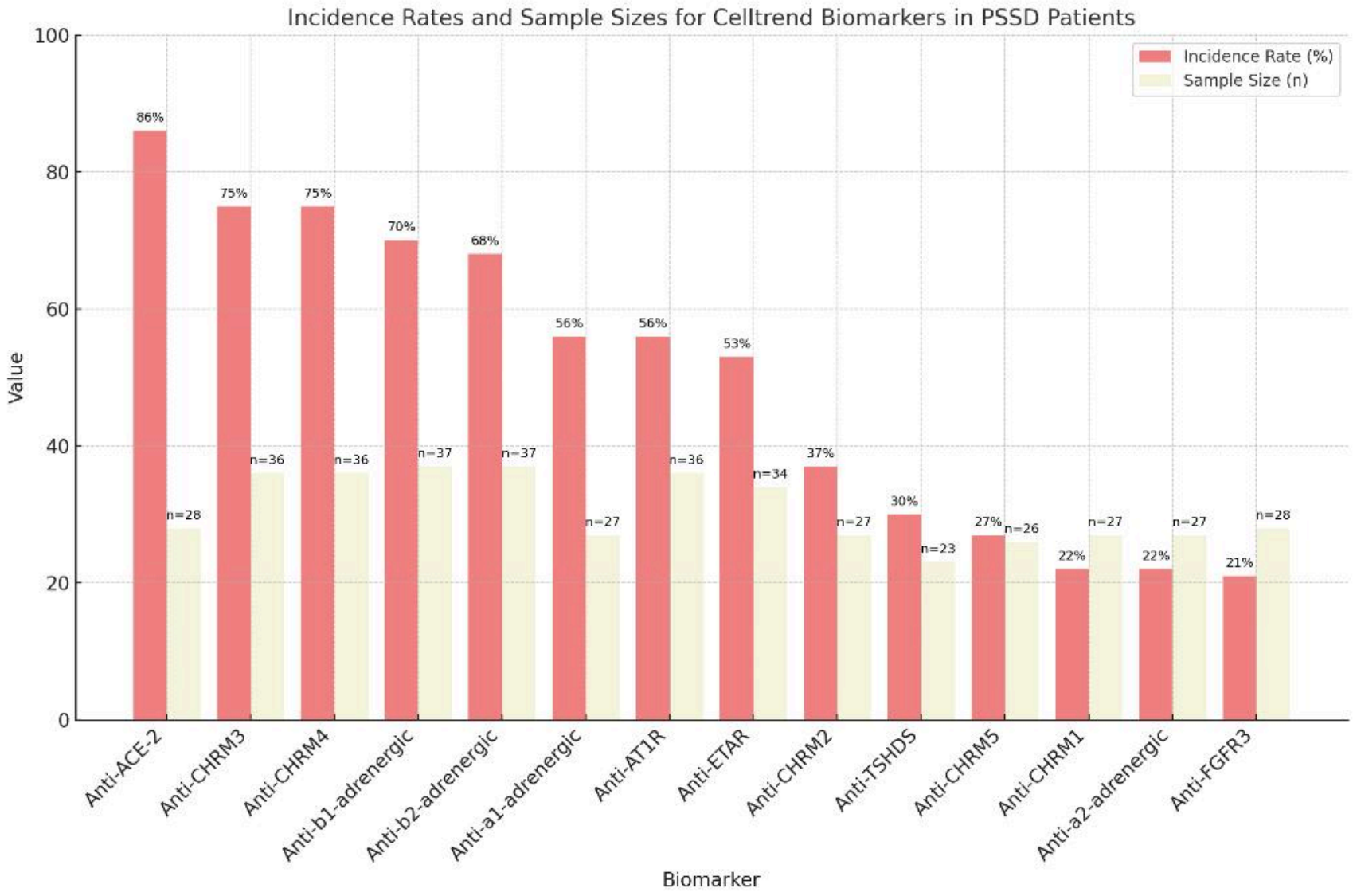
Anti-A2 Adrenergic

Alpha-2 adrenergic receptors show a 22% incidence rate based on 27 samples. These receptors are involved in vasoconstriction, decrease in smooth muscle regulation in the GI tract and influence cognitive function in the prefrontal cortex by modulating norepinephrine release, where they regulate sympathetic activity by acting as presynaptic autoreceptors, suppressing norepinephrine release via a negative feedback mechanism (Ruffolo et al. 1988). A2-Adrenergic receptors can also mediate both proinflammatory and anti-inflammatory effects of the sympathetic nervous system. The selective A2-adrenergic agonist AGN-762, which lacks A2A agonist activity, was used in a recent study to reveal that agonism of the A2B/2C-adrenergic receptors may represent a promising new therapeutic approach for the treatment of autoimmune and inflammatory diseases, without the sedative and cardiovascular side effects of current A2-adrenergic agonists (Viswanath et al. 2024).

Contrary to this, use of an A2-AR agonist might be an important pharmacologic agent in patients with COVID-19 to reduce mortality. In a retrospective analysis, use of A2-AR agonist DEX was associated with lower mortality in critically ill patients with COVID-19 requiring invasive mechanical ventilation at RUSH hospitals. The associated mortality benefit of DEX appeared to be related to earlier use closer to the time of intubation as opposed to later use (Hamilton et al. 2022).

There is no existing literature on A-2AR associated autoantibody pathologies to our knowledge. Most existing literature is antibody detection in research settings (see Thermofisher.com). By assessing the receptor functions however, one can theorize its potential implications in the presence of autoantibody activity, such as for example vascular disturbances, gastrointestinal motility issues, brain fog and sedation.

Figure 2: Summary of CellTrend results



Discussion

Autoantibodies targeting the autonomic GPCR receptors as well as Ace-2, ETAR and ET1R, could be causing significant complications in the affected individual. The research surrounding these receptors indicate that their role in autonomic function can have vast complications when dysfunction occurs. The receptors with the highest incidence rates indicate a potential significant contribution to PSSD symptomatology based on their various biological functions, such as their roles in vascular function, glandular secretion, modulation of neurotransmission and inflammation. There are many ways these (functional) autoantibodies may interfere with receptor function, and the downstream effects of that could be highly variable. Perhaps this could explain, at least in part, the variable symptomatic presentation seen between individuals, such as why one patient may end up with postural orthostatic tachycardia syndrome (POTS) on top of their typical PSSD symptoms, while another patient may simply have erectile dysfunction and loss of arousal to stimuli. As briefly mentioned in chapter 5, there are cases where patients end up with persistent genital arousal disorder (PGAD) after cessation of an SSRI (Leiblum and Goldmeier 2008), perhaps theoretically speaking, this could be a consequence from autoantibodies agonizing certain receptors rather than antagonizing, as could be the case in PSSD (where the genitals are numb and less responsive to stimuli). However, this does not rule out the possibility of other factors being involved such as SFN, and should only be taken as an example to signify the point around variable symptomatic presentations. Additionally, downstream vascular dysfunction could for example explain erectile dysfunction due decreased blood supply, such as seen in LC (Abbas et al. 2020). Perhaps this could also explain genital shrinkage which is reported by quite a few patients.

Considering the current results of the Celltrend tracker (Table1) and the resulting high incidence rates of many of these autoantibodies among community members, **we suspect it may indicate an immune-mediated dysautonomia contributing to symptomatology in PSSD**.
As mentioned earlier, it is known that dysautonomia can be triggered by an autoimmune cause, and we think autoantibodies targeting these receptors could be a main driving force behind the dysautonomia seen in PSSD based on the data presented.
Dysautonomia itself could be directly responsible for a vast amount of symptoms and could even be a central driver for the disease. This aligns with previous research on autoimmune dysautonomia, such as a paper from 2020 investigating GPCR autoantibodies in complex syndromes. In the paper, they noted that a co-occurrence of dysautonomia, anti-GPCR autoantibodies and SFN are common denominators, and they even proposed a new concept for this called «Autoimmune neurosensory dysautonomia» (Shoenfeld et al. 2020). Additionally, there is another umbrella condition that has been proposed named ASIA syndrome, a condition triggered by various environmental adjuvants that also involves autonomic dysfunction and SFN (Tervaert et al. 2023). To further showcase this point, we wanted to draw attention to a type of surgery targeting the autonomic nerves, which is known for having caused similar symptoms as PSSD: **endoscopic thoracic sympathectomy,** where literature and anecdotal reports of which alike mention side effects such as a lack of libido, sexual dysfunction, depression and decreased mental reactivity (Ojimba and Cameron 2004). This may suggest that impairment of autonomic function could not only explain symptoms such as sexual dysfunction, but perhaps certain cognitive issues such as emotional blunting and anhedonia.

8.2 Findings on skin biopsies & quantitative sensory testing (QST)

Info: 56 patients have provided SFN test results so far. 50 of the results are based on skin biopsies, while 6 results are based on quantitative sensory testing (QST). Some patients had additional diagnostic workup such as EMG, autonomic testing and SFN specific antibody tests, with some acquiring diagnoses such as immune-mediated SFN, which are all noted in the comment sections of the table. All patients that tested for SFN, either through biopsy, QST or both have the iatrogenic condition known as PSSD. Complications in assessing the results include difficulties with the comparison of exact numerical values, due to differences between the testing labs such as; different normative values (including age categories vs median method), lower limit/cut off, and the method used to analyze the sample. This means that in theory you could be negative at one lab, while positive at another one. Possible Covid and/or the Covid vaccine in addition to PSSD prior to testing is another potential complication.

Table 3. SFN Skin biopsy tracker

Skin biopsies are done to diagnose SFN by analyzing anomalies in nerve fiber density

PSSD - SFN tracking						
Small fiber skin biopsy (IENFD), QST & other diagnostic results						
Patient nr	Positive	Negative	Type/site	Side	Other sfn diagnostics	Comments
Patient 1 Biopsy #1		❌ ❌ ❌	Lower leg Upper thigh Upper back	Left Left Left	**TSHDS** & **FGFR3** positive **TTT** positive **Sudoscan** negative	• Diagnosed immune-mediated sfn and POTS with hyperventilation • Second biopsy distal left was borderline
Patient 1 Biopsy #2		❌ ❌ ❌ ❌	Lower leg Upper thigh Lower leg Upper thigh	Right Right Left Left		
Patient 1 Biopsy #3		❌	Lower leg	Left		
Patient 1 Biopsy #4	✅	❌ ❌	Lower leg Upper thigh Neck	Left Left Left		
Patient 2	✅		Lower leg	Right	**TBA**	Diagnosed immune-mediated sfn
Patient 3	✅		Lower leg	Right	**TSHDS** & **FGFR3** positive	
Patient 4		❌ ❌ ❌	Lower leg Upper thigh Upper back	Left Left Left		
Patient 5		❌ ❌	Leg Thigh	Left Right		
Patient 6		❌	Lower leg	Right		
Patient 7	✅ ✅		Lower leg Upper thigh	Right Right		
Patient 8 Biopsy #1		❌	Lower leg	Right	**CCM** - Negative **Sweat gland biopsy** - positive **TTT** - negative **Gut motility test** - positive	
Patient 8 Biopsy #2	✅ ✅		Calf Thigh	Left Left		
Patient 9	✅		Lower leg	N/A		
Patient 10	✅		Lower leg	N/A		
Patient 11	✅		Lower leg	N/A		
Patient 12	✅		Lower leg	N/A		
Patient 13		❌	Lower leg	N/A		
Patient 14	✅		**QST**			
Patient 15	✅		Lower leg	Left	**QST** - positive, **CCM** - Negative	Diagnosed immune-mediated sfn
Patient 16		❌ ❌ ❌	Lower leg Thigh Neck	Left Left Left		
Patient 17	✅		Ankle	Right	**TSHDS** - positive	Diagnosed immune-mediated sfn
Patient 18	✅		Lower leg	Right		
Patient 19	✅		Lower leg	Right	Positive SFN specific antibodies	Diagnosed immune-mediated sfn
Patient 20	✅		**QST**			
Patient 21		❌ ❌	Lower leg Upper thigh	Right Right		
Patient 22	✅ ✅		Ankle Thigh	Right Right	Gut motility test	Diagnosed immune-mediated sfn
Patient 23	✅	❌	Lower leg Upper thigh	Right Left		
Patient 24		❌ ❌	Lower leg Upper thigh	Right Right		Diagnosed immune-mediated sfn based on clinical picture.
Patient 25	✅		Lower leg	Right		***revisit later**
Part 1/2						

Patient 26		❌	Lower leg	Right		
Patient 27	✅	❌	Lower leg Upper thigh	Right Left		
Patient 28		❌ ❌	Lower leg Upper thigh	Right Right		
Patient 29	✅		**QST**			
Patient 30		❌	Ankle	Right		
Patient 31	✅	❌	Leg Thigh	Right Left		
Patient 32	✅		Unknown	N/A		
Patient 33		❌	Lower leg	Left	**Colon transit time** - Negative, **NCS** - Negative, **partial QST** - negative (but anomalies in pain threshold)	Borderline positive leg biopsy.
Patient 34	✅	❌ ❌	Foot Calf Thigh	Right Right Right		
Patient 35		❌ ❌ ❌	Wrist Lower thigh Foot	Left Left Left		
Patient 36		❌	Unknown	N/A		Diagnosed sfn based on symptomatic presentation.
Patient 37		❌	Unknown	N/A		
Patient 38	✅		Unknown	N/A		
Patient 39	✅		Unknown	N/A		
Patient 40		❌	Unknown	N/A		
Patient 41	✅		Unknown	N/A		
Patient 42	✅ ✅		Calf Thigh	Left Left		
Patient 43	✅		TBA	TBA		
Patient 44	✅	❌	Calf Thigh	Right Right		
Patient 45	✅		TBA	TBA		
Patient 46	✅	❌	Calf Thigh	Right Right		
Patient 47		❌ ❌	Calf Thigh	Right Right	**EMG** - No abnormalities **QST** - Severely abnormal in temperature sensitivity, low-normal in vibration sensitivity **QSART** - Normal in legs, abnormal in forearm **TTT** - Abnormal (Confirmed severe POTS) **Valsalva Breathing Test** - Normal	Clinical impression/diagnoses: patchy SFN, patchy autonomic neuropathy and POTS.
Patient 48	✅		TBA	TBA		
Patient 49	✅ ✅		Calf Thigh	TBA TBA	**EMG** - Slightly positive	
Patient 50 Biopsy #1 **Biopsy #2**	✅ ✅	❌	Lower leg Thigh Lower leg	Right Right Left		
Patient 51	✅		**TBA**		**QST -** Positive	
Patient 52	✅		Unknown	N/A		
Patient 53	✅		TBA	TBA		
Patient 54	✅		Distal leg	Left		
Patient 55	✅		**QST**		**EMG** - Negative	
Patient 56		❌ ❌	Lower leg Lower leg	Left Right		

Results	
Total positive:	**39**
Total negative:	**17**
Total positive ratio:	**39/56 = 70%**
Total positive includes 6 QST results	
Disclaimer: This table is meant for research purposes only. All subjects has the iatrogenic condition 'PSSD'. *Biopsy values have been redacted to protect patient privacy. Further info to be added. Tracker is WIP.	

Notes

• Skin Biopsy ranges are categorized and divided by age groups (i.e 20-29, 30-39 and so on) by some labs. Non-age specific labs have a borderline between 6.9 to 11.3 depending on the lab used. There seem to be no universal standard for both the technique of testing the sample and the ranges applied to them.
• NLD sfn makes skin biopsies a bit hit or miss due to the variable atypical pattern as opposed to LD type. This means that a negative biopsy doesn't necessarily rule out sfn. Therefore, other diagnostics are often useful to diagnose sfn (such as QST and autonomic testing)

Abbreviations:
• QST = Quanti sensory tracking
• CCM = Corneal Confocal Microscopy *Questionable accuracy as diagnostic tool for NLD type-sfn.
• TTT = Tilt table test
• NCS = Nerve conduction study
• QSART = Quantitative sudomotor axon reflex test

Part 2/2

The SFN tracker shows a high incidence rate, with **39 out of 56 patients (70%) being positive for SFN.**

Considering all the variables and difficulties with diagnosing NLD SFN due to the patchy and asymmetric patterns of the affected areas in this subtype, the results show a staggering amount of positives**.** The differences between the testing labs such as variable reference ranges and method of analyzing samples adds a source of inconsistency to the overall results. This means that one could in theory test negative at one lab while positive at another one, which is a factor to consider with regards to potential errors such as false negatives. The specificity of skin biopsies has been stated to be 91% (Fabry et al. 2020), so the possibility of a false positive is very low. Therefore it is reasonable to consider skin biopsies and QSTs as promising diagnostic tests for PSSD patients, as the current results indicate SFN to be a common diagnosis among this demographic. For comparison, a cross-sectional retrospective study on SFN found an incidence of 12 cases per 100,000/year, with a prevalence of 53 cases per 100,000. (Cascio & Mukhdomi 2022).

8.3 Neuroimaging findings on MRI scans

Magnetic resonance imaging (MRI) is an important diagnostic tool to detect physical or functional abnormalities that may be causing or contributing to symptoms. It is a noninvasive medical imaging test producing detailed images of almost every internal structure in the human body (organs, bones, muscles and blood vessels). It is often the first diagnostic used to assess patients for potential CNS pathologies. See John's Hopkins for more.
Info: 40 patients have provided 54 results (33 Brain MRIs and 21 spine MRIs), with some having had both brain and spine MRIs. All patients reported have the iatrogenic condition known as PSSD. Complications involve lack of data specifying variables (such as use of contrast fluid) and other non PSSD related health issues potentially contributing to findings.

Table 4. MRI tracking

An MRI scan checks for lesions and other anomalies in brain, cervical and spine

PSSD - MRI tracker				
	MRI	Brain	Spine	
Patient	Type	Lesion(s)		Other findings & comments
Patient 1	Brain x2, cervical, spine	Yes	No	**Brain:** 4 small lesions - T2 focus (no change since last mri 6 months prior).
Patient 2	Brain, cervical, spine	No	No	**Spine:** Retrolisthesis of L4- L5 and L5-S1, tarlov cyst S2/S3. Peripheral nerve sheath tumor in thoracic.
Patient 3	Brain x3, cervical	Yes	-	**Brain:** Few small remote white matter insults without specific pattern. No change on second mri.
Patient 4	Spine	-	No	
Patient 5	Brain	No	**N/A**	**Brain:** Impression of more sulcal prominence at the convexity (considering age) particularly affecting the parietal lobes.
Patient 6	Brain, cervical	No	-	
Patient 7	Brain	No	-	
Patient 8	Brain, cervical	No	-	
Patient 9	Brain, spine	No	No	**Spine:** L4-L5 & L5-S1: Slight diffuse posterior disc bulging causing slight compression on anterior surface of dural sac.
Patient 10	Spine	-	No	**Spine:** 3 herniated discs including L3-L4, L4-L5 and L5-S1. 'Left aic pattern». Mild stenosis.
Patient 11	Brain, Spine	No	No	**Old spine mri:** Had a laminectomy discectomy 20 years ago at L5/S1 after an injury (Ruptured disc L5/S1). **Spine:** Multilevel degenerative disc disease and facet arthrosis. Worst levels are L4-L5 and L5-S1 with potential sources of radiculopathy at both levels. Grade 1 retrolisthesis of L5 on S1.
Patient 12	Brain, cervical, Spine	Yes	No	**Spine:** Scoliosis. No other findings. MRI #2: **Brain:** Lesions (location not disclosed.
Patient 13	Spine	-	No	**Spine:** Small disc herniation in L5-S1
Patient 14	Brain, cervical, spine	No	No	**Spine:** Cervical spine shows bulging discs and spondylitis. Back showed something minor.
Patient 15	Brain	No	**N/A**	**Brain:** Cavernoma (vascular tumor). Could be idiopathic or related to uncommon side effect of Zoloft (see leaflet).
Patient 16	Brain, spine	No	No	**Spine:** After PSSD; 3 herniated lumbar discs including L5/S1.
Patient 17	Spine	-	No	**Kaleb case:** MRI showed small annular tear in L5-S1. Surgery successfully improved sexual sensation.
Patient 18	Brain	Yes	-	**Brain:** T2 flair hyperintensity appeared in the base of the left posterior ventricle.
Patient 19	Brain, cervical, spine	Yes	No	**Brain:** Some small white spots in right frontal lobe area noticed by the patient upon viewing images (confirmed by neurologist).
Patient 20	Brain, cervical, spine	No	No	**Spine:** Mild bilateral foraminal stenosis at L4-5 and minimal left foraminal stenosis at L5-S1. **Extracranial structures:** Multifocal mucus retention cyst within right and left maxillary sinuses.
Patient 21	Brain	No	-	
Patient 22	Brain x2	Yes	**TBA**	**Brain (no contrast):** Lesion in right cerebellar white matter. **Brain #2 (w/contrast):** 7 mm chronic encephalomalacia in the right cerebellar hemisphere white matter as described.
Patient 23	Spine	-	No	**Spine:** Herniated disk in thoracic. Something minor in lower back.
Patient 24	Brain	No	-	
Patient 25	Brain	No	-	
Patient 26	Brain, cervical, spine	No	No	**Spine:** Mild facet joint artrophy at T12/L1. Small facet joint effustion at L4/L5 and L5/S1. Tiny bilateral femoral head neck junction cam deformaties.
Parient 27	Brain, cervical, spine	No	No	
Patient 28	Spine	**N/A**	No	**Spine:** Stenosis. Got surgery that improved symptoms (need more info)
Patient 29	Brain, spine	Yes	No	**TBA**
Patient 30	Brain, spine	Yes	No	**Brain:** Hyperintensity lesion in the brain where the patient had pinpoint pain during a TIA (mini stroke). **Spine:** Central canal cyst
Patient 31	Brain	No	-	
Patient 32	Brain, Cervical	No	-	
Patient 33	Brain, TBA	Yes	**TBA**	**Brain:** Lesions (tba). Diagnosed with CIS 15 years ago and eventually MS.
Patient 34	Spine	**N/A**	No	**Spine:** Herniated disc in L3-4.
Patient 35	Brain	No	-	
Patient 36	Brain, Cervical	No	No	
Patient 37	Brain	No	-	
Patient 38	Brain, cervical, Spine	Yes	No	**Brain:** One pinpoint lesion in the white matter in the right temporoparietal junction, supratentorial region, non-specific leucopathy (hypersignal T2). **Cervical:** Aneurysm of 2.5 millimeters in diameter at the level of the medial wall of the left C2-C3 union
Patient 39	Brain	No	-	
Patient 40	Brain	No	**N/A**	
Patient 41	Brain	No	-	**Brain:** Significantly enlarged perivascular spaces

Info	Stats & disclaimer
Magnetic resonance imaging (**MRI**) is a medical imaging technique used in hospitals and clinics for medical diagnosis, staging and follow-up of a wide range of various diseases affecting the brain, spine, joints and soft tissue. Examples include demyelinating CNS disease such as MS and CIDP, neurodegenerative disease such as ALS and various other disease states such as for example detecting tumors and spinal issues. An mri can be done with or without contrast fluid (gadolinium). Using contrast increases clarity and details of imaging, potentially detecting additional anomalies (smaller lesions and vascular flow issues) that might not be picked up using a non contrast technique. Gadolinium is generally considered safe but is defined as a toxic chemical and potentially cause side effects and allergic reactions in susceptible individuals.	**Brain:** • **10/33 (30%)** of brain mri's show variable lesion findings in the brain • **Lesion area:** Base of the left posterior ventricle, the parietal lobes, cavernoma, right cerebellar white matter, right frontal lobe **Spine:** • **15/21 (71%)** of spine mri's show variable issues (disc bulges and herniation, stenosis, tear etc). • **9/21 (43%)** shows issues specifically in the L5-S1 area • **Spine issues reported:** Stenosis (3), Herniated disc (4), Disc bulges (2), Spondylitis (2), Retrolisthesis (2), Scoliosis (1), Arthrosis (1), Radiculopathy (1), Tarlov cyst, Peripheral nerve sheath tumor (1), tear (1), Central canal cyst (1), Aneurysm (1) **Disclaimer:** This tracker is meant for research purposes only. All subjects have the iatrogenic condition known as ''PSSD''. Most patients performed MRI without contrast. **WIP***

40 patients have reported 54 MRI results so far (33 brain MRIs and 21 Spine MRIs). There are no clear findings indicating demyelinating disease, such as lesions with specific patterns that are often seen in MS. With that said, some interesting observations have been noted, especially regarding spine MRIs which show a large number of patients **(71% based on 15/21) with various potentially clinically validated findings in their spine, such as herniations, disc bulges, and stenosis.** The fact that **60% of these cases (9/15) are specific to the L5-S1** area is of interest due to it potentially explaining symptoms such as sexual dysfunction and genital numbness, because compression or irritation (inflammation) of these nerves can disrupt normal nerve signaling. Some potential problems leading to sexual dysfunction and genital numbness are herniated discs, spinal stenosis, cauda equina syndrome, and other spine issues such as ankylosing spondylitis have been reported in Long Covid patients as well (Mondal et al. 2021, Sh et al. 2023).

Discussion

It is hard to interpret what the various spine MRI findings might mean, but their high incidence rate could potentially indicate a possible connection to the etiology. Are these findings totally separate entities or could they somehow be a secondary downstream consequence of the underlying cause? One possibility could be **myelitis** (inflammation of the spine) or a so-called transverse myelitis, a neurological disorder causing inflammation of the spine, which could be contributing to certain symptoms in PSSD. Myelitis is known to cause a variety of symptoms such as numbness and loss of function depending on the area affected, disrupting nerve signaling through other pathways, and perhaps either worsening pre-existing injuries or other predispositions which could end up pressing on the lower spine. Interestingly, there have been reports from the community of a couple of patients improving in symptoms of genital numbness and sexual dysfunction through corrective spine surgeries.
Transverse myelitis is sometimes seen in inflammatory disorders such as MS, neuromyelitis optica, acute disseminated encephalomyelitis (ADEM) and neurosarcoidosis. Sjögren's syndrome and systemic lupus erythematosus (SLE) can in some instances also lead to transverse myelitis (Simone and Emmady 2022, Zun Swe et al. 2018).

Interpreting the brain MRI results is challenging due to the relatively nonspecific nature of the brain lesions observed thus far, but due to the amount of commonalities, as well as the potential clinical implications, especially regarding the spine findings, we believe that these observations deserve further investigation.

8.4 Neuroimaging findings on PET-scans

An FDG-PET scan is another possible imaging technique, which provides additional information about brain function by assessing metabolic uptake of glucose in the brain. It can complement other diagnostic tests, adding to the overall clinical assessment especially if other tests are inconclusive. It may be used in detecting functional changes in disorders of the brain such as dementia and Alzheimer's disease (Johnson et al. 2012). Additionally it is seen as an invaluable diagnostic tool and biomarker in the early stages of certain conditions such as Autoimmune encephalitis (AE), especially when autoantibody assays (and MRI) are inconclusive (Khanna et al. 2024). While TSPO-PET (another radiotracer) imaging is considered the most accurate diagnostic tool to specifically measure neuroinflammation by looking at activation of microglia and astrocytes (immune cells) (Chauveau et al. 2024), it is rarely used for that purpose in clinical settings and is most often used in research settings. FDG-PET scans on the other hand, are more often used and may indicate processes such as neuroinflammation by how metabolic uptake is associated with microglial activation, especially when seen holistically with the symptomatic presentation and strengthened by other diagnostic tools.

Info: 10 patients have provided FDG-PET scan results. All patients reported have the iatrogenic condition known as PSSD. Complications assessing the results include lack of data specifying certain variables and other non PSSD related health issues contributing to positive results.

Table 5. PET-scan tracking

An FDG-PET scan checks for metabolic disturbances in the brain

PSSD - Pet scan tracking				
Patient	**Type**	**Abnormal?**	**Result**	**Info**
Patient 1	**FDG-PET**	**Yes**	Hypometabolism in temporal-parietal lobes indicating neuroinflammation.	PSSD from Lexapro. No vax or covid prior.
Patient 2	**FDG-PET**	**Yes**	Hypometabolism in the bilateral-parietal cortex and bilateral temporal cortex consistent with neuroinflammation seen in encephalopathy, toxin exposure and Alzheimers disease.	Long covid + PSSD. Diagnosed seronegative AE.
Patient 3	**FDG-PET**	**No**		PSSD case + akathisia. Other findings indicate seronegative AE.
Patient 4	**FDG-PET**	**Yes**	PET-MRI: Mild hypometabolism of posterior of the brain.	PSSD + PFS + Covid + BPC (peptide)
Patient 5	**FDG-PET**	**Yes**	Mildly reduced metabolic activity in the occipital lobe and cerebellum.	Covid Vax injury + PSSD.
Patient 6	**PET-CT**	**Yes**	Relatively preserved metabolism at the temporal cortex. Small zone of mild hypometabolism at the level of the occipital cortex bilaterally, but with normal metabolism at the level of the primary visual cortex. Mild hypometabolism high parietal bilaterally. Prominent cortical subcortical atrophy mainly bilateral frontal and insular for the patients age.	PSSD from Lexapro and Cymbalta.
Patient 7	**FDG-PET**	**No**		TBA
Patient 8	**FDG-PET**	**Yes**	PET Scan indicating a cortical hypometabolism in two brain locations: the bilateral mesial frontal site and the left dorsal-lateral prefrontal site. In these two areas, neuronal activity is lacking.	PSSD from Paxil.
Patient 9	**FDG-PET**	**No**		TBA
Patient 10	**FDG-PET**	**Yes**	Report: increased activity anteriorly and decreased activity posteriorly with relative hypometabolism in the parietal and occipital lobes.	PSSD from Lexapro. Diagnosed with anti-NMDA encephalitis after Lexapro.

10 patients with PSSD have reported FDG-PET scans so far (Table 5). The results show that **7 out of 10 patients (70%) had hypometabolism detected in various areas of the brain, possibly indicating neuroinflammation, neuronal dysfunction or damage (loss of function).** The most common affected areas in the PET scan tracker are the temporal-parietal lobes and frontal cortex, both of which are linked to neuroinflammatory and neurodegenerative conditions. Hypometabolism has been seen in conditions such as Long Covid (Zawilska and Kuczyńska 2022), Parkinson's (Albrecht et al. 2019), MS and Autoimmune limbic encephalitis (Kaprelyan 2015). In a retrospective analysis from 2022, results showed that 85% of participants with AE had abnormal FDG-PET scans even when brain MRIs were normal in 60% of cases (Probasco et al. 2017). Furthermore, 69% of them demonstrated only hypometabolic patterns. These numbers are interesting as they are fairly consistent with both our PET-scans and MRI findings.

The sample size is small and thus further research on the role of these findings is needed to see if this is a consistent pattern in PSSD patients. With that said, the results so far are probably one of the strongest indicators of a CNS involvement and subsequent neuroinflammation.

Discussion

SSRIs have been linked to an increased risk of Alzheimer's (Kodesh et al. 2019). A new cohort study further underscores this, where it was shown that current antidepressant use was associated with faster cognitive decline; furthermore, higher dispensed doses of SSRIs were associated with higher risk for severe dementia, fractures, and all-cause mortality (Mo et al. 2025).
This is interesting considering two of the PSSD patients with hypometabolic findings in the PET-scan tracker got a diagnosis of Alzheimers and early-onset dementia based on their doctor's interpretation of their results. One of these patients also got the same diagnosis based on a SPECT scan (Single photon emission computed tomography), which is an imaging method that produces a three-dimensional (3D) image to provide functional information about organs and tissues, enabling the detection of functional abnormalities before anatomical changes occur (Bouchareb et al. 2024).

Among additional symptoms reported in the community, Visual snow syndrome (VSS), has been a frequent complaint among a subset of patients. VSS is a neurological condition involving visual disturbances such as static noise (visual snow), floaters (muscae volitantes), light sensitivity (photophobia) and double vision (diplopia). The precise pathophysiology is currently unknown, but recent studies have identified abnormal neuronal activity through different brain scans such as metabolic abnormalities in FDG-PET scans of VSS patients (Laere et al. 2022), consistent with the findings of brain hypometabolism in our anecdotal reports collected from PSSD patients, potentially suggesting a neuroinflammatory component. Several vision related symptoms reported in PSSD are consistent with VSS and SSRI-induced VSS have just recently been formally documented in a case study (Eren et al. 2020).

Note: A select number of patients have reported having done a **Quantitative electroencephalography screening (QEEG)** which is a neuroimaging technique that measures electrical activity in the brain using sensors placed on the scalp. It quantifies EEG data to produce detailed brain maps, highlighting patterns associated with different cognitive states and neurological conditions. It is often used for diagnosing and guiding treatment for various brain disorders, including epilepsy, ADHD, and anxiety. Additionally, it can detect neuroinflammation by identifying abnormal brain wave patterns. Neuroinflammation serves as a significant example of QEEG's diagnostic capabilities. A majority of the PSSD cases have reported results showing dysfunctional brain activity in various regions of the brain indicating severe neuroinflammation.
We have currently not been compiling data on this (tracking).

8.5 Findings in cerebrospinal fluid (lumbar puncture)

As with MRI, a lumbar puncture (LP) is another important diagnostic tool to exclude other conditions and potentially pick up other findings that could be relevant to the overall clinical assessment. It is a test where a variable amount of cerebrospinal fluid is drained from the patient's lower back and for lab analysis. LPs are often used to look for inflammatory markers for neurological disorders, infections and intracranial pressure (Jane and Wray 2023). Positive lumbar punctures often lead to clinical diagnosis and treatment, so this test has been of high importance in many PSSD cases that ended up acquiring a diagnosis and treatment (see chapter 9 for case reports). Table 6 shows our community data on lumbar punctures.

Info: 24 patients have provided lumbar puncture results (21 regular and 3 with specific screening for BH4 deficiency or neurosteroid levels).
All patients reported have the iatrogenic condition known as PSSD. Complications involve lack of data specifying variables (due to for example inaccessibility) and other non-PSSD related health issues potentially contributing to findings and positive results. Differences in testing markers also pose a challenge as it makes it harder to get consistent profiles to compare and analyze for correlations.

Table 6. Lumbar Puncture tracking

A lumbar puncture (spinal tap) checks for blood cell count, infections and inflammatory markers in the cerebrospinal fluid (CSF)

PSSD - Lumbar puncture tracking					
	Biomarkers				
Patient nr	**IgG index**	**Oligoclonal bands**	**Total protein**	**Leukocytes**	**Other CSF findings & relevant info**
Patient 1	Elevated	Normal	Normal	Elevated	
Patient 2	Elevated	Positive	Normal	Elevated	
Patient 3	Normal	Normal	Elevated	Normal	Anti-neurochondrin antibodies found in blood plasma indicating possible AE.
Patient 4	Normal	Normal	Normal	Normal	
Patient 5	Normal	Normal	Normal	Normal	Specific antibody for encephalitis detected (no indication for tx)
Patient 6	Normal	Normal	Normal	Normal	
Patient 7	Normal	Normal	Normal	Normal	
Patient 8	Normal	Normal	Normal	Normal	
Patient 9	Normal	Normal	Normal	Normal	There were anomalies in terms of globulin composition in csf.
Patient 10	Normal	Normal	Normal	Normal	Neuro-antibodies not tested. PT on IVIG during LP and results show treatment sides. Elevated lymphocytes and low levels of monocytes.
Patient 11	Normal	Positive	Normal	Elevated	Elevated lymphocytes.
Patient 12	Unknown	Positive	Slightly elevated	Unknown	Slightly elevated albumin.
Patient 13	N/T	N/T	N/T	N/T	NT test: Low dopamine and serotonin levels. BH4 deficiency
Patient 14	N/T	N/T	N/T	N/T	NT test: Low dopamine and serotonin levels. BH4 deficiency
Patient 15	Normal	Positive	Elevated	Normal	Diagnosed seronegative AE.
Patient 16	Normal	Normal	Elevated	Normal	High count of RBC.
Patient 17	Normal	Positive	Normal	Normal	
Patient 18	Normal	Positive	Normal	Unknown	Diagnosed with MS.
Patient 19	Normal	Inconclusive	Slightly elevated	Borderline	Slightly elevated albumin and high IgG
Patient 20	Elevated	Normal	Normal	Normal	**LP #1:** High RBC in only one tube, said to be irrelevant. Borderline high lymphocytes and borderline low monocytes. **LP# 2:** IgG index elevated.
Patient 21	Normal	Normal	Normal	Normal	
Patient 22	N/T	N/T	N/T	N/T	Neurosteroids tested in CSF. The levels of allopregnanolone and DHT (both metabolites of the 5AR2 enzyme) were almost absent.
Patient 23	N/T	N/T	Normal	Normal	
Patient 24	Normal	Normal	Normal	Normal	Positive for anti-NMDA encephalitis through both CSF and serum
	Abbreviations: N/T= Not tested				All patients have the iatrogenic condition PSSD. The table contains the most reported biomarkers. Some data is missing. This table is WIP

So far, 21 patients have gotten a regular lumbar puncture, while 2 patients have undergone a specific neurotransmitter LP that is used to diagnose issues such as BH4 deficiencies (patient 13 & 14). Additionally, one patient tested specifically for the neurosteroid Allopregnanolone and DHT levels in their CSF (patient 22). **71% had at least one abnormal/elevated finding in their CSF, with 52% (11/21) being positive for one or more of the 4 main markers in the table.** 4 patients had only other types of findings noted in the table's comment section.

From the patients that had a regular lumbar puncture, the most significant finding so far has been **elevated oligoclonal bands in 6 out of 20 patients (30%).** Elevated oligoclonal bands are an inflammatory marker often seen in conditions such as multiple sclerosis and other inflammatory disorders of the CNS (Chu et al. 1983).

Elevated protein is another valuable finding observed in **5 out of 21 patients (24%).**
Elevated protein can indicate inflammation and disruption of the blood-brain-barrier, and is often linked to conditions such as various forms of Meningitis (bacterial, viral and tuberculous), autoimmune encephalitis and GBS (Shahan et al. 2021, Zrzavy et al. 2021). Additionally, according to the Internet Book of Critical Care, if there is suspicion of seronegative autoimmune encephalitis but a neuronal antibody panel taken in CSF and plasma

comes back normal, elevated protein is often considered an essential diagnostic finding in combination with other relevant diagnostics such as a positive PET-scan.
16% (3 out of 19 patients) had elevated leukocytes (white blood cells) detected in their CSF, which is referred to as pleocytosis. Elevated levels of leukocytes usually indicate inflammation or infection in the CNS. Many infectious causes can lead to pleocytosis, including bacterial meningitis, encephalitis, Lyme neuroborreliosis and demyelinating diseases (Egelund et al. 2017).

3 out of 19 patients (16%) had elevated IgG Index, which is another inflammatory marker indicating possible infection or autoimmune disease. 2 cases had **elevated albumin**, which can indicate a compromised blood-brain-barrier (BBB), a structure that protects the CNS from harmful substances circulating in the blood (such as toxins, pathogens and antibodies) while still letting nutrients pass through. Elevated albumin is associated with CNS pathologies such as MS (LeVine 2016).
2 patients reported elevated lymphocytes, which is a type of white blood cell that can migrate to areas of inflammation or infection and differentiate into macrophages or dendritic cells. Elevated lymphocytes can indicate infections (such as bacterial, viral, fungal and parasitic) (Hamad and Mangla 2024).

The two BH4 deficient patients in the tracker are interesting findings due to how implicated dopaminergic dysfunction seems to be in PSSD. In MS, a study showed that cytokines decrease the availability of the cofactor tetrahydrobiopterin (BH4), thereby limiting the turnover of the precursors phenylalanine and tyrosine, which are all crucial for synthesizing dopamine, a key neurotransmitter in regards to motivation and reward processing (Heitmann et al. 2022).

One patient reported testing positive for anti-NMDA encephalitis after using an antidepressant. With that said, most patients that were tested for neuronal autoantibodies (antibodies that specifically target components of the brain such as seen in certain types of autoimmune encephalitis) were negative.

The patient who tested for neurosteroids in his CSF will be discussed in chapter 10.3.2.

Discussion

The current incidence rate with only one-third of PSSD patients showing abnormal CSF findings likely reflects the heterogeneity of the condition, the limitations of current diagnostic methods, and the possibility that the underlying pathophysiology of PSSD varies between patients. Some patients may have neuroinflammatory or autoimmune processes that are detectable in the CSF, while others may have localized or peripheral processes that do not significantly affect CSF composition. Additionally, the timing of sampling, the sensitivity of detection techniques, and the role of compensatory mechanisms could all contribute to the variability in CSF findings.

While incidence rates seen here are not as high as with other tests such as skin biopsies and GPCR autoantibodies, there are still a noticeable portion of patients showing inflammatory markers in their CSF, which further hints at a possible neuroimmune etiology.

8.6 Cytokine findings

Cytokines are signaling molecules that play a critical role in the body's immune response, mediating inflammation and regulating the balance between pro-inflammatory and anti-inflammatory states. In neuroimmune disorders, an imbalance in cytokine levels can contribute to neuroinflammation, which is increasingly recognized as a key factor in various CNS-related conditions, including Multiple Sclerosis (MS), and Parkinson's disease (Rothaug et al. 2016). Cytokine panels are most often used in research settings but in certain clinical practices they are sometimes used to help diagnose and monitor various immune-related conditions. These panels are also considered to have potential to support diagnosis for infections and inflammatory diseases due to its lack of invasiveness and low cost (Monastero and Pentyala 2017).

Info: 9 patients have provided cytokine test results. All patients reported have the iatrogenic condition known as PSSD. All panels were tested in blood plasma. Complications assessing the results include: Different panels, different assays and different methods (serum vs CSF) of analyzing, and lack of data specifying certain variables and other non-PSSD-related health issues contributing to positive results.

Table 7. Cytokine tracking

Cytokine panels check for immune, infection and inflammatory markers in blood or CSF

Cytokine results tracking									
Biomarkers									
Name	IL-2	IL-4	IL-6	IL-8	IL-10	IL-13	IL-17a	TNF-A	Info
Patient 1	Low	Normal	Very high	N/A	High	N/A	Normal	Normal	PSSD
Patient 2	N/A	High	High	High	High	High	N/A	High	PSSD + MCAS
Patient 3	High	High	Normal	Normal	High	High	High	N/A	PSSD
Patient 4	Normal	Normal	Very high	N/A	High	N/A	Normal	Normal	PSSD
Patient 5	N/A	Normal	N/A	N/A	High	Normal	N/A	N/A	PSSD + Long Covid
Patient 6	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	PSSD + Lyme. Fasted before test.
Patient 7	Normal	Normal	Very high	N/A	High	N/A	Normal	Normal	PSSD
Patient 8	N/A	N/A	Low	N/A	N/A	Normal	Normal	Normal	PSSD
Patient 9	Normal	N/A	Normal	Normal	Normal	N/A	N/A	Normal	PSSD

Of the 9 patients that tested for cytokine levels, **67% (6/9) had at least one abnormal marker.** Among these, the most consistent positive results so far have been **Interleukin 10 (IL-10) at 6/8 (75%)** and **Interleukin 6 (IL-6) 4/8 (50%).**

Interleukin-10 is a potent anti-inflammatory cytokine critical for preventing inflammatory and autoimmune pathologies (Iyer and Cheng 2012). Elevated IL-10 levels often reflect an inflammatory process, as one of its primary roles is to suppress immune responses and limit tissue damage caused by infection or microbiota (Islam et al. 2021). However, severe conditions like COVID-19 reveal a paradox: despite its anti-inflammatory role, IL-10 may contribute to inflammation. Islam et al. 2021 suggest this could result from IL-10's non-classical pro-inflammatory effects or a resistance to its (anti-inflammatory) regulatory actions. Whether these notions somehow link to PSSD as well is beyond the capacity of our layman research but perhaps similar mechanisms apply here as well.

Elevated levels of interleukin-6 can indicate inflammation or infection in the body. This finding is particularly noteworthy, as IL-6 is a potent pro-inflammatory cytokine that can cross the blood-brain barrier, influencing both central and peripheral nervous system functions (Rothaug et al. 2016). Elevated IL-6 levels are associated with the activation of microglia—the brain's resident immune cells—which can lead to a cascade of neuroinflammatory responses that potentially contribute to the symptoms observed in PSSD (Erta et al. 2012). The role of IL-6 in neuroinflammation has been well-documented in various disorders. In MS, for example, IL-6 is involved in the pathological process that leads to demyelination and the disruption of normal neural signaling, contributing to both physical and cognitive impairments.

The findings suggest a potential dysregulation in the immune system's attempt to control inflammation. While IL-10 typically acts to suppress inflammation, insufficient levels or a failure to effectively counterbalance pro-inflammatory cytokines could allow chronic inflammation to persist. Furthermore the relatively high incidence rate of the pro-inflammatory cytokine IL-6 supports the notion of immune dysregulation and inflammation. Acknowledging the small sample size, the results so far indicate a potential inflammatory component in the etiology of PSSD, but further test results and research are needed to see if this is a consistent pattern in PSSD, and to ultimately understand its role in the condition.

8.7 Cunningham panel findings

Neuronal autoantibodies (serum)

The gold standard for detecting neuronal autoantibodies (antibodies that target the brain) involves CSF analysis obtained through lumbar puncture combined with serum testing (Fernández-Fournier et al. 2022). In addition to this, some specialized tests can detect specific receptor autoantibodies. **The Cunningham Panel** (now referred to as the Autoimmune Brain Panel), is one such panel, and was initially designed specifically to detect PANS/PANDAS, an autoimmune neuropsychiatric disorder commonly seen in children following streptococcal infection. The panel screens for autoantibodies targeting specific receptors in the basal ganglia of the brain, which includes the following markers: Anti-D1 (dopamine 1), Anti-D2 (dopamine 2), Anti-GM1 (Lysoganglioside 1) and Anti-Tubulin and CamKII. In contrast to the Celltrend GPCR autoantibody panel, which only detects presence of autoantibodies in serum, the Cunningham Panel uses so-called functional assays to analyze the blood plasma samples, which means that it actually evaluates whether the antibodies are actively targeting the receptors or not. The sensitivity of the panel is stated as being 88%, with specificity being 83% and the overall accuracy being 86% (Shimasaki et al. 2020). This indicates that false positives are rather rare.
For more visit: https://www.moleculera.com/autoimmune-brain-panel/.

Info: 6 patients have reported Cunningham panel results. All patients reported have the iatrogenic condition known as PSSD. Complications assessing the results include lack of data specifying certain variables and other non-PSSD-related health issues contributing to positive results. To our knowledge, at least 1 of the patients has no history of infectious disease (patient 1). Patient 2 has a suspicion of PANS from childhood based on clinical history but without ever having been diagnosed with it in the past. Patient 3 has been diagnosed with Lyme while patient 4 has reactivated Epstein-Barr virus (EBV). The fifth patient has confirmed PANDAS through previous diagnosis. Due to 4 out of 5 patients having confirmed or suspected infectious disease on top of their PSSD, this complicates the assessment of the results.

Table 8. Cunningham Panel tracking

The Cunningham Panel checks for autoantibodies targeting receptors in the basal ganglia

Cunningham Panel tracking									
	Biomarkers								
Name	Anti-D1	Anti-D2	Anti-GM1	Anti-Tubulin	camKII	Result	Disease/infection	Covid/vax prior	Disclaimer
Patient 1	ELEVATED	NORMAL	BORDERLINE	BORDERLINE	NORMAL	Positive	None	No/No	•This table is purely meant for research purposes only. •All test subjects have the iatrogenic condition known as PSSD •Some patients have had infections in the past that are known to create antibodies towards these receptors. This complicates the assessment of the results •Borderline results may be significant and could indicate symptoms depending on the overall results.
Patient 2	BORDERLINE	NORMAL	NORMAL	ELEVATED	NORMAL	Positive	PANS (suspected), inactive	Yes/Yes	
Patient 3	BORDERLINE	NORMAL	ELEVATED	BORDERLINE	ELEVATED	Positive	Lyme, active	Yes/No	
Patient 4	ELEVATED	BORDERLINE	ELEVATED	BORDERLINE	ELEVATED	Positive	Reactivated EBV	Yes/No	
Patient 5	ELEVATED	BORDERLINE	BORDERLINE	ELEVATED	NORMAL	Positive	PANS/PANDAS	Yes/Yes	
Patient 6	BORDERLINE	NORMAL	NORMAL	BORDERLINE	ELEVATED	Positive	Mycoplasma, strep a	Yes/Yes	
					Total pos ratio: 6/6 100%				

Only 6 patients have tested for the Cunningham panel so far, but with that said, **all 6 patients tested positive for at least one marker**. According to Moleculera, the company behind the Cunningham panel; borderline values are considered significant, potentially contributing to symptomatology. With this in mind, a very interesting observation is that **all 6 patients had either positive or borderline results for the dopamine-1 receptor (D1)** (3 positives and 3 borderlines) and the **anti-tubulin marker** (2 positives and 4 borderline).

Anti-Dopamine 1 (50% positive, 50% borderline)

The dopamine 1 receptor (D1) is the most abundant dopamine receptor in the CNS and plays a crucial role in modulating neurotransmission, motor control, cognition, and behavior. D1 receptors are heavily expressed in the striatum, where they regulate motor control and are implicated in movement disorders such as Parkinson's disease. They are essential for cognitive functions such as working memory and learning, particularly in the prefrontal cortex. More interestingly, the D1 receptor also plays a key role in the brain's reward system, influencing motivation and reward-seeking behaviors. D1 is linked to several neurological and neuropsychiatric conditions such as Parkinson's disease, bipolar disorder, ADHD, schizophrenia and addiction (Mishra et al. 2018, Zhuang et al. 2021). Considering D1's extensive role in various processes, disruption by autoantibodies could have major implications. Functional autoantibodies can either mimic or block the receptor's activity, potentially causing a range of neurological and psychiatric symptoms, such as movement disorders, cognitive impairments, mood disturbances, and changes in motivation and reward processing such anhedonia. Given that Anhedonia and cognitive impairment are frequently reported in the community, the high incidence rate of anti-D1 could potentially make this a significant finding.

CamKII (50% positive)

CaMKII (Calcium/Calmodulin-dependent protein kinase II) is an enzyme in the brain that plays a significant role in synaptic plasticity, learning, and memory. CaMKII is widely expressed in the brain, especially in regions like the hippocampus, where memory and learning are processed. It influences multiple cellular processes, including gene expression and neurotransmission. To exemplify the latter, CaMKII activation increases the activity of tyrosine hydroxylase, an enzyme that produces dopamine, resulting in increased dopamine output, a key neurotransmitter involved in movement disorders such as PANDAS, which has been show to to have increased activity of CaMKII (Shimasaki et al. 2020). CaMKII is also involved in the regulation of *N*-methyl-D-aspartate (NMDA) receptor excitability via glutamate transmission which is being recognized in syndromes which include OCD, tics, and Tourette Syndrome, and being recognized as a treatment target in OCD (Shimasaki et al. 2020).

Mutations in CAMK2A and CAMK2B, the genes that code for CaMKII, have been associated with intellectual disability and ASD-related behaviors such as hyperactivity, social interaction deficits, and repetitive behaviors. Other studies have linked CaMKII to the pathogenesis and symptoms in a variety of mental and neurological illnesses, including learning disorders, cognitive impairment, schizophrenia, ischemia, Alzheimer's disease, epilepsy and Parkinson's disease (Shimasaki et al. 2020). CaMKII is also involved in a process called long-term potentiation (LTP), which is a process believed to be involved in memory and learning (Lisman et al 2012). According to Moleculera, elevated levels of CamKII are often associated with involuntary movements and any symptom of adrenergic activation. Other symptoms include: fight or flight behaviors, sensory abnormalities, fatigue, sleep disturbance, mood instability, enuresis and mydriasis. In cases where CaMKII is elevated, this might reflect an autoimmune or inflammatory state that interferes with dopamine receptor function or downstream signaling, compounding or sustaining the symptoms observed in PSSD.

Anti-tubulin (33% positive, 67% borderline)

Tubulin is a protein that is contained on the inside of cells and acts like internal scaffolding giving the cells their shape and is highly abundant in brain tissue. The tubulin protein is used in the Cunningham panel to determine if autoimmune antibodies are present at high enough levels to interfere with its function. Tubulin autoantibodies have been identified in chronic inflammatory demyelinating polyneuropathy (CIDP) and Guillain-Barré syndrome, Graves' disease and Hashimoto's thyroiditis (Shimasaki et al. 2020).

According to Moleculera's website, symptoms of antibodies interfering with tubulin are associated with OCD, brain fog and cognitive difficulties such as memory impairment, confusion and low energy. PSSD often presents with cognitive difficulties. In addition, many patients report fatigue and low energy. The fact that anti-tubulin is associated with CIDP is an interesting observation as well, given the high number of positive SFN cases and the previous discussion in this document of a sensory subtype of CIDP potentially being connected to PSSD.

Anti-GM1 (33% positive, 33% borderline)

Lysogangliosides, particularly GM1, are involved in crucial cell signaling pathways that regulate various physiological processes, such as cell growth, differentiation, and apoptosis (programmed cell death). These molecules also play important roles in modulating immune responses and have been implicated in inflammatory processes. GM1 is abundantly found in motor neurons in both the brain and peripheral nervous system, where it helps protect nerve cells and maintain neuronal function. Disruption in GM1 metabolism or function can contribute to neurodegenerative diseases such as Parkinson's disease (Schneider, 2023), as it plays a critical role in maintaining the structural integrity and signaling functions of neurons. Antibodies against GM1 are associated with tics and OCD (Connery et al. 2018), as well as neuropathy (Sadiq et al. 1990), and connective tissue issues, headaches and joint pain according to Moleculera's website. In the context of PSSD, neuropathy may be the most relevant association with GM1.

Anti-D2 (2 borderline)

The **dopamine D2 receptor** (D2R) is a critical regulator of dopamine signaling in the brain, particularly in areas like the basal ganglia, where it influences movement, motivation, and cognition. Functional autoantibodies targeting D2R are implicated in several autoimmune and neuropsychiatric disorders. In conditions like autoimmune basal ganglia encephalitis, anti-D2R antibodies can disrupt dopamine signaling, leading to movement disorders and parkinsonism-like symptoms such as involuntary movements, stiffness and tremors (Giri et al. 2022). These antibodies are also associated with PANDAS and Sydenham Chorea (Shimasaki et al. 2020). Moleculera mentions that patients with elevated levels of autoantibodies against the D2 receptor typically experience movement disorders and impulsivity, hyperactivity and tremors.

Discussion

The findings, especially the markers with the highest incidence rates (Anti-D1, Tubulin and GM1), suggest a potential basal ganglia autoimmune encephalitis component, and correlates with certain symptoms seen in PSSD such as cognitive, hedonic and sensory disturbances.

Given the receptors biological functions and associated disease pathologies (such as neurological and neuropathic), the results adds further value to the overall assessment of all the clinical findings in this document, given that cognitive impairment and neuropathy are linked to several other test results in this document (such as SFN diagnostics, Celltrend and results from lumbar punctures).

Considering known consequences of autoantibodies targeting neuronal receptors, the results indirectly point towards potential evidence of neuroinflammation. With the small sample size in mind, as well as complications with comorbid infections in some of the test subjects, only further tests can probe any clear correlation between PSSD and these biomarkers.

8.8 Findings on gut microbiome dysbiosis

This table focuses on the levels of **Faecalibacterium prausnitzii** (F. prausnitzii) tested through GI map panels.
Faecalibacterium prausnitzii is one of the most abundant bacterial species found in the gut, and has an important role in promoting gut health.
F. prausnitzii is one of the main producers of butyrate in the intestine, a short chain fatty acid (SCFA) with several key functions, such as being the main energy source for colonocytes (cells lining the colon) and having significant anti-inflammatory effects where it has been shown to have protective properties against colorectal cancer and inflammatory bowel disease. Low levels of F. prausnitzii are linked to various disease pathologies such as IBD, irritable bowel syndrome (IBS) and colorectal cancer (CRC). Due to several studies showing strong links between gut disorders and low levels of F. Prausnitzii, it has been proposed that F. Prausnitzii monitoring may serve as a biomarker to assist in gut disease diagnostics (Lopez-Siles et al. 2017).

Info: 16 patients have provided GI-map panel results. All patients reported have the iatrogenic condition known as PSSD. Complications assessing the results include lack of data specifying certain variables and other non PSSD related health issues contributing to positive results. We have observed issues regarding the accuracy and specificity of different gut microbiome tests. Due to time constraints as well as big differences between the gut panels (variable markers and ref methods) we have not been able to assess the 16 samples further.

Table 9. F. Prausnitzii tracking

Tracker looks specifically at the bacteria strain "F. prausnitzii" from various GI Map panels

PSSD - GI map bacteria strain tracking - F. Prausnitzii			
Name	**F. prausnitzii**	**Comment**	**Definition and and associated diseases**
Patient 1	**Very low**		**Species: F. prausnitzii** **Class: Clostridia** **Domain: Bacteria** **Phylum: Bacillota** **Family: Ruminococcaceae** **Genus: Feacalibacterium** **Info:** In healthy adults, *Faecalibacterium prausnitzii* represent approximately 5% to 15% of the total fecal microbiota, making it one of the most common gut bacteria. It has anti-inflammatory properties and may improve the imbalance in intestinal bacteria that leads to dysbiosis. It is one of the main producers of butyrate in the intestine and this makes them an important member of the gut microbiota in fighting against inflammation. Lower than usual levels of *F. prausnitzii* in the intestines have been associated with Crohn's disease, obesity, asthma and major depressive disorder, and higher than usual levels have been associated with psoriasis. **Diseases associated with low levels of F. Prausnitzii:** **• IBS and IBD** **• Major depression, Bipolar, anxiety, psychosis and Schizophrenia** **• Parkinsons, Alzheimers and Multiple sclerosis** **• ME/CFS** **• Post Finasteride Syndrome** **• Covid 19** **Disclaimer:** This table is meant for research purposes only. All subjects have the iatrogenic condition called 'PSSD'. Values have been removed for easier viewing due to differences in GI map test reference ranges. This will eventually be added.
Patient 2	**Very low**	**Old test** after pssd. Improved to within range with AIP diet on second screening.	
Patient 3	**Low**		
Patient 4	**Very low**		
Patient 5	**Low**	Borderline low results.	
Patient 6	**Very low**		
Patient 7	**Very Low**		
Patient 8	**Very low**		
Patient 9	**Normal**		
Patient 10	**Normal**		
Patient 11	**Normal**		
Patient 12	**Very low**		
Patient 13	**Normal**		
Patient 14	**Normal**		
Patient 15	**Very low**		
Patient 16	**Very low**		
Results: 11/16 low ratio (69%)		***Tracker is WIP**	

The data shows a high incidence rate of gut microbiome dysbiosis. This is in alignment with the findings from the work of professor Roberto Melcangi and his group (Giatti et al. 2022, Giatti et al. 2024b). In their paper (Giatti et al. 2022) show that the SSRI (in this case Paroxetine) is linked as a causative factor for a dysbiosis of the gut microbiome. While our data on this area is very limited at the moment, the interesting observation regarding the high incidence of low levels of **Faecalibacterium prausnitzii (table 9)** is noteworthy**,** with **11 out of 16 patients (69%)** showing low levels of this particular strain.

Low levels of F. prausnitzii has been linked to ME/CFS (König et al. 2022, Guo et al. 2023, Xiong et al. 2023), where F. prausnitzii was considered a top biomarker with potential diagnostic value. Additionally, reduced abundance of F. prausnitzii has been associated with neurological diseases like MS (Thirion et al. 2023a) and Parkinson's disease (Zhang et al. 2023c), as well as psychiatric disorders such as major depression (Kovtun et al. 2022), and Schizophrenia (Thirion et al. 2023b). Bipolar disorder has been associated with low levels of the Faecalibacterium genus, which includes F. prausnitzii. In alignment with this, a paper from 2019 (Hao et al. 2019) proposed that F. prausnitzii has significant potential as a psychobiotic. In their study, they found that F. prausnitzii has anxiolytic and antidepressant-like effects in rats.

Lastly, F. prausnitzii has also been linked to COVID-19, where it was reported to have decreased in the gut microbiota of severe COVID-19 patients compared to non-severe COVID-19 patients (Demirci 2022). Additionally, proinflammatory cytokines such as interleukin-6 were high and the anti-inflammatory response was suppressed in severe COVID-19 patients compared to non-severe COVID-19 patients. This was correlated with a decrease in F. prausnitzii amounts in the gut microbiota. In addition, F. prausnitzii was found to increase IL-10 levels, reduce corticosteroid and IL-6 levels. These findings are interesting as they correlate with our data on IL-6, as well as IL-10 in PSSD patients.

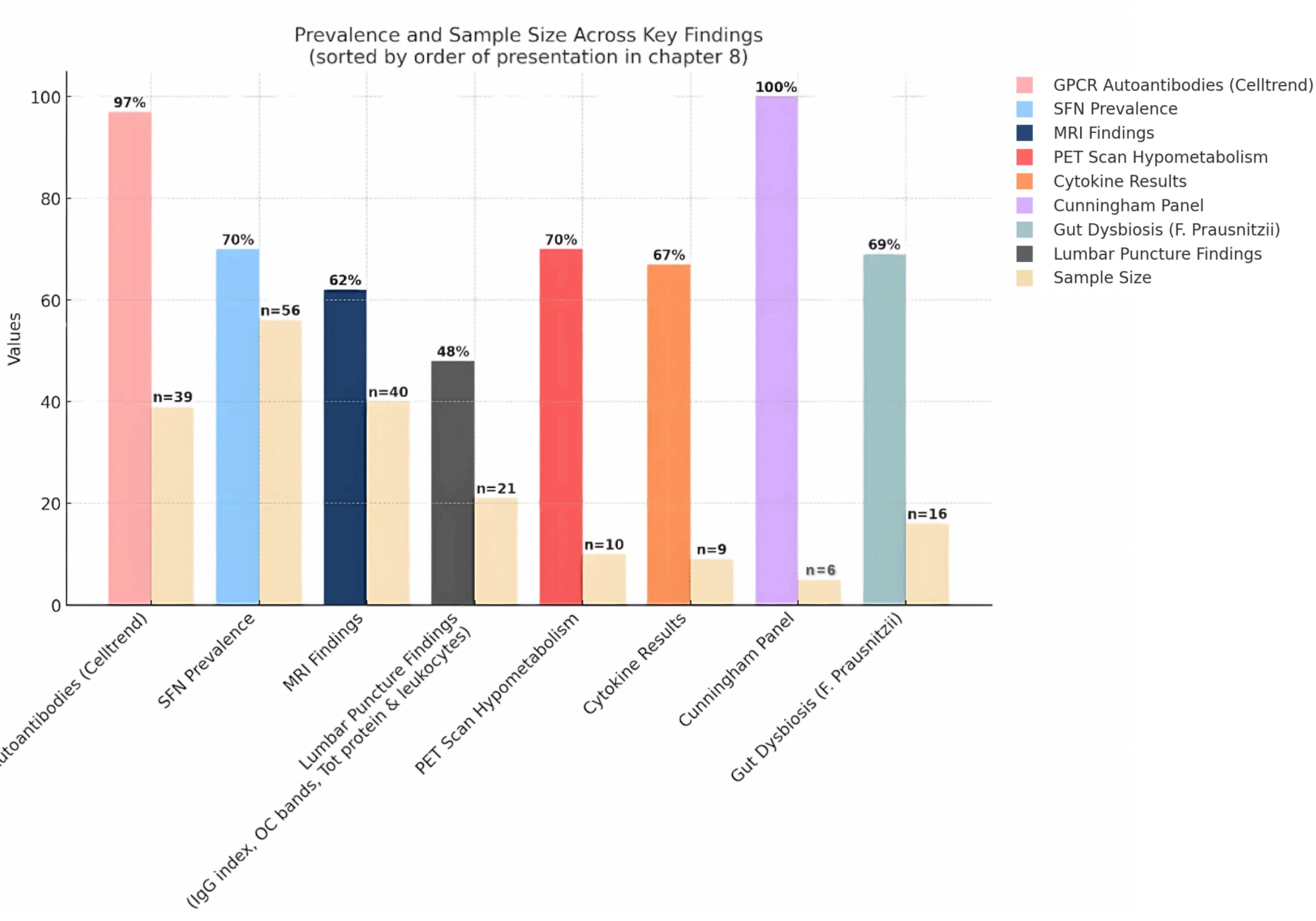
While our data on this area is limited, the clinical findings of gut dysbiosis in PSSD (table 9) are reinforced by our survey data that indicates a prevalence of gastrointestinal symptoms (see PSSD SFN Research - Survey, 2023 in appendix). While further research is needed to formally establish the high prevalence of gastrointestinal disorders in PSSD, anecdotal reports, including the community survey, report comorbid diagnosis of conditions like Small Intestinal Bacterial Overgrowth (SIBO), Gastroesophageal Reflux Disease (GERD), and Irritable Bowel Syndrome (IBS) in a notable subset of patients.

Note: A large number of patients in the community (reddit and other platforms) have reportedly tested positive for **Small Intestinal Bacterial Overgrowth (SIBO)**, a condition where excessive bacteria grow in the small intestine. It is linked to dysbiosis and can lead to symptoms such as bloating, abdominal pain, and malnutrition, and is often associated with conditions such as IBS and Crohn's disease and may be exacerbated by autonomic dysfunction, which impairs gut motility. SIBO has been one of the most reported tests in the community. We do not currently have data on this but might start tracking these results eventually.

8.9 Summary of clinical findings

The findings presented in this chapter illustrate the multi-systemic nature of PSSD, with significant contributions from autonomic, central, and peripheral nervous system dysfunctions, as well as immune and gut microbiome dysregulation. High rates of GPCR autoantibodies and small fiber neuropathy highlight the involvement of the autonomic and somatic nervous systems. CNS findings, such as MRI and PET abnormalities, elevated cytokines and Cunningham Panel results further point to central neuroinflammation. Lastly, the reduction of F. prausnitzii underscores the role of gut-brain interactions in PSSD. Collectively, these findings provide quantitative evidence supporting the hypothesis of PSSD as a complex, multi-systemic condition.

Figure 3: Summary of data



9. Treatment anecdotes & case reports

A small number of community members have been diagnosed with immune-mediated small fiber neuropathy, inflammatory polyneuropathy or other autoimmune conditions such as «Polyimmunopathy», and have thus been able to acquire immunotherapies. The treatments have shown some promise in alleviating symptoms, but as of now the sample size is too small and the length of time has been too short to draw any conclusions.
In addition to this, we have acquired four "case reports" with detailed medical reports from neurologists. This section will explore these aspects.

Disclaimer: *We are not medical professionals and are just reporting on these trials. We are not recommending patients to try out any of these treatments on their own. These are serious medications with potentially significant complications and side effects. We want to encourage patients to seek out medical professionals that can guide them in acquiring the correct diagnosis and treatment.*

9.1 Reported treatment trials

Certain treatments have shown a more favourable outcome than others. It is worth noting that most of these treatments are inaccessible for a majority of patients due to the issues surrounding the acknowledgement of PSSD as being a real illness by medical professionals, where symptoms are often attributed to psychiatric or psychosomatic causes where patients are not offered a basic diagnostic process to rule out other causes prior to drawing such conclusions. Additionally due to the limitations in knowledge on this complex condition, doctors may understandably have a hard time knowing how to interpret symptoms and findings, and thus, will have to give treatments off-label unless the patient fits certain criteria for an established diagnosis.

IVIG (intravenous-immunoglobulin)

IVIG is a treatment that involves the infusion of donated pooled immunoglobulin G (IgG) antibodies from the plasma of thousands of donors. It is used in various autoimmune, inflammatory, and immune deficiency disorders to modulate and normalise the compromised immune system (Arumugham and Rayi, 2024). Although a large number of clinical trials have demonstrated that immunoglobulin is effective and well tolerated, various adverse effects have been reported. The majority of these events, such as flushing, headache, malaise, fever, chills, fatigue and lethargy, are transient and mild. However, some rare side effects, including renal impairment, thrombosis, arrhythmia, aseptic meningitis, hemolytic anemia, and transfusion-related acute lung injury (TRALI), are serious. These adverse effects are associated with specific immunoglobulin preparations and individual differences (Guo et al. 2018b).

Trials: 11 patients have been, or are, currently being treated with IVIG. Results so far are mixed. One patient had a very favourable response where they were taken off after around 8-9 months still feeling largely recovered. One patient noted that it halted the progression of their neuropathy, but that it wasn't strong enough on its own to relieve symptoms overall, so additional treatments were added. Some patients have reported improvements in certain symptoms for a brief period of time after administration but that these fade fairly quickly over the following days. 3 patients have been discontinued after a few months and up to a year of treatment, noting it didn't work. Assessing the results at this time is challenging due to several factors: Dosing and length of time has been highly variable, ranging from under 1g/kg to 2g/kg, and length of time ranging from a month to 2 years. As with any disease state, treatment responses will vary due to the complexity of variables for each case. More people have recently been approved for IVIG, so within a year we should have a better understanding of its potential in treating/improving symptoms in PSSD.

Rituximab

Rituximab is a monoclonal antibody that targets CD20 on B cells, leading to their depletion, thus suppressing the immune system. It is primarily used to treat certain autoimmune diseases, such as rheumatoid arthritis and multiple sclerosis, and some types of cancer, like non-Hodgkin's lymphoma (Hanif and Anwer 2024, Edwards et al. 2004). Since Rituximab is an immunosuppressant, it can increase risks of infections. Hypersensitivity reactions (HSR) are commonly seen with rituximab infusions. In a retrospective study on long term safety of Rituximab from 2022, the authors found that the rate of serious infections in patients receiving Rituximab varied from 2.2 to 9.8/100 person-years in the studies published over the last 5 years and did not significantly differ between abatacept, Rituximab, tocilizumab in those with underlying rheumatic diseases. Additional risk factors for infection, included infection with first treatment of Rituximab in those undergoing retreatment, previous or current smoking, switches between biologic therapy, which may help identify patients who require closer monitoring (Varley and Winthrop 2021)

Trials: Only 2 patients have been treated with Rituximab so far. This has per reports been the most promising treatment overall in alleviating symptoms, where relief in cognitive difficulties and anhedonia have been particularly noteworthy. Additionally, one patient has recently started using a similar drug named Kesimpta (ofatumumab), which has also shown promise by improving symptoms such as anhedonia. With that said, sample size is particularly small and this medication also carries serious risks, so caution should be warranted if considering this option.

Plasmapheresis

Plasmapheresis is a procedure which involves removal, return or exchange of blood plasma, resulting in a filtered plasma product that returns to the patient's body. It is used to treat various diseases such as autoimmune diseases like GBS, CIDP and anti-NMDA autoimmune encephalitis. The preferred method of plasmapheresis in most clinics worldwide is by automated **centrifuge-based technology**, in which filtered plasma is discarded, and RBCs and replacement fluid (donor plasma or colloids) are returned. However, in certain hospitals plasmapheresis is done using **membrane plasma separation**, where it selectively removes undesired macromolecules; hence, filtered, processed plasma is returned to the patient, eliminating the need for replacement fluids. Generally, risks and side effects are mild, most common being transient hypotension and related symptoms (Sergent and Ashurst 2024).

Trials: 4 patients have tried plasmapheresis and 1 patient has tried Inuspheresis (a similar treatment). Plasmapheresis seems like a promising first line treatment for PSSD patients, based on the overall positive anecdotal reports so far. Symptoms such as derealization and mental clarity, as well as "Cognition, hedonic tone, connectedness with body, improved blood flow and improvements in gastroparesis" have been reported. Dysautonomia symptoms seem to respond favourably. However, since PSSD seems to generally involve ongoing immune dysregulation for many, symptoms will return within weeks to a couple of months after treatment when autoantibodies have reached a certain level in the blood again.

HELP-Apheresis

Heparin-induced Extracorporeal LDL Precipitation (HELP) Apheresis is a technique used to lower lipoprotein levels in the blood by filtering and removing LDL cholesterol and fibrinogen. It also helps improve plasma viscosity and microcirculation. It is used in patients such as those with severe hypercholesterolemia, hyperlipidemia and certain autoimmune disease (Seidel 1996). HELP-apheresis is also frequently used in the treatment of long covid (Achleitner et al. 2023).

Trials: 2 patients have tried HELP-Apheresis. Reports were that it slightly helped with some symptoms for a period of a couple of months.
Both patients (case report 1 and 2) did 5 sessions of HELP-apheresis as recommended by the treating clinic. They both reported that their «vein function was very poor» and that their arms had to be heated up for an extended period of time in order for the blood to flow properly through the machine. Blood consistency was reportedly very thick and dark coloured, flowing poorly which made the first 2-3 sessions particularly complicated. Initially patient 2's doctor requested him to drink more water on the suspicion that he might be dehydrated (suspected low blood volume?), but despite drinking several liters of water, there was no apparent improvement in blood circulation.
The most notable discovery was a buildup of a yellow/white opaque substance that came out of their veins and accumulated in the container after filtration. The rheumatologists from the rheumatology department at this clinic discussed this at their meeting in the central hospital, where macroglobulinemia was initially suggested, until they drew a conclusion that it was most likely a buildup/accumulation of protein.
Patient 2 has speculated that this protein buildup could potentially be in-line with the etiology of fibrin protein mediated microthrombosis that's found in Long Covid (Ryu et al. 2024), (see chapter 11 for more).
Recently another report came in of a patient with the same findings, so this will need further investigation.

Immunoadsorption

Immunoadsorption (IA) is a procedure that selectively removes pathogenic antibodies from the blood through the use of specific adsorbers. It is used in the treatment of autoimmune diseases such as MS, CIDP and GBS. IA has a low risk of infections, but has repeatedly been described as a safe and well-tolerated procedure (Dorst et al. 2020).

Trials: Only one patient has reported trialing immunoadsorption. Report stated it helped improve symptoms such as cognitive difficulties including memory, thinking and dysautonomia. Ability to sweat returned and bradycardia stopped where heart rate returned to normal, something the patient hadn't felt since the onset of the disease.

Corticosteroids (Prednisone)

Corticosteroids such as Prednisone, are a class of steroid hormones that are used to reduce inflammation and suppress the immune system in various conditions, including autoimmune diseases, allergies, and asthma. It is generally considered a short term treatment during early disease onset and during flare ups, and may also function as a "probe" to determine etiology of symptoms where for example improvements may suggest immune-mediated etiology if other test results and clinical picture suggests the same. Corticosteroids are associated with serious risks, especially with long term use. Osteoporosis, adrenal suppression, hyperglycemia, dyslipidemia, cardiovascular disease, Cushing's syndrome, psychiatric disturbances and immunosuppression are among the more serious side effects noted with systemic corticosteroid therapy, particularly when used at high doses for prolonged periods (Liu et al. 2013).

Trials: A number of patients have tried Prednisone with overall positive reports so far. Patients have noted improvements especially in cognitive symptoms, but also sexual symptoms like sensitivity and libido. Both tablet form and IV have been trialed. IV form has given greater improvements as per patient reports due to its application and high dose, though a couple of reports have stated that it did not lead to any symptom improvements for them. Why this is the case is hard to say given the complexity of factors involved. In some instances for example, patients that have comorbid infections may get worse due to how Prednisone lowers the immune system. It would be crucial in such cases to treat the infection as well, such as with antivirals for example. Interestingly, a few patients have recently reported improvements several weeks after initially not having a positive effect, from trialing short courses of high dose IV methylprednisolone.

Low dose naltrexone (LDN)

Low-dose naltrexone (LDN) is an opioid receptor antagonist used in very low doses to modulate immune function and reduce neuroinflammation. LDN has shown promise in treating conditions involving chronic pain, inflammation, and immune dysfunction, such as fibromyalgia, Crohn's disease,, multiple sclerosis and complex regional pain syndrome. While its mechanisms and applications are still being studied, LDN is considered a low-risk, cost-effective therapy for these conditions (Younger et al. 2014).

Trials: At the moment it is unclear how many have tried this medication, but we have received reports from a handful of people. Some have noted certain benefits and minor improvements, consisting mainly of less brain fog, better gut motility, slightly increased libido and return of nocturnal erections. Generally though, it does not seem potent enough to reach broad symptomatic remission. Additionally, some patients have reported crashing and temporary worsening of symptoms from this substance. More trials are needed to determine its usefulness in this condition.

Fecal microbiota transplantation (FMT)

FMT is an experimental treatment aimed to correct gut dysbiosis and thereby improve various conditions such as Clostridium Difficile (CID), gastrointestinal disorders such as IB and IBD as well as certain autoimmune diseases such as MS (Laeeq et al 2023).
A healthy donor stool is usually transplanted by colonoscopy or enema but may also be ingested through oral capsules.
The most serious risk that has been reported with respect to lower gastrointestinal tract administration is perforation. Theoretically, bleeding, adverse reaction to sedative drugs, cardiovascular events, transient fevers, or infections could occur, as with any colonoscopy procedure.
All forms of upper tract delivery increase the risk of vomiting or aspiration. The 2 most common side effects of FMT are bloating and loose stools for the first 24 hours, which usually resolve soon thereafter. Due to lack of research, long-term risks are currently unknown. Screening of donors by means of a thorough history may not reveal all future risks. Most FMT protocols aim to exclude donors with metabolic syndrome, obesity, neuropsychiatric disorders, and malignancies; however, a disease might emerge in the donor at a later date. This represents both a concern about FMT and a justification for the existence of stool banks, as follow-up of donors and maintenance of records would be more likely in stool banks, allowing the earlier identification of risks (Kim and Gluck 2019).

Trials: While it showed some early promise from a few anecdotes in the community, it has unfortunately been largely ineffective in most patients that sought out this treatment. Some patients have reported transient improvements in some symptoms that faded with time, but most patients have reported little to no benefit. We do not currently have an exact number of trials but we are aware of at least 10 members which have tried this method. Many have sought out specific protocols offered at professional clinics which involve numerous FMT's to increase probability of success. Despite a few positive anecdotes, FMT has not yielded success overall so far.

Note: *Due to time constraints as well as concerns regarding patients potentially trialing medications that may be risky we decided for this iteration of the document not to include discussions around pharmaceutical trials in the community. We do however, view it as an area of interest due to anecdotal reports of transient symptomatic improvements from certain drug classes in some patients. These anecdotes have underscored our observations around the hypothesised dopaminergic dysregulation discussed in this document. If we can find a proper and responsible way to discuss it, we may present this investigation in the next iteration (3.0).*

Discussion

The treatment trials reported by the PSSD community provide valuable anecdotal insights into potential therapeutic options, albeit with limitations due to small sample sizes, variability in outcomes and short duration of time. The interventions mentioned, such as Rituximab, plasmapheresis and corticosteroids, show some promise in alleviating symptoms, although overall responses and outcomes have been mixed so far, such as seen with IVIG. However, it is known that treatment of autoimmune disease often requires trial and error as many variables can make it harder to predict effect and outcome. Paradoxical reactions may even occur in patients with autoimmune disease and have been noted in the literature (Kremenevski et al. 2022). Thus, the mixed results and occasional reports of symptom "crashes" highlight the complexity of PSSD and the need for cautious, research-driven approaches. With that said, we believe there are enough favourable responses reported to strengthen our suspicion that PSSD could be, at least in part, an immune-mediated disease.

Another potential factor worth discussing is how the initial inflammatory insult (onset of PSSD) may leave residual damage for some, where the initial immune dysregulation has ceased completely or become low grade, where some may not have any ongoing activity of immune dysregulation after the initial onset. Residual symptoms are seen in for example Clinically isolated syndrome (CIS) (one time MS attack), where certain symptoms such as cognitive impairments can linger after the initial inflammatory insult has ceased. In addition, many patients that had Autoimmune encephalitis (AE), including patients successfully treated with early interventions, may still suffer from lingering symptoms. A retrospective study on AE highlights this, where the authors noted that despite good recovery, several residual symptoms persisted ≥24 months post-AE, including **cognitive deficits (53%)**, seizures (26%), **depression (23%)**, sleep disorders (25%), brainstem/cerebellar symptoms (13%), other movement disorders (14%) and **autonomic symptoms (12%)** (Thakolwiboon et al. 2025). If something similar could be the case for some with PSSD, remains to be seen.

Note: It is important to mention that the severity of the symptoms and desperation to find a cure can sometimes lead to patients seeking quick answers and immediate relief. This may result in trialing treatments using dietary supplements, other medication (including different antidepressants) or even recreational drugs. While there may be testimonies on various internet forums about individual people benefiting from a substance X, there often are reports of trials with the same substance leading to a so-called «crash», which is a rapid and sudden worsening of symptoms. In addition, tapering too fast or the discontinuation of the medication itself may often lead to a crash as well. Thus, we must encourage caution on any trials with both legal and illegal substances. For safe tapering of antidepressants, please consider The Maudsley Deprescribing Guidelines (Horrowitz and Taylor 2024, pdf available online: https://content.e-bookshelf.de/media/reading/L-22849603-bfafeef8c5.pdf).

We cannot stress enough the desperate need for accurate information, medical research and proper research based treatment at health care facilities.

9.2 Case reports

We asked some of the patients that provided us with data to write up short case profiles so we could dive deeper into a few examples of cases with different severity, test results and treatment experiences. Four of the write ups which we have termed “case reports”, include detailed medical reports from the patient’s neurologists. We believe this adds a significant value to this document by offering a unique perspective when investigating PSSD in relation to its possible neuroimmune etiology. Case profiles 5 and 6 have been moved to the appendix to limit the length of this section.

Note: *All patients agreed to the inclusion of their report in this document.*

Case report 1

Reported by patient

Tracker identification

Celltrend: Patient 6

Skin biopsy: Patient 2

MRI: Patient 1

Lumbar puncture: Patient 1

PET-scan: Patient 1

Patient profile:

Gender: Male

Age: 32

Medication causing PSSD: Lexapro

Length of time medicated: 5 weeks

When PSSD presented: Within the first few days

Length of time with PSSD: Almost 3 years

Symptoms: Emotional blunting, anhedonia, sexual dysfunction, loss of libido, muted orgasmic sensation, genital numbness, tremors, fatigue

Testing: MRI, lumbar puncture, skin biopsy, celltrend, PET-Scan

Diagnosis: Immune-mediated SFN, Polyimmunopathy, (suspected) Seronegative autoimmune encephalitis

Treatment: IVIG, Immunoadsorption, Rituximab, IV-prednisone, Prednisone tablets, Plasmapheresis, FMT

Post treatment outcome: IVIG: Stopped progression of sensory issues and neuropathy, improved breathing issues, some cognitive improvements at the 4 month mark. Immunoadsorption: Normalized heart rate, more sensation, sweating returned, significant improvements in brain fog. Rituximab started eight after IA. 6 weeks post Rituximab infusion my vision and cognition became much better and my sense of atmosphere improved. Anhedonia got better as did emotional blunting. Resolved muscle weakness.

FMT has corrected some GI issues. (Still undergoing treatment).

Additional info (known disease pathologies, previous infections etc prior to PSSD): Nothing.

Report from neurologist:

Slightly altered to protect patient privacy

«The patient is a previously healthy person. In October 2021 the patient developed a sudden immunological reaction to Escitalopram medication, which was prescribed to the patient without convincing psychiatric indication (undiagnosed sleep apnea). The patient developed severe autoimmune small fiber neuropathy and autonomic neuropathy within a few days of starting the Escitalopram. The symptoms progressed severely after discontinuation of Escitalopram. The patient originally was told that these symptoms were SSRI withdrawal symptoms. Unfortunately within few weeks after Escitalopram discontinuation the patient developed circulatory disturbances, livedo reticularis, vertigo, difficulty breathing, fasciculations, tremors, total anhidrosis, bradycardia, severe cognitive dysfunction, visual snow, stiff muscles (in Stiff Person`s type manner) and the small fiber neuropathy spread to the whole body (pain, paresthesia, numbness, severe nausea). Cranial neuropathy caused swallowing difficulties and gastroparesis. The patient became bed-bound. In December 2022 the patient was admitted to the Neurology department.
Both the neurologists and rheumatologists made very careful evaluations of the patient. A strong immunological disease was suspected based on symptoms and the rapid onset of the disease.

Lumbar puncture indicated an inflammatory finding with positive IgG index (0.8) and leukocytosis (9). Spinal MRI, Body CT, Myositis and autoimmune encephalitis autoantibodies were normal. However, brain FDG-PET showed hypometabolism temporo-pariteally, possibly suggesting seronegative autoimmune encephalitis. Brain MRI was considered within Normal Limits. Skin biopsy from the distal part of the lower leg revealed a significant small fiber neuropathy compared to age matched controls with IENFD results of 2,3 / mm. Large GPCR autoantibody package came back with extraordinary high positive results, indicating severe autoimmunity against the autonomic nervous system and endothelium:
Anti-AT1R: POSITIVE 50.7 u/ml (Ref. <10 u/ml), Anti-ETAR: POSITIVE 58.3 u/ml (Ref. <10 u/ml), Anti-a-1-adrenergic: POSITIVE 50.7 u/ml (Ref <7 u/ml), Anti-b-1-adrenergic: POSITIVE 55.6 u/ml (Ref. <15 u/ml) , Anti b-2-adrenergic: POSITIVE 72.1 u/ml (Ref <8 u/ml), Anti-muscarinic receptor 3: POSITIVE 54.4 u/ml (Ref <6 u/ml), Anti-muscarinic receptor 4: POSITIVE 38.4 u/ml (Ref. <10.7 u/ml).

In a comprehensive rheumatological evaluation no clear rheumatological diagnosis could be made. The chief rheumatologist stated however that the patient might have a so-called ”polyimmunopathy”. Cardiologist also confirmed cardiovascular / autonomic neuropathy based on 24h Holter evaluation and clinical symptoms. The patient had to be taken as an inpatient due to constant breathing difficulties and severe arrhythmias.
The team of immunologists made a diagnosis of immune-mediated (unspecified inflammatory) polyneuropathy and started high dose IVIG treatment (2g/kg) together with 40mg/day Prednisone in January 2023. Within 3 weeks the patient started to feel significantly better and was able to start walking short distances. The high dose IVIG was continued every four weeks as a rapid deterioration in all symptoms was seen when the treatment interval was extended. Corticosteroids were tapered, which again resulted in worsening both in cognitive functioning and memory. As the autoantibody load was huge, the patient consulted specialists in neuroimmunology departments around the EU. The patient was recommended to go through plasmapheresis or immunoadsorption in order to neutralize the autoantibody levels. The patient received five immunoadsorption- plasmapheresis treatments as an outpatient in a private clinic with very good response and no side effects. The anhidrosis, weakness, gastroparesis, bradycardia and severe pain all resolved after the third treatment. One week after these treatments the patient was much improved even cognitively. The plasma IgG was under reference value after immunoadsorption and the patient received his regular IVIG infusion shortly after. In October 2023 the neuroimmunological team added Rituximab to IVIG in order to keep the autoantibody production low. 6 weeks after the Rituximab infusions the patient reported significant recovery in functioning and cognition. Plasmapheresis was done 8 times 5 months after Rituximab infusion, which made the patient significantly better in all symptoms. The patient has regained memory, cognitive functions and the severe anhedonia and depression is mostly resolved. The sexual functioning is also improved as there is significant improvement in neuropathy. Heart rate variability has increased about 150% since starting the treatment, confirming significant regeneration in the autonomic nerves. The sweating of the skin has now normalized and temperature sensation has returned.

It seems that this disabling disease needs aggressive immunological treatments and the possible remission might only be reached by combination treatments. Luckily there has been a clear response to treatments. Compared to January 2023, the patient is much improved. The patient has since moved abroad to continue treatment elsewhere due to new treatment guideline restrictions in his country of origin.»

Comment: We have been in contact with this patient for over a year at this point and have gotten continuous feedback on his treatment trials. One of the most severe cases we have seen, with symptoms going way beyond the classic PSSD presentation. Although he has recovered to a significant degree through heavy immunotherapies, he still struggles with lingering symptoms. We won't be able to draw any conclusions on his real treatment outcome until another year of immunological treatment (IVIG and Rituximab).
This person has given us valuable input and great insight into his treatment trials, providing interesting insights and thoughts on etiology as well as connecting us with important people in the PSSD and medical scene. We owe a lot to this person for starting the ball rolling on this, by reporting his Celltrend results to the community, and ultimately examinations and diagnostics with his neurologist.
This patient’s profile and medical summary/report is the most valuable we have due to being the only known PSSD patient with a positive celltrend test (as well as other labs) without ever getting the Covid Vaccine or contracted Covid-19 prior to testing. This adds a lot of value and validity to PSSD as a neuro-immune condition, as Lexapro was the clear trigger in his case.
We believe he could potentially be a great candidate for a case study one day if that would be possible.

Case report 2

Written by patient

Tracker identification

Celltrend: Patient 21

Skin biopsy: Patient 15

MRI: Patient 14

Lumbar puncture: Patient 4

Cytokine panel: Patient 1

Patient profile:

Gender: Male

Age: 20

Medication causing PSSD: Sertraline, Risperidone

Length of time medicated: Sertraline: 1,5 years, Risperidone 4 days

When PSSD presented: Gradual onset of symptoms on Sertraline with a worsening and onset of PSSD with discontinuation, intense and quick worsening of symptoms with the addition of Risperidone

Length of time with PSSD: ~4-5 years

Symptoms: Full body peripheral numbness of skin, tingling & burning in extremities. Anhedonia, severe cognitive dysfunction affecting memory, speech, spatial awareness, aphantasia, visual snow. Abdominal cramps, bloating, constipation, food intolerances. Sexual dysfunction, erectile dysfunction, pressure headache, vertigo, PEM, chronic fatigue, muscle atrophy, weakness, dry skin, shortness of breath, circulatory dysfunction (Dysautonomia & POTS).

Testing: IENF Skin biopsy: 1.8/mm, QST: positive, ENMG: normal, brain/spine/neck/abdominal MRIs: normal except intermediate radiculopathy and disc degeneration in the neck, ALT: alternating between 100-300, GPCR autoantibodies: positive, TS-HDS: highly positive, SIBO breath test: positive methanogen overgrowth

Diagnosis: Small Fiber Neuropathy/Peripheral Neuropathy, Dysautonomia

Treatment: H.E.L.P Apheresis, Fecal Microbiota Transplantations

Post treatment outcome: Transient improvement in majority of symptoms over a 4 month period, reaching a state of stability in disease progression. Treatments neccesite repetition post the 3-4th month mark as the improvements staggered.

Prednisone 10-30mg: significant but transient alleviation in symptoms especially with peripheral neuropathy and cognition related symptomatologies. Works well as a management treatment.

Additional info (known diseases, previous infections etc prior to PSSD): IBS, OCD, strep infections as a child, several courses of antibiotics

Report from neurologist:

Slightly altered to protect patient privacy

“Diagnosis: G62.8 Inflammatory Small Fiber Neuropathy G90.8 Dysautonomia

I hereby confirm that *name censored* has been my patient since 2023 and has a severe autoinflammatory condition with dysautonomia and small fibre neuropathy.

20 year old university student who has previously suffered from generalized anxiety disorder and OCD. Sertraline treatment for these conditions in November 2018-April 2020 100mg, tapered down spring 2020. Neurological symptoms started while use of Sertraline, brain zaps with accompanying headache, cranial nerve pain with burning, intermediate chronic fatigue with post exertional malaise, loss of sensitivity for peripheral touch and temperature, genital paresthesia, burning across the body, emotional blunting, cognitive decline affecting perception, memory, concentration and reading comprehension. Symptoms continued progressing despite withdrawal of the drug.

Risperidone 0.5mg treatment for insomnia in December 2020 significantly exacerbated the condition with acute worsening. Thereafter symptoms have been clinically consistent with small fiber neuropathy and autonomic dysfunction as well as suspected neuroinflammatory components of the condition.

Neuropathic and autonomic symptoms consisting of numbness, burning and tingling paresthesia throughout the body. Diminished peripheral temperature and touch sensitivity. Lack of skin moisture, hypohidrosis, dysphagia, dysfunctional temperature regulation, loss of hunger & thirst, shallow breath, tachycardia, exercise intolerance with PEM, chronic fatigue, tunnel vision & blurry vision. Sexual dysfunction with erogenous genital paresthesia, erectile dysfunction, watery semen consistency, loss of orgasm and libido. Endothelial dysfunction with poor peripheral circulation,

vasoconstriction, weak heartbeat, vascular head pressure in connection to physical exertion, blood pooling with bulging vasculature in extremities. Gastrointestinal symptoms with gastroparesis, hypomotility, cramps, reflux and nutrient malabsorption, loss of natural stool odor and form.
New onset food intolerances consistent with Mast Cell Activation Syndrome.
Additional neurological symptomatology presents a potential neuroinflammatory etiology, including severe deficits in higher cognitive abilities, loss of spatial awareness, coordination, perception, memory, speech, thought processing, inability to form thoughts and mental imagery as per aphantasia, emotional anhedonia and loss of emotional response, hypomimia. Visual deficits consistent with visual snow syndrome, decreased color perception, blurry vision and after-images. Inner restlessness, vibrations, tremors and irregularity of the patient's pattern of thought as per akathisia. Altogether these symptoms inhibit all ordinary functioning, the patient can not work nor perform academically and is on disability leave for the moment being.

The condition can be characterized as iatrogenic, it is a drug-induced multi-system autoimmune inflammatory response. The condition has continued to progress post drug withdrawal in December of 2020 and has worsened without signs of remission in the patient's symptoms. The patient is interested in assessment of possible immunotherapy with therapeutic plasma exchange, Rituximab or intravenous corticosteroid therapy for the diagnosis of inflammatory small fiber neuropathy, dysautonomia and the neuroinflammatory components of the disorder.

Diagnostics:
Corneal Confocal Microscopy: "Elevated immature (5 – 6x the normal level) and mature dendritic cells (10x the normal level) indicate low-grade chronic inflammation and immune activation." Significantly reduced Epidermal Nerve Fiber Density (Skin Biopsy): 1.8/mm (normal values matched for males aged 20-29 are: >:6.7/mm)
GPCR autoantibodies: elevated alpha-1 adrenergic, AT1AR, ETAR, b-2 adrenergic and muscarinic cholinergic 3. TS-HDS autoantibodies associated with inflammatory small fibre neuropathy elevated.
Highly elevated Inflammatory cytokines: Interleukin-6> 5.000pg/ml (norm: 300-1750), Interleukin-10>228,9pg/ml (norm:10-60). Elevated IgG4: 3.72g/l (norm: 0.08-1-4 g/l), IgE344 kU/l (norm: 0-110). Elevated ALT 150 (norm:<50). CSF regular. A PET brain scan has been considered to detect neuroinflammation and associated metabolic changes but not done, due to lack of availability of gliands suitable for detection of glial immunoactivation.

Censored, January 8th, 2024"

Comment: We have also been in continuous contact with this person as well for about a year now and followed their case closely, getting updates on their neurology testing as well as treatment trials. They have reported unique immunological trials such as HELP-apheresis, Plasmapheresis and IV-prednisone which have been valuable anecdotes. The patient has also given us valuable input on possible etiology and we've had a lot of discussions around this.

Case report 3

Written by patient

Tracker identification

Celltrend: Patient 30

MRI: Patient 36

Patient profile:

Gender: Female

Age: 23

Medication causing PSSD: Effexor (Venlafaxine)

Length of time medicated: 7 months (January - July 2022)

When PSSD presented: from the first pill I had symptoms, then big withdrawals symptoms, then I got slightly better and 2 months after my health started to decline extremely quickly

Length of time with PSSD: 22 months

Symptoms: Full body neuropathy, tingling/burning, erythromelalgia, sexual dysfunction, dysautonomia, arrhythmias, blood pooling, visual snow syndrome, extreme fatigue, PEM, cognitive dysfunction, memory loss, anxiety, intense head pressure, ice pick headaches, muscle twitching +++ and stiffness and pain, blood sugar variations, anhedonia, diarrhea/constipation, jerks, shortness of breath, muscular weakness, vertigo dizziness, tremors, internal vibrations +++, tinnitus, dryness, red eyes, joint pain

Testing: MRIs of brain and cervical, QSRT, tilt test, holter monitoring, classic blood works, neurological antibodies in blood, celltrend GPCR panel

Diagnosis: Possible seronegative autoimmune encephalitis and autoimmune dysautonomia, diagnostic rejected in France. MCAS, pots.

Treatment: One round of IVIG November 2023. Got aseptic meningitis, now waiting for further help.

Additional info (known diseases, previous infections etc prior to PSSD): Migraine sufferer, IBS, ADHD. I had a thyroid problem for 8 months, certainly autoimmune (July 2023 - mars 2024). Surgery for a toe infection just before symptoms became worse and developed (October 2022). COVID vax x3, COVID infection in march 2022.

Referral to a specialist from neurologist:

Slightly altered to protect patient privacy

«I am writing to recommend further evaluation and specialized care for my patient, *name censored*, who is presenting with a clinical picture highly suggestive of seronegative autoimmune encephalitis and autoimmune dysautonomia.

Name censored, a 23 year-old Female, has been under my care since 05/23, during which she has exhibited a range of neurological and autonomic symptoms. Despite extensive diagnostic efforts, including laboratory tests, imaging studies, and consultations with various specialists, her condition remains undiagnosed. Her symptoms are severely impacting her quality of life and daily functioning.

The patient's neurological manifestations include episodes of confusion, memory disturbances, and intermittent focal neurological deficits. These episodes have been evaluated with standard testing for autoimmune encephalitis, including MRI, and serological markers for common autoimmune antibodies, all of which have returned within normal limits aside from a slightly positive TPO antibody which could indicate HE (Hashimoto's Encephalopathy). Given the absence of serological evidence, but in the presence of a compelling clinical presentation, her condition is suggestive of seronegative autoimmune encephalitis, a known entity where patients may not exhibit typical antibodies but still suffer from an autoimmune attack on the central nervous system. Additionally, the patient has been experiencing significant dysautonomia. Symptoms such as orthostatic intolerance, heart rate variability, and gastrointestinal dysmotility indicate a dysfunction in her autonomic nervous system. These symptoms, which align with autoimmune dysautonomia, have further complicated her clinical picture and management.

Given the complexity and severity of the patient's condition, I recommend her for a multidisciplinary approach involving neurology, immunology, and possibly rheumatology, essential for a thorough assessment and targeted treatment plan. First line therapy for Seronegative Autoimmune Encephalitis is typically High dose Steroids (1g daily for 3-5 days), High dose IVIG (2G/kg) and 3-5 sessions of plasmapheresis. If first like modalities are only partially effective, or not helpful at all, it can sometimes be beneficial to do a combination of therapies such as 3-5 rounds of plasmapheresis followed by Rituximab. If a combination of first line therapy continues to fail, second line immunotherapy should be considered, which usually includes Rituximab (375 mg/m2 weekly IV infusion for 4 weeks) and/or Cyclophosphamide 750 mg/m2 monthly for 3-6 months.

The patient has shown remarkable resilience throughout her medical journey, and I believe that with the appropriate specialized care, there is a significant potential for improvement in her health and quality of life. I Am confident that further investigation and management in a specialized setting will provide the insights and therapeutic strategies needed to address her complex condition. Thank you for your attention to this matter. Please feel free to contact me if you require further information or wish to discuss the patient's case in more detail. Sincerely, Dr *name censored*».

Comment: This patient has newly joined the scene. Sadly, despite efforts they have not been able to acquire treatment as of yet.

Case report 4

Written by patient

Tracker identification

Celltrend: Patient: 20

Skin biopsy: Patient 33

MRI: Patient 19

Lumbar puncture: Patient 19

Cytokine panel: Patient 7

Cunningham panel: 2

F. Prauznitsii: 1

Patient profile:

Gender: Male

Age: 33

Medication causing PSSD: Zoloft (sertraline), Lexapro (Escitalopram)

Length of time medicated: About a few weeks on Zoloft, then a year, followed 3 years later by a 3 months of Lexapro (Escitalopram actavis)

When PSSD presented: Unclear but i think on medication (long time ago), and got worse the following months after quitting Lexapro

Length of time with PSSD: 19 years

Symptoms: Severe Anhedonia & emotional blunting, low to zero sex drive and fluctuating issues with ED, severe brain fog/cognitive dysfunction, genital numbness, anorgasmia, fatigue, muscle weakness and pain on exertion, GI issues, weak motility and dyssynergia.

Testing: Multiple blood tests, full body MRI, EMG (negative), thermotest (abnormal), skin biopsy (negative but low), lumbar puncture (elevated igg, albumin and protein. Borderline high leukocytes), cytokine panel (negative), positive Celltrend and Cunningham panel, multiple colonoscopies and endoscopies, GI map and SIBO breath testing

Diagnosis: Dysautonomia, ME/CFS & PSSD

Treatment: None other than LDN and some pharmaceuticals (MAOI's, stimulants, Pregabalin etc).

Post treatment outcome:

Additional info (known diseases, previous infections etc prior to PSSD and so on): Possible PANDAS, although unconfirmed.

Report from neurologist:

Slightly altered to protect patient privacy

«The patient has suffered from PSSD for over 18 years. For context, PSSD (Post-SSRI sexual dysfunction) is an underdiagnosed medical condition that involves persistent symptoms of genital numbness, sexual dysfunction, emotional blunting, anhedonia and cognitive impairment following exposure to (and withdrawal from) a psychiatric medication such as SSRI's.

Based on multiple patient profiles it could be classified as an iatrogenically triggered multisystem immune-mediated neurological condition, involving dysautonomia, small fiber neuropathy and possibly a CNS involvement (neuroinflammation).

The condition was triggered by Zoloft (max 150mg-200mg) at the age of 15 (2006).

The medication was prescribed for OCD indication. The patient has also suffered from depression and anxiety, and had psychotherapy on and off for years. PSSD was considerably worsened from Lexapro (escitalopram max 15mg) given for depression at age 18 (2010). Since then it has severely impacted his life where he has eventually ended up on disability, unable to function in any meaningful capacity.

Zoloft was tapered slowly, escitalopram was stopped abruptly.

Description of symptoms:

Anhedonia and apathy

Emotional blunting

Cognitive impairment (extreme memory problems, difficulty thinking clearly, slow mental processing, "brain fog," difficulty focusing, difficulty learning new things)

Sexual dysfunction (erectile dysfunction, genital numbness, loss of arousal, decreased/absent libido, anorgasmia)

Gastrointestinal disturbances (IBS, bloating, slow motility, impaired peristalsis, signs of puborectalis syndrome, dyssynergia)

Chronic fatigue

Muscle weakness (cramps easily on exertion)

Tremors (when exerting arms, legs and facial muscles + holding objects)

Various sensory loss and disturbances in the skin (scalp, hands, other areas of the body)
Back Pain (especially lower back) that comes and goes
No feeling of hunger
Problems with regulating body temperature

The patient has had 2 mRNA vaccines in 2021 and 2022, no long term symptoms. Covid infection in 01/2023 for 10 days, some fatigue for some weeks, clearly no temporary worsening of current symptoms. No CV19 nucleotide or spike protein antibodies tested.
Other infections not clearly identified. PANS/PANDAS have been retrospectively suspected to have occurred around age 11, possibly triggered by a streptococcal infection, with symptoms of anxiety and OCD debuting after that
The patient has reduced exercise intolerance since 2011, worsened in 2020, still getting worse and fluctuating a lot. Exercise window varies, typically he can walk for 3 km without PEM and flu-like symptoms, but with increased muscle ache and weakness, tremors.
Physical exercise capacity is around 30-40%. Cognitive is lower, maybe 20-30%, with short rest breaks.
Dysautonomia symptoms include elevated exercise heart rate but it has not been measured, some evidence of intolerance of supine position but no heart rate, standing test or NASA Lean test - should be done by a physiotherapist. Oura or similar data needed, especially overnight heart rate and HRV. Temperature regulation is severely disturbed, fluctuating between not tolerating heat and feeling too cold despite normal surrounding temperature. Underactive bladder and intestine, not overactive. Gut motility and peristalsis severely affected. No accommodation disturbance.
Overexcitability in the evening, no panic attacks as before. This is clear dysautonomia although some data is lacking and needed.
Sensory loss, sexual dysfunction, anhedonia, emotional blunting and cognitive difficulties, recently also dysautonomia. Diagnosis of IBS, GERD and various symptoms like tremors, muscle pain and weakness as well.
ME/CFS was suspected by a GP in 2018 but never formally diagnosed, as the referral to the ME clinic was denied due to a previous diagnosis of depression. The patient has previously been diagnosed with ADD, major depression (2012) and GAD (2018).
He has been unable to work since 2021. More or less bedbound most of the time and severely disabled.
Over the past year tests for autoantibodies have demonstrated autoimmunity, linked to SFN. A rheumatologist and neurologist previously involved.

Summary of neurological results:
Very weak reflexes in the knees. Patchy sensitivity on examination of the skin sensory nerve, a slight low-amplitude response is seen.
Thermotest: shows two abnormal cold thresholds, but with an atypical pattern for length-dependent small
fiber neuropathy (may be non-length-dependent?). Findings are limited to hypoaesthesia for cold on the
hand and medial leg on the right side.
MRI: Potential lesions in the right frontal lobe (not mentioned in the report, but confirmed by the
neurologist upon closer examination of specific MRI images during appointment 19.08.24).
Spine MRI reported as normal with no signs of narrowing of the spinal canal.
Biopsy: Negative biopsy of 5.6/mm. The lower limit is 5.2/mm and the average normative value for age is set to 10.3/mm.
Lumbar puncture: Elevated protein (0.55), IgG (55) and Albumin (0.36). Leukocytes (5). Oligoclonal bands noted as «not detected» on report but noted as «abnormal» in patient journal.
Other test results:
Positive Cunningham Panel (positive Anti-tubulin and borderline anti-D1) indicating basal ganglia encephalopathy.
Positive Celltrend GPCR autoantibody panel (Anti-ACE-2, CHRM3, CHRM4, A-1 adrenergic, B-2 adrenergic and at risk for AT1R and ETAR).
Weak positive Myositis antibody (anti-PM-Scl-75) tested at rheumatologist office 11.2023. It was retested in 02.2024 and was negative.
Cytokine panel tested 12.2024. IL-2, IL-6, IL-8, IL-10 and TNF-A was negative.
Cunningham panel and CellTrend panel results show moderate autoimmunity but do not lead to immune therapy in *redacted*, therefore a second opinion is needed. Autonomic nervous system ab's demonstrate the mechanism of dysautonomia, although the levels are not particularly high.
FGFR3 and TS-HDS also tested and negative (they are very insensitive and not very useful).
CSF unremarkable except for 5 leukocytes, no PAD, slightly elevated albumin, negative IgG-index and negative oligoclonal bands, although stated as abnormal in patient journal, this needs to be verified. S-Borrelia antibodies neg.

TSPO PET to demonstrate neuroinflammation could be an option here, if available. The patient clearly has at least mild immune dysfunction, typical for PSSD. I would like to see SC2 and spike protein antibodies. Immunotherapy might be indicated off-label, not available for this indication in *redacted* except for one patient who has also benefited from IVIG + Rituximab. Autoantibodies could be removed by immunoadsorption or apheresis. The patient is likely to have immune activation in the CNS that might be possible to be imaged by TSPO PET that is not available for clinical use in *redacted*. Since the CSF is slightly aberrant, retesting might be beneficial."

Comment: This patient is still in the process of acquiring help and treatment. For more patient profiles see the appendix.

10. Summary & speculation on etiology

Based on interpretation of data, established PSSD research & layman research

NOTE: This section is meant to be taken as surface level interpretation and speculation surrounding the data and layman research, and how it might connect to the disease etiology. We are not professionals of these fields and thus ask that this is taken as layman interpretations and ideas.

The following section is speculation around potential etiological components of the disease, based on our data interpretation, layman research and established PSSD research in the literature. As seen throughout this paper we have focused on the following components as some of the possible outcomes we strongly suspect may be occurring in this condition: **Autoimmune dysautonomia, immune-mediated small fiber neuropathy, Neuroinflammation and Gut microbiome dysbiosis.** In this section we will summarize the findings and expand on certain aspects surrounding these processes.

10.1 Autoimmune dysautonomia

Related tables: 1 & 2

The high prevalence of autoantibodies targeting GPCRs in PSSD patients (Table 1) suggests that autoimmune dysautonomia could be a significant contributing factor to the syndrome. **97% of patients tested positive for at least one biomarker, with an 86% incidence rate for ACE-2** (among 27 test samples), a crucial enzyme regulating important for body processes such as blood pressure and has been heavily linked to COVID-19, suggesting potential overlaps in the underlying mechanisms between the conditions. Furthermore, **75% of 37 samples were positive for the Muscarinic-Acetylcholine receptors 3 and 4 (M3 & M4)**, which play critical roles in smooth muscle contraction, glandular secretion, and cognitive function, indicating a possible contributing factor to autonomic and cognitive symptoms seen in PSSD. Additionally, **The Beta-1 and Beta-2 adrenergic receptors which also showed significant incident rates at 70% and 68% respectively**, suggests that these autoantibodies might contribute to cardiovascular, and other dysfunctions in PSSD based on their known biological functions and associated pathologies. The presence of these autoantibodies may explain many of the diverse symptoms seen in PSSD, from sexual dysfunction and cognitive impairment to more systemic issues such as fatigue, cardiovascular and gastrointestinal disturbances. The high prevalence of clinically diagnosed dysautonomia and SFN in the community further supports these findings and adds a certain validity to the high incidence rates seen in this panel. Based on the data, information and discussions presented in Table 1 and 2, viewed in conjunction with the overall clinical picture of PSSD and the high prevalence of diagnosed dysautonomia and small fiber neuropathy (SFN) in the community; we propose that an autoimmune-mediated dysautonomia could be a central component of the condition.

10.1.1 Endothelial Dysfunction

The endothelium is a crucial regulator of vascular tone, immune signaling, and barrier integrity. Endothelial dysfunction can occur when these functions are impaired, **leading to reduced nitric oxide (NO) availability**, oxidative stress, and increased vascular permeability (Cyr et al. 2020) A potential driver of this dysfunction are autoantibodies targeting G-protein coupled receptors (GPCRs), such as those seen in the Celltrend results. These autoantibodies may disrupt vascular homeostasis by affecting adrenergic, cholinergic, and angiotensin receptors, leading to vasoconstriction, **chronic low-grade inflammation**, and impaired microcirculation (Binda et al. 2024) . Downstream consequences of endothelial dysfunction may include autonomic instability, tissue hypoxia, **increased blood-brain barrier permeability**, and **neuroinflammation**, all of which could contribute to the persistence of PSSD symptoms, such as for example erectile dysfunction (Bivalacqua et al. 2013). Endothelial dysfunction has been linked to various disease states, such as Systemic lupus erythematosus (SLE), where endothelial progenitor cells (EPCs), which play a crucial part in vascular repair, neovascularization and maintenance of endothelial function, are quantitatively and functionally reduced in patients with SLE (Mak and Chan 2022). Additionally, endothelial dysfunction is considered a hallmark symptom of Long Covid (Kuchler et al. 2023).

10.1.1.2 Fibrin & thromboinflammation?

Thromboinflammation is a complex, immune-driven response involving both blood clotting (thrombosis) and inflammation. It occurs when the immune system and coagulation pathways interact in a way that can lead to the formation of clots, inflammation, and tissue damage. This response plays a role in many conditions, including infections, autoimmune diseases, and trauma, as well as in vascular disorders like atherosclerosis and sepsis (Mack et al. 2024). **Fibrin (Fibrinogen)** is the central structural component of blood clots and is abundantly deposited in the lungs and brains of patients with COVID-19. The amount of fibrin correlates with disease severity and is a predictive biomarker for post-COVID-19 cognitive deficits. A recent article in Nature (Ryu et al. 2024) showed that fibrin binds to the SARS-CoV-2 spike protein, forming proinflammatory blood clots that drive systemic thromboinflammation and neuropathology in COVID-19. It has been concluded that spike protein is pathogenic from both SARS-CoV-2 and vaccine mRNA (Parry et al. 2023) and that stabilised prefusion spike proteins can be found from human bodies months after vaccination (Brogna et al. 2023). Furthermore, both viral and vaccine-encoded spike proteins have been shown to play a direct role in cardiovascular and thrombotic injuries

from both COVID-19 and vaccination (Hulscher et al. 2023). (Ruy et al. 2024) showed that coagulopathy is not merely a consequence of COVID-19 infection but that it serves as a driver of the infection, inducing thromboinflammation and neuropathology. Additionally, they suggest that spike delays fibrinolysis, which may explain why blood clots in COVID-19 patients remain resistant to degradation despite anticoagulation.

The findings of the two PSSD patients that got removed a substantial quantity of yellow/white matter from their blood while treated with HELP-apheresis (chapter 9), may suggest a potential thromboinflammation in PSSD individuals with a possible link to fibrin as the main causative factor. It is worth mentioning that (Ruy et al. 2024) suggest measuring the fibrinogen plasma levels as it is a predictive biomarker for cognitive impairment in long-COVID and thus, could be used to select patients as candidates for future fibrin-targeting immunotherapies. So far it is unknown how antidepressants interact with fibrin and/or spike and how the increased BBB permeability may affect PSSD patients. However, as (Ruy et al. 2024) point out, **even in the absence of spike, fibrin is deleterious in diseases such as multiple sclerosis**, Alzheimer's disease, rheumatoid arthritis, colitis and periodontitis. Thus, it may not be too bold to assume that whatever is the underlying mechanism of PSSD, spike protein from either COVID-19 infection or from mRNA vaccine may increase the severity of symptoms. Further research on the matter will be needed.

10.2 Immune-mediated small fiber neuropathy

Related table: 3

Given SFN's impact on sensory and autonomic nerves, combined with the high incidence rate of diagnosed SFN among PSSD sufferers, which stands at an alarming **70% incidence rate from 56 patients** (Table 3), we consider it highly likely that SFN plays a significant role for a majority of individuals with PSSD. Based on the additional clinical findings in combination with the typical symptomatic presentations and the group of diagnosed patients in treatment, we are fairly certain that the SFN seen in PSSD is of immune-mediated NLD type. Further research is needed to uncover the mechanisms behind SFN's role and development in PSSD.

10.3 Neuroinflammation

Related tables: 4, 5, 6, 7, 8

The data on brain imagings and inflammatory markers presented in this document (Tables 4-8) suggests that a neuroinflammatory process could be occurring in PSSD individuals. To further investigate neuroinflammation's potential role in PSSD, we will discuss and elaborate on some key aspects we believe may support this suspicion, given the overall clinical presentation together with interpreting the community findings and their indications.

Brain imaging of PSSD patients supports the implication of neuroinflammation, revealing a **high incidence rate of hypometabolism on FDG-Pet scans (70% of 10 patients)**—findings reminiscent of other neuroinflammatory conditions such as MS and Autoimmune encephalitis.

Lumbar puncture results from a subset of PSSD patients have shown elevated inflammatory markers in their cerebrospinal fluid (CSF), including the **presence of oligoclonal bands (30%)** and **elevated protein levels (24%)**, which are indicative of central nervous system inflammation. There are also signs of a compromised BBB based on markers such as elevated Albumin and igg. A disrupted BBB has been implicated in many similar diseases such as LC (Jernbom et al. 2024). Additionally, the cytokine panel results show that **IL-6, a pro-inflammatory cytokine closely associated with many inflammatory disorders, was elevated in several patients (50%)**. IL-6 is known to cross the blood-brain barrier and influence microglial activation (Recasens et al. 2021), further supporting the notion that neuroinflammation could play a central role in the pathogenesis of PSSD. Additionally, IL-6 can reduce BBB integrity and functionality, allowing antibodies and proinflammatory cells to infiltrate the CNS. In response to stimulation by proinflammatory cytokines, astrocytes produce IL-6 which promotes demyelination and contributes to oligodendrocyte and axon damage (Fujihara et al. 2020). **The even higher incidence rate of IL-10 (75%) supports the notion of inflammation** as this is a key anti-inflammatory cytokine, and its activation thus suggests it is trying to modulate inflammation.

While the sample size is small, **The Cunningham panel results further reinforce the suspicion of neuroinflammation, where autoantibodies against neural antigens were detected in all patients (6/6)**, which are commonly associated with neuroinflammatory and neuropsychiatric disorders.
Lastly, as shown in table 1, a significant percentage of PSSD patients tested positive for the Celltrend panel (autoantibodies targeting autonomic GPCR's), which may indirectly support the suspicion of neuroinflammation in how autoimmunity can trigger neuroinflammation.
Additionally, as shown in table 3, a substantial proportion of PSSD patients exhibit Small Fiber Neuropathy (SFN), particularly the non-length dependent subtype, which is highly associated with an autoimmune causation and subsequent neuroinflammation.
This data combined suggest that neuroinflammation may play a significant role in PSSD.

10.3.1 Autoimmune encephalitis?

One potential etiological component that may contribute to neuroinflammation is autoimmune encephalitis (AE), a condition where the body's own immune system mistakenly attacks specific neuronal brain cells triggering neuroinflammation (Kelley et al. 2017). As previously alluded to throughout this paper, certain lab results like elevated leukocytes, protein and oligoclonal bands in the CSF, metabolic disturbances on PET scans, positive cytokine panels and positive Cunningham panels may indicate that a possible **subtype of autoimmune encephalitis (AE**) could be involved in the pathophysiology of PSSD.

With the symptomatic presentation commonly seen in PSSD - with an emphasis on the cognitive symptoms in particular; it could be hypothesised that specific receptor sites involved in emotional, cognitive and reward processing are being targeted by autoantibodies. For example, as seen in some PSSD patients that tested positive for the Cunningham Panel, various receptors in the basal ganglia are being targeted by functional autoantibodies (agonizing or antagonizing the receptors) causing a disruption in their function which leads to neuroinflammation, possibly presenting as - or contributing to - symptoms like anhedonia, emotional blunting and cognitive impairment.
The basal ganglia are involved in reward, emotional processing and cognition such as memory. Similar symptoms such as apathy have been noted in other subtypes of AE such as Limbic encephalitis (Gerace et al. 2013). Keeping in mind that these are complicated processes involving complex brain systems with potential downstream complications, it is difficult to pinpoint one specific region without further research and data. As such, perhaps a part of the emotional and cognitive difficulties seen in **SSRI apathy syndrome** (Sansone and Sansone 2010, Padala et al. 2020) as well as PSSD could be analogous with already characterized conditions involving basal ganglia dysfunction, such as the **athymhormic syndrome** or **auto-activation deficit**, which have also been characterized by passivity as well as emotional blunting (Habib 2004). Additionally, inflammatory cytokines have been proposed to directly affect the basal ganglia and dopamine function. In a review paper from 2012 investigating cytokines and the basal ganglia, the authors noted that chronic inflammation and exposure to inflammatory cytokines appears to lead to persisting alterations in the basal ganglia and dopamine function reflected by **anhedonia**, fatigue, and psychomotor slowing (Felger and Miller 2012). **Elevated levels of the cytokine marker IL-6, which has frequently been elevated in PSSD patients, is often associated with AE** and could further suggest a possible AE component in PSSD considering our data (Zhang et al. 2023a).
Aside from a plethora of possible cognitive symptoms, **AE can also cause autonomic dysfunction** through targeting and inflaming brain regions critical for autonomic regulation, such as the brainstem and hypothalamus. This inflammation can impair the brain's ability to control autonomic functions, resulting in symptoms of dysautonomia, which has been discussed at great length in (Ohrn et al. 2024).
In certain instances, **AE can occasionally overlap with peripheral neuropathy** such as seen in case reports on anti-AMPA and anti-NMDA encephalitis, although it is less common than central nervous system involvement (Wei et al. 2017).
Another interesting factor worth mentioning is that studies have shown that patients with conditions like anti-NMDA receptor encephalitis exhibit **altered gut microbiota composition** compared to healthy individuals (Gong et al. 2019), which aligns with our findings on gut dysbiosis in PSSD patients, as well as Prof. Melcangis research on the gut microbiome.
Aside from the basal ganglia we have discussed if other brain regions could be involved as well (such as the limbic system), but have been limited by lack of data and AE panels that would include a more comprehensive set of receptors in the brain, as **this condition could represent a new, novel form of AE**. A lot of tests for certain receptors of interest are still not in clinical use and can only be found in research settings at this time, such as for example serotonin receptors. Current existing encephalitis panels used in clinical practice today (such as anti-NMDA and anti-DPPX, have consistently turned out negative when testing PSSD cases (besides one case testing positive for anti-NMDA), so if it is indeed the case, this subtype is most likely not discovered yet. In the absence of such tests and in the presence of other indicators such as elevated oligoclonal bands, protein and IgG Index in the CSF, hypometabolic findings on PET scans, positive Cunningham panels and elevated levels of IL-6, together with the clinical presentation this could possibly qualify for a diagnosis of **seronegative autoimmune encephalitis**. To date at least 3 patients in the community have been diagnosed with seronegative AE. Furthermore, several patients have reported that seronegative AE has been >suspected in their case, as for example seen with the patient in case report 1, that ultimately got the diagnosis of Polyimmunopathy.

Recently, a patient reported sending in a CSF sample to a top European hospital which performed an analysis to examine whether the patient sample contained known or new IgG antibodies against brain antigens that are not detected in routine diagnostics. Their method was to mix a thin section of an unfixed mouse brain with the human sample and the attachment of IgG antibodies, made visible using a staining reaction. Depending on the binding pattern (e.g. neuronal surfaces), a prediction of the pathogenicity of the antibody could possibly be made, even with a previously unknown antibody. The result in this case turned out to be negative. With that said, it does not necessarily rule out an AE component entirely considering the fluctuating nature of autoimmune disease in general (Nicholson 2016), and autoantibodies may have not been detected at the time of sampling. Additionally, most cases of autoimmune encephalitis demonstrate a high serum to cerebrospinal fluid (CSF) antibody ratio, and thus autoantibodies are theorized to be of peripheral origin that subsequently penetrate the blood-brain-barrier (BBB) (Ding et al. 2020).
This could perhaps explain the relatively low incidence rate of CSF findings in PSSD patients compared to other tests, such as Celltrend and Cunningham. One study showed that 27% of patients with AE had normal levels of white blood cells and protein in their CSF (Hébert et al. 2020)

which are often abnormal in AE. Perhaps something similar could be the case with PSSD, and explain why only a subset of patients show abnormal labs when testing their CSF. In a study on long covid on CSF autoantibodies against neuronal surface antigens, they found that such autoantibodies were rare, and that there was no evidence for a clinical correlation of these antibodies, so the authors concluded that rather than specific autoimmune neuronal injury, non-specific effects of critical illness including an impaired blood–brain barrier were more likely to contribute to neuro-COVID (Nersesjan et al. 2023). With that said, Covid-19 Infection has been seen to sometimes trigger encephalitis (Siow et al. 2021), with a subset of patients with LC occasionally presenting with autoimmune encephalitis (Valencia Sanchez et al. 2021). A similar thing could be the case with PSSD patients, given that the syndrome is a spectrum with patients presenting with differences in symptoms and severity, and the condition also seems to have a systemic nature in general, such as seen in LC. Perhaps AE could also be a component present in only a subset of patients with PSSD. Diagnosing AE is generally challenging due to many overlaps in symptoms with other disorders and differential diagnosis.
To underscore this final point, a retrospective study of 50 patients diagnosed with autoimmune encephalitis (as mentioned in chapter 3), revealed that two out of three patients were originally suspected of having a different condition such as a primary psychiatric illness, a neurodegenerative disease, or epilepsy. This highlights the challenges of proper accurate diagnosis, and formal research is needed to see if AE may be a component in PSSD individuals (Ding et al. 2020).

10.3.2 Dysregulation of neurosteroids

Studies by Professor Roberto Melcangi's research group at the University of Milan has provided significant insights into the role of neurosteroids in PSSD. Their findings (Giatti et al. 2021) indicate that **individuals with PSSD may have altered neurosteroid levels and expression of key enzymes of steroidogenesis in the brain** (e.g. in the hippocampus, hypothalamus, and cerebral cortex)**.** Neurosteroids are crucial for regulating brain functions including mood, anxiety, and sexual behavior (King 2008), and the study of (Giatti et al. 2021) suggest that long-term SSRI treatment can impair neurosteroidogenesis, the process by which neurosteroids are synthesized in the brain, leading to persistent changes in brain function even after discontinuation of SSRIs. Impairment in neurosteroidogenesis (neurosteroid synthesis) has been implicated in several disease pathologies, such as MS and autoimmune encephalomyelitis (Noorbakhsh et al. 2011). The same paper shows that levels of important neurosteroids, including allopregnanolone, were suppressed in the white matter of the brain in patients with Multiple Sclerosis. They further suggest that allopregnanolone and perhaps other neurosteroid-like compounds could be potential biomarkers or therapies for MS, whereas Yilmaz et al. (2019) propose that synthetic analogs of neurosteroids could be candidates for the management of neuroinflammation.

Besides playing crucial roles in modulating brain function, including neuroprotection, neurotransmitter regulation, and the maintenance of mood and behavior, neurosteroids possess anti-inflammatory properties, reducing the production of pro-inflammatory cytokines and mitigating neuroinflammation (Balan et al. 2024). By regulating the activity of microglia, the primary immune cells in the central nervous system, neurosteroids help balance protective and detrimental effects of inflammation in the brain, contributing to neurogenesis and neuroprotection (Lanussa et al. 2015). Interestingly, allopregnanolone has been widely shown to protect against physiological, biochemical and functional alterations associated with peripheral neuropathy (Mendell and MacLusky 2018). Allopregnanolone has also been shown to reduce demyelination, axonal injury, microglial reactivity and lymphocyte infiltration in an experimental autoimmune encephalomyelitis (EAE) mouse model. Furthermore, allopregnanolone induces myelin synthesis in oligodendrocytes, indicating that it supports remyelination (Yilmaz et al. 2019).
Due to allopregnanolone's potent anti-inflammatory properties, it has been proposed as a potential treatment for neurodegenerative conditions that also has a clear neuroinflammatory component, such as MS and ALS (Mendell and MacLusky 2018). The synthetic forms of allopregnanolone Brexanolone and the newer oral form Zuranolone (Maguire and Mennerick 2024), a GABA-A receptor positive allosteric modulator (PAM), could perhaps be potential candidates for improving PSSD symptoms. At the moment however, they are only indicated for Postpartum depression (Azhar and Din 2024, Azhar et al. 2024). With that said, various studies have shown promise in alleviating symptoms in other disorders as well, such as seen in a phase-2 clinical trial where Zuranolone was given as an adjunct treatment for tremors in Parkinson's disease (Bullock et al. 2021).
Additionally, some studies have investigated their potential roles as treatments for major depression (Clayton et al. 2023).
Neurosteroid synthesis can be substantially affected by neuroinflammation, contributing to neurodegenerative diseases like MS, Alzheimer's and Parkinson's (Yilmaz et al. 2019). Inflammatory processes, particularly the release of cytokines like IL-6, can reduce the synthesis of neurosteroids such as allopregnanolone by downregulating the enzymes responsible for their production (Parks et al. 2020). Additionally, chronic inflammation can alter the metabolism and receptor function of neurosteroids, diminishing their neuroprotective effects. This disruption can lead to a vicious cycle where decreased neurosteroid activity exacerbates inflammation, contributing to neurological and psychiatric conditions such as Alzheimer's disease and multiple sclerosis (Yilmaz et al. 2019).
Regarding sexual function, neurosteroids can have immediate and specific effects on select neuronal pathways to regulate sexual function (King 2008). Neurosteroids are proposed to be interconnected with the hypothalamic-pituitary-gonadal (HPG) axis to regulate neurosteroid synthesis in the brain, which is crucial for sexual function and health. Neurosteroids can also modulate either positively or negatively, neurotransmitter receptor-coupled ion channels and can therefore directly affect synaptic activity and/or neuronal excitability (Meethal et al. 2009). Thus this could potentially indicate downstream detrimental effects on sexual function if neurosteroids are altered or impaired in some way, such as could be the case in the presence of chronic neuroinflammation.

Prof.Melcangi's research group has also demonstrated neurosteroids like allopregnanolone plays a significant role in Post finasteride Syndrome (PFS), a near identical condition to PSSD where individuals end up with long lasting and often permanent symptoms such as sexual dysfunction and cognitive impairments. In a paper investigating both PSSD and PFS, Melcangi noted not only the similarities regarding the alteration of neurosteroids, but also that PFS (like PSSD), involves altered gut microbiota composition and that neurosteroids like Allopregnenolone has direct anti-inflammatory effects on inflammation in the gut. Additionally, he mentions the following:*«…dopamine is under the inhibitory tone of serotonin, whereas neuroactive steroids integrate, among others, peripheral and central stimuli to control dopamine circuits (through serotonin action). Therefore, perturbation of sex steroid levels induced by finasteride or SSRIs might be responsible for alterations of these neurotransmitters, thus producing the sexual dysfunction observed during treatment, and possibly the persistent sexual dysfunction occurring in PFS and PSSD.»* (Giatti et al. 2024b). The link to other inflammatory conditions, such as Long Covid and MS showing similar alteration of neurosteroids, as mentioned by Melcangi in the same paper, further suggests the significance of a potential impairment of neurosteroidogenesis, as well as inflammatory component in the etiology of PSSD.

Recently, a patient reported having tested his neurosteroids in CSF through a lumbar puncture (see table 6), which showed in his own words «almost absent levels of allopregnanolone». While this is the only relevant test result data we have, we think it is important to highlight the implications of neurosteroids and its link to the etiology due to the already established research on this area, which indicates a potential significant role in PSSD.

Based on the data (table 4-8) as well as research into the role of neurosteroids in inflammatory conditions **strongly suggests a potential role of neuroinflammation in the pathogenesis of the syndrome.** Additionally, the correlations and similarities to other neuroimmune disorders (as discussed in chapter 3 and 6) suggest that PSSD may share common etiological components with these conditions, further strengthening our hypothesis of neuroinflammation in PSSD.

10.4 Gut microbiome dysbiosis

Related tables: 9

In addition to our limited data on gut microbiome findings (Table 9) with **69% of 16 patients showing low levels of F. Prausnitzii**, Prof. Melcangi's research on the involvement of the gut microbiota in PSSD indicates it may play a significant role in the condition. The data on F. Prausnitzii indicates a potential significant complication given its extensive role in the gut with its anti-inflammatory action. Similar conditions like MS, Parkinsons, Long Covid and ME/CFS also show correlation with both gut dysbiosis and more specifically reduced abundance of F. Prausnitzii, and given their clinical manifestations this further strengthens our view of PSSD as a possible systemic inflammatory condition.

10.4.1 Gut Neurosteroids

Finasteride treatment and its withdrawal have been shown to significantly alter gut steroid levels in the experimental model, namely by an increase in pregnenolone (PREG) and a decrease in allopregnanolone (ALLO) (Diviccaro et al. 2022a). Changes presented in both gut steroids and brain neuroactive steroid levels, highlighting the bidirectional role of the gut-brain axis. Both PREG and ALLO are neuroactive steroids that play a key role in modulating inflammation. PREG, a precursor to various neurosteroids, can influence immune responses and inflammatory pathways, while ALLO has well-documented anti-inflammatory properties, particularly through its action on GABA-A receptors and its ability to modulate cytokine release (Noorbakhsh et al. 2014). The neurosteroid changes were associated with persistent microbiome alterations and increased proinflammatory cytokines, showcasing a link between altered neurosteroid levels and inflammation. This shift in steroid balance may contribute to neuroinflammation, as both peripheral and central inflammatory responses are interconnected through the gut-brain axis. Interestingly, repletion of ALLO showed a positive therapeutic effect (Diviccaro et al. 2022a), potentially restoring anti-inflammatory signaling and alleviating the inflammatory burden, both in the gut and brain.

Prof.Melcangi has planned to examine in a future clinical study whether allopregnanolone would exert a similar therapeutic effect in PSSD & PFS patients (PFS Foundation). The neurosteroid changes may suggest a mechanism in the onset of PFS & PSSD, particularly where the reduction of ALLO would disrupt immune tolerance and lead to autoimmunity by impairing the regulatory mechanisms that normally prevent excessive immune activation.

Based on the data (table 9), our researching and research by Prof. Melcangi, as well as anecdotal reports on gastrointestinal disturbances and the various complications of a gut dysbiosis elaborated on in chapter 7, we believe gut dysbiosis could play a significant role in the etiology of PSSD.

11. Beyond the data

Additional thoughts & speculation based on community anecdotes and layman research

11.1 Susceptibility and causation

At the moment, very little is known about susceptibility and predispositions in PSSD individuals. What's been discussed among team members and the community as possible contributing factors includes; a history of previous infections, antibiotic use, immune issues such as immunodeficiency as well as a family history of autoimmune disease and/or pre-existing autoimmune diseases such as PANDAS/PANS prior to taking the psychotropic drug.

Certain individuals may have genetic predispositions that make them more susceptible to acquiring this condition. Variations in genes related to immune function, barrier integrity, and inflammatory responses could possibly increase the likelihood of developing conditions associated with these weakened barriers, which as discussed earlier, is often linked to gut dysbiosis, systemic inflammation, neuroinflammation and autoimmune disease.

A compromised BBB could increase susceptibility to drug-induced injuries such as seen in a review paper (Hernández-Parra et al. 2023), where they discuss alteration of the BBB in Covid-19 and the effects of drugs. This could potentially explain what happens in PSSD as well.

Another interesting topic of discussion in the community has been the potential correlation between PSSD and neurodevelopmental comorbidities, including diagnoses such as autism (ASD) and ADHD. Some community members have reported such diagnoses, as well as some suspecting having the condition without being formally diagnosed. Both ASD and ADHD have been linked to various abnormalities such as immune issues and inflammation (Onore et al. 2012, Zhou et al 2017), as well as gut dysbiosis (Mehra et al. 2023, Steckler et al. 2024), which is often seen in PSSD as well.

A recent study showed that prenatal inflammation and SSRI exposure reshape the signaling milieu of the maternal-fetal interface and offspring brain, potentially impacting neurodevelopment in offspring (Zengeler et al. 2023), which highlights a potential correlation with SSRI drugs and neurodevelopmental disorders.

It could be interesting to do a survey that specifically screens for susceptibilities in PSSD sufferers in an attempt to gain more insight into which potential factors come into play with acquiring this condition. However, with such investigations, potential confounding issues regarding commonly used medication protocols would need to be taken into account, as patient groups that are more likely to be medicated with antidepressants than the general population are also more likely to have higher incidence rate of unwanted side effects and harm as well.

11.2 Potential triggering mechanisms

Theoretical speculation based on principles

At the moment it is impossible to say how PSSD happens and why (seemingly) only a minority of antidepressant users acquire the condition.

Many theories have been proposed in the community and literature over the years, ranging from epigenetic changes (Csoka and Szyf 2009, Kanherkar et al. 2018), persistent downregulation of the 5HT1A receptor, silencing of androgen receptors and more.

It has been guesswork for decades, but given the last years developments with the findings on autoimmunity and neuropathy, we might now be a step closer to suggesting potential mechanisms involved. Many proposed PSSD theories have understandably solely focused on the serotonergic system given SSRIs' main mechanism of action, but given the fact other antidepressant drug classes can trigger the syndrome, as well as the extreme similarities with Post-Finasteride syndrome (PFS) (Giatti et al. 2024b), it may suggest that the drug's main mechanism of action is not as relevant as the body's overall (immune) response to the drug. As briefly discussed in chapter 3, Iatrogenic syndromes similar to PSSD happen from various types of medicine, including Post Accutane Syndrome, post acute covid vaccine syndrome, and to a lesser extent fluoroquinolone antibiotic toxicity ("floxxies"), which may suggest potential shared etiological mechanisms. Interestingly, PAS has been linked as a potential environmental trigger for autoimmunity in genetically susceptible individuals. In a case report it was proposed to have triggered autoimmune hyperthyroidism (Nugroho and Schweiger, 2017). Perhaps the immune system is the common denominator here.

Some speculative statements have been proposed off the record by certain medical professionals with a background in immunology and neurology. One of the proposed ideas is that **the immune system forms an antigen to the medication, basically viewing the drug as a «foreign body» and thus triggering an immune response (antibodies).** Many drugs are too small to be directly recognized by the immune system, so they bind to larger proteins to form complexes that can be detected. Immune cells called antigen-presenting cells (APCs) process these complexes and present fragments to T cells, which then activate B cells. These B cells produce antibodies specific to the drug, marking it for elimination. Such immune reactions can sometimes lead to permanent diseases through several mechanisms. **One way is through molecular mimicry, where the immune response against the drug may cross-react with the body's own tissues.** This mechanism has been proposed to play a role in

autoimmune diseases like **MS, GBS and Systemic Lupus Erythematosus (SLE),** where various infections are linked as the triggering mechanism (Rojas et al. 2018). A similar mechanism has been suggested to take place in **drug-induced Lupus (DIL)** (Uetrecht 1997, Tetikkurt 2016).
In addition to adaptive (peripheral) immune mechanisms, innate immune dysregulation may also play a significant role. Prof. Melcangi's recent paper demonstrated that inflammatory signatures and immune activation were present in the hypothalamus and nucleus accumbens of affected individuals (Giatti et al. 2024a), indicating innate immune involvement. Dysregulated innate immune responses, such as excessive activation of microglia and macrophages, can sustain chronic inflammation through cytokine release (e.g., IL-1β, IL-6, TNF-α). These cytokines not only cause tissue damage but also activate adaptive immune cells, creating a feedback loop that perpetuates inflammation. This interaction between innate and adaptive immunity is a key feature of autoimmune diseases like MS, where innate inflammation in the central nervous system primes adaptive T cell-mediated attacks on neural tissues (Van Kaer et al. 2019). A similar interplay between innate and adaptive immunity is observed in severe COVID-19 cases, where dysregulation of cytokines such as IL-6, IL-8, and IL-10 disrupts the balance of innate immunity and indirectly impacts adaptive immune responses (Davitt et al. 2022. This dysregulation contributes to excessive inflammation, tissue damage, and long-term immune dysfunction.

Melcangi's paper also showed alterations in genes involved in neurotransmission, such as ST8SIA3 (dopamine signaling), GRID2 and GRM5 **(glutamate pathways)**, and GAD2 (GABA synthesis). Dysregulation of genes related to brain-derived neurotrophic factor (BDNF) signaling was also observed, implicating impairments in synaptic plasticity and connectivity (Giatti et al. 2024a).
These alterations may be downstream effects of immune dysregulation and neuroinflammation. Pro-inflammatory cytokines, such as IL-1β, IL-6, and TNF-α, can influence gene expression (Foran et al. 2010), suppressing genes involved in synaptic transmission and neurotransmitter synthesis. Chronic microglial activation may further exacerbate this by pruning synapses and suppressing neuronal signaling pathways (Geloso and D'ambrosi 2021). Furthermore, data have suggested that **cytokines have a significant impact on dopamine pathways** as well. Neuroimaging studies have indicated **altered blood flow and metabolic activity in basal ganglia nuclei during exposure to inflammatory stimuli** (Haroon et al. 2012). Additionally, neuroinflammation can disrupt BDNF signaling, impairing synaptic plasticity and contributing to long-term neuronal dysfunction (Lima Giacobbo et al. 2019). Epigenetic changes induced by chronic inflammation could sustain these effects, perpetuating gene silencing and neurotransmitter dysregulation (Komada and Nishimura 2022). Together, these processes provide a plausible link between immune activation and the persistent symptoms seen in PSSD.

The immune reaction could, in theory, persist even after discontinuation of the drug due to several factors.
Autoimmunity may sustain the response if the immune system starts targeting self-tissues. Memory B and T cells can quickly reactivate if they encounter similar antigens again. Persistent antigens from drug-protein complexes can continue to stimulate the immune system. Epitope spreading can occur, where initial tissue damage exposes new self-antigens, broadening the immune attack. Additionally, drugs like **SSRIs, which are known to be immunomodulatory** (Georgetown University Medical Center, 2006), **may induce epigenetic changes**, such as DNA methylation, histone modification, or non-coding RNA expression, leading to long-lasting alterations in immune function. These epigenetic changes, coupled with chronic inflammation, may create a self-perpetuating pro-inflammatory environment, contributing to persistent symptoms even after the drug is discontinued. Understanding this interplay between immune responses, epigenetic modifications, and inflammation could potentially help provide a unifying explanation for PSSD and its parallels in other iatrogenic conditions.

11.3 Alternative hypotheses

There are several routes through which SSRIs could lead to autoimmune reactions, neuropathy, or both. Here is an outline of some ideas:

Covalent interactions: a well-known cause of immune reactions

Covalent interactions and ”irreversible” binding between medications and their targets are typically avoided in the field of drug discovery due to toxicity concerns (Potashman and Duggan 2009), particularly in terms of causing unwanted immune reactions in a minority of people. As such, the SSRIs were not designed to interact in this manner with their targets. However, they are known to occasionally arise by accident, and may not be discovered until later. Due to the complexity of the human body, even seemingly implausible reactions are known to occur, such as fluorine acting as a leaving group (Kyzer and Martens 2021), even in the absence of favorable structures such as fluorobenzyl moieties. It is therefore possible that the medications have covalent interactions with an unknown target, which could explain reports (Karasowska et al. 2007) of Stevens-Johnson syndrome and toxic epidermal necrolysis associated with SSRI use, which are known examples of immune-mediated toxic reactions. As for other post-drug syndromes, finasteride is known to covalently inhibit its target, and although the covalent interaction itself is technically with a co-substrate while the binding to the protein is not, the inhibition of 5α-reductase is only reversible in theory and effectively irreversible in practice (Keserü et al. 2015). As with allergies, most people would not be affected, but repeat or prolonged exposures will increase the risk of an adverse reaction, which would explain why many people do not develop PSSD until their second or third time on the same or a different SSRI.

The SSRI pharmacophore: connection to antihistamines & immunomodulation

Several post-drug syndrome triggers from antidepressants to antipsychotics and antihistamines share certain structural commonalities and how said structures align with their targets, which are also known as pharmacophores. Specifically, the presence of two aromatic rings, one hydrophobic, and one positive ionizable group such as nitrogen appears to be a common factor. As antihistamines modulate the immune system, possibly through routes (Canonica and Blaiss 2011) beyond histamine, perhaps the same could be true for similar drugs, and it could have unintended consequences in some cases.

Latent infection reactivation

The reactivation of latent infections is a hypothesis that has been discussed in the community in recent years, where dormant pathogens may resurface under conditions of immune dysregulation. Reactivation can occur when antidepressants alter the immune system, either through direct mechanisms or as part of their withdrawal effects, creating an environment conducive to infection relapse. The majority of research reports immunosuppressive effects of SSRIs such as decreased lymphocyte proliferation and reduced pro-inflammatory cytokine secretion (Gobin et al. 2014). Additionally, the same paper showed that fluoxetine has an effect on neutrophil adhesion and recruitment to inflammatory sites, demonstrating that not only cellular but also innate immunity is impacted by SSRIs.

This hypothesis could potentially reflect the different types of onsets seen in PSSD patients (during treatment, during tapering and upon withdrawal). Additionally, due to the immunosuppressive effects of SSRIs, a rebound effect may occur upon discontinuation of the SSRI, where the immune system becomes overactive and cytokine levels rapidly increase causing inflammation, such as seen in Immune reconstitution inflammatory syndrome (ICIS) (Thapa and Shrestha 2023). Common infections like Epstein-Barr Virus (EBV) and Herpes Simplex Virus (HSV) have been implicated in various neuroinflammatory and autoimmune disorders, where for example HSV-1 reactivation can trigger encephalitis (Thellman and Triezenberg 2017). Interestingly, a study showed that heightened serologic reactivation of EBV increases the probability of transitioning to systemic lupus erythematosus (SLE) in unaffected SLE relatives (Jog et al. 2019), implying there is some genetic susceptibility involved.

CNS injury via excitotoxicity or oxidative stress

Another possible mechanism worth discussing is that these drugs render the central nervous system vulnerable to excitotoxic or oxidative injury. SSRIs are known to disrupt glutamate–GABA balance, potentially lowering inhibitory tone (Giatti et al. 2024a). Accutane (isotretinoin), meanwhile, has been shown to induce oxidative stress and DNA damage in both clinical and laboratory studies (Erturan et al. 2012, Georgala et al. 2005).

Upon drug withdrawal, the abrupt loss of neuroprotective or inhibitory modulation may lead to a rebound state of excitotoxicity, particularly in already sensitized neural circuits. This could result in subtle or localized injury to dopaminergic neurons, sensory/autonomic fibers, or neural substrates critical for sexual and emotional function—injuries that may not be easily detected by standard neuroimaging but could contribute to the persistence of symptoms in PSSD, as well as possibly PFS, and PAS. Such neural injury may also play a role in triggering immune dysregulation. Excitotoxic or oxidative damage can expose normally hidden intracellular antigens and danger-associated molecular patterns (DAMPs), which may initiate or perpetuate an immune response. Inflammatory cytokine release and blood-brain barrier disruption may further facilitate immune cell infiltration and antigen presentation (Varatharaj & Galea. 2017). Microglial activation in this context can promote adaptive immune responses by acting as antigen-presenting cells and activating T lymphocytes (Becher et al. 2017, Dalmau & Graus. 2018). These processes could be one possible explanation for the detection of GPCR autoantibodies observed (CellTrend, Cunningham) in a subset of patients, potentially pointing to a neuroimmune cascade initiated by early CNS stress or injury.

Mitochondrial dysfunction

Mitochondrial dysfunction could be another potential mechanism underlying the complex multisystemic symptoms of PSSD. Antidepressants, particularly SSRIs and SNRIs, have been shown to affect mitochondrial function (Abdel-Razaq et al. 2011), including impairments in oxidative phosphorylation and ATP production (L'upták et al. 2023). Disrupted energy metabolism may contribute to fatigue, cognitive impairment, and neuropathy seen in PSSD patients. Furthermore, mitochondrial dysfunction can exacerbate oxidative stress and neuroinflammation, potentially amplifying damage to neural tissues (Picca et al. 2020).

Mitochondrial dysfunction may contribute to downstream immune system dysregulation by affecting both innate and adaptive immunity. Damaged mitochondria release molecules like mitochondrial DNA (mtDNA) and reactive oxygen species (ROS), which can activate the immune system through receptors such as Toll-like receptors (TLRs) and the NLRP3 inflammasome. This process triggers the release of pro-inflammatory cytokines, leading to chronic inflammation. Over time, this inflammatory environment can also activate adaptive immunity, including T and B cells, potentially contributing to the complex multisystemic symptoms seen in PSSD (Chen et al. 2023, Mohanty et al. 2019).

Neuropathy: chicken or egg?

What if the neuropathy occurs first and the autoimmunity is a consequence of it instead? This would explain why most people experience these side effects while on the medication, but only a minority fail to recover after cessation. It is known that some cases of SFN may recover or improve to an extent (Oaklander and Nolano 2019) perhaps even completely if the damage is mild enough to only cause dysfunction rather than cell death. However, an inflammatory reaction could interfere with this process and there are case studies of conditions such as NMDAR encephalitis being seemingly triggered by nerve injuries (Prüss et al. 2014) for example. This may also be the reason why some patients only have numbness while others get more varied physical, emotional or cognitive symptoms. In other words, in the presence of certain susceptibilities, the injury could cause the immune system to inappropriately attack the nerves, which would interfere with recovery.

Ion channel effects

While SSRIs were designed to bind to the serotonin transporter, they were later found to have interactions with other proteins such as sigma receptors, enzymes such as phenylethanolamine N-methyltransferase (Giatti et al. 2022), or ion channels. The latter have been hypothesized to be responsible for their pain relieving properties, and due to their significance in nerve function, it would be plausible if this was the cause of temporary genital numbness while on the medication. It may be possible that certain mutations related to ion channel structure or metabolism of the drugs themselves could lead to increased binding, and perhaps excessive blockage of the channels could lead to nerve dysfunction or even damage. The receptor structure is probably self-explanatory, but regarding metabolism specifically, we are alluding to a potential scenario in which an off-target enzyme is added to a methyl group. The significance of adding methyl groups would lie in increased water-repelling properties of the drug, and if they happen to align with similar functional groups in the target protein, this may increase the binding by up to 100x, an effect fittingly dubbed ”magic methyl effect” in the field of medicinal chemistry.

Hyponatremia

Hyponatremia or low sodium level in the blood is a known side effect of SSRIs that may be completely asymptomatic in some cases. However, it can still be dangerous, and sudden changes in the salt balance of the body can damage the myelin sheaths of nerves, which can arise both when the concentration increases or decreases. This in turn could explain why the syndrome can arise both while starting and while stopping the drug, and why sudden discontinuation may be particularly risky. Notably, Dr. David Healy first proposed this idea on a RxISK blogpost. Although he has not since written on this, it remains worth consideration, particularly because genital numbness is a known symptom of demyelinating disorders.

Many of these hypotheses are not mutually exclusive, and therefore it is possible that more than one can occur at the same time, or that one may exacerbate the other. The immune dysregulation could also be a secondary downstream effect and doesn't necessarily have to be the main mechanism. These are just meant as ideas to inspire discussions around this, and to potentially offer clues to both professional and non professional readers with much more knowledge on these subjects than we have.

13. Conclusion

From our extensive layman research the past two years as well as the community data and anecdotal reports presented in this document, we think it is reasonable to suggest that PSSD may be, at least in part, an iatrogenically triggered systemic immune-mediated neurological (neuroimmune) disorder, involving both the central and peripheral nervous system, given the condition's multifaceted presentation in symptomatology, as well as the broad range of positive test results reported in the community (including autoantibody panels, skin biopsies, brain imaging, inflammatory markers and GI tests). This is further strengthened by the case reports, as well as official statements made by certain medical professionals (names have been redacted to protect their privacy).
The data, anecdotal reports and research correlations further suggest that the etiology may involve; immune-mediated dysautonomia, neuroinflammation, small fiber neuropathy (SFN), as well as gut microbiome dysbiosis and dysregulation of neurosteroids such as allopregnanolone (as shown in the research by Prof. Melcangi). Additionally some labs indicate a possible autoimmune encephalitis component in some individuals.
No conclusions can be drawn at this point, and professional research is urgently needed to understand, define and ultimately come up with effective treatments for this complex condition.

12. Closing Words

This data collection, initiated by community member «Goldenhour», aimed to uncover insights into PSSD to help patients access adequate testing and treatment, especially for those who don't have the time to wait years for official research to catch up. Many of us have had PSSD for years, and in some cases even decades. Our lives have been entirely put on hold due to the debilitating nature of this condition. It is worth noting that PSSD does not only profoundly affect the lives of us patients but also the lives of our loved ones as well. The severity of this condition simply cannot be overstated. Our symptoms are often attributed to psychiatric or psychosomatic causes without a proper investigation, and thus, a lot of us feel neglected by our healthcare. We hope this document may improve our chances of being recognized and treated as a group of patients with a real and serious condition that needs urgent care and treatment.

As stated in the introduction, our objective was to provide a comprehensive overview of PSSD. This involved identifying and evaluating verifiable, established tests from community-collected data, and reviewing existing scientific literature. We aimed to bring creativity and critical thinking to explore the various directions for future inquiry based on this knowledge.
The document expanded a lot in the process, both in scope and goal posts, where the community data and reported anecdotes was complemented by the research and discovery of correlations with related conditions.
Ultimately we wanted to present all of this through interpretation, discussion of our findings, and speculation on potential etiology that have been partly facilitated by certain health care professionals with relevant backgrounds that some of us have had the privilege to meet.
Despite our best intentions to be as accurate and thorough as possible, we do acknowledge our standpoint as laymen of these topics and want to highlight that **all errors made in this document are purely our own.** Also, we stress that we are not, nor can our, expertise be compared to professionals in neurology and immunology. We also hope for an understanding of the fact that we wish to remain anonymous, as we do not want to risk any potential publicity that could complicate our access to care and potential treatment.

We hope that this work may inspire professional researchers to get involved with PSSD, as we desperately need a broader scope of focus on the official research that includes a neuroimmune angle, to gain further understanding of the condition. Based on our work presented in this document we believe that immune dysregulation and downstream outcomes such as SFN and dysautonomia are currently the most promising areas for future research directions. We hope this document can be useful in some way to whoever may be reading it.
Thank you for taking the time to read this document, and a big thanks to everyone in the community who provided their information and test results to us. We couldn't have done this without you!

Kind regards,
Jonny, on behalf of INIDA

Team members:
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Visit our website for updates and more: **https://inida.info**

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Other sources

Chapter 8.2:

GPCR results: B1-AR and AT1R - Valonen, 2022

Appendix

1. PSSD SFN RESEARCH- SURVEY RESULTS

Participants: 115

Male: 79 (69%)

Female: 34 (30%)

Prefer not to answer: 2 (2%)

Uncategorized

- PSSD presented immediately on medication: 35 (30%) PSSD presented at some point during treatment: 27 (23%) PSSD presented during tapering: 8 (7%)
- PSSD presented after discontinuation: 48 (42%)
- PSSD presented during reinstatement: 5 (4%)
- (Some answered more than one option for when they presented PSSD) PSSD for under 1 year: 23 (20%)
- PSSD for 1-2 years: 29 (25%)
- PSSD for 3-5 years: 24 (21%)
- PSSD for 5-7 years: 12 (10%)
- PSSD for 8-10 years: 7 (6%)
- PSSD for 10-15 years: 10 (9%)
- PSSD for 15+ years: 10 (9%)
- Cannot feel the effects of alcohol: 42 (37%)
- Can feel the effects of alcohol: 33 (29%)
- Unsure if they can feel the effects of alcohol: 39 (34%)
- Cannot feel the effects of pain medications: 12 (10%)
- Can feel the effects of pain medication: 43 (37%)
- Unsure if they can feel the effects of pain medication: 60 (52%) Cannot feel hunger: 45 (39%)

Vasculitis

- Muscle or joint pain: 39 (34%) Red or sore eyes: 28 (24%) Loss of appetite: 46 (40%) Flu-like symptoms: 25 (22%) Fever: 6 (5%)
- Weight loss: 28 (24%)
- Small red or purple dots: 16 (14%)
- Itchy, lumpy rashes which can be painful or tender: 11 (10%)
- Open sores (ulcers): 2 (2%)
- Small black spots around the toes, fingernails, or ends of the fingers: 2 (2%) Cramps: 19 (17%)
- Stomach pain: 27 (23%)
- Bloating: 37 (32%)
- Blood pooling in extremities/ hands and feet: 19 (17%)
- None: 33 (29%)
- Autoimmune Conditions (known)
- Celiac: 4 (3%)
- Hashimoto's: 4 (3%)
- Lupus: 2 (2%)
- Sjogren's: 4 (3%)
- Small Fiber Neuropathy: 16 (14%)
- CFS/ME: 9 (8%)
- Fibromyalgia: 6 (5%)
- Vasculitis: 1 (1%)
- Diabetes: 1 (1%)
- Pandas: 1 (1%)
- Colitis: 1 (1%)
- IBS/ IBD: 16 (14%)

- SIBO: 13 (11%)
- POTS: 12 (10%)
- Dysautonomia: 26 (23%) Rheumatoid Arthritis: 1 (1%) Connective Tissue Disease: 3 (3%) Raynaud's Syndrome: 7 (6%) Encephalitis: 5 (4%)
- No known: 57 (50%)

Immune System:

- Swollen lymph nodes: 14 (13%)
- New allergies since PSSD: 31 (27%) New infections since PSSD: 16 (14%)
- (Reported: Klebsiella, UTIs, stronger colds, interstitial cystitis, chronic inflammation, red/ itching/ burning skin, strep, candida, wounds/ sores that won't heal in normal time), skin irritation, difficult healing, rubbery skin, blisters/ dyshidrosis, hand/ foot/ groin infections
- Antibodies reported in survey: AT1R: 4
- ETAR: 4
- α-1 adrenergic: 4
- α-1 adrenergic: 4
- β-1 adrenergic: 5
- β-2 adrenergic: 4
- Muscarinic cholinergic (M1): 3 Muscarinic cholinergic (M2): 3
- Muscarinic cholinergic (M3): 5 Muscarinic cholinergic (M4): 4 Muscarinic cholinergic (M5): 2 FGFR3: 2
- TSHDS: 2
- ACE2: 8
- TPO: 4
- TG: 1
- ANA: 2
- IgG Index CSF: 1 IgA: 1
- SS-B/ LA: 1

Small Fiber Neuropathy

- Numbness: 97 (84%)
- Tingling: 28 (24%)
- Burning: 21 (18%)
- Pain: 30 (26%)
- Shocks: 12 (10%)
- Other parts of the body besides genitals: 63 (55%)
- Listed: Legs, butt, thighs, face, whole body, hands, feet, wrists, chest, back, scalp, rectum, stomach, fingertips, lips, nipples, fingers, pelvic area, head, arms, limbs, armpits, toes, pinky fingers, shins, ankles, neck, cranial nerves, stomach, bladder, tongue, groin, knees, perineum, anus
- Possible issues of blood flow problems: Color of genitals changed: 32 (28%) Size of genitals changed: 46 (40%)
- Erectile dysfunction: 66 (84% of males)
- Loss of genital sensitivity: 103 (90%)
- Ejaculation disorder: 35 (44% of males)
- Loss of lubrication: 36 (32% total) (24 women 71%)
- Orgasmic disorder: 65 (57%)
- Loss of sexual desire: 103 (90%)
- Loss of erotic sensation: 98 (85%)
- Loss of feeling during intercourse: 81 (70%)
- Ejaculatory disturbances (premature, delayed, absent, dribbling): 44 (56% of males) Difficulties in reaching orgasm: 71 (62%)
- Changes in sensation of orgasm: 88 (77%)
- Pain during intercourse: 24 (21%)
- Semen color or consistency changes: 38 (48% of males)
- Sperm count changes: 14 (18% of males)
- Fertility changes: 5 (4%)
- None: 0

Dysautonomia

- Sensation of coldness (unable to feel warmth in body): 35 (30%)
- Pain that gets worse at night: 11 (10%)
- Skin tightness: 17 (15%)
- Unable to feel pain: 19 (17%)
- Feeling of dullness in skin anywhere in the body: 44 (38%)
- Loss of taste: 22 (19%)
- Loss of smell: 28 (24%)
- Dry eyes and mouth: 32 (28%)
- Urinary symptoms of hesitancy, incomplete emptying: 42 (37%) Frequent urination, incontinence: 34 (30%)
- Facial flushing: 13 (11%)
- Skin rashes or discoloration: 25 (22%)
- Increased/ decreased sweating: 51 (44%)
- Dizziness, lightheadedness, vertigo: 37 (32%)
- Ringing in ears: 40 (35%)
- Vision problems (blurred vision, vision loss, tunnel vision): 48 (42%)
- Enteric symptoms of constipation, diarrhea, abdominal distension, food intolerance: 38 (33%)
- Anxiety: 44 (38%)
- Abnormally fast or slow heart rate: 38 (33%)
- Fatigue: 73 (63%)
- Feeling short of breath (especially when you exercise): 37 (32%) Feeling thirsty all the time: 22 (19%)
- Having trouble swallowing: 16 (14%)
- Headaches: 29 (25%)
- Insomnia: 47 (41%)
- Nausea: 26 (23%)
- Balance problems: 28 (24%)
- Chest pain/ discomfort: 14 (12%)
- Weakness: 56 (49%)
- Large swings in heart rate and blood pressure: 16 (14%)
- Noise/light sensitivity: 35 (30%)
- Low blood sugar: 5 (4%)
- Swings in body and skin temperature: 19 (17%)
- Brain “fog”/ forgetfulness/can’t focus: 76 (66%)
- Mood swings: 40 (35%)
- Sleeping problems: 60 (52%)
- Exercise intolerance (heart rate doesn’t adjust to changes in activity level): 36 (31%) None: 5 (4%)

Autoimmune Encephalitis

- Impaired memory and understanding: 76 (66%)
- Unusual and involuntary movements: 20 (17%)
- Involuntary movements of the face (facial dyskinesia): 9 (8%)
- Difficulty with balance, speech or vision: 46 (40%)
- Insomnia: 44 (38%)
- Weakness or numbness: 61 (53%)
- Seizures: 4 (3%)
- Severe anxiety or panic attacks: 30 (26%)
- Compulsive behaviors: 28 (24%)
- Altered sexual behaviors: 55 (48%)
- Behavior changes such as agitation, fear or euphoria: 27 (23%)
- Loss of inhibition: 18 (16%)
- Hallucinations: 5 (4%)
- Paranoid thoughts: 22 (19%)
- Loss of consciousness or coma: 3 (3%)

- None: 14 (12%)

Neuroinflammation/ Anhedonia/ Cognition

- I have emotional blunting/ anhedonia of positive and negative emotions: 67 (58%)
- I have emotional blunting/ anhedonia of only positive emotions: 26 (23%)
- I have emotional blunting/ anhedonia of only negative emotions: 3 (3%)
- None: 19 (17%)
- I have reduced memory ability: 77 (67%)
- I have have issues with speech, communication, word-finding: 70 (61%)
- I have lost ability for visual thinking and creativity: 70 (61%)
- I have a blank mind: 56 (49%)
- I have lost inner dialogue: 41 (36%)
- I have confusion in everyday life: 55 (48%)
- My cognitive issues have impacted my daily life: 69 (60%)
- I am unable to function from my cognitive symptoms: 37 (32%)
- I am unable to work due to my cognitive symptoms: 38 (33%)
- I am unable to go to school due to my cognitive symptoms: 27 (23%)
- I am unable to pursue my desired or previous career path due to my cognitive symptoms: 55 (48%)
- None: 21 (18%)

Covid

- I did bad with Covid since PSSD: 32 (28%) I got Long-Covid after PSSD: 15 (13%) Covid made my PSSD worse: 22 (19%) Never had Covid: 33 (29%)
- My PSSD got worse after Covid vaccination: 17 (15%) Never had vaccine: 37 (32%)
- Survey Comments
- #1 “I took Lexapro for 3 months only and had horrible GI issues, blunting, sexual dysfunction and ideation. I went off and everything got much worse. Within months I had Hashimoto’s, Sjogren’s (Seronegative), Small Fiber Neuropathy, Dysautonomia and then eventually Long Covid. Then during PSSD I got reconstruction surgery from a preventative double mastectomy for a cancer gene. Within 3 months I developed over 40 breast implant illness symptoms where I almost died. I explanted but still suffer. I started IVIG in June and I am seeing improvement but it is very slow.”

Quotes from survey participants:

- #9 “Antidepressant lexapro has ruined my sex life, only took it for 3 weeks when all my symptoms started and have persisted for over a year. It has done damage to both my body and my mind. These drugs are so much more powerful and dangerous than doctors think. Please help those who are suffering.”
- #11 “I was completely unable to feel hunger for a year but that has since passed and my appetite is fully back.” “My mouth burns”
- #12 “I was 100% healthy before Escitalopram. (5 weeks)”
- #18 “Reinstated for a few days before quitting due to bad anxiety. First 2 weeks after quitting I felt sick and agitated (negative for covid) and I had neck, back, pelvis and testicle pain. The pain happened mostly at night. When the 'sickness' and agitation (possibly akathisia) wore off I noticed the emotional and body numbness + other symptoms. I can no longer feel the effects of cannabis. I also developed muscle spasms everywhere and they hurt sometimes.”
- #25 “When I started taking Voritoxetine I got high blood pressure and now that I am 2 years off of this medication I still have high blood pressure so now I am on medication to lower it.
- Its also worth mentioning that I do not have genital numbness but I have most of the other symptoms of PSSD (Erectile Dysfunction, Severe premature ejaculation,Anhedonia, DPDR, Cognitive Impairment)”
- #26 “Muscle joint pain likely work related, and getting older.” #27 “I may have some mild emotional blunting, it's hard to tell”
- #40 “I also have POIS from PSSD. Every orgasm makes me way worse.
- Also, as may others, CPPS symptoms. The whole pelvic area does no longer work right.”
- #42 “ No libido, limited and very weak morning erections, weaker sensitivity in penis. Shrinkage, hard to visualize sexual thoughts - mind wanders off. Cant get any erection with thoughts and visual stimulation. Symptoms worse since few days ago when i started to have extreme stress due to having PSSD. Due to discovering all the stories from other people, now i think and read about it every day for many hours. No appetite because of stress and anhedonia of any positive thoughts, I since I began realizing its not gone after 8 months. I’m in despair and suicidal every day now.”
- #52 “Regained about 30% genital feeling within 3 years, then progress halted. Regained ability to get drunk after approximately 7 years. My reaction to cannabis and nicotine changed permanently, now it's unpleasant.”

- #55 “Abnormal movements only occur during sleep and were pre-existing (periodic limb movement disorder), but got worse after SSRIs, now affecting all limbs not just the legs. A year of working with a sleep specialist more or less ruled out other causes.
- I also have other sensory issues that weren't mentioned on the survey, mostly other paresthesias:
- -feelings of vibration, usually on the scalp
- -the sensation of being splashed with cold water, usually on the legs
- -mild feet discomfort, like the sensation of socks being too tight even if they aren't -general clumsiness/proprioception issues not related to balance”
- #63 “I have tried many supplements/medications but none have improved my symptoms in the 3+ years I've had this.”
- #73 “I still experience brain zaps, especially with lateral eye movements.”
- #74 “Have not had the hiccups since PSSD, used to get them about once per week.”
- #78 “I don’t know if it’s pssd because I found these symptoms 2 months after ssri quit and had a lot so stress during that time. Maybe it’s depression again or some traumatic event initialized this.”
- #79 “Took sertraline in past once when 14 and again when 20, did not notice anything change, took one dose of dapoxetine in 2022 October, completely destroyed from that, also developed gynocomastia, didn't see this as a listed symptom.”
- #81 “Lost all of my imagination and visualization ability.”
- #82 “My appetite has decreased, but I still feel hunger.
- Basically everything related to emotions has numbed down significantly, sexuality is non- existent and I don’t react to stimuli as I once did, both physically and mentally/emotionally”
- #85 “Hair loss and dull skin”
- #88 “I didn't have these symptoms prior to Lexapro.”
- #89 “Tremors in the hand and occasional dropping things or loss of balance. Not very severe, but started while on SSRIs and was told it would go away after withdrawal. I has not gone away and has been with me for around 24 years.”
- #92 “I had pretty strong anxiety and a high sex drive for must of my adult life. I could often be a slave to my emotions. Since stopping Cymbalta most of my anxiety has gone away but my ability to get sexually excited or feel love are either gone or severely limited. I describe it as the difference between a flickering pilot light on a gas stove and a burner on high. Before Cymbalta my libido was a burner on high now it is a flickering pilot light.”
- #97 “Pssd came over night 4 months after quitting in horrible withdrawal (Akathisia, insomnia, terror anxiety). Woke up with numb and shrinkage in genitals”
- #107 “Stomach motility reduced post pssd and covid along with appetite and have been diagnosed with sibo as part of attempts to resolve PSSD.
- Most stark and noticeable issues for me which cannot be explained as part of 'mood' are:
- - no high or 'endorphins' after exercise - no ability to feel drunk
- - premature ejaculation
- Others which are part of pssd but can be considered less easy to define
- - anhedonia and emotional blunting positive and negative - quick to anger
- limited or no feelings of joy, excitement, nervousness etc”
- #112
- “burning penis, anus and perineum, recurring groin ulcers, rubbery skin, bleeding gums, eye floaters, random irritation and swelling in different areas of the body, and all the other symptoms I have listed”
- #114
- “Anhedonia began alongside lichen sclerosus after 2 years on fluoxetine. Linked strongly to mir155 which is key in autoimmune disease.
- Amitriptyline caused emotional blunting and nortriptyline caused dysautonomia “ #115
- “I don't get execise high. I don't feel good after going to sauna or cold water. I didn't get any good feeling when I tried mushrooms (only 0,1 g of Golden teacher). Neither did I feel anything of Extacy, have trieda few times after pssd (I did feel before pssd). I have had a pleasureless orgasm -there wasn't even 0,000001 sensation of pleasure, but there were all other symptoms of orgasm.“

Notes

- One survey was eliminated for not taking an SSRI and stating that they did not answer questions truthfully (in the comments).
- 2 surveys that answered “biological female” answered with symptoms that were not female symptoms and so those answers were omitted from results.

Credit: Goldenhour

2. Ancillary symptoms reported by Yassie Pirani (RSW RCC - PSSD clinical counsellor and researcher) with conversations with over 100 PSSD sufferers

Emotional Symptoms of PSSD:

- Emotional blunting or anesthesia (on a spectrum from mild to severe)
- Generalized anhedonia (loss of pleasure, motivation, and enjoyment - on a spectrum from mild to severe)
- Muted emotional spectrum
- Ability to feel negative emotions (e.g., anger or sadness) but not joy or positive emotions
- Lack of rewarding feelings from activities
- Inability to process emotions effectively
- Mental fear without physical sensation of fear
- Lowered or reduced ability to laugh or experience humour
- Difficulty feeling deeper emotional connections with people (social anhedonia)
- Apathy or lack of interest
- Romantic anhedonia (reduced or eliminated interest in romantic connection specifically)
- Diminished or reduced ability to feel emotions in the body
- Diminished or reduced ability to cry
- Diminished or reduced ability to feel love for previously loved ones
- Diminished or reduced ability to empathize or experience empathy
- Empathy experienced only cognitively as an intellectual belief rather than a visceral embodied feeling
- Diminished or reduced ability to feel excitement or anticipation
- Diminished or reduced ability to connect with music or art

Cognitive Symptoms of PSSD:

- Memory retention issues
- Delayed cognitive processing
- Disorganized thoughts
- Concentration and focus problems
- Difficulty communicating
- Loss of motivation
- Inattention
- Loss of ability to access creativity
- Loss of ability to experience humour
- Lack of imagination and visualization
- Loss of dreaming
- Dulled or diminished fantasy (sexual and non-sexual)
- Poor memory
- Struggles with reading, writing, and functioning
- Difficulty learning new things
- Information retention issues
- Depersonalization and derealization
- Challenges with deep comprehension
- Lack of spontaneity
- Brain fog
- Brain zaps or popping sensations**
- Reduced enjoyment of and connection to music
- Loss of connection to spirituality and transcendence**
- Persistent mental fatigue
- Speech impairment and word retrieval difficulties

Miscellaneous Symptoms:

- Sleep disturbances and lowered sleep quality
- Insomnia
- Chronic fatigue
- Diminished skin sensitivity
- Numbness in specific body areas (e.g., forehead or arms)
- Full body numbness
- Diminished senses
- Dry skin
- Head pressure
- Visual snow
- Decreased visual acuity or blurriness
- Reduced ability to feel the effects of substances (e.g., alcohol, caffeine, nicotine)
- Dry mouth
- Dysautonomia symptoms
- POTS (Postural Orthostatic Tachycardia Syndrome) or heart rate issues
- Akathisia
- Tinnitus
- Cold extremities and poor temperature regulation
- Loss of balance
- Loss of physical strength or muscle weakness
- Muscle pain
- Post-exertion malaise
- Tremors
- Protruding veins popping
- Damage to fascia and connective tissues
- Reduced blood flow
- Stomach pains or digestion problems
- IBS symptoms
- Constipation
- Pelvic floor issues
- Sensory loss and muscle coordination issues related to bathroom use
- Loss of sense of smell
- Loss of hunger sensation
- Lack of sweating, temperature regulation, and breath control
- Hair loss and thinning (facial and body hair)
- Cold extremities (hands and genitalia)

3. Additional patient profiles

Patient profile 5

Written by patient

Tracker identification

Skin biopsy: Patient 22

MRI: Patient 35

F. Prausnitzii: Patient 5

Gender: Male

Age: 21

Medication causing PSSD: Prozac (Fluoxetine), Lexapro (Escitalopram)

Length of time medicated: 3 months on Prozac, followed by a few days of Lexapro

When PSSD presented: During the use of Prozac, and worsened around a week after discontinuation

Length of time with PSSD: 2 years

Symptoms: Anhedonia/loss of emotion/inability to feel pleasure, low to zero sex drive and inability to maintain an erection, food and environmental intolerances, severe brain fog/cognitive dysfunction, severe mood swings and and inability to shut off fight or flight mode, fatigue, recurring genital and full body numbness, gastritis and GI issues, joint issues, hair loss and face changes (in the beginning), on and off Sjögren's symptoms

Testing: Multiple blood tests, MRI, Small Fiber neuropathy biopsy (positive), multiple endoscopies (found gastritis all three times), GI pathogen testing/SIBO breath testing, cognitive testing done by a neuropsychologist

Diagnosis: Small Fiber neuropathy, long covid diagnosis, gastritis

Treatment: IVIG infusions, on and off prednisone use, supplements for gut health

Post treatment outcome: IVIG: Occasional relief from cognitive issues, occasional relief from sexual dysfunction and anhedonia (positive results are more apparent when combined with prednisone. Prednisone: Major relief from cognitive dysfunction, relief from mood swings, occasional relief from anhedonia, calms sensitivities and reactivity

Gut health supplements (Probiotics, herbals): Apparent fluctuations of symptoms, some positive some negative

Additional info (known diseases, previous infections etc prior to PSSD and so on): Possible PANDAS, although unconfirmed.

Comment: We have been in contact with this patient since last fall. His overall state so far since commencing treatment is considered marginally improved but with fluctuations of functioning state.

Patient profile 6

Written by patient

Tracker identification

Celltrend: Patient 24

Skin biopsy: Patient 34

MRI: Patient 11

F. Prausnitzii: Patient 3

Gender: Male

Age: 39

Medication causing PSSD: Sertraline

Length of time medicated: 3.5 years on Sertraline, 1 tablet 25mg seroquel

When PSSD presented: during the use of Sertraline and got much worse 3 weeks after stopping

Length of time with PSSD: 14 months since stopping (full blown PSSD), 2 years since symptoms started while still on meds (mainly genital numbness)

Symptoms: anhedonia, numb genitals, extremely muted sensation of full bladder and bowel movement, muted thirst, hunger and tired signals, zero libido, very diminished orgasm sensation and intensity, diminished physical sensation on most of body, no interoception, blank mind, light headed and dizziness spells, PEM type crashes from over
exertion, visual changes, sensitivity to light, slurred speech at times, full body muscle twitches, insomnia, loss of coordination at times, dry skin, less sweating, very impaired memory and recall.

Testing: Various micro biome tests, Cunningham panel (positive), Celltrend (positive), SFN biopsy (positive for NLD), many immune blood and DNA tests (positive for HAE gene, low IgG subclasses, low C1 esterase inhibitor which also points to HAE hereditary angioedema) various blood tests (low T), reactivated EBV, abnormal EMG, some positive blood markers for Sjogren's and awaiting a lip biopsy.

Diagnosis: HAE although not typical symptom pattern, SFN, Common variable immunodeficiency (CVID), Mild cognitive impairment (MCI), CIDP based on abnormal EMG. The rheumatologist thinks I have neuro Sjogren's based on my symptoms and blood markers. She is awaiting a lip biopsy for an official diagnosis.

Treatment: FMT, LDN 1mg, IVIG infusions 600mg/kg, Ruconest

Treatment outcome: No significant relief at this moment

Additional info (known diseases, previous infections prior to PSSD and so on): Not reported (TBA).

Comment: We have been in close contact with this patient since last fall. So far no changes since receiving treatment. With that said, the IVIG dosage the patient is receiving is very low compared to what's normally given in immune-mediated SFN cases.