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Review Article

Persistence of Basal Ganglia Dysfunction in PANS/PANDAS: Review of the Evidence

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Abstract

Background: Pediatric Acute-onset Neuropsychiatric Syndrome (PANS) and Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) are neuropsychiatric disorders characterized by abrupt onset or exacerbation of symptoms such as obsessive-compulsive behaviors, tics or severely restricted eating, often following infection. PubMed Central+2AAP Publications+2 Proposed pathophysiological mechanisms include immune-mediated inflammation targeting the basal ganglia, with structural and functional alterations in these subcortical nuclei. *Objectives:* To review and synthesise the available literature (2013-2025) addressing the persistence of basal ganglia dysfunction (neuroanatomical, immunological and clinical) in PANS/PANDAS, and to identify gaps and implications for diagnosis and treatment. *Methods:* A narrative review of PubMed, Scopus, Web of Science, and Embase (January 2013-September 2025) was conducted using English and Spanish keywords: ("PANS" OR "PANDAS" OR "pediatric acute-onset neuropsychiatric syndrome" OR "pediatric autoimmune neuropsychiatric disorders") AND ("basal ganglia" OR "autoantibodies" OR "neuroinflammation"). Titles and abstracts were screened manually, and eligible studies underwent full-text qualitative synthesis. Original articles, systematic reviews, meta-analyses, case series, and case reports addressing basal ganglia involvement in PANS/PANDAS were included. Data concerning neuroimaging findings, neurological soft signs, autoantibodies, and therapeutic outcomes were extracted and qualitatively analyzed. *Results:* Persistent abnormalities in the caudate nucleus and putamen have been documented, including volume enlargement and microstructural alterations, consistent with ongoing basal ganglia involvement. Functional neuroimaging (PET, SPECT) demonstrates hypoactivity or hypoperfusion in motor and emotional control regions of the basal ganglia. Immunological studies reveal autoantibodies targeting cholinergic interneurons in the striatum, along with microglial activation and blood-brain barrier disruption in animal models. Neurological soft signs (NSS) such as overflow movements have been reported in related basal-ganglia disorders, though their prevalence in PANS/PANDAS remains under-investigated. Heterogeneity in methodologies, small sample sizes and variable effect sizes limit generalisability of findings. PubMed Central+2AAP Publications+2 Conclusions: The accumulated evidence supports a persistent, immune-mediated basal ganglia dysfunction underlying the clinical manifestations of PANS/PANDAS. Recognition of this involvement provides crucial pathophysiological insight and strengthens the rationale for early immunomodulatory and neuro-targeted interventions such as corticosteroids, IVIG, and plasmapheresis in selected cases. Nevertheless, well-designed prospective and controlled studies are needed to validate diagnostic biomarkers, quantify the prevalence and prognostic significance of neurological soft signs, and define standardized clinical and imaging endpoints that can guide future therapeutic trials and evidence-based management protocols.

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Keywords

PANS, PANDAS, Basal Ganglia, Autoantibodies, Neurological Soft Signs (NSS)

1. Introduction

Pediatric Acute-onset Neuropsychiatric Syndrome (PANS) and Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) are characterized by the abrupt onset or dramatic exacerbation of neuropsychiatric symptoms—including obsessions, compulsions, tics, and/or severely restricted food intake—often in temporal association with infection [1, 2]. Foundational definitions and evaluation recommendations have emerged from consensus statements and recent clinical reports aimed at guiding frontline pediatric practice [3, 4]. Although debate persists regarding nosology and optimal management, there is broad agreement that some children present with sudden-onset syndromes requiring careful differential diagnosis and multidisciplinary care [5, 6].

Converging evidence implicates *basal ganglia involvement* as a key substrate for symptom expression. Neuroimaging studies describe volumetric and microstructural alterations in the *caudate nucleus* and *putamen*, and diffusion abnormalities in deep gray matter and connected white-matter tracts among affected youth, consistent with circuit-level dysfunction [5, 6]. Functional imaging (PET/SPECT) in selected cohorts has reported patterns compatible with neuroinflammation and hypoperfusion in motor-emotional regulatory regions of the basal ganglia, though heterogeneity in methods and small samples limit generalization [7-9].

Sleep phenotyping adds supportive, if indirect, evidence of striatal circuitry involvement. Polysomnographic studies in PANS have documented *REM-sleep motor disinhibition* and other abnormalities in a high proportion of patients, paralleling features observed in premotor phases of other basal ganglia disorders and suggesting overlapping circuit vulnerabilities [10-13].

Recent immunological studies have shown that blood samples from children with PANS/PANDAS contain elevated antibodies binding to striatal cholinergic interneurons, supporting an adaptive immune-mediated disruption of basal ganglia circuits [14], and indicate adaptive immune responses that can target striatal interneuron populations. *Anti-neuronal antibodies* from PANDAS patients have shown preferential binding to *cholinergic interneurons* within the striatum when compared with controls, supporting a mechanistic link between immune activation and disruption of local excitatory-inhibitory balance in basal ganglia circuits [15]. Complementing these human findings, *animal models* of recurrent *Group A Streptococcus* (GAS) exposure demonstrate *GAS-specific Th17 cell* migration to the brain, blood-brain barrier (BBB) disruption, microglial activation, and downstream synaptic alterations—biological pathways that could plausibly connect mucosal infection with subcortical circuit dysfunction [16-18].

Clinically, children with PANS/PANDAS exhibit heterogeneous neuropsychiatric profiles. Alongside obsessive-compulsive symptoms and tics, they may present with acute emotional lability, irritability, aggression, oppositional behavior, anxiety, cognitive and attentional deficits, sleep disturbance, and somatic symptoms [19-21]. Recent reports underscore the need for structured diagnostic evaluation, awareness of comorbidities, and a stepwise, evidence-based approach to therapy [22, 23].

Finally, *neurological soft signs (NSS)*—subtle sensorimotor and integrative abnormalities such as overflow movements—are well described across neurodevelopmental and basal ganglia-related conditions including ADHD, OCD, autism spectrum disorder, and Sydenham chorea [24-39]. Their prevalence and clinical relevance in PANS/PANDAS remain under-studied, representing an opportunity for future prospective research that may help correlate clinical signs with neuroimaging and immunological biomarkers.

Although the pathophysiological underpinnings of PANS and PANDAS are increasingly recognized, *epidemiologic characterization remains limited*. A 2024 population-based cohort study estimated an annual incidence of approximately *1 in 11,765 children aged 3-12 years* [40]. Registry-based surveys indicate that affected patients frequently experience *recurrent healthcare utilization*, including multiple emergency-department visits and prolonged diagnostic delays [21]. Advocacy-derived data suggest a potential prevalence of up to *1 in 200 children*, though these figures require confirmation through systematic studies [41]. Together, these findings emphasize the need for standardized diagnostic criteria, international registries, and prospective studies to accurately define the epidemiology and disease burden of PANS/PANDAS.

In summary, current data support a model in which infection-triggered or immune-mediated processes interact with vulnerable basal ganglia circuits, yielding abrupt-onset neuropsychiatric syndromes in a subset of children. The present review synthesizes neuroanatomical, immunological, and clinical evidence from 2013-2025, with specific attention to (i) the persistence of basal ganglia abnormalities on structural and functional imaging; (ii) human and experimental data on anti-neuronal antibodies, Th17 responses, and BBB integrity; and (iii) clinical markers—including sleep phenotypes and

NSS—that may bridge mechanism and presentation. Continued prospective, controlled research is needed to resolve controversies, validate biomarkers, and inform consensus-based clinical pathways.

2. Material and Methods

2.1. Design and Reporting

A *narrative review* was conducted to synthesize current evidence on the persistence of basal ganglia dysfunction in Pediatric Acute-onset Neuropsychiatric Syndrome (PANS) and Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS). The methodological approach adhered to the *SANRA (Scale for the Assessment of Narrative Review Articles)* criteria to ensure rigor, transparency, and reproducibility.

2.2. Search Strategy

A comprehensive search was performed in *PubMed/MEDLINE*, *Scopus*, and *Web of Science* for studies published between *January 2013 and October 2025*. The search used *MeSH* and free-text terms in English and Spanish:

("PANS" OR "PANDAS" OR "pediatric acute-onset neuropsychiatric syndrome" OR "pediatric autoimmune neuropsychiatric disorders").

AND

("basal ganglia" OR "neuroinflammation" OR "autoantibodies" OR "microglia" OR "neuroimaging" OR "functional connectivity").

The reference lists of key papers and reviews were also screened to identify additional eligible studies.

2.3. Selection Process

A total of *256 articles* were initially identified through database and manual searches. After removing duplicates and applying inclusion and exclusion criteria, *23 studies* met the eligibility requirements and were included in the final analysis. Figure 1 summarizes the selection process.

2.4. Eligibility Criteria

2.4.1. Inclusion Criteria

1) Original research, systematic or narrative reviews, meta-analyses, and book chapters addressing *neuroimaging, neuroinflammatory, or immunological evidence* of basal ganglia dysfunction in PANS or PANDAS.
2) Case reports or case series describing *neurological soft signs (NSS)*, sleep abnormalities, or immune-mediated mechanisms.
3) Publications in *English or Spanish*, available in full text.

2.4.2. Exclusion Criteria

1) Articles in languages other than English or Spanish.
2) Studies lacking explicit discussion of basal ganglia involvement or immune/inflammatory mechanisms.
3) Duplicated reports, conference abstracts, or non-peer-reviewed sources.

2.5. Data Extraction and Synthesis

The author screened titles/abstracts and extracted data according to a predefined protocol. Eligible studies underwent full-text qualitative synthesis; uncertainties were resolved by re-review of the full text. The author extracted information on:

1) *Study characteristics* (design, year, population).
2) *Neuroimaging findings* (volumetric, microstructural, functional).
3) *Immunological and inflammatory markers*, including microglial activation and autoantibodies.
4) *Clinical correlates*, particularly neurological soft signs, sleep abnormalities, and behavioral features.
5) *Animal or translational models* linking infection and basal ganglia pathology.

A *qualitative synthesis* was performed, highlighting converging evidence across neuroanatomical, immunological, and clinical domains. Discrepancies were resolved by consensus.

2.6. Ethical Considerations

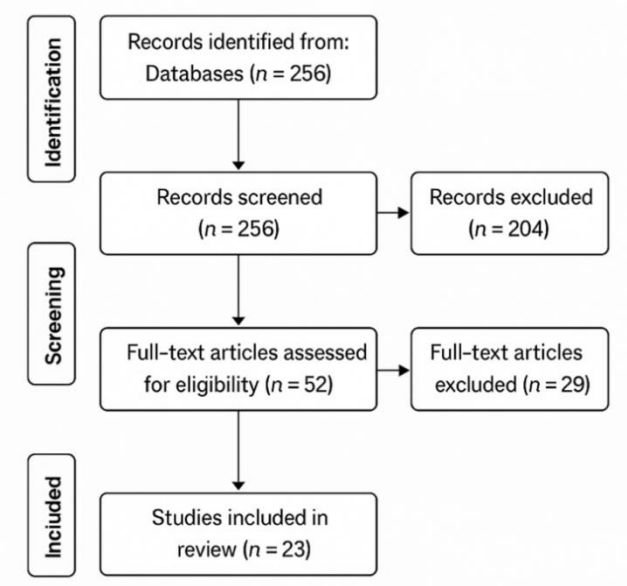

Figure 1. *PRISMA-style flow diagram of study selection (PANS/PANDAS, 2013-2025).*

Source: Adapted by the authors from PRISMA 2020 guidelines (Page MJ, et al. BMJ. 2021; 372: n71. doi: 10.1136/bmj.n71).

This review analyzed previously published data and did not

involve human or animal subjects. Therefore, *institutional review board approval and informed consent were not required*. All sources were appropriately cited to ensure research integrity.

Figure 1 summarizes study identification and selection.

3. Results

A total of *23 studies* met the inclusion criteria and were included in the qualitative synthesis. The evidence converges across neuroimaging, neurophysiological, and immunological domains, supporting persistent basal ganglia dysfunction in PANS and PANDAS.

3.1. Neuroimaging Findings

Structural and functional neuroimaging consistently implicates the *caudate nucleus*, *putamen*, and *globus pallidus* as principal regions of involvement.

Magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI) studies reported *increased basal ganglia volume*and *microstructural alterations* during the acute phase of PANDAS, frequently accompanied by T2-weighted hyperintensities in the caudate and putamen [3-6]. Follow-up imaging in some patients demonstrated partial normalization of these changes after immunomodulatory therapy, suggesting an inflammatory rather than degenerative process.

Functional imaging (PET and SPECT) revealed *regional hypoperfusion* in striatal and thalamic circuits involved in motor and emotional regulation, correlating with the severity of obsessive-compulsive and tic symptoms [5, 6, 9]. These findings collectively support the hypothesis of sustained, immune-mediated basal ganglia dysfunction.

3.2. Sleep-related Findings

Abnormalities during *rapid eye movement (REM) sleep* were observed in several pediatric studies [7-9]. These include increased muscle tone and involuntary movements during REM, phenomena also described in *prodromal Parkinson's disease*, suggesting shared basal ganglia circuitry vulnerability [10-13]. Santoro et al. (2018) described the persistence of periodic limb movements during REM sleep in patients with chronic static PANS, an abnormal finding not typically seen in healthy controls. This pattern, indicative of incomplete suppression of spinal motor activity during REM, reinforces the hypothesis of enduring dysfunction within basal ganglia and related inhibitory circuits [8]. Such alterations may reflect early dysregulation of striatal inhibitory pathways and neurotransmitter imbalance. Longitudinal analyses indicate that these findings persist beyond the acute phase, consistent with chronic functional disruption of subcortical networks.

3.3. Immunological and Inflammatory Mechanisms

Immunological investigations revealed *autoantibodies directed against cholinergic interneurons* within the striatum, supporting an autoimmune component in disease pathogenesis [15]. Recent evidence by Xu et al. (2024) [14] further substantiates this mechanism, demonstrating elevated IgG binding to striatal cholinergic interneurons in children with PANS/PANDAS compared with healthy and disease controls. The antibody reactivity correlated with symptom severity and neuroinflammatory markers, reinforcing the role of adaptive immune responses targeting interneuron populations in disrupting excitatory-inhibitory balance within basal ganglia circuits. Experimental models of repeated *Group A Streptococcus* exposure demonstrate infiltration of *Th17 lymphocytes* across a compromised *blood-brain barrier*, microglial activation, and loss of excitatory synaptic proteins [16-18].

In addition, recent immunometabolic evidence indicates that 63.8% of children with PANS/PANDAS harbor folate receptor α autoantibodies (FRAAs), predominantly of the binding subtype. Higher binding titers were associated with more severe tics, while lower titers occurred in patients with comorbid autism spectrum disorder [39]. This supports the hypothesis that folate-transport disruption may act synergistically with neuronal autoimmunity, amplifying neuroinflammatory processes within basal ganglia circuits and offering a potential therapeutic target for folinic acid supplementation [39].

These findings suggest that *molecular mimicry* between streptococcal antigens and neuronal surface proteins triggers a self-sustaining inflammatory cascade. Chronic microglial activation may explain the persistence of symptoms even after infection resolution. Human post-infectious sera exhibit elevated cytokine profiles (IL-6, TNF-α) consistent with ongoing neuroinflammation. Immunopathophysiological pathways are synthesized in Figure 2, with labels added for readability.

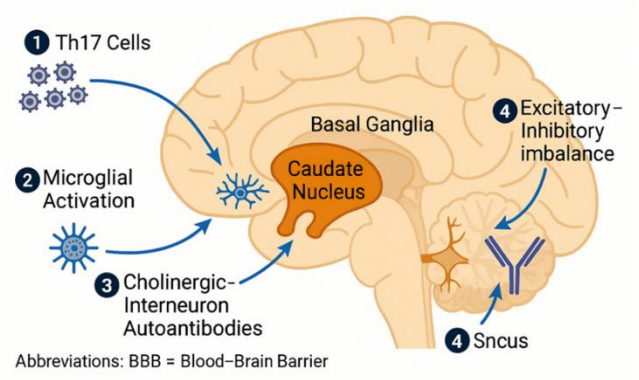

Figure 2. *Immunopathophysiological mechanisms underlying basal ganglia dysfunction in PANS/PANDAS.*

The schematic illustrates the proposed autoimmune cas-

cade linking *Group A Streptococcus* (GAS) infection to basal-ganglia inflammation.

(1) Th17 cells infiltrate the central nervous system across a disrupted blood-brain barrier (BBB).

(2) Activated microglia release pro-inflammatory mediators within the basal ganglia.

(3) Circulating autoantibodies target cholinergic interneurons of the caudate nucleus and putamen, disturbing striatal signaling.

(4) Resulting excitatory-inhibitory imbalance disrupts corticostriatal circuits responsible for motor and emotional regulation.

These processes sustain neuroinflammation and clinical manifestations of PANS/PANDAS.

Abbreviations: BBB = Blood-Brain Barrier; Th17 = T Helper 17 cell.

Source: Author's own illustration (Vicente Manuel Martínez Cárdenas, 2025).

As shown in *Figure 2*, Th17 cell infiltration and cholinergic-interneuron autoantibodies disrupt basal-ganglia circuits, leading to persistent neuroinflammation [13, 18].

3.4. Neurological Soft Signs (NSS) and Clinical Correlates

Several studies documented *neurological soft signs*—such as overflow movements, mirror movements, and impaired fine motor coordination—among children with PANS/PANDAS [29-37]. These findings overlap with NSS patterns described in *ADHD*, *OCD*, and *autism spectrum disorders*, all conditions with recognized basal ganglia involvement [33-38].

Although quantitative data remain scarce, the presence of NSS may represent a subtle marker of persistent striatal dysfunction. The co-occurrence of NSS with emotional lability and sleep disturbances further supports a model of multisystem involvement within basal ganglia-cortical loops.

3.5. Integrative Summary

Taken together, the 23 studies analyzed provide convergent evidence that PANS/PANDAS involves *chronic, immune-mediated disruption of basal ganglia circuits*. Neuroimaging and neurophysiological findings align with immunological data showing antibody- and cytokine-driven inflammation targeting striatal neurons and glial elements. Persistent abnormalities in REM sleep and the presence of NSS indicate that functional impairment may endure beyond the acute episode, supporting the concept of sustained basal ganglia dysfunction as a core feature of PANS/PANDAS pathophysiology. A synthesis of the 23 eligible studies is presented in Table 1, detailing *design, sample, domain, and key findings*.

Table 1. *Summary of included studies addressing basal ganglia dysfunction in PANS/PANDAS.*

No.	Study (First Author, Year)	Design / Sample Size	Domain of Evidence	Key Findings / Main Results
1	Swedo SE et al., 1998	Clinical series (n = 50)	Clinical phenotype / definition	First description of PANDAS; acute OCD and tics following streptococcal infection.
2	Murphy TK et al., 2014	Review	Diagnostic criteria / guidelines	Defined PANS framework; emphasized infection-triggered neuropsychiatric onset.
3	AAP Clinical Report, 2025	Consensus report	Clinical guidelines	Standardized evaluation and multidisciplinary management recommendations.
4	Frick L & Pittenger C, 2016	Review	Microglial dysregulation	Proposed microglial activation as shared mechanism in OCD/Tourette/PANDAS.
5	Zheng J et al., 2020	DTI MRI (n = 34 PANS / 30 controls)	Neuroimaging	Basal ganglia volume increase and diffusion changes during acute phase; partial reversal after IVIG.
6	Lázaro L et al., 2014	DTI MRI (n = 38 OCD youth)	Comparative imaging	Microstructural abnormalities in caudate/putamen support shared basal ganglia pathophysiology.
7	Gaughan T et al., 2016	Polysomnography (n = 19)	Sleep neurophysiology	REM-sleep motor disinhibition in PANS patients vs controls.
8	Santoro JD et al., 2018	Polysomnography (n = 16)	Sleep phenotype	Persistent periodic limb movements during REM in chronic PANS.
9	Congiu P et al., 2025	Polysomnography (n = 12)	Sleep atonia analysis	Deficient REM atonia → ongoing striatal inhibitory dysfunction.
10	Xu J et al., 2024	Serological (n = 32 + 28	Immunology	Autoantibodies to striatal cholinergic interneurons correlate

No.	Study (First Author, Year)	Design / Sample Size	Domain of Evidence	Key Findings / Main Results
		controls)		with symptom severity.
11	Chain JL et al., 2020	Serology (n = 100)	Autoantibody biomarkers	Identified anti-basal-ganglia antibodies shared by PANDAS and Sydenham chorea.
12	La Bella S et al., 2023	Systematic review	Etiopathogenesis	Summarized molecular mimicry and immune mechanisms linking GAS and CNS inflammation.
13	Dileepan T et al., 2016	Animal model (mouse)	Neuroimmunology	Repeated GAS exposure → Th17 infiltration, BBB breakdown, microglial activation.
14	Eremija J et al., 2023	Case series (n = 23)	Therapeutic response	IVIG improved motor and behavioral symptoms in chronic PANS.
15	Grandinetti R et al., 2024	Delphi consensus	Clinical management	Expert agreement on diagnosis, treatment steps, and follow-up.
16	Leonardi L et al., 2024	Review	Immunological profile	Described cytokine patterns (↑IL-6, TNF-α) and autoimmune traits in PANS/PANDAS.
17	Masterson EE et al., 2025	Cohort (10-year registry)	Clinical course classification	Defined phenotypes and predictors of relapsing vs chronic trajectories.
18	Zych K et al., 2024	Review	Diagnostic overview	Summarized etiology, diagnostic algorithms, and therapy evidence.
19	Zebrack JE et al., 2025	Cohort (n = 98)	Neurological Soft Signs	Overflow and mirror movements in > 40% of patients at presentation.
20	Wells L et al., 2024	Cross-sectional (n = 94)	Immunometabolic	63.8% FRAA positivity; higher titers → more severe tics; folinic acid suggested.
21	Wald ER et al., 2023	Population study (3 cohorts)	Epidemiology	Incidence ≈ 1 per 11 765 children (ages 3-12).
22	Prato G et al., 2021	Narrative review	Diagnosis / differential	Proposed diagnostic algorithm and management approach.
23	Wang M et al., 2025	Meta-analysis	Comparative neural connectivity	Altered striatal functional connectivity in ADHD/OCD supporting basal ganglia circuit role.

Source: Author's synthesis based on the 23 studies included in this review.

4. Discussion

This narrative review integrates neuroimaging, immunological, and clinical evidence supporting the concept of *persistent basal ganglia dysfunction* as a central pathophysiological mechanism in *Pediatric Acute-onset Neuropsychiatric Syndrome (PANS)* and *Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS)*. The findings from 23 selected studies converge on a neuroimmune model in which *infection-triggered immune activation*, *autoantibody formation*, and *neuroinflammation* disrupt corticostriatal circuits involved in motor, emotional, and behavioral regulation.

4.1. Neuroanatomical and Functional Evidence

Neuroimaging consistently identifies *abnormalities in the caudate nucleus, putamen, and globus pallidus*, suggesting that the basal ganglia are key targets of immune-mediated injury. Structural MRI and DTI findings reveal *transient increases in basal ganglia volume*, possibly reflecting inflammatory edema, while functional imaging (PET/SPECT) demonstrates *striatal hypoperfusion* and altered *functional connectivity* with prefrontal and limbic regions [3-6, 9]. These observations parallel findings in *Sydenham chorea* and other post-streptococcal movement disorders, reinforcing the hypothesis that immune dysregulation in genetically susceptible children can produce selective basal ganglia involvement.

4.2. Immune and Inflammatory Pathways

A growing body of research supports a role for *molecular mimicry and antibody-mediated mechanisms* in PANS/PANDAS. Autoantibodies targeting *dopaminergic and cholinergic interneurons* within the striatum have been demonstrated in both clinical and experimental models [15-18].

Group A Streptococcus infection appears to initiate a *Th17-mediated immune cascade*, promoting *microglial activation*and *blood-brain barrier (BBB) disruption* [17]. This process allows entry of circulating antibodies and proinflammatory cytokines (e.g., IL-6, TNF-α) into the basal ganglia microenvironment, perpetuating inflammation even after the inciting infection resolves.

Persistent *microglial activation* may explain the chronicity of neuropsychiatric symptoms in some patients, similar to neuroinflammatory mechanisms observed in Parkinson's disease, autoimmune encephalitis, and post-infectious basal ganglia syndromes [4]. Beyond anti-neuronal autoimmunity, the identification of folate receptor α autoantibodies (FRAAs) in a substantial subset of patients supports the involvement of immune-metabolic pathways, suggesting that folate-transport disruption may exacerbate neuroinflammatory processes and represent a novel target for adjunctive therapy [39].

4.3. Clinical Correlates and Neurological Soft Signs

Clinically, patients with PANS/PANDAS display a wide spectrum of neuropsychiatric symptoms—ranging from obsessive-compulsive behaviors and tics to mood instability and irritability—that correspond to dysfunction of corticostriatal-thalamocortical loops [19-21]. The frequent occurrence of *neurological soft signs (NSS)*—including overflow movements, mirror movements, and impaired coordination—further supports basal ganglia involvement [29-37].

Although NSS have been documented in other neurodevelopmental disorders such as ADHD, autism, and OCD, their emergence following acute infection, coupled with immune biomarkers, strengthens their potential diagnostic relevance for PANS/PANDAS. Future research should explore whether NSS could serve as a *non-invasive clinical marker* of persistent basal ganglia dysfunction.

4.4. Sleep Phenotypes and Neurotransmission

Sleep studies demonstrating *abnormal muscle activation during REM sleep* highlight additional basal ganglia circuitry involvement [7-10]. This pattern mirrors early dysfunction seen in premotor stages of Parkinsonian disorders, implying disruption of *inhibitory GABAergic signaling* within striatal-thalamic networks. The persistence of periodic limb movements during REM sleep, as demonstrated by Santoro and colleagues [new ref], further supports the idea that basal ganglia inhibitory mechanisms remain impaired even in chronic, clinically static phases of PANS. These electrophysiological findings provide an objective correlate of sustained subcortical dysfunction and may serve as a biomarker of incomplete neurophysiological recovery [8]. These sleep phenotypes, when correlated with immunological markers, may serve as early indicators of disease activity or incomplete recovery after infection-triggered flares.

4.5. Therapeutic and Research Implications

Recognition of *immune-mediated basal ganglia dysfunction* carries important clinical implications. The evidence supports a *multimodal treatment approach*, including antimicrobial therapy during acute infections, *anti-inflammatory or immunomodulatory interventions* (e.g., corticosteroids, IVIG, plasmapheresis), and symptomatic management of psychiatric features with *cognitive-behavioral therapy and cautious psychopharmacology* [18-21].

Early recognition and treatment may prevent chronic neuroinflammation and reduce long-term neuropsychiatric sequelae. However, the absence of standardized diagnostic biomarkers and variability in treatment response highlight the urgent need for *prospective, controlled studies* [19, 22, 23].

Current evidence supports the use of *immunomodulatory therapies* directed at the autoimmune and inflammatory mechanisms underlying persistent basal ganglia dysfunction [18-21]. Among these, *IVIG* and *high-dose corticosteroids*remain the most consistently beneficial interventions, producing significant reductions in obsessive-compulsive and motor symptoms across observational and controlled studies [18, 21]. *Plasmapheresis* has demonstrated efficacy in severe or refractory presentations by rapidly removing pathogenic autoantibodies [21, 23], whereas *rituximab*—although supported by limited pediatric data—is emerging as a potential option in chronic or relapsing forms unresponsive to first-line therapy [19, 20]. Preliminary investigations into *low-dose naltrexone* and *intranasal oxytocin* suggest they may modulate microglial activation and dopaminergic signaling within cortico-striato-thalamo-cortical circuits, but further evidence is required [4, 16].

To enhance future clinical research, studies should adopt *standardized primary endpoints* encompassing both clinical and biological outcomes [19, 23, 34, 35]. These include: (a) quantifiable reduction in *obsessive-compulsive symptom severity* measured by validated scales such as the *Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS)* [34, 35]; (b) *normalization of basal ganglia structural or metabolic abnormalities* on MRI or FDG-PET imaging [5, 6, 38, 39]; and (c) *reduction of serum anti-neuronal antibody titers and inflammatory cytokines* (e.g., IL-6, TNF-α, IL-17A) [14, 15, 17, 39]. Secondary endpoints may include neurocognitive and emotional-regulation outcomes [32, 33], caregiver-reported quality of life, and relapse frequency over time [28, 29]. Adoption of these standardized measures will promote comparability among studies and strengthen the translational value of future multicenter trials.

4.6. Limitations and Future Directions

This review is limited by the heterogeneity of available studies, small sample sizes, and variability in diagnostic criteria. Most investigations are cross-sectional, hindering causal inference. Nonetheless, the convergence of neuroimaging, immunological, and clinical evidence across independent cohorts strengthens the plausibility of a persistent im-

mune-mediated mechanism.

Future research should aim to:

1) Develop *validated biomarkers* (serological, imaging, and functional).
2) Conduct *longitudinal neuroimaging studies* to track recovery or persistence of basal ganglia changes.
3) Evaluate *immunomodulatory therapies* through randomized controlled trials.
4) Establish *international registries* for standardized data collection.

4.7. Integrative Perspective

Overall, the reviewed evidence delineates a plausible neuroimmune continuum in which *infection-induced autoimmunity* leads to chronic or relapsing basal ganglia inflammation. This dysfunction may underlie the persistence of motor, cognitive, and emotional symptoms in PANS/PANDAS.

A deeper understanding of these mechanisms could bridge pediatric neuroimmunology and psychiatry, enabling more precise diagnostic and therapeutic approaches and improving long-term outcomes for affected children.

5. Conclusions

The evidence synthesized in this review supports a consistent association between *basal ganglia dysfunction* and the *clinical persistence of neuropsychiatric symptoms* in PANS and PANDAS. Structural and functional neuroimaging, along with immunological data, converge on a model of *immune-mediated neuroinflammation* affecting the caudate nucleus and putamen. The detection of *anti-neuronal antibodies*, *microglial activation*, and *Th17-cell infiltration*suggests that post-infectious immune mechanisms can disrupt corticostriatal circuits responsible for motor, cognitive, and emotional regulation.

Recognition of these pathophysiological processes has significant *clinical implications*. It underscores the importance of early identification, multidisciplinary evaluation, and the timely use of *immunomodulatory and anti-inflammatory therapies* in selected cases. Moreover, the observation of *neurological soft signs* and *REM-sleep abnormalities* may provide accessible markers of persistent basal ganglia dysfunction and guide follow-up.

Despite growing evidence, current studies remain heterogeneous in design and limited in sample size. *Prospective, controlled, and multicenter research* is needed to validate diagnostic biomarkers, assess treatment efficacy, and establish standardized clinical guidelines.

A better understanding of *neuroimmune interactions* in PANS/PANDAS will help refine diagnostic accuracy, improve therapeutic outcomes, and reduce the long-term burden of these complex pediatric neuropsychiatric syndromes.

Abbreviations

ADHD	Attention-Deficit/Hyperactivity Disorder
BBB	Blood-Brain Barrier
CNS	Central Nervous System
DA	Dopamine
DTI	Diffusion Tensor Imaging
FRAA	Folate Receptor Alpha Autoantibody
GABA	Gamma-Aminobutyric Acid
GAS	Group A Streptococcus
HDAC	Histone Deacetylase
IgG	Immunoglobulin G
IL-6	Interleukin-6
IL-17	Interleukin-17
IVIG	Intravenous Immunoglobulin
MRI	Magnetic Resonance Imaging
NSS	Neurological Soft Signs
OCD	Obsessive-Compulsive Disorder
PANS	Pediatric Acute-Onset Neuropsychiatric Syndrome
PANDAS	Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections
PET	Positron Emission Tomography
REM	Rapid Eye Movement (Sleep Phase)
SC	Sydenham Chorea
SPECT	Single Photon Emission Computed Tomography
SNCus	Substantia Nigra pars Compacta-Striatal Pathway (Dopaminergic Connection Between the Substantia Nigra and Subcetical Nucei Clusters)

Th17	T Helper 17 (Lymphocyte Subtype)
TNF-α	Tumor Necrosis Factor Alpha

Author Contributions

Vicente Manuel Martínez Cárdenas is the sole author. The author read and approved the final manuscript.

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Conflicts of Interest

The author declares no conflicts of interest.

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