Mini-Review
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Connections Between Prefrontal Cortex Anatomy and Autism Spectrum Disorder: A Literature Review

Efthalia Tzila[1], Eleni Panagouli[1, 2], Maria Tsouka[3], Amir Shihada[1], Dionysios Venieratos[1], Dimosthenis Chrysikos[1], Theodore Troupis[1]

[1]Department of Anatomy, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece, [2]Department of Basic and Clinical Sciences, Medical School, University of Nicosia, UNIC Athens, 16777, Athens, Greece, [3]Department of Psychology, Université Lumière Lyon 2, Lyon, France

Correspondence: *eleni72000@yahoo.gr*; Tel.: + 30 210 7462394

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Abstract

Objective. This review examines the existing literature on the structural and functional changes in the anatomy of the prefrontal cortex (PFC) associated with autism spectrum disorder (ASD), focusing on the roles of molecular signaling disruptions and trace element imbalances. **Methods.** A literature review was performed through a structured search of academic publications from 2010 to 2025. **Discussion.** Anatomic variations and structural and functional abnormalities within the PFC, including disruptions in neural connectivity, synaptic plasticity, and neurochemical balance, significantly contribute to the cognitive, social, and emotional deficits observed in ASD. The interplay between brain-derived neurotrophic factor dysregulation, oxidative stress, and trace element imbalances further exacerbates these dysfunctions. **Conclusion.** According to our findings, the anatomy of the PFC appears to play a crucial role in the pathophysiology of ASD, given its involvement in executive function, emotional processing, and social cognition, suggesting a multifactorial pathophysiology that demands a multidimensional research approach.

Key Words: Anatomy ▪ Autism ▪ Brain Structure ▪ Synapse.

Introduction

Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder that emerges in early childhood and persists throughout an individual's lifetime. ASD is characterized by deficits in social interaction, communication difficulties, and the presence of restricted and repetitive behaviors. ASD significantly affects cognitive, emotional, social, and physical health, with an estimated prevalence of 1 in 36 children and a higher occurrence in males than in females (1). The prefrontal cortex (PFC) is anatomically located in front of the frontal lobe of the brain. This anatomical part of the brain, which governs high-level cognitive and social processes, has emerged as a critical region in ASD research. Impairments in activity-dependent neural signaling pathways and disruptions in trace element homeostasis within the PFC may underlie the cognitive and behavioral deficits characteristic of ASD (1).

This mini-review examines the existing literature on the structural and functional changes in the anatomy of the PFC associated with ASD, focusing on the roles of molecular signaling disruptions and trace element imbalances.

Methods

This literature review was developed through a structured search of academic publications published between 2010 and 2025. The databases searched were PubMed, Scopus, and Google Scholar. Relevant sources were identified using the search terms "Prefrontal Cortex Anatomy", "Autism Spectrum Disorder", "BDNF" (brain-derived neurotrophic

factor), "Oxidative Stress", "Neuroanatomy", and "Neurodevelopment". The reference lists of the selected articles were manually screened to identify further pertinent literature.

Inclusion Criteria: Studies were selected based on language (English), relevance to PFC morphological and anatomical alterations in ASD, and scientific rigor. Priority was given to research incorporating anatomical, neuroimaging, and neuropathological findings. *Exclusion Criteria:* Studies that examined connections between different brain regions or multiple disorders were excluded from the present review. Additionally, studies written in a language other than English or published before 2010 were excluded.

Data Extraction and Analysis

A data extraction form was used to extract data from eligible articles, which were reviewed simultaneously and independently by three reviewers (E.P., E.T., and M.T.). Disagreements were resolved through discussions among the reviewers and by team consensus.

Discussion

The etiology of ASD is multifaceted, involving a combination of genetic, epigenetic, and environmental factors that contribute to its heterogeneous presentation (1). Studies suggest that brain neuroanatomy, disruptions in neural circuits, synaptic plasticity, and neurotransmitter imbalances play significant roles in the pathophysiology of ASD (2). The PFC, a brain anatomical region responsible for executive functions, decision-making, and social cognition, has been identified as a critical area of interest in ASD research due to its involvement in higher-order cognitive processes (2).

BDNF Levels as a Potential Diagnostic Marker

Emerging human studies have investigated serum and plasma BDNF concentrations as possible biomarkers for ASD. Barbosa et al. (3) analyzed serum BDNF in 49 children with classical autism and 37 typically developing controls, finding that BDNF levels were statistically significantly elevated in ASD children ($P<0.000$). Their analysis included ROC modeling, suggesting moderate discriminatory ability between groups—though notable overlap and outliers cautioned against using BDNF alone as a diagnostic tool (3). A more recent study by Farmer et al. (4) emphasized that higher peripheral BDNF levels in ASD may largely reflect increased platelet counts rather than direct neural secretion. This finding highlights an important confounding factor when interpreting peripheral BDNF measurements and suggests that any biomarker development must account for platelet contributions (4). Taken together, while elevated peripheral BDNF in ASD is a reproducible finding, its standalone diagnostic utility remains uncertain without adjustments for biological confounders, such as platelets, age, and cognitive severity.

Structural and Functional Implications in the Prefrontal Cortex

Recent neuroimaging and histopathological studies have revealed abnormalities in the structure and function of the PFC in individuals with ASD, including altered neuronal connectivity, reduced dendritic spine density, and imbalances in excitatory and inhibitory neurotransmission (5). Additionally, recent studies have focused on the medial prefrontal cortex (mPFC), a crucial anatomical part of the "social brain" involved in social behaviors. These studies suggest that mPFC dysfunction may contribute to the changes in social behaviors observed in individuals with ASD (6). Furthermore, studies have indicated that mPFC dysfunction is associated with impaired emotional regulation and difficulties in interpreting social cues, further exacerbating the core symptoms of ASD (7, 8).

The functional connectivity between the PFC and other brain regions, such as the basal ganglia, thalamus, and cerebellum, plays a crucial role in the execution of complex motor, cognitive, and emotional functions. Disruptions in these connections have been associated with ASD symptoms,

highlighting the importance of large-scale brain network alterations in this disorder (8). Moreover, neuroanatomical and neurophysiological alterations in amygdala-PFC connectivity, particularly reduced connectivity between the amygdala and the right ventrolateral PFC during the processing of fearful faces, have been implicated in emotional dysregulation in ASD, further emphasizing the role of PFC dysfunction in socio-emotional impairments (9).

In a volumetric MRI study of children and adults with ASD, no significant differences in gross dorsolateral prefrontal cortex (DLPFC) volume were observed relative to typically developing controls, and volumetric measures did not correlate with executive task performance. These results suggest that executive dysfunctions may stem more from functional rather than structural gross abnormalities in this region (10).

In addition to the medial and ventrolateral PFC, there is strong evidence for the involvement of the DLPFC in ASD. For example, Courchesne et al. examined postmortem PFC tissue in children with ASD and neurotypical controls, focusing on the DLPFC (DL-PFC) and mesial PFC (M-PFC). They found that children with ASD had ~79% more neurons in the DL-PFC than controls, as well as an increased number in the M-PFC (~29%). These findings suggest that neuronal overpopulation in the DLPFC may play a role in the early brain overgrowth observed in ASD and that DLPFC abnormalities should be considered in models of structural PFC alterations (11). However, post-mortem examination has revealed microglial activation and altered neuron-microglia spatial organization in the DLPFC of individuals with autism. Microglia were found in closer proximity to neurons (e.g., 25–100 μm), potentially reflecting neuroinflammatory or homeostatic disruptions from early childhood onward (12).

In vivo proton magnetic resonance spectroscopy (MRS) investigations targeting adults with ASD have measured elevated gamma-aminobutyric acid (GABA)/water ratios in the left DLPFC, despite no significant difference in $GABA_A$ receptor density (13). This suggests that inhibitory neurotransmission in this region may be altered in ASD and could contribute to the functional atypicalities reported in executive control and inhibition tasks (13, 14). Functional magnetic resonance imaging (fMRI) studies, including those assessing temporal discounting, show reduced activation in both the right ventrolateral and dorsolateral PFC in adolescents and adults with ASD. Importantly, whereas typically developing individuals display increased activation with age in these regions, individuals with ASD exhibit attenuated functional maturation, which correlates with task performance and clinical indices, such as repetitive behaviors (15).

Together, these findings encourage a more integrative view: even in the absence of gross anatomical differences, the DLPFC exhibits functional under-activation, neurochemical alterations, and microglial–neuronal reorganization in ASD. These subtle changes likely underlie impairments in executive control, planning, inhibitory behavior, and cognitive flexibility. Including the DLPFC completes the anatomical and functional mapping of key PFC subregions implicated in ASD, offering a richer foundation for understanding the neural heterogeneity of the disorder.

Trace Element Dysregulation and Oxidative Stress

Neurochemical studies have also revealed significant alterations in the metabolic profile of the mPFC in individuals with ASD. Specifically, reduced levels of total N-acetylaspartate (tNAA) and total creatine, along with an increased Glx (mixed signal of glutamate and glutamine)/tNAA ratio, indicate underlying neurometabolic dysfunctions in the mPFC. These findings suggest potential disruptions in neuronal viability and energy metabolism, which may contribute to the cognitive and behavioral impairments observed in ASD (9). Additionally, emerging evidence suggests that oxidative stress and trace element imbalances, such as altered levels of copper (Cu), zinc (Zn), magnesium (Mg), and iron (Fe), may further influence neuronal function and exacerbate symptoms associated with ASD (7).

Recent studies have highlighted the role of glutathione (GSH), the primary antioxidant in the brain, in maintaining redox homeostasis within the PFC. Decreased GSH levels in individuals with ASD suggest impaired antioxidant defenses, leading to increased neuronal vulnerability and oxidative damage (16). Furthermore, trace elements are known to influence neurotransmitter systems—zinc plays a role in GABAergic transmission and synaptic inhibition, while iron is essential for dopamine synthesis, both of which are critical for emotional regulation and social behavior (17). Disruptions in these systems may intensify core ASD symptoms. In addition, trace element imbalances may affect epigenetic processes such as DNA methylation and histone modification, thereby altering the expression of genes linked to neurodevelopment (18). Notably, sex-based differences in oxidative stress responses and trace element metabolism may help explain the higher prevalence of ASD in males, underscoring the importance of individualized approaches in future research and therapy (19).

Key Morphological Findings or Alterations in Specific Prefrontal Cortex Regions

Morphological alterations of the PFC in ASD have been increasingly recognized as a central component of the neuroanatomical profile of the disorder. Beyond global volumetric changes, research emphasizes the importance of disentangling distinct morphological indices, such as cortical thickness, cortical surface area, and gray/white matter volumes. For example, Ecker et al. (20) reported that adults with ASD exhibit increased cortical thickness in the pars opercularis of the inferior frontal gyrus, coupled with reduced cortical surface area in regions such as the rostral middle frontal gyrus. These results suggest that atypical prefrontal development in ASD is not uniform but instead reflects a dynamic interplay between thickness and surface area that may follow distinct developmental trajectories. Importantly, such findings also highlight that volume-based measures alone may mask region-specific alterations that could be directly linked to behavioral phenotypes (20).

In addition, lifespan research indicates that these morphological differences are dynamic. Walsh et al. (21), for instance, demonstrated that reductions in hippocampal volume and increases in extracellular free-water are strongly associated with cognitive decline in older adults with ASD. While hippocampal changes were central to their study, the authors also underscored evidence of structural alterations in the prefrontal regions, particularly in the integrity of both gray and white matter, thereby suggesting that the PFC may undergo age-related modifications that interact with the clinical expression of ASD. This perspective underscores the necessity of adopting a developmental and longitudinal lens when examining prefrontal morphology (21).

It is worth noting, in comparison, that in adults with ASD, corresponding data reveal different trajectories: Braden and Riecken (22) demonstrated accelerated age-related cortical thinning, particularly in the pars opercularis of the frontal lobe, as well as in temporal, parietal, and occipital cortices. Although these adult findings do not provide detailed volumetric measures of gray and white matter, they highlight that cortical morphology in ASD is not static but evolves dynamically across the lifespan (22).

Finally, more recent neuroimaging data highlight that structural variability in the dorsolateral and orbitofrontal cortices is closely associated with symptom severity in ASD. Alterations in both gray and white matter organization within these regions—long recognized as critical for executive functioning, social cognition, and emotion regulation—point to the anatomical substrates of clinical heterogeneity across individuals (23). Taken together, these studies converge to demonstrate that the PFC in ASD is characterized by region-specific and age-dependent alterations in cortical thickness, surface area, and gray/white matter volumes.

Key Findings from Neuroimaging Studies of the Prefrontal Cortex in ASD

Neuroimaging research has provided substantial evidence of PFC dysfunction in individuals with

ASD. fMRI studies have revealed that individuals with ASD exhibit reduced activation in the right ventrolateral and dorsolateral PFC during tasks involving temporal discounting (15). Specifically, Murphy et al. (15) demonstrated that males with ASD had significantly lower brain activation in these regions than typically developing controls. This hypoactivation was associated with poorer task performance and suggests that deficits in PFC function may underlie decision-making impairments observed in ASD (15). In addition to functional abnormalities, structural differences in the PFC have been observed in ASD. Irimia et al. conducted a study using diffusion tensor imaging to assess white matter integrity in the PFC of individuals with ASD. Their findings indicated reduced fractional anisotropy in the left dorsolateral PFC, suggesting compromised white matter integrity in this region. These structural abnormalities may contribute to the functional deficits observed in the PFC and further support the notion of PFC dysfunction in ASD (24).

Future Research

Future investigations should prioritize longitudinal studies that integrate neuroimaging, molecular biology, and electrophysiology to establish causal links between PFC anatomical morphology and ASD symptomatology. Furthermore, exploring personalized therapeutic interventions, such as targeted neuromodulation and metabolic regulation strategies, may pave the way for more effective treatments. Addressing the heterogeneity of ASD through precision medicine approaches will be crucial for developing tailored interventions that enhance neurodevelopmental outcomes and improve the quality of life of individuals with ASD and their families. In summary, the anatomy of the PFC plays a critical role in the neurobiology of ASD, affecting cognitive, social, and emotional functions. Structural and functional abnormalities in the anatomy of this region, including disrupted connectivity, synaptic dysfunction, and neurochemical imbalances, contribute to the core symptoms of ASD. Studies additionally indicate that impairments in BDNF signaling and trace element homeostasis exacerbate these disruptions, further impacting neuronal plasticity and metabolic regulation. Given the complexity of ASD and the multifaceted involvement of PFC functions and anatomy, future research should focus on integrating neuroimaging, molecular, and electrophysiological approaches to develop targeted therapeutic strategies. Investigating the roles of oxidative stress, neuroinflammation, and genetic factors may provide deeper insights into the mechanisms underlying the pathophysiology of ASD. Additionally, personalized interventions based on an individual's neurobiological profile could enhance treatment efficacy, ultimately improving the quality of life of individuals with ASD.

Conclusion

The findings reviewed in this paper highlight the pivotal role of the PFC in the neurobiological mechanisms underlying ASD. Anatomic variations and structural and functional abnormalities within this region, including disruptions in neural connectivity, synaptic plasticity, and neurochemical balance, significantly contribute to the cognitive, social, and emotional deficits observed in ASD. The interplay between BDNF dysregulation, oxidative stress, and trace element imbalances further exacerbates these dysfunctions, suggesting a multifactorial pathophysiology that requires a multidimensional approach to research. In conclusion, the anatomy of the PFC plays a crucial role in the pathophysiology of ASD, given its involvement in executive function, emotional processing, and social cognition. Structural and functional disruptions, including impaired connectivity, synaptic alterations, anatomical variations, and neurochemical imbalances, highlight the complexity of the neurological basis of the disorder. Abnormal BDNF signaling and trace element dysregulation appear to aggravate these disturbances, indicating their potential as therapeutic targets. Advancing our understanding will require integrative approaches that combine neuroimaging, molecular biology, and electrophysiology to uncover

the underlying mechanisms. Ultimately, personalized, biology-driven treatment strategies may offer more effective interventions and significantly improve outcomes for individuals living with ASD.

What Is Already Known on This Topic:

ASD is a complex neurodevelopmental disorder with an increasing incidence and multiple impacts. Several hypotheses and mechanisms have been under investigation to identify the possible causes of ASD. The prefrontal cortex (PFC), an anatomical part of the brain that governs high-level cognitive and social processes, has emerged as a critical region in ASD research.

What This Study Adds:

After reviewing the available literature, this study clarifies that the anatomy of the PFC plays a crucial role in the pathophysiology of ASD and presents the possible mechanisms. Our findings could lead to further investigations and studies to improve outcomes for individuals living with ASD.

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Conflict of Interest: The authors declare that they have no conflict of interest.

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