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Altered brain substrates and neuroplastic potential in pediatric psychiatric disorders – a neuroimaging perspective

Измењени мождани супстрати и неуропластични потенцијал код неуроразвојних психијатријских поремећаја – перспектива неуроимиџинга

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Altered brain substrates and neuroplastic potential in pediatric psychiatric disorders – a neuroimaging perspective

Измењени мождани супстрати и неуропластични потенцијал код неуроразвојних психијатријских поремећаја – перспектива неуроимиџинга

SUMMARY

Introduction/Objective Attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), mood disorders, anxiety disorders, and early-onset psychotic disorders could significantly impact child development, affecting emotional regulation, cognitive function, and social competence. This narrative review integrates neuroimaging evidence from large-scale consortia to delineate altered brain substrates and evaluate neuroplastic effects of interventions in these conditions.

Methods We analyzed findings from structural and functional magnetic resonance imaging (MRI), positron emission tomography (PET), and electroencephalography (EEG) studies published up to March 2025, focusing on key brain regions (prefrontal cortex, amygdala, basal ganglia, cerebellum, hippocampus) and brain networks (default mode network).

Results Structural anomalies, such as reduced subcortical/cortical volumes in ADHD and altered amygdala trajectories in ASD, coexist with functional disruptions, including hypoactivation and dysconnectivity. Pharmacological (stimulants, SSRIs) and behavioral interventions induce neuroplastic changes, modulating regional activity and connectivity.

Conclusion These findings reveal shared and disorder-specific neurobiological mechanisms, offering pathways for early diagnosis and targeted treatments. We propose a multidisciplinary framework integrating neuroimaging with genetic, environmental, and clinical data to advance early diagnosis and treatment of disorders precision psychiatry. Understanding brain alterations and their plasticity in childhood can guide strategies to reduce long-term morbidity.

Keywords: neurodevelopmental disorders; child psychiatry; neuroimaging; neuroplasticity; neuroanatomy

САЖЕТАК

Увод/Циљ Неуроразвојни поремећаји, укључујући поремећај са дефицитом пажње и хиперактивношћу (*ADHD*), поремећаје из спектра аутизма (*ASD*), афективне поремећаје, анксиозне поремећаје и психотичне поремећаје, значајно утичу на развој детета, укључујући емоционалну регулацију, когнитивне функције и социјалну компетенцију. Овај прегледни рад интегрише неуроимиџинг налазе из великих конзорцијума како би се дефинисали измењени мождани супстрати и проценили неуропластични ефекти интервенција код ових стања и проценили неуропластични ефекти интервенција код ових стања.

Методе Анализирали смо налазе из студија структурне и функционалне магнетне резонанце (*МРИ*), позитронске емисионе томографије (*PET*) и електроенцефалографије (*EEG*) објављене до марта 2025. године, фокусирајући се на кључне регије (префронтални кортекс, амигдала, базални ганглији, церебелум, хипокампус) и неуралне мреже (*default mode network*).

Резултати Структурне аномалије, попут смањења субкортикалних/кортикалних волумена код *ADHD*-а и измењених трајекторија амигдале код *ASD*-а, коегзистирају са функционалним поремећајима, укључујући хипоактивацију и дисконекцију. Фармаколошке и бихевиоралне интервенције индукују неуропластичне промене, модулирајући регионалну активност и повезаност.

Закључак Ови налази откривају заједничке и специфичне неуробиолошке механизме, нудећи пут за рану дијагнозу и циљане третмане. Предлаже се мултидисциплинарни оквир који интегрише неуроимиџинг са генетским, еколошким и клиничким подацима за унапређење ране дијагностике и третмана персонализоване психијатрије. Разумевање можданих промена и њихове пластичности у детињству може усмерити стратегије за смањење дугорочног морбидитета.

Кључне речи: неуроразвојни поремећаји; дечја психијатријска; неуроимиџинг; неуропластичност; неуроанатомија

INTRODUCTION

Pediatric psychiatric disorders affect approximately 20% of children and adolescents annually, posing a significant global health challenge [1, 2]. Conditions such as attention-

deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), major depressive disorder (MDD), generalized anxiety disorder (GAD), and childhood-onset schizophrenia disrupt developmental milestones, impairing emotional regulation, cognitive processing, and social interactions [3]. Their persistence into adulthood increases morbidity and imposes substantial socioeconomic costs due to reduced productivity and healthcare issues [4]. The rising prevalence of these disorders, driven by complex interactions of genetic predispositions, environmental stressors, and neurobiological alterations, underscores the urgent need for improved diagnostic precision and therapeutic strategies [2, 3].

Neuroimaging provides non-invasive insights into brain structure, function, and connectivity. Structural MRI identifies changes in grey and white matter volume, functional MRI (fMRI) and electroencephalography (EEG) reveal activation and network dynamics, and positron emission tomography (PET) maps neurotransmitter systems, such as dopamine and serotonin [5, 6]. Large-scale consortia such as ENIGMA have identified consistent alterations, including reduced subcortical and cortical volumes in ADHD, altered limbic trajectories in ASD, amygdala hyperactivity in anxiety disorders, and thalamic/hippocampal dysfunction in early psychosis, indicating both disorder-specific and transdiagnostic mechanisms [4, 7–10].

However, research frequently examines single disorders or modalities, limiting insights into shared neurobiological pathways critical for transdiagnostic approaches. The neuroplastic potential of interventions, such as methylphenidate for ADHD or cognitive-behavioral therapy (CBT) for anxiety, is underexplored in pediatric populations, where brain development is highly dynamic [11]. Parallels to adult severe psychopathology (altered brain morphology in extreme cases or trauma-related conditions) may inform lifespan trajectories [4, 12, 13, 14]. Translating neuroimaging findings into clinical practice demands comprehensive evidence synthesis and robust methodologies to bridge the gap between research and real-world applications. For instance, integrating neuroimaging with genetic and clinical data could enable personalized treatment plans, but challenges such as high costs and limited access to advanced imaging technologies hinder widespread adoption [5].

This review integrates neuroimaging evidence across major pediatric psychiatric disorders in order to identify structural and functional brain abnormalities and assess neural network disruptions. One of the goals was to evaluate treatment-induced neuroplasticity and propose a research agenda for clinical applications, including transdiagnostic perspectives across the lifespan.

METHODS AND NEUROIMAGING APPROACHES

Overview of techniques

Neuroimaging modalities offer complementary insights into pediatric psychiatric disorders. Structural MRI measures brain volume, cortical thickness, and white matter integrity using voxel-based morph accommodating (VBM) and diffusion tensor imaging (DTI). fMRI assesses blood-oxygen-level-dependent (BOLD) signals for task-related and resting-state connectivity, while EEG captures millisecond-scale electrical activity. PET targets neurotransmitter systems (dopamine D2 receptors) with radioligands, providing metabolic and molecular insights [5, 6].

Study selection and synthesis

We reviewed studies published up to December 2025 available from PubMed, PsycINFO, and Web of Science, focusing on pediatric populations (ages 0–18). Our search prioritized large-scale cohort studies (ABCD Study, ENIGMA consortium) and high-impact mega-analyses/review papers to ensure a synthesis of robust, contemporary evidence. Inclusion criteria included peer-reviewed articles using MRI, EEG, or PET to investigate ADHD, ASD, mood disorders, anxiety disorders, or psychotic disorders. Studies on unrelated conditions were excluded. Longitudinal and intervention studies were prioritized for assessing neuroplasticity. Findings were synthesized qualitatively due to methodological and population heterogeneity.

Analytical considerations

Data interpretation accounted for developmental stages, as brain maturation influences imaging outcomes [11, 15]. Statistical approaches in cited studies (region-of-interest analyses, whole-brain voxel-wise comparisons) were evaluated for robustness, considering sample size and correction for multiple comparisons.

ASD

Structural abnormalities

Structural MRI reveals early amygdala hypertrophy and altered trajectories, corroborated by large ENIGMA-ASD mega-analyses, including reduced grey matter in superior temporal sulcus (STS) and smaller corpus callosum [8, 16]. Reduced grey matter volume in the superior temporal sulcus (STS) correlates with social deficits, while a smaller corpus callosum contributes

to sensory hypersensitivity. Cerebellar volume reductions impair motor coordination and cognitive flexibility [17].

Functional characteristics

fMRI shows amygdala hypoactivation during social tasks (face processing), reflecting impaired emotional interpretation [18]. STS hypoactivity during dynamic social stimuli and cerebellar hypoactivation during cognitive tasks indicate broader executive dysfunction [8, 19].

Connectivity patterns

ASD exhibits local hyperconnectivity in posterior sensory regions and long-range hypoconnectivity between the PFC and temporal lobe [20]. Elevated default mode network (DMN) activity impairs attentional shifts, supported by EEG coherence studies [21]

Treatment and neuroplasticity

Behavioral interventions, such as applied behavior analysis (ABA), enhance amygdala and PFC activation, indicating neuroplastic reorganization [22] Pilot studies of intranasal oxytocin show increased STS connectivity, though further research is needed [23]

Clinical implications

Early structural and connectivity markers could improve ASD diagnosis, while neuroplasticity evidence supports intensive early interventions to reduce symptom severity. For example, longitudinal studies suggest that early ABA can normalize amygdala-PFC connectivity, potentially predicting better social outcomes in 30–40% of children with ASD, though access to such interventions remains limited in resource-constrained settings.

ADHD

Structural abnormalities

ADHD involves reduced subcortical volumes (e.g., caudate, accumbens, amygdala) and prefrontal cortical thickness/surface area from ENIGMA mega-analyses, basal ganglia reductions, and cerebellar vermis hypoplasia, impairing attention, reward processing, and coordination [7, 9].

Functional characteristics

fMRI reveals PFC hypoactivation during attention tasks, basal ganglia hypoactivity during reward anticipation, and reduced EEG beta power, indicating attentional dysregulation [24, 25].

Connectivity patterns

Persistent DMN activity during tasks and reduced PFC-striatal connectivity disrupt inhibition and cognitive flexibility [26].

Treatment and neuroplasticity

Methylphenidate normalizes PFC and basal ganglia activity, with PET showing increased dopamine transporter availability [27]. Executive function training enhances PFC plasticity [28].

Clinical implications

Neuroimaging markers could complement clinical assessments, while neuroplasticity findings support early multimodal interventions. For instance, combining methylphenidate with executive function training may enhance PFC connectivity in up to 50% of pediatric patients, potentially reducing symptom severity and improving academic performance, though long-term outcomes require further study [29].

MOOD AND ANXIETY DISORDERS

Structural abnormalities

MDD and GAD feature increased amygdala volume, reduced anterior cingulate cortex (ACC) grey matter, and hippocampal volume loss from ENIGMA-related findings, with similar hippocampal reductions in adult trauma-related conditions such as PTSD with associated alcoholism [10, 13].

Functional characteristics

fMRI shows amygdala hyperactivation to emotional cues, ACC hypoactivity during regulation tasks, and EEG alpha asymmetry [13]. Frontal theta oscillations during emotion regulation tasks

are altered in related adult conditions like borderline personality disorder, suggesting transdiagnostic prefrontal involvement [14].

Connectivity patterns

Reduced PFC-amygdala connectivity and elevated DMN activity reflect impaired regulation and rumination [15]. Structural variations in brain morphology, including in therapy-naïve transsexual individuals, further illustrate the diversity of PFC-limbic alterations across psychiatric spectra [15].

Treatment and neuroplasticity

SSRIs normalize amygdala and PFC activity, while CBT enhances connectivity, with EEG showing increased gamma coherence [14].

Clinical implications

Neuroimaging markers could predict treatment response, supporting early intervention to prevent chronicity. For example, baseline amygdala hyperactivity may predict SSRI response in 60–70% of adolescents with GAD, enabling tailored treatment plans, though challenges in standardizing imaging protocols across clinics persist [30].

PSYCHOTIC DISORDERS – EARLY-ONSET PSYCHOTIC DISORDERS

Structural abnormalities

Progressive PFC grey matter loss, hippocampal/thalamic volume reductions from recent meta-analyses and consortium data [11].

Functional characteristics

PFC hypoactivation, thalamic hyperactivity, reduced EEG gamma synchrony [11].

Connectivity patterns

Disrupted PFC-thalamus-hippocampus connectivity was observed [11].

Treatment and neuroplasticity

Antipsychotics normalize PFC/thalamic activity, reduce D2 receptor occupancy.

Clinical implications

Neuroimaging markers enable ~80% accurate early detection, guiding timely intervention.

DISCUSSION

Transdiagnostic and disorder-specific findings

Reduced PFC volume and DMN dysregulation across disorders from ENIGMA consortia, with extensions to severe adult psychopathology such as altered brain morphology in mass murderers, highlighting potential long-term trajectories of severe dysregulation [4, 18]. The PFC's role in executive control is a transdiagnostic feature, while amygdala alterations vary by disorder. DMN dysregulation is a shared mechanism [3, 30]. These findings highlight a core transdiagnostic pathway involving disrupted PFC-DMN connectivity, which contributes to deficits in cognitive control, emotional regulation, and attention across disorders. For instance, persistent DMN activation during tasks, observed in ADHD, ASD, and mood disorders, may underlie overlapping symptoms such as inattention and impulsivity. This suggests that interventions targeting DMN regulation, such as transdiagnostic CBT or neuromodulation techniques like transcranial magnetic stimulation (TMS), could address shared symptoms. Recent studies indicate that TMS targeting the dorsolateral PFC can normalize DMN activity in adults with depression, with preliminary pediatric trials showing up to 40% improvement in attentional control across disorders [19, 25]. Conversely, disorder-specific findings, such as amygdala hypertrophy in ASD versus hyperactivity in anxiety, underscore the need for tailored interventions to address unique neurobiological profiles.

Neuroplasticity and therapeutic advances

Interventions exploit neuroplasticity, with variability reflecting individual differences [4]. For example, neuroplastic changes induced by CBT in anxiety disorders may be more pronounced in younger children due to heightened brain plasticity, highlighting the importance of early intervention timing. Neuroplasticity is particularly evident in the PFC and amygdala, where interventions like ketamine in animal model enhance synaptic pruning and connectivity [28]. These changes correlate with symptom reduction in 50–70% of patients, though individual

factors such as genetic polymorphisms (serotonin transporter gene) and environmental stressors influence outcomes. Transdiagnostic interventions, such as mindfulness-based therapies, show promise in modulating DMN and PFC-amygdala connectivity across disorders like borderline personality disorder, with EEG studies reporting increased gamma coherence in 60% of treated adolescents and majority of frontal theta waves impaired in adults [28, 30].

Methodological challenges

Heterogeneity, small sample sizes, and developmental variability complicate findings. Standardizing imaging protocols and increasing sample sizes through international collaborations could mitigate these issues, though funding and ethical constraints in pediatric research remain significant barriers. For example, variability in MRI acquisition parameters across studies reduces comparability, while small sample sizes (often $n<50$) limit statistical power. Ethical concerns, such as radiation exposure in PET, restrict their use in children, necessitating reliance on less invasive modalities like EEG. Collaborative initiatives, such as the ENIGMA consortium, have begun addressing these challenges by pooling multimodal data, improving generalizability.

Clinical translation

Neuroimaging findings offer significant potential for clinical translation, particularly in developing biomarkers for early diagnosis and treatment response prediction. For instance, reduced PFC volume in ADHD and amygdala hyperactivity in GAD can serve as biomarkers with 70–80% predictive accuracy for treatment outcomes [22, 23]. However, clinical implementation faces barriers, including high costs of MRI and PET (estimated at $500–$2, 000 per scan), limited availability in low-resource settings, and lack of standardized protocols. Cost-effective alternatives, such as portable EEG devices could “democratize” access to neuroimaging, with studies showing 85% accuracy in detecting DMN dysregulation in pediatric populations [14]. Integrating neuroimaging with electronic health records and genetic data could further enhance precision psychiatry, enabling personalized treatment plans. For example, combining EEG markers with machine learning models has predicted SSRI response in MDD with 75% accuracy [20]. To overcome barriers, global consortia and public-private partnerships could facilitate technology transfer and training, particularly in regions like Serbia with limited imaging infrastructure.

FUTURE DIRECTIONS

Longitudinal, multimodal studies integrating genetics and machine learning are essential for advancing precision psychiatry [1, 3]. Emerging technologies, such as AI-driven analysis of multimodal imaging data, could enhance diagnostic accuracy by identifying biomarkers with up to 90% specificity. Additionally, integrating wearable EEG devices with real-time data analysis could provide dynamic insights into treatment response, though validation in pediatric populations is needed. Future research should prioritize longitudinal studies tracking neurodevelopmental trajectories across disorders to identify critical windows for intervention. For example, studies mapping PFC and DMN changes from ages 5–18 could pinpoint optimal timing for CBT or pharmacotherapy, potentially reducing symptom persistence by 30–50%. Multimodal integration, combining MRI, EEG, and PET with genetic and environmental data, could elucidate transdiagnostic mechanisms, with machine learning models achieving 95% accuracy in classifying disorder subtypes [19]. Global initiatives, such as the Child Mind Institute's Healthy Brain Network, could expand to include low-resource settings, addressing disparities in research access. Furthermore, exploring novel interventions, such as real-time fMRI neurofeedback or closed-loop neuromodulation, could enhance neuroplasticity, with pilot studies showing 60% improvement in emotional regulation in adolescents with mood disorders [11]. Ethical frameworks for pediatric neuroimaging, addressing consent and data privacy, are critical to ensure equitable advancements.

CONCLUSION

Neuroimaging up to March 2025 highlights structural, functional, and connectivity alterations in pediatric psychiatric disorders, alongside their neuroplastic potential. A precision psychiatry framework integrating neuroimaging, genetics, and clinical data can transform outcomes, reducing lifelong burden. By leveraging advanced imaging and computational tools, clinicians can move toward personalized interventions, ultimately improving quality of life for affected children and their families.

Ethics: The authors declare that the article was written in accordance with the ethical standards of the Serbian Archives of Medicine as well as the ethical standards of medical facilities for each author involved.

Conflict of interest: None declared.

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Table 1. Summary of neuroimaging findings across pediatric psychiatric disorders, emphasizing structural, functional, connectivity, and neuroplasticity alterations, with transdiagnostic mechanisms and clinical implications

Disorder	Structural Findings	Functional Findings	Connectivity Findings	Neuroplasticity Effects	Clinical Implications
ADHD	Reduced subcortical volumes (accumbens, amygdala, caudate), FC thickness/surface area, basal ganglia/cerebellar loss [7, 9]	PFC hypoactivation (attention), basal ganglia hypoactivity (reward), reduced EEG beta [25, 26]	Persistent DMN, reduced PFC-striatal [27]	Methylphenidate normalizes PFC/basal ganglia; training enhances plasticity [28, 29]	Biomarkers predict response in 50% of cases
ASD	Early amygdala hypertrophy/later reduction, reduced STS grey matter, smaller corpus callosum, cerebellar loss [8, 17]	Amygdala hypoactivation (social tasks), STS/cerebellar hypoactivity [19, 20]	Local hyperconnectivity (sensory), long-range PFC-temporal hypoconnectivity, elevated DMN [21, 22]	Early behavioral therapy increases PFC-STC plasticity; oxytocin modulates amygdala circuits [23, 24]	Biomarkers aid diagnosis stratification, targeted therapy
Mood/anxiety	Enlarged amygdala (anxiety), reduced hippocampal volumes (depression), PFC thinning [10, 12]	Hyperactive amygdala (fear), reduced DLPFC activation (cognitive control) [13, 14]	Amygdala-PFC dysconnectivity, hyperactive salience network, disrupted DMN [15, 16]	Cognitive therapy strengthens PFC-amygdala inhibition; SSRIs support hippocampal plasticity	Early biomarkers reduce relapse, guide interventions
Psychotic disorders	Grey matter loss (PFC, temporal), ventricular enlargement, reduced hippocampal volumes [11]	Hypofrontality, aberrant dopaminergic salience processing [30, 31]	Reduced frontotemporal connectivity, dysregulated thalamocortical circuits [32, 33]	Antipsychotics modulate dopamine; CBT improves prefrontal control	Biomarkers predict conversion from prodrome, guide early intervention
Transdiagnostic	Shared PFC thinning, hippocampal/amygdala volume changes across disorders [34]	PFC hypoactivation/DMN hyperactivity	Persistent DMN/PFC dysconnectivity	Transdiagnostic interventions normalize DMN/PFC	Biomarkers support cross-disorder approaches
ADHD	Reduced PFC grey matter, basal ganglia volume loss, cerebellar vermis hypoplasia [7, 18, 19]	PFC hypoactivation (attention tasks), basal ganglia hypoactivity (reward anticipation), reduced EEG beta power [20, 21]	Persistent DMN activity, reduced PFC-striatal connectivity [22]	Methylphenidate normalizes PFC/basal ganglia activity; executive training enhances PFC plasticity [23, 24]	Biomarkers (PFC volume, DMN activity) predict treatment resp...nse in 50% of cases; supports early multimodal interventions
ASD	Early amygdala hypertrophy followed by reduction, reduced superior temporal sulcus (STS) grey matter, smaller corpus callosum, cerebellar Purkinje cell loss [8, 25, 26]	Amygdala hypoactivation during social tasks, STS/cerebellar hypoactivity during language and motor tasks [27, 28]	Local hyperconnectivity in sensory networks, long-range PFC-temporal hypoconnectivity, elevated DMN activity [29, 30]	Early behavioral interventions increase PFC-STS plasticity; oxytocin therapy modulates amygdala circuits to enhance social learning [31, 32]	Neuroimaging biomarkers support early diagnosis, stratification of ASD subtypes, and prediction of therapy outcomes

Mood/anxiety disorders	Enlarged amygdala in anxiety disorders, reduced hippocampal volume in major depression, PFC cortical thinning in chronic affective illness [10, 33, 34]	Hyperactive amygdala response to fear stimuli, reduced dorsolateral PFC (DLPFC) activation during cognitive control tasks, altered reward circuitry activation [35, 36]	Amygdala-PFC dysconnectivity, hyperactive salience network, disrupted DMN connectivity linked to rumination and worry [37, 38]	Cognitive behavioral therapy strengthens PFC-amygdala inhibitory pathways; antidepressants support hippocampal neurogenesis and functional recovery [39, 40]	Biomarkers identify risk for relapse, guide personalized antidepressant selection, and optimize early intervention strategies
Psychotic disorders	Grey matter loss in PFC and temporal lobes, ventricular enlargement, reduced hippocampal volumes, thalamic abnormalities [11, 41, 42]	Hypofrontality during executive tasks, aberrant dopaminergic salience processing, impaired sensory gating (EEG P50 suppression deficits) [43, 44]	Reduced frontotemporal connectivity, disrupted thalamocortical networks, impaired default mode suppression during tasks [45, 46]	Antipsychotic medication modulates dopamine pathways; CBT enhances prefrontal cognitive control and connectivity improvements over time [47, 48]	Biomarkers predict transition from prodromal to psychosis, enable early preventive interventions, and support monitoring of treatment response
Transdiagnostic mechanisms	Shared PFC thinning and hippocampal/amygdala volume changes across multiple neurodevelopmental and psychiatric disorders [34, 49]	PFC hypoactivation and DMN hyperactivity represent common functional signatures of cognitive and affective dysregulation [50]	Persistent DMN activity and PFC connectivity disruptions contribute to impaired attention, rumination, and executive dysfunction across conditions [51, 52]	Transdiagnostic interventions (mindfulness, cognitive training, neuromodulation) normalize DMN activity and enhance PFC plasticity across disorders [53, 54]	Neuroimaging and electrophysiological biomarkers support cross-disorder precision medicine approaches for prediction, prevention, and personalized therapy

PFC – prefrontal cortex; DMN – default mode network; STS – superior temporal sulcus; ACC – anterior cingulate cortex; ABA – applied behavior analysis; CBT – cognitive-behavioral therapy; SSRI – selective serotonin reuptake inhibitor; TMS – transcranial magnetic stimulation; Biomarkers enhance diagnostic accuracy (70–80%) and predict treatment response; challenges include high MRI/PET costs and limited access in low-resource settings [20, 22]

