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BRAIN STRUCTURAL AND FUNCTIONAL ALTERATIONS ASSOCIATED WITH EXTRAPYRAMIDAL SYMPTOMS IN ANTIPSYCHOTIC-TREATED PATIENTS (REVIEW)

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Abstract. Extrapyramidal symptoms (EPS) remain among the most clinically significant and treatment-limiting adverse effects of antipsychotic pharmacotherapy. Although dopamine D_2-receptor blockade within the nigrostriatal pathway represents the classical pharmacodynamic mechanism, recent multimodal neuroimaging and translational findings demonstrate that EPS result from complex alterations involving cortical–subcortical network integration, microstructural white-matter integrity, and neurofunctional connectivity. Structural MRI, diffusion tensor imaging (DTI), functional MRI (fMRI), and positron emission tomography (PET) studies reveal consistent associations between EPS and morphological changes in the basal ganglia, thalamic and cerebellar dysfunction, as well as disruption of cortico-striato-thalamic circuitry. These mechanisms have important clinical implications for risk assessment, early detection, and individualized pharmacotherapy.

Keywords: extrapyramidal symptoms; antipsychotics; basal ganglia; white matter; MRI; DTI; fMRI; PET; precision psychiatry.

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СТРУКТУРНЫЕ И ФУНКЦИОНАЛЬНЫЕ ИЗМЕНЕНИЯ ГОЛОВНОГО МОЗГА, СВЯЗАННЫЕ С ЭКСТРАПИРАМИДНЫМИ СИМПТОМАМИ У ПАЦИЕНТОВ, ПОЛУЧАЮЩИХ АНТИПСИХОТИЧЕСКИЕ ПРЕПАРАТЫ (ОБЗОР)

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Аннотация. Экстрапирамидные симптомы (ЭПС) остаются одними из наиболее клинически значимых и ограничивающих лечение побочных эффектов антипсихотической фармакотерапии. Хотя блокада дофаминовых D_2-рецепторов в нигростриарной системе традиционно рассматривается как классический

фармакодинамический механизм, современные мультимодальные нейровизуализационные и трансляционные исследования показывают, что ЭПС возникают в результате сложных нарушений интеграции корково-подкорковых сетей, микроструктурной целостности белого вещества и нейрофункциональной коннективности. Данные структурной МРТ, диффузионно-тензорной томографии (DTI), функциональной МРТ (fMRI) и позитронно-эмиссионной томографии (ПЭТ) демонстрируют устойчивые связи между ЭПС и морфологическими изменениями в базальных ганглиях, дисфункцией таламуса и мозжечка, а также нарушениями кортико-стриато-таламических цепей. Эти механизмы имеют важное клиническое значение для оценки риска, раннего выявления и индивидуализации фармакотерапии.

Ключевые слова: экстрапирамидные симптомы; антипсихотики; базальные ганглии; белое вещество; МРТ; DTI; fMRI; ПЭТ; персонализированная психиатрия.

Introduction. Extrapyramidal symptoms (EPS) — including drug-induced parkinsonism, acute dystonia, akathisia and tardive dyskinesia (TD) — continue to compromise long-term antipsychotic treatment adherence and functional outcome [1,2]. The classical concept linking EPS to D_2 blockade in the nigrostriatal pathway is necessary but not sufficient to explain phenotypic heterogeneity, delayed onset and sometimes irreversible course of certain syndromes, notably TD [3,4]. Over the past decade, advances in structural and functional neuroimaging have revealed that EPS are associated with alterations beyond focal receptor effects, involving basal ganglia morphometry, thalamocortical circuits, cerebellar systems, and white-matter pathways; these observations support a systems (network) view of EPS pathophysiology [5–8]. This review briefly integrates contemporary evidence and outlines implications for clinical practice.

Neuroimaging evidence Basal ganglia and subcortical morphometry. Volumetric MRI studies have repeatedly reported alterations in striatal structures (caudate, putamen) among antipsychotic-treated patients with motor side effects. Several investigations document early increases in striatal volume during antipsychotic exposure—interpreted as compensatory or gliotic responses to receptor blockade—followed by progressive atrophy in long-term treated cohorts, suggesting a time-dependent remodeling process [6,9,10]. Thalamic volume reductions, reported in cohorts with drug-induced parkinsonism, implicate thalamocortical relay dysfunction in bradykinetic phenotypes [8,11].

White-matter microstructure (DTI). Diffusion tensor imaging reveals decreased fractional anisotropy (FA) and increased mean diffusivity (MD) in motor-relevant tracts (internal capsule, corona radiata, corpus callosum) among patients with EPS compared to matched

controls or non-EPS patients [12,13]. Such microstructural disorganization correlates with EPS severity and cumulative antipsychotic exposure in several studies, indicating effects on oligodendroglial integrity or axonal coherence [9,12].

Functional connectivity and task activation (fMRI). Resting-state and task-based fMRI studies converge on impaired connectivity within the sensorimotor network and disrupted cortico-striato-thalamo-cortical (CSTC) loops in EPS. Reduced functional coupling between supplementary motor area (SMA) and putamen, and altered SMA-to-thalamus interactions, have been associated with parkinsonian features and impaired motor initiation [14,15]. Additionally, abnormal engagement of the default mode and salience networks may account for co-occurring cognitive and affective symptoms observed in EPS patients [16].

Metabolic and receptor imaging (PET). FDG-PET studies demonstrate regionally specific metabolic patterns in EPS: striatal hypermetabolism in hyperkinetic TD versus thalamic/cortical hypometabolism in parkinsonian presentations [17,18]. Dopamine-receptor PET (e.g., [11C]-raclopride) documents receptor occupancy dynamics and compensatory upregulation that parallel chronicity and clinical severity of motor syndromes [19].

Integrative pathophysiological model. Collectively, multimodal imaging supports a model in which chronic dopamine antagonism precipitates synaptic and glial adaptations (receptor supersensitivity, synaptic reorganization, microglial activation) that, together with vulnerability factors (age, sex, genetic polymorphisms), produce progressive network dysfunction [3,11,20]. White-matter disruption compromises information flow across motor loops, while cortical thinning in premotor and prefrontal regions reduces top-down regulation; metabolic imbalances further destabilize network homeostasis, facilitating emergence or persistence of EPS [9,12,17].

Clinical correlations and risk factors. Clinical correlates include greater EPS incidence with high-potency D_2 antagonists and higher cumulative doses; older age, female sex, pre-existing movement abnormalities and certain pharmacogenetic variants (e.g., DRD2, COMT) increase susceptibility [2,21]. Imaging markers (striatal volume change; reduced FA in internal capsule; SMA–putamen hypoconnectivity) show potential as predictive biomarkers but require validation in prospective cohorts [6,12,14].

Therapeutic and preventive implications. Implications for clinical care are threefold: (1) **Risk stratification** — integrating imaging and genetic data could identify high-risk patients prior to chronic exposure; (2) **Monitoring and management** — imaging markers can assist decisions on dose reduction, agent switching (prefer agents with lower D_2 occupancy or fast-off kinetics), and early use of adjunctive therapies; (3) **Neuroprotective strategies** — VMAT2

inhibitors for TD, antioxidants (e.g., vitamin E) in selected cases, and neuromodulation (rTMS) as rehabilitative options merit further study in imaging-guided trials [18,19,22].

Limitations of current evidence and research priorities. Existing studies are limited by heterogeneous EPS definitions, small sample sizes, cross-sectional designs and confounding by illness-related brain changes. Priority areas include prospective multimodal imaging from treatment initiation, standardized EPS phenotyping, and combined imaging-genetic predictive modeling. Large multicentre longitudinal studies are essential to differentiate treatment effects from disease progression and to validate candidate biomarkers for clinical use [10,20,22].

Conclusion. The contemporary evidence base reframes EPS as network disorders resulting from the interplay of dopaminergic pharmacodynamics, adaptive synaptic/glial responses and white-matter integrity loss. Multimodal neuroimaging has identified plausible biomarkers (striatal morphometry, tract-specific FA, SMA–putamen connectivity, metabolic signatures) that may enable prediction, prevention and personalized management of antipsychotic-induced motor syndromes. Translation of these findings into routine clinical practice requires rigorous longitudinal validation and cost-effectiveness analyses.

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