



Neuroimaging in Huntington's Disease

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Abstract

Huntington's disease (HD) is an autosomal dominant progressive neurodegenerative disorder for which effective disease-modifying treatments have not yet been developed. Current diagnosis of HD relies on clinical criteria and genetic testing. However, neuroimaging plays a crucial role in differentiating HD with similar phenotypes and, most importantly, in objectively monitoring the neurodegenerative process, particularly during the development of disease-modifying therapies. Novel technologies and imaging protocols have significantly advanced neuroimaging capabilities in HD patients in recent years. This review presents a range of promising neuroimaging modalities (magnetic resonance morphometry, functional MRI, diffusion tensor imaging, positron emission tomography, etc.) that assess HD neurodegenerative patterns from multiple perspectives and clarify disease mechanisms and their correlation with clinical manifestations. Further development of these technologies is important not only for neurology but also for neuropharmacology and neurophysiology.

Keywords: Huntington's disease; neuroimaging; neurodegeneration; biomarkers; magnetic resonance imaging; positron emission tomography; resting-state functional magnetic resonance imaging; diffusion tensor magnetic resonance imaging; magnetic resonance tractography

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Технологии нейровизуализации при болезни Гентингтона

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Аннотация

Болезнь Гентингтона (БГ) – аутомомно-доминантное прогрессирующее нейродегенеративное заболевание, эффективные патогенетические методы лечения которого пока не разработаны. Диагностика БГ в настоящий момент основывается на клинических критериях и данных генетического анализа, но методы нейровизуализации могут иметь большое значение для дифференцирования БГ со сходными фенотипами и главным образом – для объективного мониторинга нейродегенеративного процесса, в том числе на фоне разрабатываемых подходов болезнь-модифицирующей терапии. Возможности нейровизуализации у пациентов с данным заболеванием существенно выросли в последние годы в связи со всё более широким применением ряда новых технологий и режимов исследования. В обзоре представлен спектр наиболее перспективных нейровизуализационных методик (магнитно-резонансная морфометрия, функциональная и диффузионно-тензорная магнитно-резонансная томография, позитронно-эмиссионная томография и др.), которые оценивают нейродегенеративные паттерны БГ с различных сторон и уточняют патогенетические механизмы болезни и их взаимосвязь с клиническими проявлениями. Дальнейшее развитие этих технологий имеет значение не только для неврологии, но также для нейрофармакологии и нейрофизиологии.

Ключевые слова: болезнь Гентингтона; нейровизуализация; нейродегенерация; биомаркеры; магнитно-резонансная томография; позитронно-эмиссионная томография; функциональная магнитно-резонансная томография покоя; диффузионно-тензорная магнитно-резонансная томография; магнитно-резонансная трактография

Источник финансирования. Авторы заявляют об отсутствии внешних источников финансирования при проведении исследования.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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Huntington's disease (HD) is a severe progressive neurodegenerative disorder with autosomal dominant inheritance, characterized by multisystem clinical manifestations and degeneration of striatal spiny neurons as the primary target of the pathological process [1]. The classic triad of HD symptoms includes motor disorders (chorea, dystonia, myoclonus, etc.), cognitive decline (progressing to subcortical dementia), and various psychiatric abnormalities (depression, obsessive-compulsive disorder, anxiety, possible psychotic episodes, etc.) [1–3]. Additionally, HD patients often exhibit metabolic abnormalities that may lead to progressive weight loss culminating in cachexia [2, 3].

The genetic basis of HD involves the expansion of tandem polyglutamine-encoding CAG repeats in the *HTT* gene, resulting in elongation of the mutant huntingtin protein, accumulation of aberrant protein molecules in degenerating striatal neurons, and initiation of pathological cascades in brain tissue [1–3]. For over a century, this disease has been a focus of intense global research and is considered a unique genetic model for studying neurodegenerative patterns, mechanisms of brain plasticity, and possibilities of preventive neuroprotection.

Despite some promising studies (e.g., antisense oligonucleotides to suppress expression of mutant polyglutamine-encoding *HTT* alleles), effective evidence-based disease-modifying therapy for Huntington's disease (HD) remains undeveloped, and the disease continues to be largely incurable [3]. Existing therapeutic approaches are purely symptomatic and palliative in nature [2, 3]. The key prerequisite for implementing effective treatment strategies capable of slowing HD progression and preventing symptom onset in asymptomatic mutation carriers is the earliest possible initiation of pathogenetic therapy. This requires detailed investigation of HD's molecular mechanisms and development of methods for timely diagnosis of neurodegenerative processes including the preclinical stage. In this context, the current priority is identifying reliable HD biomarkers applicable in real clinical practice [4], with neuroimaging biomarkers playing a crucial role in detecting subtle structural and functional changes and neural network reorganization across all stages of mutant gene carriage [4, 5]. Numerous studies employing voxel-based morphometry (VBM), resting-state fMRI, diffusion tensor imaging (DTI), MR spectroscopy, and PET demonstrate the significant po-

tential of modern neuroimaging techniques for investigating HD neurobiology, elucidating neuroplasticity mechanisms in this condition, and evaluating novel therapeutics in clinical trials [5–9].

This review synthesizes global research experience with promising HD neuroimaging biomarkers, focusing on relatively accessible structural MRI/fMRI techniques and PET data using different radiotracers. Literature search was conducted in Scopus, Web of Science, PubMed (MedLine), and eLIBRARY.RU databases.

Positron Emission Tomography

Positron emission tomography (PET) is a functional imaging modality based on the ability of radioactive isotopes to accumulate in tissues with high metabolic activity. In HD, PET imaging with various ligands – low-molecular vectors capable of crossing membranes – allows visualization of specific targets [3]. The targets for these ligands include intermediate metabolites, protein complex components, signaling molecules, and nuclear receptors [10], with short-lived radionuclides demonstrating optimal binding properties.

In a study by C. Giampà *et al.*, an early version of a PET ligand for huntingtin – compound CHDI-180R – was presented [11]. It was demonstrated that CHDI-180R molecules exhibit strong binding to toxic huntingtin aggregates *in vitro*. CHDI-180R was successfully used to localize mutant huntingtin aggregates in brain samples of HD mice, with ligand binding to the mutant protein shown to increase with animal aging.

Thus, PET ligands can precisely localize mutant huntingtin and estimate its approximate quantity in the brain, whereas analysis of cerebrospinal fluid and other biological samples in HD does not provide reliable information about disease progression severity, clinical stage, or pathological process dissemination. Unlike PET scanning (which specifically targets the pathological polyglutamine substrate), most existing biochemical methods measure total huntingtin levels, including both mutant and normal forms [5].

Phosphodiesterase 10A (PDE10A), an enzyme expressed in medium spiny neurons of the striatum that regulates their sensitivity to glutamatergic signaling, has been identified as

a promising biomarker for HD [10]. PDE10A inhibition functionally mimics the effects of D1-like receptor agonists and D2-like receptor antagonists while modulating both direct and indirect striato-thalamo-cortical pathways in the central nervous system. To date, research has primarily characterized the effects of PDE10A inhibition, which reproduce the inhibitory effects of D2-like dopamine receptor antagonists.

An international research team from Denmark, the Netherlands, Norway, and Sweden measured PDE10A availability in patients with early-stage HD using the ^{18}F MNI-659 radioligand, revealing significantly reduced binding in the striatal region compared to healthy volunteers [11]. Data from other studies [12–15] suggest that diverse alterations in PDE10A signaling within pathomorphologically intact neural networks of the central nervous system represent the earliest neuroimaging marker detectable before the predicted onset of symptomatic HD. Changes in PDE10A expression also provide valuable information for monitoring cerebral atrophy progression in HD.

Voxel-Based Morphometry

Voxel-based morphometry (VBM) has emerged as a promising MRI biomarker for neurodegeneration, enabling quantitative assessment of atrophy in various brain regions [16, 17]. Russian researchers demonstrated that in HD, VBM not only identifies involvement of specific structures of the central nervous system but also quantifies gray matter changes, reveals subtle process characteristics (such as asymmetry), assesses potential topographic spread of neurodegeneration over time, and establishes correlations between mutation severity, clinical data, and regional brain atrophy [7].

One study in HD patients revealed more pronounced degenerative changes in the dominant hemisphere, along with an inverse correlation between CAG repeat copy number and the severity of atrophy in the caudate nucleus and putamen [18].

Correlation analysis indicates that reduced gray matter volume in the caudate nucleus, putamen, and insula constitutes an early morphometric brain change detectable in preclinical HD mutation carriers [19]. Striatal atrophy in early-stage HD patients is associated not only with motor control impairments but also with executive dysfunction, likely involving cortical regions such as the insular lobe.

A French research group [20] confirmed progressive gray matter volume loss in the basal ganglia, substantia nigra, hypothalamus, amygdala, insular, premotor, and sensorimotor cortices as HD advances to clinical stages. Atrophy was most pronounced in the basal ganglia, subsequently spreading to cortical regions predominantly involved in subcortical-thalamo-cortical pathways.

A recent study in patients with confirmed HD assessed the distribution of atrophic changes across various brain regions using automated volumetry compared to standard clinical measurement methods [21]. Automated caudate nucleus volume measurements were additionally verified using manual segmentation. This study demonstrated that new software

developments enable more accurate identification of patients with basal ganglia atrophy and determination of its severity. Prospective studies utilizing state-of-the-art software may facilitate more detailed diagnostics of pathological cerebral processes in HD patients.

It can be concluded that VBM has undeniable advantages, allowing quantitative tracking of progressive brain atrophy during longitudinal monitoring of HD patients.

Functional MRI

Functional MRI (fMRI) indirectly assesses functional activity in various brain regions. It does not measure neuronal electrical activity but instead relies on the neurovascular coupling phenomenon, i.e., regional blood flow changes in response to activation of nearby neurons, as increased neuronal activity requires greater oxygen and nutrient delivery through blood circulation [22].

The literature presents findings on the activation patterns of various brain regions in HD patients during fMRI using diverse paradigms [23]. These results indicate that fMRI is sensitive to neural dysfunction occurring more than 12 years prior to the anticipated onset of HD clinical manifestations [24]. Multiple studies have demonstrated that alterations in spontaneous neuronal activity (resting-state fMRI) within the default mode network in HD correlate with clinical features of the disease and may serve as neuroimaging correlates of visuospatial, affective, memory, executive, and motor control impairments, both at the asymptomatic mutation carrier stage and in patients with manifest HD.

Thus, fMRI is as a valuable neuroimaging tool to objectively assess the progression of neurodegenerative processes and patterns of functional neuroplastic reorganization during longitudinal monitoring of HD patients.

Diffusion tensor MRI and differential tractography

DT-MRI is used for in vivo quantitative and qualitative assessment of water diffusion directionality in the human brain, enabling the study of microscopic structure of white matter pathways in cerebral hemispheres. This technique allows reconstruction of three-dimensional images of commissural, associative, and projection tracts that ensure normal brain function [25].

When assessing white matter integrity in patients with prodromal and clinically manifest stages of HD using DT-MRI, researchers identified white matter disintegration in frontal lobes, preand postcentral gyri, corpus callosum, anterior and posterior limbs of internal capsule, and corticostriatal pathway [26]. Some HD studies also demonstrated altered structural connectivity integrity in white matter – from early manifestations to advanced stages – with most pronounced microstructural changes observed in corpus callosum. Such alterations of commissural fibers in HD patients may lead to cortical disconnection effects [27].

J.V. Barrios-Martinez *et al.* evaluated correlations between changes in white matter pathways in HD and motor, cog-

nitive, and functional assessment scores using a variant of tractography – differential tractography [27]. Unlike conventional tractography, which maps all existing pathways, differential tractography allows quantification of degeneration severity by calculating the volume of affected tract segments based on longitudinal changes in specific pathways within individual patients. Significant differences were observed between manifest and premanifest disease stages. Initial results in manifest HD patients showed substantial involvement of pathways, whereas premanifest mutation carriers exhibited either no or minimal affected pathways. Changes in the volume of affected pathways significantly correlated with disease severity on the Unified Huntington's Disease Rating Scale (UHDRS) ($p < 0.001$), and chronological changes on differential tractography also correlated with worsening scores on this scale ($p < 0.001$). Moreover, one patient demonstrated increased lesion volume prior to symptom onset. A larger

volume of involved tracts is considered indicative of reduced structural integrity.

The obtained results confirm that differential tractography can be used as a dynamic neuroimaging biomarker, allowing individualized assessment of HD progression. Importantly, this methodology serves as a quantitative tool for tracking degeneration in presymptomatic patients, with potential applications in clinical trials.

Thus, numerous methodologies have been proposed as neuroimaging biomarkers in HD. These appear to be among the most promising approaches for describing and characterizing patterns of neurodegeneration. New technologies and advances in existing methodologies will enable tracking of therapeutic responses, identification of novel drug targets, and provide deeper insights into disease pathogenesis.

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