International Journal of General Medicine

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

Multimodal Neuroimaging Mechanisms of Apathy in Alzheimer's Disease: A Narrative Review of Structural, Functional, and Molecular Evidence

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Abstract: Apathy is the most common neuropsychiatric symptom in Alzheimer's disease (AD) and is conceptualized as a pathological reduction of goal-directed motivation and behavior. It is currently believed that apathy has an independent neurobiological basis rather than merely accompanying cognitive decline. This narrative review synthesizes evidence from structural, functional, and molecular neuroimaging studies published up to 2025, identified through targeted PubMed searches and reference tracking, without applying formal systematic inclusion/exclusion criteria. Existing imaging evidence indicates that the core mechanism of apathy lies in the specific impairment of the prefrontal–basal ganglia motivational circuit: gray matter atrophy and hypometabolism in the anterior cingulate cortex (ACC) and orbitofrontal cortex are closely associated with impaired motivation integration and reward evaluation, whereas structural damage to the dorsolateral prefrontal cortex contributes to executive planning deficits. Functional network analysis further reveals suppression of the default mode network and ineffective compensation of the central executive network. Molecular imaging studies confirm that structural degeneration of the locus coeruleus, dopaminergic presynaptic transmission dysfunction, and synergistic pathological accumulation of amyloid-beta and Tau proteins in the motivational circuit collectively constitute the neurobiological basis of apathy. Furthermore, computational modeling has already been employed as an analytical framework to dissect these mechanisms, revealing altered effort-based decision-making and abnormal frontoparietal connectivity. Given the frequent impairment in self-awareness (anosognosia) regarding their own apathy in AD, informant-based assessments are essential for accurate clinical evaluation. Ultimately, integrating these multimodal biomarkers may facilitate early identification and stratified interventions, including dopaminergic and noradrenergic pharmacotherapies as well as non-invasive brain stimulation techniques such as transcranial magnetic stimulation (TMS).

Keywords: prefrontal–basal ganglia circuit, multimodal magnetic resonance imaging, positron emission tomography, default mode network, locus coeruleus, biomarker

Introduction

Apathy, the most common neuropsychiatric symptom in Alzheimer's disease (AD), is formally defined as a syndrome of reduced goal-directed behavior, decreased goal-directed cognition, and emotional blunting, distinct from depression, anhedonia, fatigue, and generalized cognitive decline. It significantly increases caregiver burden and accelerates cognitive and functional decline, predicting a particularly poor prognosis.[1–3] Although the clinical assessment of apathy still relies on standardized informant-based scales such as the Neuropsychiatric Inventory (NPI) and the Apathy Evaluation Scale (AES), their subjective nature can introduce bias, particularly in patients with impaired self-awareness. In recent years, the development of multimodal imaging technologies has provided technical support for analyzing the neuroanatomical and functional mechanisms of apathy in vivo, and has also provided an imaging basis for the objective quantification and monitoring of this symptom. This review integrates multimodal imaging findings to elucidate the neurobiological mechanisms of AD-related apathy, focusing on evidence from structural, functional, and molecular perspectives.

https://doi.org/10.2147/IJGM.S622802
Received: 8 May 2026
Accepted: 25 June 2026
Published: 30 June 2026

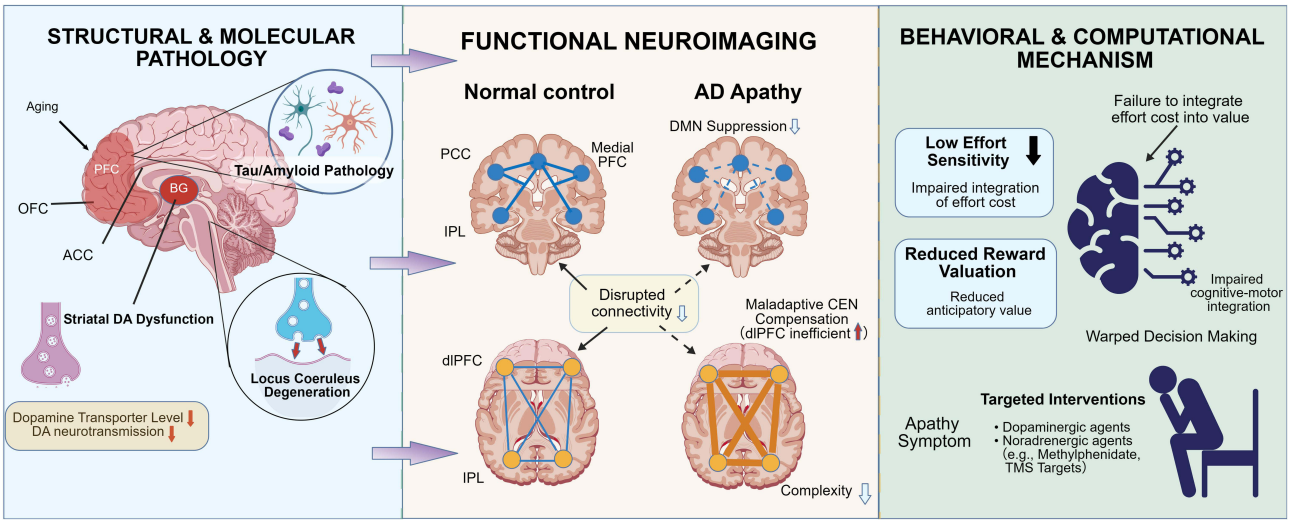

Figure 1 Multimodal neuroimaging mechanisms of apathy in Alzheimer's disease. The conceptual framework integrates structural and molecular pathology (left), dynamic resting-state functional network alterations (center), and the resulting behavioral and computational mechanisms (right).
Abbreviations: PFC, prefrontal cortex; ACC, anterior cingulate cortex; OFC, orbitofrontal cortex; BG, basal ganglia; DA, dopamine; DMN, default mode network; CEN, central executive network; PCC, posterior cingulate cortex; IPL, inferior parietal lobule; dlPFC, dorsolateral prefrontal cortex; TMS, transcranial magnetic stimulation. Created with BioGDP.com.[4]

The neurobiological substrate of apathy is thought to center on the prefrontal–basal ganglia motivational circuit, which includes the anterior cingulate cortex (ACC), orbitofrontal cortex, dorsolateral prefrontal cortex, and striatum. Disruption of this circuit at multiple levels is a recurring theme in the imaging literature (Figure 1). Given the wide scope of neuroimaging modalities and behavioral mechanisms, this review was designed as a narrative synthesis rather than a systematic review. To ensure transparency, we briefly describe the literature identification process: we searched PubMed for English-language articles published from 2000 to 2025, using combinations of terms such as "Alzheimer's disease," "apathy," "magnetic resonance imaging," "positron emission tomography," "functional connectivity," and "computational modeling." Additional studies were identified through reference lists. Articles were selected for their relevance to structural, functional, or molecular mechanisms of apathy in AD, and no formal inclusion/exclusion criteria or quality scoring were applied. In the following sections, we first summarize structural alterations in the motivational circuit, then discuss functional network dysregulation, molecular PET findings, and computational modeling approaches, and finally consider the clinical implications and targeted therapeutic strategies.

Structural Imaging Basis of Apathy in AD

High-resolution structural MRI provides morphological evidence for understanding the pathophysiological mechanisms of apathy. Studies consistently show that symptoms of apathy in patients with AD are not non-specific manifestations of diffuse whole-brain atrophy, but the direct result of specific structural degeneration occurring in motivation-related neural circuits. This structural damage mainly involves reduced gray matter volume in key cortical nodes, subcortical nuclear atrophy, and microstructural disruption of white matter connecting pathways.

Cortical and Subcortical Gray Matter Atrophy: Morphological Remodeling of the Motivational Circuit

Voxel-based morphometry studies have confirmed that the severity of apathy is significantly and positively correlated with decreased gray matter density in key nodes of the prefrontal–basal ganglia circuit. Reduced structural integrity of the ACC and orbitofrontal cortex is a core anatomical feature of apathy in AD. Multimodal imaging shows that, compared with patients without symptoms of apathy, individuals with apathy exhibit gray matter atrophy in the left orbitofrontal cortex and ACC.[5–8] As an important region integrating emotion, cognition, and drive, reduced gray matter volume of the ACC is significantly correlated with symptoms of apathy;[5,7] damage to this area may severely disrupt the generation of intrinsic motivation. The

orbitofrontal cortex is primarily involved in assessing the reward value of environmental stimuli; focal atrophy and metabolic suppression in this region are related to impaired reward prediction error coding, which may render patients unable to effectively anticipate positive rewards, manifesting as a loss of interest.[5,9]

Regarding cognitive apathy, which presents as motivation in the absence of planning ability, structural imaging studies using multidimensional assessments have found it to be significantly associated with reduced gray matter density in the frontal cortex, specifically implicating the dorsomedial prefrontal regions.[10] As a key node of the executive control network, early atrophy of the dorsolateral prefrontal cortex is closely correlated with a decline in the ability to organize and plan complex action sequences.

Among subcortical structures, the striatum is an important relay node that translates cortical motivational signals into specific behaviors. In morphological studies, patients with AD and apathy showed significant gray matter atrophy in the striatum (especially the head of the left caudate nucleus). Moreover, gray matter density in this region was significantly and negatively correlated with the severity of apathy,[11] suggesting impaired anatomical connectivity of the cortico–subcortical circuit. Meanwhile, structural MRI and diffusion tensor imaging studies have demonstrated that amygdala atrophy and microstructural alterations in its white matter connections to the prefrontal cortex (eg, the uncinate fasciculus) are significantly associated with the overall severity of apathy in AD, disrupting the anatomical basis for emotion–motivation integration.[12,13]

Disruption of White Matter Microstructural Integrity: Abnormalities in Anatomical Connections

Diffusion tensor imaging technology has revealed decreased fractional anisotropy in the white matter tracts connecting the aforementioned gray matter nodes, indicating microstructural changes such as axonal degeneration and demyelination.[13]

The uncinate fasciculus connects the orbitofrontal cortex and the anterior temporal lobe. It is a critical anatomical pathway for the integration of emotional memory and reward evaluation. Disruption of uncinate fasciculus integrity mediated by Tau protein pathology impedes the transmission of emotional information to the frontal lobe,[14] making it difficult for patients to retrieve positive emotional experiences based on past episodic memories, thereby affecting the reward value evaluation system.

In free-water corrected diffusion tensor imaging studies, the cholinergic nerve tracts projecting from the basal nucleus of Meynert to the cortex already showed a significant increase in free water content in the mild cognitive impairment stage, indicating early microenvironmental changes and axonal degeneration.[15] Structural impairment of the basal forebrain cholinergic projection system affects the attentional arousal in the cerebral cortex, which is an important neuroanatomical basis for cognitive apathy.

Structural Degeneration of the Locus Coeruleus: A Novel Structural Biomarker

The brainstem locus coeruleus is an early site of invasion in AD pathology and a key nucleus for maintaining whole-brain arousal. Neuromelanin-sensitive MRI studies have observed an association between the structural integrity of the locus coeruleus and symptoms of apathy in vivo. The MRI signal contrast of the locus coeruleus (reflecting neuronal integrity and neuromelanin density) is significantly and negatively correlated with apathy scores.[16] Recent advances have provided compelling evidence that the structural integrity of the catecholaminergic nuclei is compromised in the earliest stages of the disease.[17] This degeneration is strongly linked to noradrenergic deficits, which are increasingly recognized as a neurobiological driver of subsequent neuropsychiatric symptoms including apathy.[18] Consequently, these specific neural deficits provide a strong rationale for emerging noradrenergic pharmacological treatments.[19]

Functional Network Connectivity Abnormalities in AD Apathy

Resting-state fMRI studies indicate that apathy not only is associated with localized structural lesions in specific brain regions, but also involves synergistic dysregulation of connections within and between large-scale brain functional networks. This abnormal functional connectivity, together with ineffective compensatory mechanisms, constitutes the systems-level basis for apathy.

Abnormal Functional Connectivity in the Motivational Circuit

Micro-level functional connectivity analysis reveals node abnormalities during the generation and transformation of motivation. The generation of motivated behavior depends on the brain translating reward evaluation into specific actions. Neurocognitive framework models indicate that weakened functional connectivity between the ACC and subcortical striatal regions (including the nucleus accumbens) is critically involved in the severity of apathy.[20] Decreased functional connectivity in this prefrontal–striatal pathway may impair the transformation of reward evaluation into behavioral effort, which is a crucial step significantly correlated with a reduction in goal-directed behaviors.

Some patients clinically exhibit impaired self-awareness (lack of insight) regarding their symptoms of apathy, directly leading to a significant discrepancy between patients' subjective self-reports and the objective observations of caregivers. Recent resting-state fMRI studies demonstrate that within the AD continuum, this impaired self-awareness is closely related to abnormally enhanced functional connectivity within the salience network (particularly the ACC and between the salience network and the basal ganglia, a crucial component of the motivational circuit).[21] This abnormal hyperconnectivity may interfere with the brain's monitoring and metacognitive evaluation of internal motivational states and self-referential information, thereby providing key network-level evidence for anosognosia in patients with AD. Corroborated by metabolic imaging findings, lack of awareness of apathy essentially signifies an earlier specific disruption of the limbic network[22], further highlighting the clinical necessity of objective assessments that incorporate reports from multiple informants.

Imbalance of Large-Scale Networks: Functional Suppression and Abnormal Compensation

At the macro-network level, apathy is usually accompanied by altered connectivity patterns among the default mode, central executive, and salience networks.

The default mode network (DMN) is important in self-referential thought and intrinsic motivation generation. Extensive resting-state fMRI studies have consistently demonstrated widespread functional suppression of the DMN in the AD continuum, which is closely associated with overall cognitive and neuropsychiatric burden.[23] Building upon this, network analyses have pinpointed that functional impairment of the DMN's core midline hubs (especially the anterior cingulate) is fundamental to the motivational deficits unique to apathy.[24] Furthermore, these macroscopic network dysfunctions are not isolated; concurrent connectivity alterations within the salience network also significantly drive the behavioral symptoms seen in these patients.[25]

By contrast to the low connectivity of the DMN, the central executive network, which is responsible for cognitive control, exhibits abnormally enhanced functional connectivity in certain regions (eg, the middle frontal gyrus and supramarginal gyrus), and this enhancement is positively correlated with apathy severity[26] This phenomenon is considered a form of "maladaptive compensation," meaning that against the backdrop of insufficient endogenous motivation, the brain demonstrates overactivity in the prefrontal-dominated network. However, under the underlying neurodegenerative pathology, this compensatory neural activity is usually inefficient, reflecting a decompensated state of the network system.[26]

Regarding the salience network responsible for filtering environmental stimuli, its internal hyperconnectivity (especially between the right ACC and the insula) is mainly associated with symptoms of agitation or hyperactivity, and has no significant correlation with apathy.[25] This finding suggests that the neural mechanism of apathy is primarily functional suppression of the motivation system rather than abnormal arousal in response to environmental stimuli.[25]

Notably, this abnormal enhancement of connectivity in brain networks (eg, the DMN subsystems) is not a static final outcome, but a transient compensatory phenomenon in dynamic evolution According to the proposed cascading network failure model, in the early stages of AD, after the functional decline of highly connected core network nodes (eg, the posterior DMN), the information processing load is transferred to other network nodes (eg, the ventral and anterior dorsal DMNs), presenting as hyperconnectivity Although this enhancement may have temporary compensatory significance, it also foreshadows a broader subsequent network collapse. This model is consistent with the "pseudo-normalization" phenomenon reported in the literature, where patients with cognitive decline paradoxically show similar or even enhanced activity in specific network connections compared with healthy populations, further supporting the hypothesis of network enhancement as an early compensatory mechanism.[27] However, multimodal imaging studies reveal that this compensatory high-connectivity state actually provides a highly convenient physical conduit for spreading pathological proteins. Studies combining longitudinal Tau–positron emission tomography (PET) and resting-state fMRI have confirmed that the Tau protein accumulation rate is closely related to the

functional network architecture of the brain, and pathological proteins tend to accelerate diffusion along highly connected network hubs.[28] As Tau pathology progressively accumulates in compensatorily enhanced brain networks (eg, the DMN subsystems), the originally highly active core hub regions gradually experience functional exhaustion owing to long-term overload, ultimately manifesting as a significant reduction in the complexity of brain resting-state functional signals.[29] This change is closely related to further cognitive decline, suggesting that decreased functional signal complexity may be a functional marker of Tau-mediated neuronal damage. Ultimately, this "maladaptive compensation" driven by Tau pathology may eventually progress to exhaustion, contributing to a comprehensive collapse of macroscopic functional networks that manifests clinically as an irreversible deterioration of neuropsychiatric symptoms, including apathy.

Molecular Imaging and Metabolic Features

PET and single-photon emission computed tomography enable in vivo visualization of neurometabolism, pathological protein deposition, and neurotransmitter receptor distribution, providing direct evidence for the pathophysiological mechanisms underlying symptoms of apathy.

Glucose Hypometabolism Patterns: Localized Functional Suppression

^{18}F-fluorodeoxyglucose PET imaging indicates consistent reductions in regional cerebral blood flow perfusion and glucose metabolic suppression in the ACC, medial prefrontal cortex, and orbitofrontal cortex in patients with AD and apathy. This hypometabolic state of the frontal–limbic system has significance for differential diagnosis. Symptoms of apathy are specifically correlated with hypometabolism in the left ACC and the left orbitofrontal cortex, and this metabolic pattern differs anatomically from depressive symptoms (which primarily involve the left dorsolateral prefrontal cortex).[9]

Therefore, localized hypometabolism in the anterior cingulate and orbitofrontal cortices directly reflects an energetic failure within the prefrontal motivational network, providing a solid metabolic basis for the integration deficits observed in apathetic patients.

Spatiotemporal Distribution and Diffusion of Pathological Proteins

Pathological protein PET imaging using specific tracers has revealed the correlation between core AD pathology and symptoms of apathy.

Longitudinal imaging studies show that the baseline severity of apathy is mainly correlated with the Tau protein burden in motivational circuits such as the ventral ACC. By contrast, the rapidity of the longitudinal progression of symptoms parallels the pathological diffusion of Tau protein in regions like the supramarginal gyrus and entorhinal cortex.[30] This finding suggests that apathy is related to the initial pathological deposition in the motivational circuit, and its exacerbation reflects the diffusion of Tau protein in the cortex.

Amyloid and Tau proteins interact in the occurrence of neuropsychiatric symptoms. In amyloid-positive individuals, the severity of neuropsychiatric symptoms can predict subsequent increases in cortical Tau protein burden.[31]

Dual-tracer PET studies have shown that the severity of apathy reported by informants is significantly and positively correlated with cortical amyloid burden and Tau protein deposition in the entorhinal cortex and inferior temporal lobe, whereas this association is not reflected in patients' subjective self-rating scale scores.[32] This result suggests that informant reports possess higher clinical validity in terms of objectively reflecting pathological burden.

Recent comprehensive reviews highlight the broad synergistic role of neuroinflammation in AD-related behavioral changes.[33,34] However, some in vivo PET studies indicate that microglial activation, particularly in the medial temporal region, is primarily associated with symptoms such as agitation,[35] whereas its linear association with symptoms of apathy appears comparatively weak.[36]

Receptor and Transporter Imaging of Neurotransmitter Systems

Molecular imaging studies confirm that dopamine transporter binding rates in the striatal region of patients with AD are significantly reduced, particularly in the left caudate nucleus. The degree of decline in the transporter binding rate is negatively correlated with the severity of apathy, indicating that functional impairment of the dopamine system extends to presynaptic

terminals, affecting the transmission of motivational signals.[37] Simultaneously, reduced D3 receptor activity in the limbic system (eg, the nucleus accumbens) is also considered one of the pathological mechanisms of apathy.[1]

Computational Model Analysis of Imaging Data

By combining mathematical models with functional imaging data, computational neuropsychiatry transforms motivated behavior into quantifiable computational parameters, providing new methodological approaches for studying the mechanisms of apathy.

Computational Modeling of Motivated Behavior

This research paradigm often employs effort-based decision-making tasks, using computational models to decompose motivated behavior into independent variables such as reward sensitivity and effort cost sensitivity.

Patients with AD show significantly reduced sensitivity to changes in effort cost. This finding suggests that patients' ability to integrate effort cost during decision-making is impaired. The model-quantified decrease in effort sensitivity correlates with executive function test results but shows no significant association with traditional self-reported apathy scores.[38] This result suggests that traditional clinical scales may not fully reflect the underlying cognitive computational characteristics of patients.

Image Mapping of Computational Parameters

By correlating computational parameters with functional imaging data, researchers have explored the neural basis for behavioral variables. Analyses show that reduced effort sensitivity is significantly correlated with abnormal functional connectivity strength between the nucleus accumbens and posterior parietal regions of the frontoparietal network.[39] This result suggests that apathy may involve the disruption of connectivity between subcortical motivation centers and cortical executive regions, affecting the neural processes that integrate evaluation information into action plans.

Methodological Considerations

Although the reviewed studies converge on the prefrontal–basal ganglia circuit, several methodological limitations must be acknowledged. First, most evidence derives from cross-sectional designs with modest sample sizes, precluding causal inferences between localized neurodegeneration and apathy onset. Second, substantial heterogeneity in apathy assessment instruments (such as NPI and AES) captures distinct symptom dimensions, directly contributing to spatial inconsistencies across imaging findings. Third, the neural substrates of apathy are dynamic across the AD continuum; failure to stratify patients by disease stage often yields divergent functional results, such as early compensatory hyperconnectivity versus late-stage network suppression. Future longitudinal investigations with harmonized behavioral protocols across defined AD stages are essential to validate the proposed mechanistic models.

Future Perspectives

Existing neuroimaging studies have preliminarily revealed the neuroanatomical and functional basis of apathy in AD. Considering the heterogeneity of this symptom, deeper exploration at the levels of multimodal integration and clinical application is needed.

Deep Integration of Multimodal Imaging Data

Addressing the limitations of current cross-sectional studies, future longitudinal studies should focus on constructing comprehensive "structure–function–molecular" imaging models. The focus should be on exploring how specific molecular pathologies (eg, regional Tau protein deposition) alter topological structure and dynamic connectivity patterns in brain functional networks. In addition, applying dynamic functional connectivity analysis is helpful in elucidating the laws governing brain network evolution over time.

Application of Objective Imaging in Clinical Assessment

Given the influence of patients' cognitive and insight decline on subjective scale assessments, imaging biomarkers have important adjunctive value in clinical diagnosis. Research clearly supports the superiority of informant reports in reflecting objective pathological changes.[32] During the progression from normal cognition to mild cognitive impairment, symptoms of apathy observed by informants already correlate with early cortical pathological deposition.[32] Therefore, in clinical practice, combining reliable informant medical history with objective imaging evidence improves the accuracy of early identification.

Exploration of Targeted Interventions According to Pathological Mechanisms

With the deepening understanding of the neural mechanisms of apathy, future intervention strategies are expected to develop toward targeted therapies. For example, for patients exhibiting structural or functional abnormalities in the dorsolateral prefrontal cortex, neuromodulation technologies may have application prospects. Meanwhile, for phenotypes characterized by a significant decline in dopamine transporter function, the efficacy of dopaminergic drugs warrants further validation.[40] Furthermore, precise mapping of apathy onto specific neuroanatomical hubs, such as the dorsomedial prefrontal cortex and the supplementary motor area, could lead to individualized targets for non-invasive brain stimulation therapies (eg, transcranial magnetic stimulation), translating neuroimaging findings from pure mechanistic exploration into promising clinical interventions for psychogeriatric practice.[41–43]

Conclusion

In summary, the evidence reviewed here converges on a core mechanism: specific dysfunction of the prefrontal–basal ganglia motivational circuit, manifested as gray matter atrophy in the anterior cingulate, orbitofrontal, and dorsolateral prefrontal cortices, accompanied by default mode network suppression and maladaptive hyperconnectivity of the central executive network at the systems level (Table 1). Molecular imaging further indicates that locus coeruleus degeneration, dopaminergic deficits, and

Table 1 Summary of Multimodal Neuroimaging Mechanisms, Clinical Correlates, and Potential Interventions for Apathy in Alzheimer's Disease

Imaging Modality	Key Brain Regions & Biomarkers	Main Pathological/Functional Findings	Clinical Correlates & Computational Mechanisms	Potential Targeted Interventions
Structural MRI	Anterior cingulate cortex (ACC) & Orbitofrontal cortex (OFC)	Reduced gray matter volume and density	Impaired generation of intrinsic motivation and reward prediction error coding	Non-invasive brain stimulation (e.g., TMS targets)
	Dorsolateral prefrontal cortex (dlPFC)	Early focal gray matter atrophy	Cognitive apathy; decline in executive planning and action sequence organization	Neuromodulation technologies
	Striatum (e.g., caudate nucleus)	Subcortical nuclear atrophy; disrupted cortico-subcortical connectivity	Deficits in translating cortical motivational signals into specific behavioral effort	Dopaminergic agents
	Brainstem Locus Coeruleus	Microstructural degeneration and loss of neuronal integrity/neuromelanin	Deficits in maintaining whole-brain arousal (noradrenergic deficits)	Noradrenergic pharmacological treatments
Resting-State fMRI	Default Mode Network (DMN) (e.g., medial PFC, PCC)	Widespread functional suppression and early decoupling of core midline hubs	Diminished self-referential thought; failure to integrate effort cost	
	Central Executive Network (CEN)	Maladaptive hyperconnectivity (inefficient compensation)	Overactivity masking endogenous motivation deficits; positively correlated with apathy severity	
	Salience Network (SN)	Abnormally enhanced connectivity with the basal ganglia; internal hyperconnectivity (e.g., right ACC-insula)	Hyperconnectivity with basal ganglia linked to anosognosia; internal hyperconnectivity relates to agitation, not apathy	
Molecular Imaging (PET/SPECT)	Prefrontal-limbic system (ACC, OFC)	Localized glucose hypometabolism (FDG-PET)	Energetic failure within the motivational integration network	
	Cortical regions (e.g., supramarginal gyrus, entorhinal cortex)	Synergistic diffusion and accumulation of Tau and amyloid-beta pathology	Progressive exacerbation of apathy; strongly correlated with informant-reported symptom severity	
	Striatum (left caudate nucleus)	Significantly reduced dopamine transporter (DAT) binding rates	Impaired presynaptic transmission of motivational signals to motor output	Dopaminergic drugs (e.g., Methylphenidate)

https://doi.org/10.2147/IJGM.S622802

synergistic amyloid-β/Tau pathology collectively drive these circuit disruptions. These multimodal biomarkers not only clarify the neurobiology of apathy but also hold substantial promise for objective assessment and the development of targeted interventions.

Acknowledgments

We thank Michael Irvine, PhD, from Liwen Bianji (Edanz) (https://www.liwenbianji.cn) for editing the English text of a draft of this manuscript.

Funding

This research was supported by the Innovation Team on AD with Depression (led by Guo).

Disclosure

The authors report no conflicts of interest in this work.

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