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Brain Network Changes Underlying Non-motor Symptoms in Amyotrophic Lateral Sclerosis: A Multimodal MRI Perspective

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Abstract: Amyotrophic lateral sclerosis (ALS) has evolved in clinical understanding from an isolated motor neuron disease into a complex multisystem disorder. Current evidence firmly establishes cognitive deficits and behavioral dysfunctions as inherent, non-motor elements of ALS, factors that drastically alter clinical outcomes, life expectancy, and caregiver stress. In light of this growing recognition, multimodal magnetic resonance imaging (MRI) has emerged as a crucial tool for elucidating the multiscale neuropathology of these symptoms, capturing a trajectory from structural damage to functional reorganization. Current findings demonstrate that atrophy in frontotemporal and subcortical regions, coupled with microstructural degradation in the corpus callosum and limbic white matter tracts, underpins deficits in executive function, social cognition, and emotional regulation. Resting-state functional MRI further reveals extensive network reorganization (primarily involving the default mode, frontoparietal control, and ventral attention networks) that appears to evolve from early compensatory hyperconnectivity to late-stage decompensation. More recently, the integration of multimodal data with predictive modeling has advanced the field toward individualized patient stratification and the early detection of cognitive decline. Operating under the premise that non-motor symptoms in ALS are clinical manifestations of widespread brain network degeneration, this review synthesizes recent advances in multimodal MRI. We highlight the structural basis, functional mechanisms, and individual variability of these symptoms, and discuss the translational potential of neuroimaging biomarkers in clinical practice.

Keywords: ALS, non-motor symptoms, multimodal MRI, brain network.

1. Introduction

Classic neurology long defined amyotrophic lateral sclerosis (ALS) as a fatal disorder that predominantly affects upper and lower motor neurons in the brain and spinal cord [1, 2]. Driven by converging evidence from clinical neuropsychology and neuroimaging, ALS is increasingly conceptualized as a multisystem disorder that exists on a clinical, genetic, and TDP-43-related pathological continuum with frontotemporal dementia (FTD) [3–6]. Consequently, cognitive, behavioral, and emotional abnormalities must be conceptualized within the broader framework of the ALS-FTD spectrum [7, 8].

Within this framework, non-motor symptoms have emerged as a critical dimension for understanding the profound clinical heterogeneity of ALS. Approximately half of all patients develop cognitive, behavioral, or affective disturbances over the disease course, with common manifestations encompassing executive dysfunction, reduced verbal fluency, impaired social cognition, apathy, disinhibition, and depression [6, 9, 10]. Cohort studies utilizing specific screening tools, such as the Edinburgh Cognitive and Behavioural ALS Screen (ECAS), demonstrate that these symptoms are not merely secondary consequences of motor decline [11, 12]. Rather, they act as independent predictors of accelerated disease progression, shortened survival, and exacerbated caregiver burden. Consequently, modern investigations have moved beyond merely confirming the frequency of these non-motor manifestations. The field is now dedicated to decoding the underlying large-scale neural network alterations that trigger them, alongside tracking their progression over time [7, 13]. Recently, a comprehensive umbrella review incorporating data from over 29,000 ALS patients reaffirmed that multiparametric MRI consistently highlights widespread structural, functional, and metabolic disruptions, transitioning the field from isolated regional studies to holistic network perspectives [14].

Multimodal MRI provides a robust, non-invasive approach to address this challenge by systematically tracking structural, connective, and functional alterations within a unified disease framework [13, 14]. Guided by the idea that non-motor symptoms in ALS are the clinical expression of brain network degeneration, this review first outlines their structural basis, then discusses how functional reorganization makes these symptoms clinically visible, next considers how multimodal integration supports patient stratification and longitudinal prediction, and finally returns to the main controversies and future directions.

2. Structural Neuroanatomy

To understand non-motor symptoms as the clinical manifestation of brain network degeneration in ALS, it is imperative to first delineate their underlying structural neuroanatomy. Structural MRI and diffusion MRI show that structural abnormalities in ALS extend far beyond the motor cortex and involve frontotemporal gray matter regions and their associated white matter tracts, which serve as neural substrates critical for higher-order cognition and emotional regulation [13, 15–17]. Crucially, rather than reflecting uniform global atrophy, these structural aberrations exhibit robust topological associations with specific cognitive and behavioral phenotypes [18, 19]. To illustrate, the topographical patterns of these structural alterations differ significantly when comparing individuals who primarily

exhibit cognitive deficits (ALS-ci) with those whose main symptoms are behavioral (ALS-bi) [20]. This regional specificity underscores a pattern of network-based selective vulnerability, suggesting that the highly individualized non-motor profiles observed in clinical practice are directly dictated by the distinct anatomical trajectories of disease spread [21].

2.1. Gray Matter Degeneration

At the gray matter level, voxel-based morphometry and cortical thickness analyses consistently show atrophy in the frontal and temporal lobes and in subcortical nuclei in ALS patients with cognitive impairment. Changes in the right inferior frontal gyrus, temporal pole, and thalamus are closely related to lower scores on cognitive measures [18]. Longitudinal structural MRI studies further show that cortical thinning in the middle frontal cortex and bilateral temporal regions tracks declines in total ECAS score and in the executive and language domains [22]. Persistent atrophy in the right inferior frontal gyrus and temporal pole is more specifically related to impaired theory of mind and reduced empathy, which suggests a relatively clear anatomical basis for social cognitive deficits [18, 22].

Longitudinal tracking confirms that this gray matter degeneration is a highly dynamic process, evolving in tandem with phenotypic severity [22–24]. Extending beyond the frontotemporal cortices, progressive volume loss within subcortical hubs, namely the thalamus, caudate, and putamen, is predictive of compromised multitasking capacities and an accelerated global clinical decline [18, 25]. Furthermore, deep learning-based structural neuroimaging models indicate that patients with ALS possess a brain age approximately seven years older than their real age; notably, this accelerated aging trajectory closely parallels worsening executive function and declining ECAS scores [26]. Collectively, these multiscale morphometric findings suggest that gray matter alterations are not merely the pathological endpoints of established symptoms, but rather serve as early, objective neuroimaging biomarkers for impending cognitive decline [22, 26]. Furthermore, this structural deterioration is highly modulated by genetic heterogeneity. For instance, patients carrying the C9orf72 hexanucleotide repeat expansion exhibit a distinct, highly aggressive morphometric signature characterized by profound, widespread atrophy in the bilateral thalamus, anterior insula, and orbitofrontal cortex, which significantly exceeds the structural burden observed in sporadic ALS cohorts [27, 28]. This severe gray matter penalty in C9orf72 carriers provides a direct anatomical explanation for their heightened susceptibility to early-onset, severe executive and psychotic symptoms.

2.2. White Matter Disconnection

Concomitant with the degeneration of cortical gray matter hubs, the intricate white matter pathways interconnecting these nodes undergo extensive microstructural disruption [29–31]. Diffusion tensor imaging and higher-order microstructural models indicate that in ALS patients exhibiting non-motor phenotypes, pathological alterations extend well beyond the primary corticospinal tract to encompass broad networks of long association and commissural fibers [32, 33]. Multicenter DTI cohorts demonstrate that microstructural degradation within the corpus callosum, superior longitudinal fasciculus, and intra-hemispheric frontotemporal pathways is particularly pronounced in subgroups burdened by cognitive and behavioral impairments [34]. Beyond the assessment of isolated white matter tracts, whole-brain structural connectomics provides a macro-scale framework for quantifying these widespread disruptions. Network topology studies suggest that the presence of non-motor symptoms in ALS is closely linked to aberrant global efficiency and altered path lengths, ultimately pointing to degraded large-scale connectivity [35, 36]. Furthermore, neurite orientation dispersion and density imaging (NODDI) suggests that diminished neurite density in prefrontal and temporal white matter may precede overt macroscopic gray matter atrophy, thereby providing a highly sensitive window into early neurodegeneration [34, 37].

From a functional perspective, microstructural damage in the genu and body of the corpus callosum is closely related to executive dysfunction, whereas abnormalities in limbic tracts such as the uncinate fasciculus and cingulum are more often linked to apathy, disinhibition, and compulsive-like behavior [32, 38]. Additionally, investigations into pseudobulbar affect reveal that reduced fractional anisotropy (FA) in the superior cerebellar peduncle, coupled with brainstem volume loss, correlates with impaired emotional lability, highlighting the involvement of extensive brainstem-cerebellar regulatory circuits in emotional dysregulation [19, 39]. Mechanistically, the spatial pattern of this structural disconnection aligns closely with the hypothesized prion-like, trans-synaptic propagation of pTDP-43 aggregates, suggesting that the brain's structural wiring itself acts as a conduit for disease spread and dictates the trajectory of evolving clinical phenotypes [5, 40]. Notably, evidence indicating that these white matter tractopathies frequently antedate visually discernible gray matter atrophy posits that structural disconnection is a fundamental, early driver of non-motor pathogenesis [33, 41].

3. Functional Reorganization

While structural neurodegeneration establishes the anatomical substrate for non-motor symptoms, alterations within intrinsic functional networks elucidate the dynamic mechanisms through which these phenotypes become clinically manifest [42, 43]. Resting-state functional MRI (rs-fMRI) investigations reveal that functional brain networks in ALS do not follow a simple linear trajectory of decline over the disease course [42, 43]. Rather, they undergo a complex, dynamic reorganization characterized by an early phase of abnormal hyper-synchronous compensation followed by late-stage decompensation. This biphasic process manifests as aberrant connectivity within higher-order cognitive networks, alongside disrupted topological configurations and compromised temporal stability within circuits governing emotion and behavior [44, 45].

3.1. Cognitive Networks

In ALS cohorts presenting with cognitive impairment, functional connectivity disruptions are predominantly localized to the default mode network (DMN), the frontoparietal control network (FPCN), and the ventral attention network (VAN) [44, 46]. Furthermore, current fMRI evidence links resting-state DMN anomalies directly to defective neurovascular coupling (NVC). Such pronounced NVC deficits imply that the deterioration of advanced cognitive networks in ALS is collaboratively driven by early-stage cerebrovascular and microvascular failures. Specifically,

dysconnectivity among temporal nodes of the DMN inversely correlates with global cognitive performance, whereas pathological hyperconnectivity encompassing the thalamus, insula, and putamen within the VAN is robustly linked to deficits in attentional set-shifting [44]. Furthermore, recent comprehensive overviews emphasize that combining resting-state fMRI with other electrophysiological modalities is increasingly employed to uncover the precise cognitive neural signatures underlying these distinct network disruptions. Consequently, cognitive impairment in ALS transcends localized prefrontal dysfunction, reflecting a systemic breakdown in the synergistic coordination across multiple higher-order large-scale networks [13, 44]. Furthermore, these functional aberrations exhibit distinct frequency-specific topological patterns. Spectral analyses of functional connectivity strength indicate that within specific low-frequency oscillations (e.g., slow-4 and slow-5 bands), connectivity is significantly attenuated in the left prefrontal cortex and bilateral superior frontal gyri, concurrent with compensatory functional enhancements in the postcentral gyrus and paracentral lobule [47]. This concurrent manifestation of localized functional decrement and compensatory upregulation suggests that, during the early stages of pathogenesis, functional networks attempt to preserve cognitive output via the redistribution of neural load [43, 47]. Crucially, this biphasic pattern of functional network failure is not uniform across all etiologies, but is profoundly influenced by the underlying genetic architecture. Specifically, C9orf72 mutation carriers demonstrate exceptionally early and extensive alterations, including aberrant hyperconnectivity within the default mode and frontoparietal networks, often detectable alongside distinct atrophy patterns [27, 48]. This suggests that specific genetic drivers can instigate network-level functional excitotoxicity, accelerating the transition from transient compensation to macroscopic network collapse. However, as irreversible structural degradation accumulates, this transient compensatory scaffolding ultimately collapses, precipitating overt clinical cognitive decline.

3.2. Emotional and Behavioral Networks

In addition to cognitive deficits, the broader non-motor clinical profile of ALS is heavily characterized by the breakdown of brain networks responsible for behavioral and emotional control [45]. Recent graph-theoretical evaluations underscore that while apathy and depression are frequently conflated in clinical settings, they are underpinned by divergent network topographies. Patients exhibiting isolated apathy display increased characteristic path length, diminished local efficiency, and attenuated nodal strength specifically within the left basal ganglia network, reflecting a pronounced inefficiency of information transfer across motivation and reward circuits [42]. Conversely, cohorts with depressive symptomatology predominantly exhibit shortened path lengths within bilateral basal ganglia networks alongside whole-brain hyperconnectivity—a maladaptive topological pattern indicative of pathological neural synchronization [45, 49]. This mechanistic dichotomy is clinically critical, demonstrating that emotional and behavioral disturbances in ALS should not be subsumed under a monolithic psychiatric label, but rather delineated as distinct manifestations of selective vulnerability in different regulatory circuits. Additionally, dynamic functional connectivity (dFC) analyses have detected an aberrant dichotomy in the temporal architecture of brain networks. Specifically, ALS patients exhibit pathologically increased functional stability within the sensorimotor cortices, contrasting sharply with decreased stability (or hyper-instability) in higher-order cognitive hubs such as the right middle and inferior frontal gyri [42]. This altered temporal dynamic, characterized by maladaptive rigidity in primary motor areas and exaggerated fluctuations in cognitive regions, correlates with reduced ALSFRS-R scores and reflects accelerated global disease progression [50]. Ultimately, these findings corroborate that functional network reorganization in the ALS-FTD spectrum is profoundly disrupted across both spatial and temporal dimensions [42, 43].

4. Integrative Modeling

Although group-level comparisons of structural and functional alterations have revealed core pathological features of ALS, they often face limitations in fully capturing the marked clinical heterogeneity of the disease [51, 52]. To address this, current translational efforts focus on determining whether multimodal MRI can identify patient-specific patterns of network degeneration to predict individual symptom trajectories [51]. The field is gradually shifting from describing average cohort differences toward integrating multidimensional data. In this context, multimodal modeling provides a practical approach to link group-level findings with individualized clinical inference.

4.1. Phenotypic Stratification

In recent years, multimodal feature fusion and data-driven methods have been utilized to identify latent phenotypes of brain network injury within the ALS spectrum [52, 53]. Furthermore, the application of network-based clustering algorithms has enabled researchers to move beyond simple group-level dichotomies, revealing distinct, biologically grounded neuroimaging subtypes. Evidence from recent large-cohort MRI clustering analyses highlights three distinctly characterized trajectories of neurodegeneration in ALS patients: a pure motor (PM) cluster, a frontotemporal (FT) cluster, and a cingulate-parietal-temporal (CPT) cluster [54]. Patients within the PM cluster exhibit isolated cortical thinning restricted to the precentral gyrus, largely preserving cognition-related networks. Conversely, the FT cluster features prominent orbitofrontal and anterior temporal involvement, while the CPT cluster is characterized by widespread degradation encompassing the posterior cingulate cortex, parietal white matter, and cerebellum [54]. Crucially, these widespread topological subtypes (FT and CPT) are associated with significantly higher rates of cognitive and behavioral impairments on the Edinburgh Cognitive and Behavioural ALS Screen (ECAS) compared to the restricted motor phenotype [54]. Multimodal MRI thus shows that non-motor symptoms in ALS are not the endpoint of a single pathway. They are more likely to reflect multiple trajectories of brain network evolution [55].

4.2. Longitudinal Prediction

Building on phenotypic stratification, multimodal MRI is increasingly applied to predict individualized trajectories of cognitive decline. Investigators have combined morphometric measures from structural MRI, microstructural indices from diffusion MRI, and baseline clinical data to predict changes in executive function and global cognition over the subsequent one to two years [52, 56]. Existing

literature suggests that hybrid convolutional neural networks and automated machine learning frameworks often show improved performance in predicting cognitive deterioration compared to models based on a single modality [53, 56]. However, methodological reviews caution that in ALS cohorts with limited sample sizes, simply increasing model complexity exacerbates the risk of overfitting and does not necessarily guarantee superior predictive performance; on the contrary, robust feature selection and cross-modal extraction remain the primary ongoing challenges [57]. To optimize the predictive accuracy of these longitudinal models, determining the precise temporal interval for follow-up neuroimaging is critical. Recent longitudinal evaluations indicate that while macroscopic gray matter volumetric loss may require 12 months to yield robust predictive signals, microstructural connectomic changes—particularly along frontotemporal association tracts—can reliably stratify cognitive decline trajectories within a narrow 6-month window [24, 58]. Therefore, integrating high-frequency microstructural tracking with long-term morphometric modeling is essential for mapping the multi-stage progression of non-motor symptoms. Consequently, the utility of multimodal MRI is expanding from explaining existing structural damage to contributing to prognostic risk stratification and personalized longitudinal modeling [59]. In a highly heterogeneous disease like ALS, the proactive identification of patients at elevated risk for cognitive and behavioral deterioration represents a critical milestone in translating brain network connectomics into actionable clinical practice1.

5. Controversies and Limitations

Although multimodal MRI has significantly advanced the understanding of non-motor symptoms in ALS [14, 60], the mechanistic chain of evidence remains constrained by biological controversies and methodological limitations. Clinically, a prominent dissociation persists: a subset of patients exhibits pronounced frontotemporal network degradation while maintaining normative cognitive scores [61]. This non-linear relationship between objective imaging burden and clinical scales suggests the confounding influence of cognitive reserve [6, 62], underscoring the need for imaging markers that detect subclinical decompensation before overt phenoconversion [26]. Compounding this issue is the unresolved debate regarding the spatiotemporal trajectory of pathological spread. It remains fiercely debated whether non-motor involvement represents a prion-like, contiguous outward extension of advanced motor system degeneration [63], or if distinct cognitive and behavioral networks undergo partially independent, selective vulnerability during the nascent stages of the disease [64, 65].

Furthermore, pervasive methodological heterogeneity continues to restrict the comparability and replicability of findings across independent cohorts [59]. Discrepancies in MRI acquisition parameters, preprocessing pipelines, and clinical stratification criteria frequently yield inconsistent results within identical networks. For instance, uncorrected signal variations from reactive gliosis can systematically confound morphometric estimates [59], while divergent statistical thresholds can drastically alter the diagnostic yield of cognitive impairment [66]. Moreover, as the field increasingly relies on multicenter datasets to achieve adequate statistical power, unmitigated inter-scanner variability introduces profound batch effects that can easily overshadow subtle disease-related microstructural and connectomic alterations [67]. Consequently, the integrationof advanced statistical harmonization techniques, such as the ComBat algorithm, is becoming indispensable for pooling multi-site imaging data without eroding true biological signals [34]. Moving forward, the field must transition from isolated, exploratory discoveries to a harmonized, cumulative framework. Establishing standardized acquisition protocols, open-source postprocessing workflows, and consensus-driven clinical assessments is paramount [34, 67]. Only through rigorous methodological harmonization can these biological controversies be resolved, ultimately translating multidimensional brain network connectomics into actionable prognostic tools.

6. Future Directions

Building upon the established evidence and acknowledging current methodological bottlenecks, future endeavors must transcend the mere accumulation of cross-sectional neuroimaging correlates [13, 14, 68]. The overarching imperative is to fortify the mechanistic continuity and translational utility of the multimodal evidence chain. Consequently, future research trajectories must pivot towards detecting subclinical network aberrations earlier, elucidating phenotypical variances with higher microstructural resolution, and delivering actionable, multimodal predictive models to inform clinical decision-making [52, 69].

The advent of 7 Tesla (7T) and ultra-high-field MRI platforms offers unprecedented spatial resolution to interrogate cortical architecture and microenvironmental shifts in vivo [70, 71]. This technological leap enables the field to progress beyond macroscopic regional or network-level descriptions toward exquisite, tissue-level characterization [72]. Specifically, 7T MRI facilitates layer-specific cortical analyses and high-resolution quantitative susceptibility mapping (QSM), allowing researchers to pinpoint intracortical myelin degradation and focal iron accumulation, which are pathological hallmarks previously accessible only via post-mortem histology [70, 73]. If applied systematically, these ultra-high-field techniques could refine current macroscopic network explanations of frontal disinhibition and social cognitive deficits, grounding them in specific cortical microenvironmental pathologies and distinct cytoarchitectural vulnerabilities [70].

Given the profound heterogeneity of the ALS-FTD spectrum, a singular neuroimaging modality is insufficient to encapsulate the full pathophysiological complexity [1, 74]. A highly promising frontier involves the synergistic integration of multimodal MRI with biofluid biomarkers (e.g., neurofilament light chain and glial fibrillary acidic protein), genomic profiling, and longitudinal phenotyping [60, 75]. This fusion ensures that structural demyelination and functional network imbalance are interpreted within a unified mechanistic framework of axonal injury and astrogliosis [76]. For instance, concurrent evaluations have demonstrated that dynamic elevations in fluid neurofilament light chain quantitatively correlate with the progressive microstructural disintegration of specific white matter tracts, providing a direct molecular validation for MRI-derived network disconnection [77]. By synthesizing these multi-scale signatures through advanced longitudinal modeling, researchers can map the precise temporal sequence of pathogenesis, effectively bridging the critical lag between initial neurochemical alterations and subsequent macroscopic network collapse [59, 76]. Ultimately, harnessing this

integrated approach to detect the nascent signs of network decompensation—particularly in presymptomatic cohorts carrying highly penetrant pathogenic variants—will irrevocably transition neuroimaging into a pivotal clinical decision-making tool [78]. Pinpointing the critical "tipping point" of network failure during this latent preclinical phase is imperative, as it fundamentally defines the optimal opportunity for deploying targeted interventions before irreversible neuroanatomical exhaustion occurs [79, 80].

7. Conclusion

Overall, research on non-motor symptoms in ALS is moving from the question of whether damage exists outside the motor system to the deeper question of how these symptoms emerge as the clinical expression of brain network degeneration [7, 81]. Along this line, structural and diffusion MRI define the anatomical basis formed by frontotemporal gray matter injury and white matter disconnection, resting-state fMRI maps the dynamic reorganization of the default mode network, the frontoparietal control network, the ventral attention network, and basal ganglia circuits, and multimodal integrative modeling begins to translate these group-level findings into the identification and prediction of individual differences [22, 34, 44, 45, 51, 52].

Therefore, the value of multimodal MRI lies not only in providing more imaging evidence for non-motor symptoms in ALS, but also in helping to build a continuous explanatory chain that runs from structural degeneration to symptom expression and then to risk identification [14, 52]. As imaging precision, longitudinal design, and joint modeling continue to improve, this chain of evidence is likely to become more complete and to provide a more reliable objective basis for early identification, precise stratification, and treatment timing in non-motor symptoms of ALS [55, 70].

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