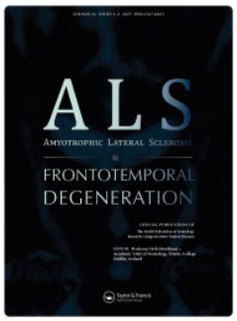

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# Subcortical grey matter involvement in ALS and PLS – vulnerable hubs of cortico-cortical and cortico-basal circuits: extrapyramidal, cognitive, bulbar and respiratory correlates

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**REVIEW ARTICLE**

# Subcortical grey matter involvement in ALS and PLS – vulnerable hubs of cortico-cortical and cortico-basal circuits: extrapyramidal, cognitive, bulbar and respiratory correlates

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**Abstract**

Evidence from neuroimaging studies suggests that the cardinal clinical manifestations of ALS stem from the dysfunction of specific neural networks. The majority of cortico-cortical and cortico-basal networks are physiologically relayed by deep cerebral and cerebellar grey matter nuclei which have been increasingly implicated in the pathophysiology of ALS. A series of recent human imaging papers revealed volume reductions, shape deformations, metabolic alterations and more recently, susceptibility changes in hippocampal subfields, thalamic, striatal, amygdalar and cerebellar nuclei. Thalamic changes have been identified in presymptomatic mutation carriers long before symptom onset and longitudinal studies have consistently confirmed progressive subcortical degeneration during the symptomatic phase of the disease. The dysfunction of circuits relayed by specific subcortical nuclei has been associated with apathy, amnestic deficits, limbic symptoms, extrapyramidal manifestations, sensory disturbances, pseudobulbar affect and cerebellar deficits. In light of emerging imaging data, the clinical heterogeneity of ALS is probably best approached from a network integrity perspective. Accordingly, the comprehensive assessment of subcortical grey matter nuclei seems imperative to untangle complex clinical phenomena in ALS.

**Keywords:** *MRI, ALS, Neuroimaging, Biomarkers*

## From focality to circuitry

ALS has traditionally been primarily associated with motor disability and accordingly, imaging studies have overwhelmingly focused on motor cortex, brain stem and corticospinal tract degeneration (1–3). Subcortical grey matter imaging is a relatively new frontier of ALS imaging and has contributed to the paradigm shift from assessing cortical grey matter regions to the evaluation of entire neural networks. Most ALS-associated clinical phenomena are underpinned by the dysfunction of specific neuronal networks as opposed to being solely driven by cortical disease burden. Networkwise cerebral degeneration has long been suggested based on clinical and neuropsychological observations (4,5). The wider recognition of cognitive (6,7), behavioral (8), extrapyramidal (9), sensory (10), pseudobulbar (11) and cerebellar (12) manifestations in ALS gave impetus to the study of subcortical grey matter nuclei which relay specific cortico-cortical and cortico-basal networks (13,14). Linking complex clinical symptoms to focal grey matter regions alone has long been regarded contentious (15) and ALS has been increasingly reconceptualised as a "network disease" (16). The shift from "focality to circuitry" to untangle clinical phenomena is supported by an ever-increasing number of studies that evaluate both functional and structural connectivity (17).

## Academic advances

Presymptomatic thalamic changes have been identified in GGGGCC hexanucleotide repeat expansion carriers many years before projected symptom onset (18,19). The *C9orf72* genotype has been initially linked to particularly severe subcortical degeneration (20,21), but large neuroimaging studies have later

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confirmed that hippocampal and thalamic degeneration is not unique to hexanucleotide repeat expansion carriers (22). Longitudinal imaging studies have consistently demonstrated relentlessly progressive subcortical degeneration in large cohorts of symptomatic patients (23). While there remains a considerable focus on supratentorial degeneration, recent studies have confirmed the involvement of deep cerebellar grey matter nuclei and have shown progressive cerebro-cerebellar uncoupling over the course of the disease (24–27). While often regarded as a relatively "benign" motor neuron disease compared to ALS, patients with PLS, also demonstrate significant subcortical degeneration (28). In addition to volumetric changes, significant susceptibility alterations have also been detected in the caudate, thalamus, and putamen of patients with ALS (29).

## Anatomic involvement and clinical correlates

Considerable thalamic involvement has been consistently demonstrated in ALS using a multitude of imaging methods, including metabolic, functional and structural approaches (21,30–32). High-resolution structural data has been interrogated along the ALS-FTD spectrum to reveal thalamic volume reductions (33), voxelwise changes, shape deformations and also used to segment the thalamus either based on cortical projections (34) or to parcellate the thalamus into histologically-defined nuclei (35,36). The amygdala has also been studies by a variety of morphometric, metabolic, diffusivity, and volumetric methods (37) and a predilection for accessory basal nucleus and the cortical nucleus involvement has been detected in sporadic cases (38). Accumbens nucleus degeneration in ALS has been consistently linked to apathy (39,40). Hippocampal degeneration in ALS has been evaluated by an array of connectivity, diffusivity, spectroscopy and volumetric approaches and consistently linked to memory deficits (40–42). Limbic networks and the integrity of Papez circuit have been assessed in dedicated functional MRI, diffusion and high-resolution structural techniques and linked to neuropsychological deficits (43,44). Caudate nucleus, putamen and pallidum degeneration is also well recognized in ALS, and has been consistently linked to extrapyramidal manifestations (9,45,46). Cerebellar imaging has confirmed the dysfunction of dentate nucleus mediated networks (24) and cerebellar disease burden has been implicated in bulbar (47), cognitive (48), respiratory (49) and pseudobulbar manifestations (11,27), but further studies are required to confirm the cerebellar components of clinical deficits in ALS.

## Methodological considerations

In contrast to the voxelwise cross-sectional statistics of early imaging studies in MND, a wide range of mathematical approaches have been utilized in more recent years, including graph-theory models (50), classification and machine-learning algorithms (51,52), longitudinal (53,54), and predictive modeling (55,56). In addition to MRI metrics, EEG and MEG data have been increasingly evaluated to assess connectivity alterations (57–60).

## Conclusions

Irrespective of their imaging techniques, MRI studies have consistently demonstrated considerable subcortical grey matter involvement in ALS. Subcortical grey matter changes can be captured decades before symptom onset, at the time of diagnosis, and these structures succumb to relentless degeneration throughout the course of the disease. Subcortical grey matter degeneration is a key driver of connectivity alterations and ensuing network dysfunction in ALS and should therefore be routinely studied in both biomarker and clinical studies.

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## Declaration of interest

No potential conflict of interest was reported by the author(s).

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