UNIVERSITY OF PADOVA

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Final dissertation

Attention Control Network Impairments in ALS: From Anatomy to Disconnections

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Abstract

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder primarily affecting motor function, but a considerable proportion of patients also exhibit cognitive deficits, particularly in attention and executive functioning. These deficits are thought to arise from disruptions in attention control networks involving frontal, parietal, and subcortical brain regions. The present study aims to investigate the structural and functional brain changes in ALS using neuroimaging techniques, with a specific focus on attention control deficits. Relevant papers which include datasets based on structural as well as functional data were selected following structured guidelines during the literature search. A direct image lesion-mapping will be implemented and Volume-of-interest (VOIs) will then be manually delineated onto a template scan. These VOIs will then be overlaid to identify patterns of gray matter atrophy or lesions associated with attention and cognitive deficits in ALS patients. The study's preliminary goal is to elucidate the presence of possible structural and functional deficits characterising ALS and possibly even specific attention control deficits in ALS by super-imposing VOIs and analysing them. It is hypothesized that ALS patients will exhibit gray matter atrophy in the frontal, parietal, and subcortical regions.

Keywords: *ALS, Cognition, Lesion-mapping, Neuroimaging, Multimodal*.

Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder characterised by the degeneration of upper and lower motor neurons, leading to progressive muscle weakness and atrophy. While motor impairments are the main symptoms, a substantial number of ALS patients exhibit cognitive and behavioural deficits, particularly in the domains of attention, executive functioning, and social cognition (Goldstein & Abrahams, 2013; Woolley & Katz, 2008). Attention is a fundamental cognitive process that enables the selective allocation of mental resources to relevant stimuli or tasks while filtering out irrelevant information (Petersen & Posner, 2012). These non-motor symptoms could predate the onset of motor symptoms and significantly impact the quality of life (Tsermentseli et al., 2012). Attention control network is a distributed neural system involving the frontal, parietal, and subcortical regions of the brain, which plays a crucial role in regulating attentional processes (Bressler & Menon, 2010). Disruptions in this network have been found in various neurological and psychiatric disorders, including ALS (Pavese et al., 2010; McMackin et al., 2019).

Since the dawn of the 21st century, neuroimaging studies have provided insights into the structural and functional brain changes associated with attention control deficits in ALS. Structural magnetic resonance imaging (MRI) studies have consistently reported gray matter atrophy in frontal, parietal, and subcortical regions, including the dorsolateral prefrontal cortex, anterior cingulate cortex, thalamus, and cerebellum (Phukan et al., 2012; Pettit et al., 2013; Qiu et al., 2019; Nigri et al., 2023). Additionally, white matter tract degeneration has been observed in corticomotor, frontotemporal, and interhemispheric pathways (Abrahams et al., 2005; Rose et al., 2012; Buchanan et al., 2015; Lillo et al., 2012), suggesting disrupted structural connectivity within the attention control network. Functional MRI (fMRI) studies have further revealed altered patterns of brain activity and functional connectivity within attention control networks during cognitive tasks in ALS patients (Mohammadi et al., 2015; Schulthess et al., 2016; Castelnovo et al., 2020). Increased functional connectivity has been observed in presymptomatic gene carriers (Menke et al., 2016), potentially reflecting compensatory mechanisms in early disease stages. However, as the disease progresses, functional connectivity decreases, mirroring the structural degeneration (Chen et al., 2021; Castelnovo et al., 2020). These neuroimaging findings suggest that Attention Control Network impairments in ALS may arise from both structural and functional disruptions in key brain regions and their interconnections. However, a comprehensive understanding of the neural correlates of attention

control deficits in ALS remains elusive, as existing studies have utilised diverse methodologies and turned out with mixed results (Goldstein & Abrahams, 2013).

Attention Control Networks and Cognitive Impairments in ALS

Attention control networks refer to the regions of the brain and the connections involved in regulating and modulating attention, particularly for higher-order cognitive functions such as executive control, working memory, and task switching. These networks consist of areas like the prefrontal cortex, parietal cortex, and subcortical structures like the thalamus and basal ganglia. The relevance of attention control networks in amyotrophic lateral sclerosis (ALS) has been increasingly recognised in the past couple of decades as cognitive and behavioural impairments are common in ALS patients. Several neuroimaging studies have investigated the integrity and functionality of these networks in ALS patients, revealing important insights. McMackin et al. (2019, 2020) found the presence of dysfunction of attention-switching networks in ALS patients compared to healthy controls using functional MRI during a sustained attention-to-response task. Their findings suggest that quantitative markers of executive impairment in ALS can be derived from the localisation of brain networks engaged by a task. Specifically, McMackin et al. (2020) reported alterations in the prefrontal, parietal, and subcortical regions involved in attention control networks. Furthermore, Trojsi et al. (2021) reported impairment in hippocampal connectivity in ALS patients compared to controls using resting-state functional MRI. This suggests that disruptions in attention control networks may extend beyond traditional frontal-parietal regions in ALS.

While amyotrophic lateral sclerosis (ALS) is primarily characterised by progressive motor neuron degeneration, there is an increasing body of evidence suggesting that a substantial proportion of patients also exhibit cognitive and behavioural impairments (Goldstein & Abrahams, 2013; Woolley & Katz, 2008). These non-motor symptoms can be present even in the absence of dementia and can manifest in various domains, including attention, executive functioning, language, and social cognition (Phukan et al., 2012; Tsermentseli et al., 2012).

Attention deficits are among the most commonly reported cognitive impairments in ALS patients (Goldstein & Abrahams, 2013). Difficulties in sustaining attention, divided attention, and attentional shifting have been documented that could potentially impact activities of daily living and overall quality of life. Executive dysfunction, characterised by impairments in

planning, decision-making, problem-solving, and cognitive flexibility, is also prevalent in ALS (Phukan et al., 2012; Pettit et al., 2013).

It is important to note that the severity and pattern of cognitive impairments can vary among ALS patients, with some individuals exhibiting relatively preserved cognitive function, while others experience more severe deficits (Tsermentseli et al., 2012). Additionally, these non-motor symptoms can precede the onset of motor symptoms or occur concurrently, further emphasizing the need to understand and address cognitive and behavioural changes in ALS.

Objectives and Hypotheses

The primary objective of this study is to understand the structural and functional brain changes in amyotrophic lateral sclerosis (ALS) using neuroimaging techniques. Specifically, the study aims to identify patterns of gray matter atrophy or lesions in ALS that focus on attention control deficits. To achieve these objectives, the study will employ a direct image lesion-mapping approach and superimpose volume-of-interest (VOI) maps derived from structural and functional neuroimaging data. By overlaying these VOIs, the study aims to identify patterns of gray matter atrophy, white matter lesions, and functional connectivity disruptions associated with attention control deficits in ALS patients.

Based on the existing literature and the hypotheses outlined in the study proposal, the following are the main hypotheses:

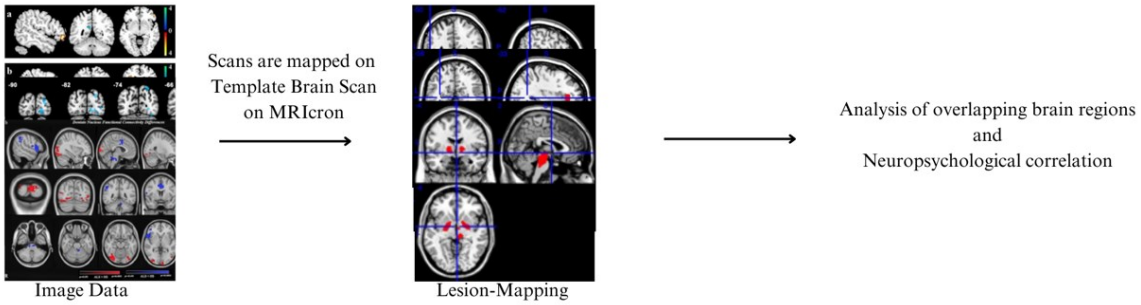
1. ALS patients will exhibit gray matter atrophy and functional disruptions in distributed frontal, parietal, and subcortical regions implicated in attention control networks, including the dorsolateral prefrontal cortex, anterior cingulate cortex, parietal lobules, thalamus, and basal ganglia.
2. ALS patients may also exhibit structural and functional changes in regions beyond the traditional frontal-parietal attention control network, such as the temporal lobes and cerebellum, reflecting the involvement of broader cognitive networks in ALS-related cognitive impairment.

These hypotheses are based on previous findings from neuroimaging and lesion-mapping studies in ALS, which have consistently reported structural and functional alterations in frontal, parietal, and subcortical regions focused on attention control and executive functioning deficits. By testing these hypotheses, the study aims to provide a comprehensive understanding of the neural correlates of attention control network impairments in ALS.

The present study aims to investigate the structural and functional brain changes in ALS by employing a direct image lesion-mapping approach. More specifically aiming to identify patterns of gray matter atrophy or lesions possibly linked to impaired performance of attention control networks and executive functioning. We first selected the contrast between controls and ALS patients in studies focusing on attention control and executive control. Then we superimposed the volume-of-interest (VOI) derived from structural and functional neuroimaging data, in order to highlight the neural correlates of attention control network impairments in ALS as shown in Figure 1. The use of lesion-mapping techniques is crucial in this study as it allows us to bridge the gap between anatomical brain changes and cognitive dysfunction, which is particularly relevant in a multifocal disorder like ALS (Menke et al., 2018; Agosta et al., 2013; Agosta et al., 2015). Based on previous literature and the multifocal aspect of ALS, we hypothesize that ALS patients will exhibit possible gray matter atrophy and functional disruptions in distributed frontal, parietal, and subcortical regions implicated in attention control.

Figure 1

Overview of Study Methodology

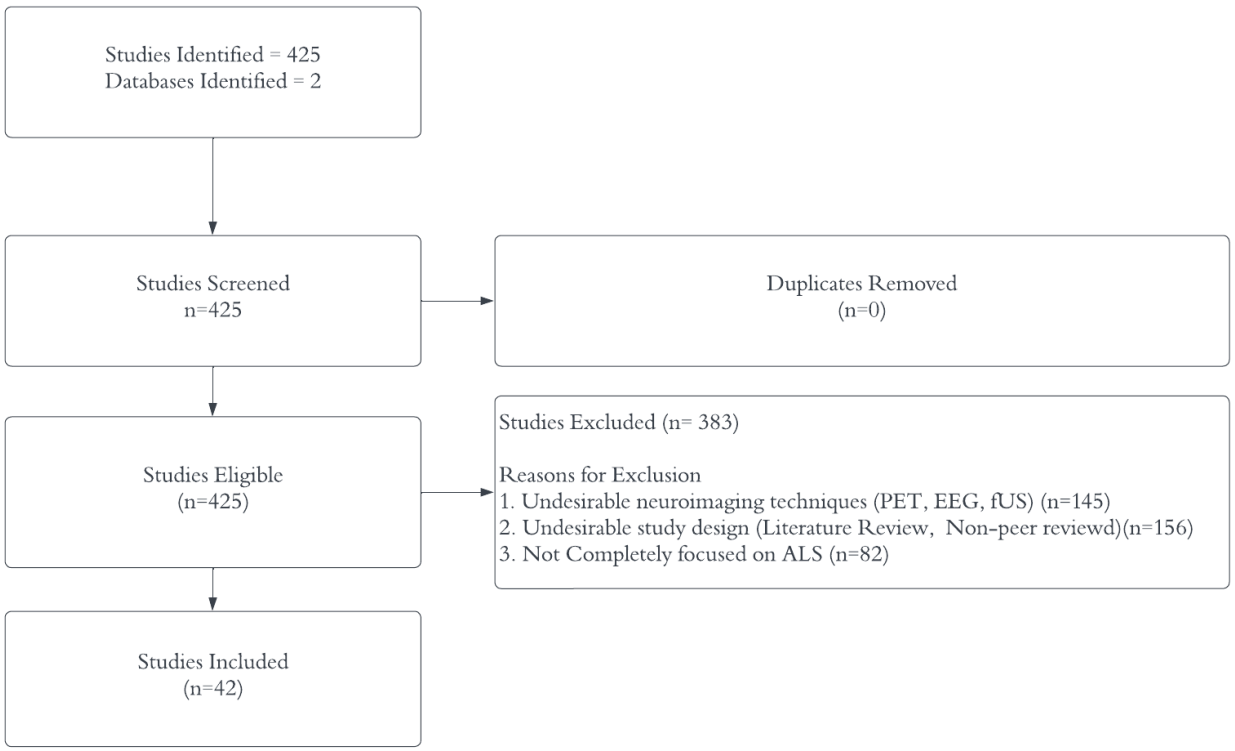


Literature Review

In the process of conducting a comprehensive literature review, a systematic search strategy was used to identify relevant studies. As shown in Figure 2, the initial search using relevant keywords (("Amyotrophic Lateral Sclerosis" OR "ALS") AND ("Attention" OR "Attentional Control" OR "Executive Function") AND ("Neuroimaging" OR "Structural MRI") OR ("Cognitive Assessment" OR "Behavioural Assessment") AND ("Lesion Studies" OR "Cognitive Dysfunction" OR "Progressive Neurodegeneration")) across the two databases (PubMed and ScienceDirect) yielded 425 studies. After screening for duplicates and applying inclusion and exclusion criteria as given in Table 1, a total of 42 studies were ultimately included for the review. The exclusion criteria comprised studies with undesirable neuroimaging techniques (n=145), studies with undesirable study designs (n=156), and those not focused specifically on ALS (n=82). The following review critically examines the findings from these 42 selected studies, providing insights into the current understanding of ALS and its associated neurological implications before proceeding with the primary goal of this study.

Figure 2

Flowchart showing the selection of studies for the literature review



Note: The flowchart shows the selection procedure followed for the studies cited and referred to in this study including the literature review. Figure 3 shows the selection of studies with the image data from the studies included following this selection procedure.

Table 1

Table showing the inclusion and exclusion criteria used

Inclusion Criteria	Exclusion Criteria
• Study population: Studies involving patients diagnosed with amyotrophic lateral sclerosis (ALS) or motor neuron disease (MND). • Study design: Original research studies involving functional/structural neuroimaging (fMRI, structural MRI, DTI) and/or cognitive/behavioural assessments of attention control processes. • Database: PubMed and ScienceDirect (Elsevier) • Language: Studies published in English. • Studies that have full-text available • Time frame: Studies published from the inception of respective databases until the date of the literature search. • Some studies may be included due to their high relevance to the topic, despite not meeting all inclusion criteria.	• Study population: Studies not focused on ALS patients or animal studies. • Study design: Non-peer reviewed; Literature Review • Outcome measures: Studies not involving relevant attention control measures through neuroimaging (PET, EEG, fUS) or cognitive/behavioural assessments.

Structural Brain Changes in ALS

Gray Matter Atrophy

Numerous neuroimaging studies have consistently reported gray matter atrophy in key brain regions associated with attention control networks in patients with ALS. Phukan et al. (2012) noted that structural MRI studies have revealed significant gray matter loss in the frontal and temporal lobes, as well as subcortical regions like the thalamus and caudate nucleus.

Likewise, Pettit et al. (2013) conducted a voxel-based morphometry (VBM) study and found that ALS patients exhibited gray matter atrophy in the dorsolateral prefrontal cortex, anterior cingulate cortex, and parietal regions compared to healthy controls. Importantly, the extent of atrophy in these areas correlated with impaired performance on neuropsychological tests of executive function, suggesting a link between structural brain changes and cognitive deficits. Qiu et al. (2019) employed a regional homogeneity analysis and reported decreased gray matter integrity in the precentral gyrus, supplementary motor area, and cerebellum in ALS patients. These findings are particularly relevant as the cerebellum has been implicated in cognitive functions beyond its traditional role in motor control.

White Matter Degeneration

In addition to gray matter atrophy, several studies have documented white matter tract degeneration in ALS patients, which may contribute to disruptions in attention control networks. Abrahams et al. (2005) used diffusion tensor imaging (DTI) and found widespread white matter changes in the corticospinal tracts, as well as frontal and temporal white matter regions in ALS patients. Similarly, Rose et al. (2012) employed ultra-high field DTI and reported degeneration of intra- and interhemispheric white matter pathways, including the corpus callosum and corticospinal tracts in ALS patients. These findings suggest impaired structural connectivity within and between brain regions involved in motor and cognitive functions. Buchanan et al. (2015) combined DTI and structural MRI data to investigate white matter tract integrity in ALS and found reduced structural connectivity within the prefrontal-motor-subcortical network, including the dorsolateral prefrontal cortex, primary motor cortex, and thalamus. This network is known to play a crucial role in attention control and executive functioning. Lillo et al. (2012) used VBM and DTI to examine gray and white matter changes across the ALS-frontotemporal dementia continuum. They found that ALS patients exhibited white matter degeneration in the corpus callosum, as well as frontal and temporal white matter tracts, which correlated with cognitive impairment.

Functional Brain Changes in ALS

Resting-State Functional Connectivity

Resting-state functional MRI (rs-fMRI) studies have provided insights into the functional connectivity alterations in attention control networks in ALS patients. Mohammadi et al. (2015) reported decreased functional connectivity in the frontoparietal network, as well as increased connectivity in the sensorimotor network in ALS patients compared to healthy

controls. Importantly, Menke et al. (2016) found increased functional connectivity in presymptomatic carriers of ALS-associated genetic mutations, suggesting that functional connectivity changes may precede clinical symptom onset. This increased connectivity could potentially reflect compensatory mechanisms in the early stages of the disease. Chen et al. (2021) conducted a longitudinal study investigating dynamic changes in functional network connectivity in ALS patients and observed a progressive decrease in functional connectivity within and between attention control networks, mirroring the structural degeneration observed in these patients.

Task-Based Functional Neuroimaging

Several studies have employed task-based functional MRI (fMRI) to examine brain activity patterns during attention-demanding cognitive tasks in ALS patients. Castelnovo et al. (2020) used fMRI during an attention control task and found altered activation patterns in frontal, parietal, and subcortical regions involved in attention control networks in ALS patients compared to healthy controls. McMackin et al. (2019) utilised the Sustained Attention to Response Task (SART) during fMRI and reported dysfunction in attention-switching networks, involving frontal, parietal, and subcortical regions, in ALS patients. In a follow-up study, McMackin et al. (2020) further localised the brain networks engaged during the SART and quantified the executive impairment in ALS patients based on these network alterations. Schulthess et al. (2016) investigated brain activation patterns during a cognitive switching task in ALS patients. They found increased activation in the dorsolateral prefrontal cortex and anterior cingulate cortex, which could be a potential compensatory mechanism for maintaining task performance in the presence of underlying neurodegeneration as discussed earlier.

Attention Control Network Disruptions in ALS

Converging evidence from structural and functional neuroimaging studies has implicated frontal lobe regions as a major component of the attention control network that are disrupted in ALS patients. Buhour et al. (2017) employed voxel-based mapping of gray matter volume revealing atrophy in the dorsolateral prefrontal cortex, ventrolateral prefrontal cortex, and anterior cingulate cortex in ALS patients. Lillo et al. (2012) reported gray matter atrophy in the frontal lobes, particularly the dorsolateral prefrontal cortex and anterior cingulate cortex, in ALS patients. These structural changes correlated with impaired performance on neuropsychological tests of executive functioning and attention. McMackin et al. (2020) specifically localised the brain networks engaged during the Sustained Attention to Response

Task (SART) and found that ALS patients exhibited dysfunction in the dorsolateral prefrontal cortex, anterior cingulate cortex, and other frontal regions involved in attention control and executive functioning.

In addition to frontal lobe alterations, the parietal lobe has also been implicated in attention control network disruptions in ALS. Lillo et al. (2012) reported gray matter atrophy in the parietal lobes, particularly the inferior and superior parietal lobules, in ALS patients. Trojsi et al. (2021) used resting-state fMRI and found impaired functional connectivity between the hippocampus and parietal regions, including the precuneus and inferior parietal lobule, in ALS patients. These regions are known to play important roles in attention and working memory processes. McMackin et al. (2019) observed dysfunction in parietal regions, such as the inferior parietal lobule, during an attention-switching task in ALS patients, further highlighting the involvement of the parietal lobe in attention control network impairments.

Also, subcortical structures and the cerebellum have been implicated in attention control network deficits in ALS. Buhour et al. (2017) reported gray matter atrophy in the thalamus and basal ganglia, which are critical components of the fronto-subcortical circuits involved in cognitive control and attention regulation. Lillo et al. (2012) found that ALS patients exhibited gray matter atrophy in the thalamus and cerebellum, regions that have been linked to attention and executive functioning processes. Meoded et al. (2015) employed resting-state fMRI and reported increased functional connectivity between the cerebellum and motor cortex in ALS patients, suggesting yet another potential compensatory mechanism for motor function impairment.

Neuroimaging Techniques and Lesion-Mapping Approaches

Researchers have employed a variety of neuroimaging techniques to investigate brain changes in ALS patients, including structural MRI, diffusion tensor imaging (DTI), and functional MRI (fMRI). Structural MRI has been widely used to assess gray matter atrophy and white lesions, while DTI allows for the evaluation of white matter tract integrity and structural connectivity. Functional MRI, both at rest (rs-fMRI) and during task performance, provides great insights into the functional activity and connectivity patterns within attention control networks. Lesion-mapping approaches, such as direct image lesion-mapping and voxel-based morphometry (VBM), have been employed to identify patterns of brain lesions or atrophy associated with cognitive deficits in ALS patients. McMackin et al. (2020) utilised the Sustained Attention to Response Task (SART) during fMRI and employed a lesion-mapping

approach to localise the brain networks engaged during this task in ALS patients. They found alterations in the frontal, parietal, and subcortical regions involved in attention control and executive functioning. Buchanan et al. (2015) combined DTI and structural MRI data to investigate white matter tract integrity in ALS, employing a lesion-mapping approach and found reduced structural connectivity within a prefrontal-motor-subcortical network, including the dorsolateral prefrontal cortex, primary motor cortex, and thalamus. Buhour et al. (2017) used voxel-based mapping of gray matter volume and glucose metabolism to identify atrophy and hypometabolism patterns in ALS patients. They reported alterations in frontal, parietal, and subcortical regions, which correlated with cognitive impairment.

Cognitive and Behavioural Correlates

As mentioned in a comprehensive review of the cognitive and behavioural changes observed in ALS and their potential neural correlates by Goldstein and Abrahams (2013), several studies have reported correlations between neuroimaging markers of brain changes and performance on neuropsychological tests assessing attention, executive functioning, and cognitive control in ALS patients. Lillo et al. (2012) found that gray matter atrophy in the frontal and parietal lobes, as well as white matter degeneration in the corpus callosum and frontal/temporal tracts, correlated with impaired performance on tests of executive functioning, attention, and processing speed in ALS patients. McMackin et al. (2020) demonstrated that the extent of brain network dysfunction during the SART, particularly in the dorsolateral prefrontal cortex, anterior cingulate cortex, and parietal regions, correlated with poorer performance on tests of executive function, attention, and cognitive flexibility in ALS patients. Trojsi et al. (2021) reported that impaired hippocampal connectivity with the parietal regions was associated with reduced performance on tests of memory and attention in ALS patients, highlighting the possibility of a broader involvement of cognitive networks beyond the traditional frontal-parietal attention control system.

Limitations of Previous Studies

While the literature has provided valuable insights into the neural correlates of attention control network impairments in ALS, several limitations should be acknowledged. Goldstein and Abrahams (2013) noted that many studies have utilised diverse methodologies and reported mixed results, making it challenging to draw firm conclusions. Tsermentseli et al. (2012) cautioned against oversimplifying the relationship between cognitive impairments and

structural brain changes, emphasizing the need for a more comprehensive understanding of the neural substrates underlying cognitive dysfunction in ALS.

Methods

The present study aims to elucidate the structural and functional brain alterations in individuals with amyotrophic lateral sclerosis (ALS) using a lesion-mapping approach focusing specifically on attention control networks. The novelty of this study lies in employing a comprehensive lesion-mapping technique to directly overlay and analyse neuroimaging data from various modalities, providing a more comprehensive understanding of the neural correlates underlying cognitive dysfunction in ALS.

Data Collection

A structured search for the image dataset was conducted from the previously included studies to identify relevant studies that included structural and functional neuroimaging data from ALS patients contrasted with healthy controls applying the inclusion and exclusion criteria as shown in Table 2. Studies utilising various imaging modalities, such as structural magnetic resonance imaging (MRI), resting-state functional MRI (rs-fMRI), and task-based functional MRI (fMRI), were included. A total of 09 studies were obtained from the selected studies. A flowchart of the selection of the studies is shown in figure 3.

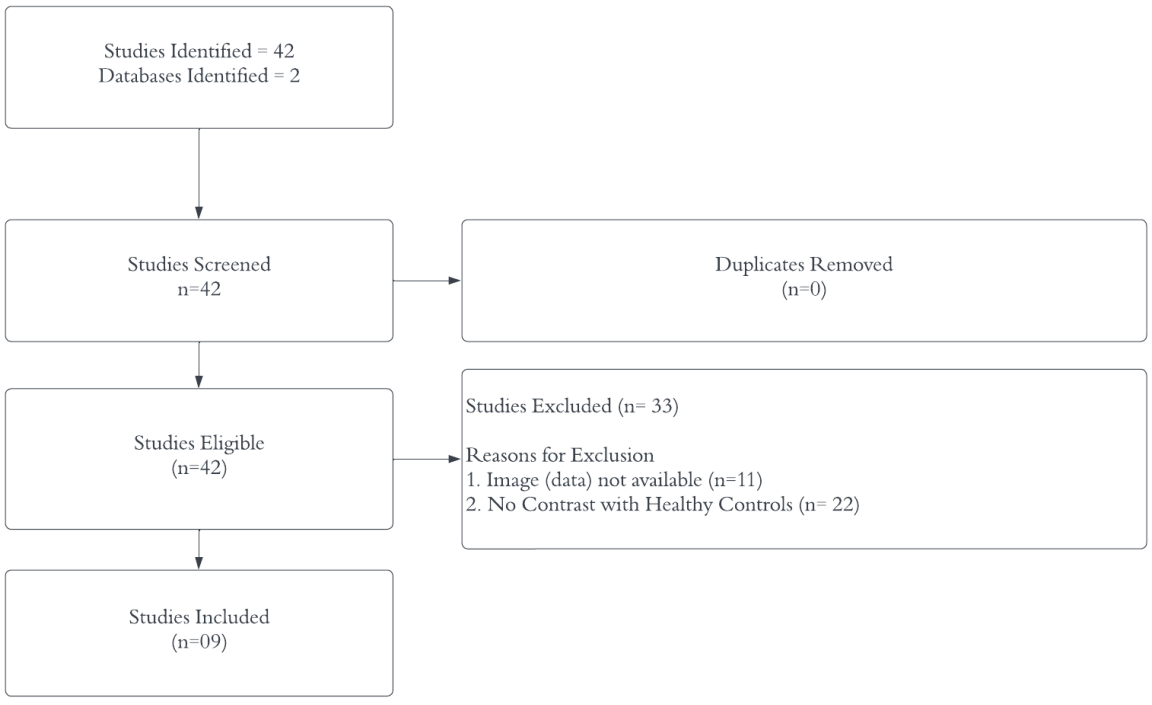
Table 2

Table showing the inclusion and exclusion criteria used

Inclusion Criteria	Exclusion Criteria
• Study population: Studies involving patients diagnosed with amyotrophic lateral sclerosis (ALS) or motor neuron disease (MND). • Study design: Original research studies involving functional/structural neuroimaging (fMRI, structural MRI, DTI) and/or cognitive/behavioural assessments of attention control processes. • Studies consisting of proper contrast with Healthy controls. • Studies that have neuroimaging data available in-text (as Images or MNI coordinates with *t*-values)	• Study population: Studies not focused on ALS patients or animal studies. • Studies that do not have a contrast with Healthy controls. • Studies which do not have have neuroimaging data available in-text (as Images or MNI coordinates with *t*-values)

Figure 3

Flowchart showing the selection of studies for Lesion-mapping



Note: The flowchart refers only to the studies that were used for lesion-mapping and overlay analysis. Refer to figure 2 for the flowchart for all studies included in the literature review.

Data Preprocessing

The neuroimaging datasets obtained from the selected studies were already spatially normalized and mapped onto a standard brain template by the respective authors. Therefore, no additional preprocessing steps were required.

Data Analysis

Direct Image Lesion-Mapping:

For each dataset, regions of interest (ROIs) or volumes of interest (VOIs) were delineated onto the template brain scan, representing areas of gray matter atrophy, white matter lesions, or functional connectivity alterations in ALS patients. The ROIs/VOIs were manually drawn using the MRIcron toolbox, guided by the findings reported in the original studies. Each mapping was saved as an individual file in VOI format, and a comprehensive table was created to compare the lesion-mapping on the template scan with the corresponding original image.

VOI Overlay Analysis:

The individual VOI files from the lesion-mapping were first overlaid onto the template scan to create a combined map using the "create overlap image" statistical tool in MRIcron, this new file was saved as a NifTI file. It comprised all individual brain-mapping files as one for easy comparison and analysis of the overlaying patterns. This step aided in highlighting the structural and functional changes across the studies which is interpreted in detail in the upcoming section. This novel approach of overlaying patterns of lesions and atrophies allowed for the visualization of brain regions consistently implicated in cognitive deficits, including attention control deficits, in ALS patients, irrespective of the imaging modality.

Results

The direct image lesion-mapping approach and subsequent overlay analysis primarily revealed consistent patterns of gray matter atrophy (figures 4 and 5) and moderate functional connectivity disruptions (figure 6) in key brain regions associated with attention control networks in amyotrophic lateral sclerosis (ALS) patients across multiple neuroimaging modalities.

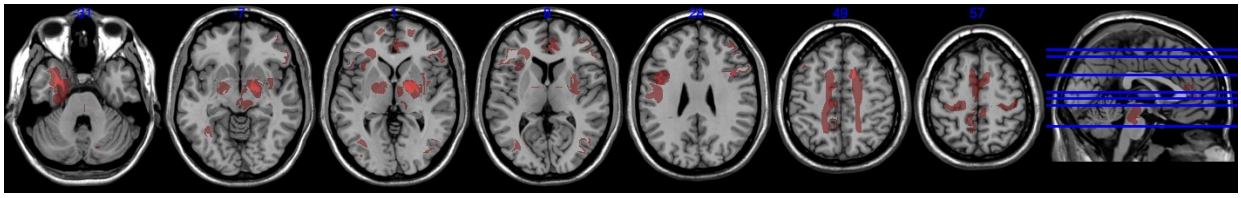
Frontal Lobe Involvement: The overlay map highlighted atrophy in several frontal regions critically involved in attention control and executive functioning. The dorsolateral prefrontal cortex (DLPFC), encompassing Brodmann areas 8, 9, and 46, exhibited gray matter loss across multiple studies as shown in figure 5 (Buhour et al., 2017; Grossman et al., 2008; Lillo et al., 2012; Qiu et al., 2019). Additionally, the ventrolateral prefrontal cortex (VLPFC), particularly Brodmann area 44/45, also showed consistent atrophy patterns in ALS patients across studies (Buhour et al., 2017; Grossman et al., 2008). Furthermore, the anterior cingulate cortex (ACC), a crucial region for cognitive control and attention regulation (Brodmann area 32), exhibited atrophy in ALS patients as shown in figure 4 (Buhour et al., 2017; Lillo et al., 2012).

Parietal Lobe Involvement: In addition to frontal lobe alterations, the overlay analysis revealed atrophy in parietal regions associated with attention control networks. The inferior parietal lobule (IPL, Brodmann area 40) and superior parietal lobule (SPL, Brodmann area 7) exhibited consistent gray matter loss in ALS patients as shown in figure 4 and as reported by Lillo et al. (2012) and Zhang et al. (2017).

Subcortical and Cerebellar Involvement: The overlay analysis also highlighted the involvement of subcortical structures and the cerebellum in attention control network disruptions in ALS patients. Atrophy was observed in the thalamus and basal ganglia structures, including the putamen and caudate nucleus as shown in figure 5 (Buhour et al., 2017; Lillo et al., 2012). Furthermore, cerebellar involvement was evident, with atrophy observed in the dentate nucleus and cerebellar hemispheres as shown in Figures 4 and 5 (Bharti et al., 2020; Qiu et al., 2019).

Figure 4

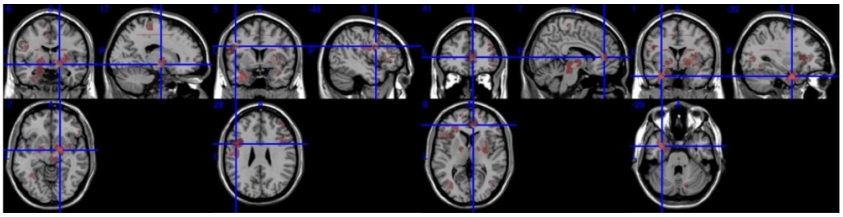
Scans showing structural changes using lesion-mapping on the template brain scan



Note: The image shows an axial-view multislice of overlapping of atrophy in ALS patients (n= 261) contrasted with healthy controls (n= 220).

Figure 5

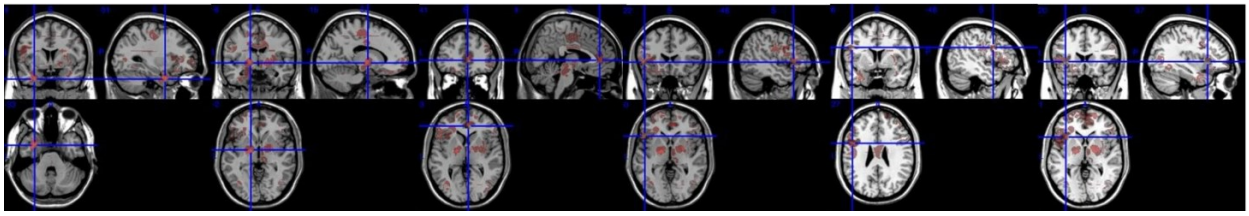
Scans showing structural changes using lesion-mapping on the template brain scan



Note: The images show a multi-axis view of overlapping of atrophy in ALS patients (n= 261) contrasted with healthy controls (n= 220).

Figure 6

Scans showing overlapping of atrophy and functional connectivity using lesion-mapping on the template brain scan



Note: The images show a multi-axis view of overlapping of atrophy and functional connectivity in ALS patients (n=390) contrasted with healthy controls (n= 315).

Functional Connectivity Disruptions: In addition to gray matter atrophy, the overlay analysis revealed functional connectivity disruptions within attention control networks in ALS patients as depicted in Figure 6. Decreased functional connectivity was observed between frontal,

parietal, and subcortical regions involved in attention regulation. For instance, McMackin et al. (2019, 2020) reported dysfunction in the DLPFC, ACC, and parietal regions during an attention-switching task, with altered connectivity patterns observed. Similarly, Trojsi et al. (2021) found impaired hippocampal connectivity with parietal regions, including the precuneus and IPL, in ALS patients, suggesting broader involvement of cognitive networks beyond the traditional frontal-parietal attention control system.

Additionally, the brain regions identified in the overlay analysis showed correlations with impaired performance on attention, executive functioning, and cognitive control, as reported in the original studies (Goldstein & Abrahams, 2013; Lillo et al., 2012; McMackin et al., 2020; Trojsi et al., 2021). For instance, Lillo et al. (2012) found that gray matter atrophy in the frontal and parietal lobes, as well as white matter degeneration in the corpus callosum and frontal/temporal tracts, correlated with poorer performance on tests of executive function, attention, and processing speed in ALS patients. McMackin et al. (2020) demonstrated that the extent of brain network dysfunction during the Sustained Attention to Response Task (SART), particularly in the DLPFC, ACC, and parietal regions, correlated with reduced performance on tests of executive function, attention, and cognitive flexibility in ALS patients. Trojsi et al. (2021) reported that impaired hippocampal connectivity with parietal regions was associated with decreased performance on tests of memory and attention in ALS patients. These findings suggest that the observed patterns of gray matter atrophy and functional connectivity disruptions in frontal, parietal, subcortical, and cerebellar regions could be linked to cognitive dysfunction, particularly in the domain of attention control, in ALS patients.

Discussion

While this study's protocols may be seen as elementary and simple, the outcomes are consistent with earlier findings in the literature, emphasising the role of frontal, parietal, subcortical, and cerebellar regions in the structural and functional changes specifically focused on attention control network deficits in ALS. The atrophy and functional connectivity alterations observed in the dorsolateral prefrontal cortex, ventrolateral prefrontal cortex, and anterior cingulate cortex are particularly noteworthy, as these regions are known to play crucial roles in various aspects of attention control, including selective attention, cognitive flexibility, and inhibitory control (Bressler & Menon, 2010; Corbetta & Shulman, 2002).

The involvement of parietal regions, such as the inferior and superior parietal lobules furthers the support for the hypothesis of a possible deficit in attention control network in ALS.

These areas have been implicated in various attention-related processes, including spatial attention, visual attention, and attentional orienting (Corbetta & Shulman, 2002; Petersen & Posner, 2012). The observed atrophy and functional connectivity disruptions in subcortical structures, such as the thalamus and basal ganglia, align with the role of these regions in attention control and executive functioning.

The present study also highlighted the involvement of the cerebellum in attention control network impairments in ALS patients. While traditionally associated with motor functions, accumulating evidence suggests that the cerebellum plays an important role in cognitive processes, including attention, working memory, and executive functioning (Strick et al., 2009; Timmann & Daum, 2007). The observed atrophy and functional connectivity disruptions in the dentate nucleus and cerebellar hemispheres may contribute to the cognitive deficits observed in ALS patients.

Conclusion

To conclude, the present study's strengths lie in its multimodal approach, combining data from various neuroimaging techniques, and the novel application of direct image lesion-mapping and overlay analysis. This approach allowed for a comprehensive examination of the neural correlates underlying cognitive dysfunction, including attention control deficits, in ALS patients, providing useful insights. The study provides preliminary evidence for the involvement of distributed brain networks, including frontal, parietal, subcortical, and cerebellar regions, in attention control network impairments in ALS patients. The observed structural and functional alterations in these regions could be associated with cognitive deficits, highlighting the potential for these neuroimaging markers to serve as biomarkers and targets for intervention. The direct image lesion-mapping and overlay analysis revealed preliminary overlapping patterns of gray matter atrophy and functional connectivity disruptions in frontal, parietal, subcortical, and cerebellar regions implicated in attention control and executive functioning. These findings support the hypothesis that ALS patients exhibit structural and functional alterations in distributed brain networks associated with cognitive deficits, particularly in the domain of attention control.

Furthermore, it is important to acknowledge some limitations of the study. First, previous studies have used diverse methodologies, leading to mixed results and making it difficult to draw firm conclusions. Second, the analysis was based on data extracted from previously published studies, which may introduce potential biases in data acquisition and analysis which

has resulted in the presence of voxel-lines which could hinder the quality of the study. The use of open-access software MRIcron even though useful, faced the lack of open-access imaging data and comprehensive supplementary data which could be considered as one of the major drawbacks of this study. The lack of individual neuroimaging data for each patient is also a considerable limitation of this study. Future studies should aim to address these limitations by conducting large-scale, open-access, multimodal neuroimaging studies in ALS patients, with a particular focus on attention control and executive functioning. Additionally, combining neuroimaging data with comprehensive neuropsychological assessments and genetic profiling could provide further insights into the underlying mechanisms and potential biomarkers of cognitive impairment in ALS.

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