Cerebellar pathology in motor neuron disease: neuroplasticity and neurodegeneration

Introduction

Amyotrophic lateral sclerosis (ALS) is a relentlessly progressive neurodegenerative condition. While it is primarily characterized by the degeneration of upper and lower motor neurons, ALS is now recognized as a multi-system disorder. Cerebellar pathology in ALS has been demonstrated by a multitude of neuropathology and neuroimaging studies (Prell and Groskreutz, 2013), but its role in the disease process is poorly characterized. Clinical reports of overt cerebellar signs are sparse, frank dysmetria, dysdiadochokinesia and ataxia are rarely reported in ALS (Machida et al., 1999; Schimke et al., 2002; Yasser et al., 2010; De Marco et al., 2015). The clinical assessment of the cerebellum in ALS is notoriously challenging due to coexistent upper and lower motor neuron degeneration. Eye-movement abnormalities, such as nystagmus (Kushner et al., 1984), pursuit (Jacobs et al., 2010) have been consistently described in ALS. Bulbar dysfunction is a pathognomonic feature of ALS (Yunusova et al., 2019) which is often exclusively linked to corticobulbar volume reductions, diffusivity studies readily detect both intra-cerebellar and cerebellar peduncle white matter alterations and functional imaging studies commonly report increased connectivity with supratentorial regions. Increased functional connectivity is commonly interpreted as evidence of neuroplasticity representing compensatory processes despite the lack of post-mortem validation. There is a scarcity of post-mortem studies focusing on cerebellar alterations, but these detect pTOP-43 in cerebellar nuclei. Cerebellar pathology is an overlooked facet of neurodegeneration in amyotrophic lateral sclerosis despite its contribution to a multitude of clinical symptoms, widespread connectivity to spinal and supratentorial regions and putative role in compensating for the degeneration of primary motor regions.

Key Words: amyotrophic lateral sclerosis; ataxia; cerebellum; magnetic resonance imaging; motor neuron disease; neuroimaging; neuroplasticity; pathology; primary lateral sclerosis; pseudobulbar affect

Discussion

Amyotrophic lateral sclerosis is a relentlessly progressive multi-system condition. The clinical picture is dominated by upper and lower motor neuron degeneration, but extra-motor pathology is increasingly recognized, including cerebellar pathology. Post-mortem and neuroimaging studies primarily focus on the characterization of supratentorial disease, despite emerging evidence of cerebellar degeneration in ALS and motor neuron disease. Cardinal clinical features of amyotrophic lateral sclerosis, such as dysarthria, dysphagia, and cognitive and behavioral deficits, saccade abnormalities, gait impairment, respiratory weakness and pseudobulbar affect are likely to be exacerbated by co-existing cerebellar pathology. This review summarizes in vivo and post mortem evidence for cerebellar degeneration in amyotrophic lateral sclerosis. Structural imaging studies consistently capture cerebellar grey matter volume reductions, diffusivity studies readily detect both intra-cerebellar and cerebellar peduncle white matter alterations, functional imaging studies commonly report increased connectivity with supratentorial regions. Increased functional connectivity is commonly interpreted as evidence of neuroplasticity representing compensatory processes despite the lack of post-mortem validation. There is a scarcity of post-mortem studies focusing on cerebellar alterations, but these detect pTOP-43 in cerebellar nuclei. Cerebellar pathology is an overlooked facet of neurodegeneration in amyotrophic lateral sclerosis despite its contribution to a multitude of clinical symptoms, widespread connectivity to spinal and supratentorial regions and putative role in compensating for the degeneration of primary motor regions.

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Results

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Conclusions

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Addendum

Amyotrophic lateral sclerosis (ALS) is a relentlessly progressive multi-system condition. The clinical picture is dominated by upper and lower motor neuron degeneration, but extra-motor pathology is increasingly recognized, including cerebellar pathology. Post-mortem and neuroimaging studies primarily focus on the characterization of supratentorial disease, despite emerging evidence of cerebellar degeneration in ALS and motor neuron disease. Cardinal clinical features of amyotrophic lateral sclerosis, such as dysarthria, dysphagia, and cognitive and behavioral deficits, saccade abnormalities, gait impairment, respiratory weakness and pseudobulbar affect are likely to be exacerbated by co-existing cerebellar pathology. This review summarizes in vivo and post mortem evidence for cerebellar degeneration in amyotrophic lateral sclerosis. Structural imaging studies consistently capture cerebellar grey matter volume reductions, diffusivity studies readily detect both intra-cerebellar and cerebellar peduncle white matter alterations, functional imaging studies commonly report increased connectivity with supratentorial regions. Increased functional connectivity is commonly interpreted as evidence of neuroplasticity representing compensatory processes despite the lack of post-mortem validation. There is a scarcity of post-mortem studies focusing on cerebellar alterations, but these detect pTOP-43 in cerebellar nuclei. Cerebellar pathology is an overlooked facet of neurodegeneration in amyotrophic lateral sclerosis despite its contribution to a multitude of clinical symptoms, widespread connectivity to spinal and supratentorial regions and putative role in compensating for the degeneration of primary motor regions.

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spino-cerebellar tract passes through the inferior peduncle. This peduncle is involved in the maintenance of posture and balance (Fitzgerald et al., 2012). (Figure 1) Neurulation is the process by which the central portion of the ectoderm forms the neural plate which is the origin of the entire nervous system. At week 3 of gestation, the neural plate folds to form the neural tube, which in week 4 undergoes flexion at the region of the mesencephalon, which is the future midbrain. Above the mesencephalon is the prosencephalon, which is the future forebrain and beneath it is the rhombencephalon, which is the future hindbrain. The caudal rhombencephalon develops into the medulla oblongata and the rostral part becomes the pons and cerebellum (Fitzgerald et al., 2012).

The cerebellar function has been traditionally associated with motor control and motor learning, however, physiological role in mediating cognitive and behavioral functions such as executive functions, language, spatial cognition, and mood regulation is also increasingly recognized (Buckner, 2013). The ‘Dysmetria of thought’ theory was coined to denote cognitive and emotional disorders arising from cerebellar pathology (Schmahmann, 1998). Cerebellar lobules are not only activated during motor and sensorimotor task, but during executive, working memory, language, and emotional processing paradigms (Stoodley and Schmahmann, 2009). Cerebellar pathology has been consistently implicated in impaired social cognition (Van Overwalle et al., 2015), pathological crying and laughing (Bede and Finegan, 2018; Finegan et al., 2019a), and language deficits (Runnqvist et al., 2016). Neuropsychological domains that show focal cerebellar activity on cerebellar imaging studies include attention (Allen and Courchesne, 2003), working memory (Desmond et al., 1998), and emotion dysregulation including irritability, disinhibition, and impulsivity has been linked to lesions of the vermis (Levshin et al., 2000). While lesions in the anterior lobe have been primarily linked to motor deficits, pathology of the posterior lobe is associated with cerebellar cognitive affective syndrome, encompassing problems with language, speech, executive and visuospatial functions and emotional affect (Tedesco et al., 2011; Argyropoulos et al., 2020). Evidence is slowly mounting that specific lobules have specific roles in mediating cognitive processes (Stoodley and Schmahmann, 2009; Argyropoulos et al., 2020). Based on the expanding spectrum of physiological roles of the cerebellum and the high number of recently published imaging studies in ALS, the main aim of this review is to summarise cerebellar neuroimaging and post-mortem findings in ALS and other motor neuron disease phenotypes. An additional objective of this manuscript is to examine the evidence for cerebellar neuroplasticity in ALS and link radiological observations to post-mortem findings.

**Search Strategy and Selection Criteria**

A systematic literature search was performed on PubMed using the core search terms “amyotrophic lateral sclerosis”, “primary lateral sclerosis” and “motor neuron disease” combined individually with each of the following keywords as search word pairs: “cerebellum”, “cerebellar”, “magnetic resonance imaging”, “positron emission tomography”, and “post mortem”. Only original research papers were systematically reviewed. Conference abstracts, review papers, opinion pieces, and editorials were excluded. No exclusion criteria were set based on the year of publication. Based on the above criteria, a total of 69 original research papers were identified, selected, and reviewed.

**Results**

**Imaging**

Only two cerebellar studies included pre-symptomatic patients (Menke et al., 2016; Papma et al., 2017). About half of the identified studies collected genetic information, but only 11 studies stratified their ALS cohort by genotype (Tanaka et al., 1993; Canosa et al., 2016; Agosta et al., 2017; Schonecker et al., 2018; Calvo et al., 2019; Abidi et al., 2020). The vast majority of identified studies were cross-sectional with only 4 longitudinal imaging studies describing cerebellar changes (Keil et al., 2012; Menke et al., 2018; Calvo et al., 2019). Sample size limitations are evident in these studies, including only a minority of subjects included in some of the studies investigated on 200 participants and most of these were PET studies (Pagni et al., 2014, 2016; Canosa et al., 2020). The majority of studies were case-control studies, with only a few exceptions. While most studies reported cerebellar atrophy, a handful of studies performed clinical-radiological correlations (Verstraete et al., 2015; Consolli et al., 2019; Sala et al., 2019; Abidi et al., 2020; Canosa et al., 2021b). A minority of studies acquired data on 1.5 Tesla (T) scanners, 3T scanners were most commonly used and only one study collected data on a 7T platform (Barr et al., 2021). Over half the studies assessed multiple imaging parameters.

**Grey matter alterations**

While the cerebellar imaging data are characteristically challenging to quantitatively interpret, novel pipelines have been developed to evaluate infratentorial structures. Cerebellar changes are often observed on cere-
describe hypometabolism (Calvo et al., 2019), the majority of PET studies identify cerebellar hypermetabolism in ALS (Cistaro et al., 2012; Canosa et al., 2016; Matías-Guiu et al., 2016; Buhour et al., 2017), both in spinal-onset diseases and in bulbar-onset (Sala et al., 2019, 2020), as well as in ALS-FTD (Canosa et al., 2020). The reports are conflicting, with another study reporting (Additional Table 3).

Post-mortem findings
While cerebellar changes are seldom evaluated specifically, cerebellar pathology is readily observed post-mortem (Ishihara et al., 2006; Kobayashi et al., 2011). UBOQN-positive cytoplasmic inclusions in the cerebellar granular layer and Purkinje cell layer (Ohmura et al., 2011), neurofibrillary tangles (Yokota et al., 2006), and neuronal and glial TDP-43 pathology have been consistently described (Geser et al., 2008). Cerebellar degeneration has been linked to bulbar ALS (Shelliikeri et al., 2017), but other studies do not identify significant cerebellar alterations in ALS (Tu et al., 1996; Additional Table 4). p62 positive, p-TDP-43 negative neuronal intranuclear inclusions (Rohrer et al., 2011) have been observed in C9orf72 and the severity of cerebellar changes depends on repeat expansion (van Blitterswijk et al., 2013). In PLS, cerebellar involvement is clearly established. Some studies observed ballooning of dendrites in molecular and Purkinje cell layers of the cerebellum (Sughrue et al., 1999), and dentate nucleus degeneration (Kao et al., 2020), while others found no significant changes (Engel and Gurnon, 2000).

Animal models
With few exceptions (Aguirre et al., 2005), animal models of ALS also exhibit cerebellar pathology. In SOD1(G93A) transgenic mice, PARP-immunoactive astrocytes (Chung et al., 2004) and pERK-immunoactive astrocytes (Chung et al., 2005) were observed in cerebellar nuclei. Reduced tau-miRNA expression was noted in the cerebellum of SOD1(G93A) transgenic mice (D’hont et al., 2007). Increased cerebellar TRPV4 expression (Lee et al., 2012) and enhanced LOX gene expression (Li et al., 2004) have also been shown. Cerebellar atrophy and Purkinje cell degeneration which were also observed in MATR3 SBSC knock-in mice (Kao et al., 2020), C9orf72 mice (Chew et al., 2015) as well as in SOD1 mice (Li et al., 2004).

Discussion
Neuroimaging and post-mortem infratentorial pathology in ALS
It is increasingly recognized that symptomatic manifestation in ALS is preceded by a long pre-symptomatic phase (Eisen et al., 2014b; Schuster et al., 2015), and to clarify the role of the cerebellum in the pathogenesis and verify proposed compensatory processes, more pre-symptomatic imaging studies are needed for a better evaluation (Ainsworth et al., 2018a, b). Cerebellar pathology and symptomatic disease burden in specific cerebellar lobules (Consonni et al., 2019; Barry et al., 2019) and hypometabolism (Carlsen et al., 2020) have also been shown.

Both increased (Qiu et al., 2019) and decreased grey matter volumes have been reported, both increased (Agosta et al., 2011; Zhou et al., 2013; Menke et al., 2016; Abidi et al., 2021) and reduced functional cerebro-cerebellar connectivity was found (Pascual-Leone et al., 2010), cerebellar hypometabolism (Canosa et al., 2016; Matías-Guiu et al., 2016; Buhour et al., 2017) and hypometabolism (Calvo et al., 2019) have been observed. Very few imaging studies assessed directly how different cerebellar lobules (Consonni et al., 2018; Kim et al., 2017; Bede et al., 2021a, Bede et al., 2021b) and cerebellar nuclei (Bharti et al., 2020) or the activation shift from primary motor areas to the cerebellum (Konczak et al., 2010) and adapt to extra-cerebellar pathologies (Mitoma et al., 2013; Proudfoot et al., 2018). The cerebellum in particular is thought to be a key component of the nervous system to adapt to insult and compensate for injury (Villamar et al., 2012). Effective neuroplasticity has been demonstrated in a multitude of neurological conditions such as traumatic brain injury (Kumar et al., 2012), stroke (Dimyan and Cohen, 2011), multiple sclerosis (Straudi and Basaglia, 2017), Alzheimer’s disease (Herholz et al., 2013) and spinal cord injury (Hutson and Di Giovanni, 2019), and similar adaptive mechanisms have also been observed in ALS (Bae et al., 2016; Prell and Grosskreutz, 2013, 2014) and overlapping clinical, radiological, and genetic features with ALS (Tanaka et al., 2014). After the initial processing of the injury, there is a notion that neural networks underlying pathogenically “recent” skills, such as fine motor skills, vocalization, ambulation, etc. are particularly vulnerable to ALS (Eisen et al., 2014a; Eisen and Bede, 2021), which may explain why cerebellar alterations, which are associated with C9orf72 carriers, remain to be elucidated. It is also unfortunate that large imaging studies of well-characterized patients do not typically offer complementary post-mortem analyses to interpret their ante-mortem imaging findings.

A multitude of functional magnetic resonance imaging studies showed increased cerebellar activation when performing motor tasks (Konrad et al., 2012; Prell and Grosskreutz, 2013), and resting-state functional magnetic resonance imaging studies often reveal increased cerebro-cerebellar connectivity (Agosta et al., 2011; Zhou et al., 2013; Menke et al., 2016; Abidi et al., 2021). These two observations are interpreted as the compensatory shift from motor cortex degeneration despite the lack of supporting structural findings and compelling post mortem evidence. Neuroplasticity is an intrinsic property of the nervous system, allowing the system to reorganize which may be impaired following injury, as these associations remain to be elucidated.

Cerebellar findings in related neurodegenerative conditions
The link between ALS and FTD is increasingly accepted based on shared clinical, genetic, and imaging features (Ömer et al., 2017; Christidi et al., 2019). Frontotemporal dysfunction related to FTD pathogenesis may be the reason for the heterogeneous in ALS and the concept of an ALS-FTD spectrum or continuum is now widely accepted. Cerebellar changes have been consistently described in GGGGCC hexanucleotide repeat carriers in C9orf72 (Mahoney et al., 2012; Rohrer et al., 2012, 2015; Bede et al., 2015). While comorbid FTD was once primarily associated with hexanucleotide repeats, recent data have shown that frontotemporal degeneration is not exclusively caused by C9orf7 repeat expansions in ALS (Westeneng et al., 2016). Cerebellar changes have also been reported in carriers of large and small hexanucleotide expansions (Bocchetta et al., 2016) for example, preferential vermis atrophy was described in MAPT carriers (Bocchetta et al., 2016). Other cerebellar studies of FTD stratified their patients by the clinical phenotype (Gellersten et al., 2017; Chen et al., 2018, 2019; McKenna et al., 2021) and associations were identified between cerebellar pathology and performance in specific cognitive domains such as attention, working memory, visuospatial skills, and language (Chen et al., 2018, 2020). Lobule VI, VIIb, VIIIb atrophy was also associated with olfactory dysfunction in svPPA and an olfactory loss in a semantic variant primary progressive aphasia (svPPA) (Chen et al., 2019). Cerebellar grey matter atrophy was captured pre-symptomatic C9orf72 carriers (Cash et al., 2018) and ALS-FTD (Bocchetta et al., 2020) and overlapping clinical, radiological, and genetic features with ALS (Bede et al., 2019; Finegan et al., 2019b, c). Very few imaging studies have specifically focused on structural changes in ALS with other neurodegenerative atypical C9orf72 variant carriers (Finegan et al., 2021), dentato-rubro-thalamo-cortical and spino-cerebellar tract diffusivity changes (Tu et al., 2019) and increased functional connectivity were reported between the cerebellum and cortical motor, frontal and temporal areas (Meoed et al., 2015). PLS patients with dementia and cognitive deficits are thought to exhibit fractional anisotropy reductions and
increased radial diffusivity in cerebellar white matter (Canu et al., 2013). In spinal muscular atrophy preferential lobule VIIIB, IX and X atrophy has been observed without notable correlations with clinical metrics (de Borba et al., 2017). The spastic paraplegic paradigm of ALS or PLS is also associated with considerable cerebellar grey and white matter degeneration (Orlacchio et al., 2004; Seidel et al., 2009; Lindig et al., 2015; Thal et al., 2015; Olivieri et al., 2019; Servele et al., 2021). Subcortical cerebellar atrophy is also commonly observed in spinal and bulbar muscular atrophy or Kennedy's disease which is an X-linked recessive, slowly progressive, LMN-predominant motor neuron disease (Pieper et al., 2013; Pradat et al., 2020). Interestingly, cerebellar integrity metrics are typically worse in ALS patients compared to healthy controls (Li Hi Shing et al., 2021b), which is often regarded as evidence of neuroplasticity and compensation for longstanding spinal anterior horn insult (Li Hi Shing et al., 2021a, c).

**Clinical relevance**

Though woefully understudied in ALS, cerebellar pathology is thought to contribute to pseudobulbar affect (Foester et al., 2014; Finegan et al., 2019a), cognitive deficits (Consonni et al., 2019; Bede et al., 2021a), behavioral dysfunction (Bae et al., 2016; Canosa et al., 2021b), bulbar symptoms (Sala et al., 2019; Yunusova et al., 2019), respiratory problems (Xu and Frazier, 2002), gait and balance abnormalities (Sala et al., 2009; De Michele et al., 2010) and eye movement abnormalities (Jensen et al., 2019). The role of the cerebellum in mediating cognitive, and behavioral processes is increasingly well established (Van Overwalle et al., 2015; Guo et al., 2016; Schmahmann, 2019; Argyropoulos et al., 2021). Multi-time point longitudinal studies have shown that both corticospinal tracts and the corpus callosum are involved very early in the disease process (Schuster et al., 2016b; Bertrand et al., 2018; Querin et al., 2019a; Wen et al., 2019), whereas cerebellar changes exhibit a pronounced overlap with the later disease phases (Menke et al., 2018). Regions that are affected early in the disease process may help diagnostic or prognostic classification (Schuster et al., 2016a; Querin et al., 2018, 2021). Furthermore, the cerebellum itself is a progressive organ where the later disease phases are better suited as tracking biomarkers (Schuster et al., 2015; Chipka et al., 2019). It is noteworthy that commonly used image analysis suites which evaluate cortical thickness profiles, such as FreeSurfer, offer only such surface-based analyses. Therefore many longitudinal ALS studies using this software do not evaluate cerebellar changes at all (Tahedl et al., 2021a). The prevailing clinical understanding of ALS-associated disability is overwhelmingly centered in UMNLMN degeneration and the wide variation in the manifestation of cerebellar pathology would also inform and refine disability is overwhelmingly centered in UMN/LMN degeneration and the new creations are licensed under the identical terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms. Additional files:

**Additional Table 1:** A selection of grey and white matter studies investigating cerebellar pathology in motor neuron disease.

**Additional Table 2:** A selection of functional magnetic resonance studies evaluating cerebellar pathology in amyotrophic lateral sclerosis; functional magnetic resonance imaging & spectroscopy.

**Additional Table 3:** A selection of positron emission tomography studies commenting on cerebellar pathology in amyotrophic lateral sclerosis.

**Additional Table 4:** A selection of post mortem studies describing cerebellar pathology in amyotrophic lateral sclerosis.

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Table 1 A selection of grey and white matter studies investigating cerebellar pathology in motor neuron disease

| Study                  | Study participants (n, patients/HCs) | Methodology                                      | Clinical assessments       | Main findings                                                                 |
|------------------------|--------------------------------------|-------------------------------------------------|---------------------------|-------------------------------------------------------------------------------|
| Bede et al., 2021d     | 161/110                              | Structural (volumetry, cortical thickness), diffusion (DTI) | ALSFRS-r, cerebellar assessment | -Cerebellar pathology confined to lobules I-V of anterior lobe in patients with sporadic ALS  
  -Considerable posterior lobe and vermis disease burden identified in C9orf72 mutation carriers  
  -Patients with intermediate ATXN2 expansions did not exhibit significant cerebellar pathology |
| Baek et al., 2020      | 96/47                                | Diffusion (DTI)                                 | ALSFRS-r                  | -Significant differences between ALS and healthy controls in cerebellar peduncle |
| De Marchi et al., 2020 | 41/0                                 | Diffusion (DTI)                                 | ALSFRS-r, FVC, MMSE, RCPM, Cognitive Estimates Test, FAB, Clock Drawing Test, Digit Span test, Short Story Test, Trail Making A-B Test, Attentive Matrices, verbal fluency and comprehension, NPI | - Significant FA reduction and ADC increase in all selected regions including cerebellar peduncle |
| Consonni et al., 2019  | 66/28                                | Structural (cortical thickness, cortical volume) | ALSFRS-R, phonemic fluency index, object naming, SET, stroop, RAVLT, FBI | -Disease severity correlated with cerebellar cortical volume reduction in anterior lobules  
  -Decreased cerebellar cortical volume in posterior lobules related to cognitive impairment |
| Qiu et al., 2019       | 60/60                                | Structural (VBM), diffusion (DTI)                | ALSFRS-r, MOCA            | -ALS patients have increased GMV in bilateral cerebellum  
  -Decreased FC in cerebellum anterior lobe |
| Tu et al., 2019        | 19/17                                | Diffusion (DTI)                                 | ALSFRS-r                  | -Significant alterations across diffusion metrics in the DRTC proximal to the motor cortex were found in both ALS and PLS patient groups  
  -PLS patients have independent diffusion abnormality in cerebellar region of DRTC and SC tracts |
| Bede and Hardiman, 2018| 32/69                                | structural (VBM, cortical thickness), diffusion (DTI) | ALSFRS-r                  | -Gradually progressive cerebellar grey matter degeneration throughout three time-points |
| Study                        | Sample Size | Imaging Techniques | Neuropsychological Tests | Findings                                           |
|------------------------------|-------------|--------------------|--------------------------|---------------------------------------------------|
| Christidi et al., 2018c      | 56/25       | structural (VBM), diffusion (DTI) | ALSFRS-r, CNS-LS, ADI-12, ADI-12, neuropsychological assessment | -WM abnormalities detected in WM associative and ponto-cerebellar tracts |
| Christidi et al., 2018e      | 50/25       | structural (VBM), diffusion (DTI) | ALSFRS-r, MMSE, TMT, SNST-CWIS, WCST, RAVLT, BSRT, RCFT, WAIS, Age-Scale Score | -Reduced GMV in cerebellar areas in ALS -Reduced GMV in cerebellum in ALS-Plus |
| Christidi et al., 2018d      | 17/22       | structural (VBM), TMS | ALSFRS-r | -Decreased GM density in cerebellar regions in ALS |
| Feron et al., 2018           | 31/14       | Structural (VBM, volumetry) | ALSFRS-R, MRC, Ashworth scale, Berg Balance scale, CVLT, Stroop, verbal fluency test, WCST, forward and backward digit span, computational gait analysis | -No cortical changes in the cerebellum |
| Menke et al., 2018           | 16/0        | Structural (VBM), diffusion (DTI), functional (rsfMRI) | ALSFRS-r, UMN score, ACE-R | -Progressive DTI changes -Increased RD, AD, MD in cerebellum |
| Schoenecker et al., 2018     | 58/19       | Structural (volumetry) | MMSE, FTD-CDR-SOB | -No significant atrophy of cerebellar regions |
| Agosta et al., 2017          | 86/22       | Structural (cortical thickness, volume), diffusion (DTI), functional (rsfMRI) | ALSFRS-r, UMN score, MMSE, RPCM, Phonemic fluency, Semantic fluency, Digit span backward, Cognitive estimation task, WCST, Weigl test, Digit span forward, Rey's list immediate recall, Rey's list delay recall, Oral noun confrontation naming | -C9orf72 patients showed cerebellar and thalamic atrophy |
| Study                          | Test/Procedure Details | Tests/Measurements                                                                 | Findings                                                                                                                                                                                                 |
|-------------------------------|------------------------|-----------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Kim et al., 2017              | 47/28                  | structural (VBM)  
ALSFRS-R, contrasting program go, no-go test, category verbal fluency test (animal item), phonemic fluency test, Stroop test color reading and backward digit span test, forward digit span test, K-BNT, auditory comprehension test, calculation, RCFT, SVLT, Korean HVLT, K-MMSE, CDR, Caregiver-Administered Neuropsychiatric Inventory | -ALSci group show decreased volume in the left cerebellum compared to healthy controls  
-ALSci show decreased brain volume in the bilateral cerebellum compared to pure ALS                                                                 |
| Papma et al., 2017            | 18/15                  | structural (VBM), diffusion (DTI)  
Neuropsychological tests                                                                 | -C9orf72RE carriers above 40 years of age, have grey matter volume loss in cerebellum                                                                                                           |
| Bae et al., 2016              | 42/37                  | Structural (VBM), diffusion (DTI), TMS  
ALSFRS-r, ACE-R, CBI-R                                                                 | -More grey-matter changes in the cerebellum in ALS compared to controls  
-In bvFTD, severe degenerative changes observed in the cerebellum                                                                                                                                   |
| Trojsi et al., 2015           | 54/18                  | Structural (VBM), diffusion (DTI)  
ALSFRS-R, ACE-R, FrSBe, UMN score, FVC                                                                 | -ALS patients had decreased FA and increased MD and RD in left cerebellar hemisphere and brainstem precerebellar nuclei                                                                          |
| Bede et al., 2014             | 27/42                  | Structural (cortical thickness), diffusion (DTI)  
ALSFRS-r                                                                 | -Higher FA in association with male gender in cerebellum                                                                                                                                          |
| Bede et al., 2015             | 36/42                  | Diffusion (DTI)  
0                                                                 | -FA and RD also captured diffusivity differences in the cerebellum  
-Bilateral symmetrical cerebellar white matter pathology detected in C9orf72 negative cohort  
-C9orf72 positive patients have reduced AD, MD and RD in comparison to C9orf72 negative patients                                                                                           |
| Floeter et al., 47/0          | Diffusion (DTI)  
ALSFRS-r, MDRS-2.  
Patients with PBA had increased MD of WM tracts underlying middle cerebellar |


| Year   | Study                                | Methods                                                                 | Measures                                      | Results                                                                 |
|--------|--------------------------------------|-------------------------------------------------------------------------|-----------------------------------------------|-------------------------------------------------------------------------|
| 2014   | Hartung et al., 2014                 | Diffusion (VBI)                                                        | ALSFRS-r                                      | -Widespread WM intensity increases in cerebellum                        |
|        | McCluskey et al., 2014               | Structural (VBM), diffusion (DTI)                                       | clinical assessment, ALSFRS-r                 | -Greater cerebellar disease in ALS-plus patients                         |
|        | Bede et al., 2013                    | Structural (cortical thickness, VBM), diffusion (DTI)                   | Executive function, letter fluency, category fluency, attention, memory, language, visuospatial skills, and behavioral domains | -WM changes in C9orf72 negative group confined to corticospinal and cerebellar pathways |
|        | Keil et al., 2012                    | Diffusion (DTI)                                                        | ALSFRS-r, MMSE, FAB, SF36                    | -Reduced FA in cerebellum in ALS                                        |
|        | Prudlo et al., 2012                  | Diffusion (DTI)                                                        | ALSFRS-r                                      | -Widespread white matter changes in all fibre groups of the brain including cerebellum |
|        | Minnerop et al., 2009                | Structural (VBM), relaxometry (VBR)                                    | 0                                             | -Reduced WM in right middle cerebellar peduncle                          |
|        | Kassubek et al., 2005                | Statistical parametric mapping (SPM) and VBM                           | NA                                            | -White matter alterations in cerebellum                                  |

ACE-R: Addenbrooke's cognitive examination score; AD: axial diffusivity; ADC: apparent diffusion coefficient; ALS: amyotrophic lateral sclerosis; ADI-12: ALS-depression inventory; ALS-FTD: amyotrophic lateral sclerosis and frontotemporal dementia; ALS-SCI: amyotrophic lateral sclerosis with cognitive impairment; ALSFRS-r: revised amyotrophic lateral sclerosis functional rating scale; ATXN2: Ataxin 2 gene; BADA: batteria per l'analisi del deficit afasico; BDI-2: Beck depression inventory-II; BSRT: Babcock story recall test; bvFTD: Behavioral variant frontotemporal dementia; C9orf72: chromosome 9 open reading frame 72 gene; CBI-R: Cambridge behavioural inventory revised; CDR: clinical dementia rating; CNS-LS: center of neurologic study lability scale; CVLT-II: California verbal learning test II; DRTC: dentato-rubro-thalamo-cortical; DTI: diffusion tensor imaging; FA: fractional anisotropy; FAB: fronto-occipital atrophy; FBI: frontal behavioral inventory; FC: functional connectivity; FrSBe: frontal systems behavioral evaluation; FTC-CDR-SOB: FTD modified clinical dementia rating scale; MMSE: mini mental state exam; MOCA: Montreal cognitive assessment; MRC: the medical research council score; NPI: neuropsychiatric inventory; PBA: Pseudobulbar affect; PLS: primary lateral sclerosis; RAVLT: Rey auditory verbal learning test; RCF: Rey’s complex figure test-immediate recall; RD: radial diffusivity; RPCM: Raven’s progressive colored matrices; rsfMRI: resting state functional magnetic resonance imaging; SC: spino-cerebellar; SET: story-based empathy task; SF36: 36-item short form health survey; SNST-CWIS: stroop neuropsychological screening test-color word interference score; SPM: statistical parametric mapping; SVLT: Seoul verbal learning test.
TMS: transcranial magnetic stimulation; TMT: trail making test; UMN: upper motor neuron; VBM: voxel based morphometry; VBR: voxel-based relaxometry; WAIS: Wechsler adult intelligence scale; WCST: Wisconsin card sorting sest; WM: white matter.
Table 2 A selection of functional magnetic resonance studies evaluating cerebellar pathology in amyotrophic lateral sclerosis: functional magnetic resonance imaging & spectroscopy

| Study                  | Study participants (n, patients/HCs) | Methodology                  | Clinical assessments                                           | Main findings                                                                                                                                                                                                 |
|------------------------|--------------------------------------|------------------------------|----------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Abidi et al., 2021     | 31/14                                | Structural, functional (fMRI) | ALSFRS-r, CVLT II, Stroop, Verbal fluency test, WCST, digit span, MIQ-rs | -UMN predominant ALS patients show increased cerebellar signal during imagined locomotion  
-Increased effective connectivity of striato-cerebellar and parieto-cerebellar circuits may represent compensatory process                                                                                           |
| Barry et al., 2021     | 12/9                                 | Functional (fMRI)            | ALSFRS-R, SVC, quantitative muscle strength test using hand-held dynamometry | -Disruption in long range functional connectivity between superior sensorimotor cortex and bilateral cerebellar lobule VI                                                                                         |
| Abidi et al., 2020     | 31/14                                | Structural, functional (fMRI) | ALSFRS-r, CVLT II, Stroop, Verbal fluency test, WCST, digit span | -Increased cerebellar activation in UMN predominant ALS patients in comparison to healthy controls and LMN predominant ALS  
-Increased effective connectivity between cerebellum and caudate  
-Decreased connectivity between SMA and cerebellum when performing self-initiated movement  
-UMNp patients, a positive correlation detected between clinical variables and striato-cerebellar connectivity                                                                                   |
| Bharti et al., 2020    | 71/56                                | Structural, functional (rsfMRI), diffusion tensor imaging (DTI) | ALSFRS-r, ECAS, finger tapping, foot tapping, UMN burden | -No dentate nucleus (DN) volumetric changes  
-DN rsFC correlated with WM abnormalities at superior cerebellar peduncle  
-Altered cerebellar rsFC connectivity with motor and extra-motor regions in ALS & impaired rsFC likely due to observed cerebellar peduncular WM damage                                                                 |
| Hu et al., 2020        | 42/21                                | Structural (VBM), functional (rsfMRI) | ALSFRS-r, ACER-R | -Alterations of ReHo in the right inferior cerebellar area in ALS with cognitive impairment                                                                                                                   |
| Trojsi et al., 2020    | 32/21                                | Structural (VBM), functional (rs-fMRI), diffusion (DTI) | ALSFRS-r, MMSE, ECAS, digit span, Stroop, fluency, RAVLT-immediate and delayed recall, RCPM, HADS, ALS-FTD-Q | -Reduced functional connectivity between bilateral hippocampus, bilateral parahippocampal gyri and cerebellum in ALS patients                                                                                   |
| Menke et al., 2021     | 24/12                                | Structural (VBM), diffusion  | ALSFRS-R | -FC between cerebellum and a network comprising precuneus, cingulate & middle                                                                                                                               |
| Year    | Sample | Methodology | Outcome                                                                 |
|---------|--------|-------------|-------------------------------------------------------------------------|
| 2016    | Zhou et al., 2016 | 43/44 Functional (rsfMRI) ALSFRS-r | - ALS patients showed significant increase of DC in the left cerebellum posterior lobes & bilateral cerebellum crus in comparison to controls |
| 2013    | Fekete et al., 2013 | 40/30 Functional (rsfMRI) ALSFRS-r | - Widespread alterations in motor functional connectivity including in cerebellum |
| 2013    | Zhou et al., 2013 | 12/12 Functional (rsfMRI) ALSFRS-r | - Increased FC between bilateral superior parietal lobule and right anterior inferior cerebellum found to be correlated with disease severity |
| 2011    | Agosta et al., 2011 | 26/15 Functional (rsfMRI) ALSFRS-r, MRC score | - Significantly increased functional connectivity between left SMC and right cingulate cortex, parahippocampal gyrus, and cerebellum-crus II |
| 2006    | Han and Ma, 2006 | 15/15 Functional (fMRI) NA | - Activation areas in ipsilateral cerebellum significantly larger in ALS in comparison to HCs |
| 2006    | Konrad et al., 2006 | 10/10 Functional (fMRI) 0 | - Activation increase observed in the cerebellum |
| 2005    | Schoenfeld et al., 2005 | 6/6 structural, functional (fMRI) ALSFRS-R, motor task | - Difficulty-related activity in the left cerebellum observed in patients |
| 1997    | Gredal et al., 1997 | 10/8 spectroscopy (MRS) NA | - Concentration of NAA in the cerebellum unaltered in MND patients |
| 1993    | Tanaka et al., 1993 | 13/13 regional cerebral blood flow (rCBF) and oxygen metabolism (rCMRO2) NA | - Significant reduction in the mean rCBF was also found in the cerebellar hemispheres in progressive dementia with ALS |

ACE-R: Addenbrooke's cognitive examination score; ALS: amyotrophic lateral sclerosis; ALS-FTD-Q: amyotrophic lateral sclerosis-frontotemporal dementia-questionnaire; ALSFRS-r: revised amyotrophic lateral sclerosis functional rating scale; CVLT-II: California verbal learning test II; DC: degree centrality; DN: dentate nucleus; DTI: diffusion tensor imaging; ECAS: edinburgh cognitive and behavioural ALS screen; FC: functional connectivity; fMRI: functional magnetic resonance imaging; HADS: hamilton depression rating scale; HC: healthy control; LMN: lower motor neuron; MIQ-rs: movement imagery questionnaire revised 2nd version; MMSE: mini mental state exam; MRC: the medical research council score; NAA: N-acetylaspartate; RAVLT: Rey auditory verbal learning test; rCBF: regional cerebral blood flow; ReHo: regional homogeneity; RPCM: Raven’s progressive colored matrices; rsfFC: resting-state functional connectivity; rsMRI: resting state functional magnetic resonance imaging; SMA: supplementary motor area; SVC: slow vital capacity; UMN: upper motor neuron; VBM: voxel based morphometry; WCST: Wisconsin card sorting test; WM: white matter.
| Study                        | Study participants (n, patients/HCs) | Methodology                          | Clinical assessments                                                                 | Significant findings                                                                 |
|-----------------------------|--------------------------------------|--------------------------------------|--------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|
| Canosa et al., 2021b        | 165/0                                | F-FDG PET                            | FrsBe                                                                                | -FrsBe apathy before-after gap positively correlated with cerebellar and pontine clusters |
| Canosa et al., 2021a         | 111/40                               | 18F-FDG-PET                          | ALSFRS-r, ECAS                                                                       | -Negative correlation between medial frontal cluster and cerebellum found in ALS patients may reflect cerebellar compensation |
| Canosa et al., 2020          | 274/0                                | 18F-FDG-PET                          | ALSFRS-r, MMSE, The Letter and Category Fluency Test, FAB, Digit Span Forward and Backward, The Trail-Making Test (TMT) A and B, RAVLT, BSRT, ROCF, RPCM (CPM47) | -ALS-FTD patients showed cerebellar relative hypermetabolism                           |
| Calvo et al., 2019           | 101/0                                | Structural, diffusion (DTI), 123I-ioflupane (123I-FP-CIT) SPECT, 18F-FDG-PET18 F-FDG-PET | ALSFRS-R, MRC score, Ashworth scale, neuropsychology battery, MDS-UPDRS               | -ALS-PK patients showed a relative hypometabolism in left cerebellum                  |
| Sala et al., 2019            | 95/0                                 | 18F-FDG-PET                          | ALSFRS-r, cognitive tests                                                            | -Hypermetabolism in cerebellum in both spinal onset and bulbar onset ALS patients -Severity of motor symptoms correlates with cerebellar hypermetabolism in bulbar-onset ALS |
| Buhour et al., 2017          | 37/37                                | Structural (VBM), FDG-PET            | ALSFRS-r, MRC, Muscle Strength Scale; TMT, letter verbal fluency, episodic memory, theory of mind, Mattis | -Hypermetabolism in cerebellum                                                        |
| Canosa et al., 2016          | 170/NA                               | 18F-FDG-PET                          | NA                                                                                  | -Hypometabolism in frontal regions was associated to hypermetabolism in cerebellum    |
| Matias-Guiu et al., 2016     | 18/24                                | F-FDG PET, amyloid-PET with (18)F-florbetaben | ALSFRS-r, ACE-III, MMSE, memory span, visuospatial span (Corsi block-tapping test), TMT, ROCF, Free and Cued Selective Reminding Test, VOSP, Stroop Color-Word Interference Test, letter verbal fluency, category fluency test, Tower of London | -ALS exhibit hypometabolism in frontal area and hypermetabolism in cerebellum compared to healthy controls -Changes in metabolism in cerebellum in ALS with or without cognitive impairment |
| Study                  | Patient Group | Methodology | Result/Findings                                                                 |
|-----------------------|---------------|-------------|--------------------------------------------------------------------------------|
| Pagani et al., 2016   | 259/40        | FDG-PET     | ALSFRS-r                                                                         |
|                       |               |             | - Cerebellar/midbrain component accounted for highest accuracy in separating ALS patients from controls |
| Pagani et al., 2014   | 195/40        | (18)F-FDG-PET | 0                                                                               |
|                       |               |             | - Spinal patients have relative hypermetabolism in the right cerebellum         |
| Cistaro et al., 2012  | 32/22         | F-FDG PET   | Phonological verbal fluency test (FAS), TMT, Stroop, WCST                        |
|                       |               |             | - Highly significant relative increases in glucose metabolism distribution in cerebellum in ALS compared to HC's |
| Ludolph et al., 1992  | 18/NA         | PET         | Neuropsychological assessment                                                    |
|                       |               |             | - No changes seen in cerebellum                                                 |
| Dalakas et al., 1987  | 12/11         | [18F]FDG-PET | 0                                                                               |
|                       |               |             | - Hypometabolism did not extend to cerebellum                                   |

ACE-III: Addenbrooke's cognitive examination III; ALS: amyotrophic lateral sclerosis; ALS-FTD: amyotrophic lateral sclerosis and frontotemporal dementia; ALS-PK: amyotrophic lateral sclerosis with parkinsonian symptoms; ALSFRS-r: revised amyotrophic lateral sclerosis functional rating scale; BSRT: Babcock story recall test; CBI-R: Cambridge behavioural inventory revised; DTI: diffusion tensor imaging; ECAS: Edinburgh cognitive and behavioural ALS screen; F-FDG: [18F]-fluorodeoxyglucose; FAB: frontal assessment battery; FrSBe: frontal systems behavioral evaluation; HC: healthy control; MDS-UPDRS: movement disorders society unified Parkinson’s disease rating scale; MMSE: mini mental state exam; MRC: the medical research council score; PET: positron emission tomography; RAVLT: Rey auditory verbal learning test; ROCF: Rey-Osterrieth complex figure; RPCM: Raven’s progressive colored matrices; SPECT: single-photon emission computerized tomography; TMT: trail making test; VOSP: visual object and space perception battery; WCST: Wisconsin card sorting test.
Table 4 A selection of post mortem studies describing cerebellar pathology in amyotrophic lateral sclerosis

| Study                           | Summary of findings                                                                                                                                   |
|---------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|
| Jones et al., 2021              | HML6 3p21.31c consistently upregulated in ALS in cerebellum tissue                                                                               |
| Yang et al., 2019               | Similar levels of nonphosphorylated TDP-43 were found in all 3 regions (motor cortex, spinal cord, cerebellar vermis) between ALS groups (ALS with repeat expansions in the ATXN2 or C9orf72 genes and sporadic disease) |
| Blitterswijk et al., 2013       | - Repeat lengths in the cerebellum were smaller than those in the frontal cortex and those in blood in C9orf72 symptomatic patients  
                                | - Substantial variation in repeat sizes between samples from the cerebellum, frontal cortex, and blood  
                                | - Longer repeat sizes in the cerebellum associated with survival disadvantage                                                       |
| Brettschneider et al., 2012     | UBQLN pathology showed a highly distinct pattern in ALS and FTLD-TDP cases with the C9orf72 expansion, with UBQLN-positive cytoplasmic inclusions in cerebellar granular layer |
| Kobayashi et al., 2011          | Degeneration in posterior cerebellar tract                                                                                                         |
| Rohrer et al., 2011             | Abundant p62 positive, p-TDP-43 negative neuronal intranuclear inclusions (NIIs) observed in 6 out of 14 cases in the cerebellar granular layer in C9orf72 symptomatic patients |
| Geser et al., 2008              | Neuronal and glial TDP-43 pathology present in multiple areas of the central nervous systems of ALS patients, including cerebellum                          |
| Ishihara et al., 2006           | Severe and widespread degeneration in CNS including in cerebellum                                                                                  |
| Petri et al., 2006              | No disease-specific differences of the mRNA expression of the investigated subunits in cerebellar cortex                                               |
| Yokota et al., 2006             | Neurofibrillary tangles (NFTs) found in cerebellum                                                                                                  |
| Przedborski et al., 1996        | Glutathione peroxidase activity not significantly altered in the cerebellar cortex in ALS compared to controls                                          |
| Plaitakis et al., 1988          | Glutamate levels significantly decreased in all areas investigated (frontal and cerebellar cortex and two areas of spinal cord)                      |

ALS: Amyotrophic lateral sclerosis; ATXN2: Ataxin 2 gene; C9orf72: chromosome 9 open reading frame 72 gene; NFTs: neurofibrillary tangles; TDP-43: TAR DNA-binding protein 43; UBQLN: ubiquilin like.