Clinical and preclinical evidence of somatosensory involvement in amyotrophic lateral sclerosis

Javier Riancho1,2,3 | Lucía Paz-Fajardo4 | Adolfo López de Munaín3,5,6,7

1Service of Neurology, Hospital Sierrallana–IDIVAL, Torrelavega, Spain
2Department of Medicine and Psychiatry, University of Cantabria, Santander, Spain
3Centro de Investigación en Red de Enfermedades Neurodegenerativas, CIBERNE, Instituto Carlos III, Madrid, Spain
4Service of Internal Medicine, Hospital Sierrallana–IDIVAL, Torrelavega, Spain
5Neurosciences Area, Biodonostia Research Institute, San Sebastián, Spain
6Neurology Department, Donostia University Hospital–OSAKIETZA, San Sebastián, Spain
7Neurosciences Department, Basque Country University, San Sebastián, Spain

Correspondence
Javier Riancho MD, PhD, Service of Neurology, Hospital Sierrallana–IDIVAL, Barrio Ganzo, Torrelavega 39300, Spain.
Email: javier.riancho86@gmail.com

Funding information
Institute of Research Valdecilla (IDIVAL), Grant/Award Number: NVAL 16/21

Amyotrophic lateral sclerosis (ALS) is the most common motor neuron neurodegenerative disease. Although it has been classically considered as a disease limited to the motor system, there is increasing evidence for the involvement of other neural and non-neuronal systems. In this review, we will discuss currently existing literature regarding the involvement of the sensory system in ALS. Human studies have reported intradermic small fibre loss, sensory axonal predominant neuropathy, as well as somatosensory cortex hyperexcitability. In line with this, ALS animal studies have demonstrated the involvement of several sensory components. Specifically, they have highlighted the impairment of sensory–motor networks as a potential mechanism for the disease. The elucidation of these “non-motor” systems involvement, which might also be part of the degeneration process, should prompt the scientific community to re-consider ALS as a pure motor neuron disease, which may in turn result in more holistic research approaches.

LINKED ARTICLES: This article is part of a themed issue on Neurochemistry in Japan. To view the other articles in this section visit http://onlinelibrary.wiley.com/doi/10.1111/bph.v178.6/issuetoc

KEYWORDS
amyotrophic lateral sclerosis, clinical, preclinical, sensory disorders

1 | INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is the most common neurodegenerative disease involving motor neurons (MNs) (Riancho, Gonzalo, Ruiz-Soto, & Berciano, 2019). The incidence of ALS ranges between 0.7 and 3 cases per 100,000 habitants and is more frequent among Caucasians (Chio et al., 2013; Riancho et al., 2016). ALS is characterised by progressive muscular atrophy and weakness, which commonly leads to death within 2–3 years after diagnosis, which is usually related to respiratory failure (van Es et al., 2017). Histologically, ALS shows MN loss accompanied by atrophy at both the motor cortex and the anterior horn of the spinal cord, as well as corticospinal tract sclerosis (Zufiria et al., 2016). With the exception of cases related to superoxide dismutase-1 (SOD1) and FUS (fused in sarcoma, a nuclear DNA/RNA binding protein), typically, ALS MNs exhibit intracytoplasmic aggregates of the TAR DNA-binding protein 43 (TDP43), which have been considered the hallmarks of ALS (Riancho et al., 2019).

ALS cases can be divided into familial ALS (fALS) and sporadic ALS (sALS) (Zufiria et al., 2016). fALS cases, which represent 5–10% of total cases, are related to mutations in specific causative genes (C9ORF72, SOD1, TARDBP, FUS), which directly induce MN degeneration (Al Chalabi & Hardiman, 2013). sALS cases are considered to be secondary to the interaction between the individual genetic risk and
environmental conditions. According to this hypothesis, ALS would develop in individuals in whom the sum of genetic risk, ageing and environmental exposure would reach a particular threshold, beyond which specific disease mechanisms would be triggered and subsequently auto-perpetuated (Riancho et al., 2018).

Although fALS represents a small percentage of cases, its study is of great importance because it can help to shed light on the pathogenesis of the disease, both in the familial cases and in the sporadic cases. Although the pathogenesis of ALS has not been fully elucidated yet, our knowledge about disease mechanisms has significantly improved during the last decade. In this context, several crucial cellular pathways, such as gene processing disorders, energetic metabolism, proteostasis, axonal transport, hyperexcitability, or surrounding glial cell disorders, have been associated with degeneration of MNs (Riancho et al., 2019). Regarding hyperexcitability, it was the rationale for the use of riluzole, an anti-glutamate agent approved for the treatment of ALS patients with a modest effect in survival.

In recent years, our paradigm of the disease has also changed, and ALS is now increasingly being considered as a multisystem disease rather than an MN-circumscribed disorder.

From its initial description by Professor Charcot in the 19th century, ALS had been classically considered as a neurodegenerative disease exclusively affecting MNs (van Es et al., 2017). However, during the past few decades, an increasing number of investigations have been published supporting the theory that ALS might not only be a “motor system disease.” In this sense, a non-motor constellation of manifestations, including dysautonomic, Parkinsonian, cognitive, and sensory problems, has been reported in ALS patients (Geser et al., 2009; McCombe, Wray, & Henderson, 2017; Ringholz et al., 2005; Shimizu et al., 2000; Van der Graaff, de Jong, Baas, & de Visser, 2009). Probably, the most reliable evidence for this multisystem involvement came from the identification of the C9orf72 hexanucleotide expansion as a shared pathogenic condition for frontotemporal lobar degeneration (FTLD) and ALS. Currently, we all admit that FTLD and ALS are not two independent disorders but two conditions of the same disease spectrum which, in up to 15% of cases, may occur in the same patient (Ringholz et al., 2005). Furthermore, in ALS patients not meeting FTLD criteria, some degree of cognitive impairment has been reported. In different clinical series, cognitive impairment seems to be present in up to 50% of cases and has been characterised as an unfavourable independent prognostic factor (Chio et al., 2019; Phukan, Pender, & Hardiman, 2007). Cognitive disorders and their relationship with ALS have been extensively studied and reviewed. However, we also consider the sensory manifestations of ALS of great importance (previously reviewed by Tao, Wei, & Wu, 2018), because of two reasons. First, awareness of sensory disturbances might help clinicians to manage patient symptomatology better, in a holistic manner. Second, a better understanding of non-motor symptoms will potentially provide new perspectives for new diagnostic and therapeutic strategies.

In this article, we will review the existing literature, both from clinical and preclinical perspectives, supporting the involvement of the sensory system in ALS patients and trying to incorporate it into the pathogenesis of the disease. For drug/molecular target nomenclature, BJJ’s Concise Guide to Pharmacology has been followed (Alexander et al., 2019).

2 CLINICAL EVIDENCE SUPPORTING THE COEXISTENCE OF SENSORY DISORDERS IN ALS PATIENTS

2.1 Pain and sensory symptomatology in ALS patients

Most clinicians agree that a large proportion of ALS patients have pain or minor sensory symptomatology during the disease (Chio, Mora, & Lauria, 2016; Hammad, Silva, Glass, Sladky, & Benatar, 2007). This has been reported to be particularly frequent in fALS cases, secondary to SOD1 mutations (Abe et al., 1996). The first reports in the literature suggesting some degree of sensory alteration in patients suffering from ALS come from the 1960s, when Fincham and Vanallen (1964) assessed sensory nerve conduction in patients with MN disease.

Globally, up to 20–30% of ALS patients may refer to the occurrence of sensory symptoms, although sensory examination is usually normal in most patients (Hammad et al., 2007). Among sensory symptoms, tingling paraesthesia is the most frequently complaint. Occasionally, objective sensory loss may occur as a part of a MN “plus” syndrome (including paraneoplastic and other complex syndromes) and might precede or follow motor symptoms.

Pain was a mainly neglected symptom in ALS until about 15 years ago (Chio et al., 2016). However, the importance of identification and assessment of pain in patients with ALS cannot be overlooked due to the fact that it has profound detrimental effects on the quality of life of ALS patients (Wallace et al., 2014). Indeed, pain management is considered in the main guidelines of ALS treatment (Miller et al., 2009). The epidemiology of pain in the ALS spectrum has not been fully elucidated yet. There are few systematic studies on pain in patients with ALS, and a few longitudinal studies have reported the frequency of pain to be between 15% and 85% (Chio et al., 2016). Regarding pain characteristics, there is also a great variability in both clinical manifestations and localisation depending on whether the pain represents primary mechanisms or results from the secondary effects of MN degeneration. Primary causes of pain in ALS include pain with neuropathic features, spasticity, and cramps. Among them, cramps are the major cause of pain in a substantial proportion of patients, particularly in those with spinal onset (Caress, Ciarlone, Sullivan, & Griffin, Cartwright, 2016), while spasticity is typically observed at advanced stages. Secondary causes of ALS develop as the disease progresses, and progressive paresis induces immobility and degenerative changes in connective tissue, bones, and joints, leading to musculoskeletal pain. In this context, joint contractures, periscapular arthritis and decubitus ulcers are causes of pain, particularly towards the end of the disease (Chio et al., 2016). Non-invasive ventilation may be another cause of pain in ALS patients for two reasons. The first reason...
is that some patients present poor adaptation to ventilatory devices, while the second possible reason is the fact that non-invasive ventilation is commonly associated with skin lesions on the nasal bridge. In addition, dyspnoea itself is known to activate several nociceptive pathways (Bouvier, Laviolette, Kindler, et al., 1985). Treatment strategies for pain in ALS should be directed to reduce its intensity and, if possible, prevent it from becoming chronic. Pharmacological treatments, sometimes combined with physiotherapy, constitute the main approach for primary types of pain, whereas non-pharmacological strategies are generally indicated for the secondary sources of pain. (Chio et al., 2016).

2.2 | Involvement of sensory components in ALS patients

According to the different components of the sensory pathway, we have divided existing reports into three distinct categories: (a) sensory peripheral nervous system; (b) sensory ascending spinal tracts; and (c) somatosensory cortex (Figure 1). Most relevant studies are summarised in Table 1.

2.2.1 | Sensory peripheral nervous system

The peripheral sensory pathway is made up of different components, including posterior spinal roots, plexus, peripheral nerves, and sensory peripheral receptors.

Two main types of studies have focused on this level of the sensory system. First, there are a large number of studies assessing sensory peripheral nerve conduction, some of which included sural nerve biopsy. Complementarily, other researchers have investigated peripheral sensory receptors, as well as intraepidermal nerve fibres at the skin level. Regarding neurophysiological studies assessing sensory involvement in ALS patients, some important issues that might potentially bias the obtained results should be mentioned. First, the vast majority of reported studies have involved only a small number of participants. Second, as ALS is typically a disease of adults, most of the included patients may also exhibit other co-morbidities such as diabetes (and consequently diabetic polyneuropathy) or cervical myelopathy that might influence both nerve conduction studies and somatosensory evoked potentials, thus behaving as confounding factors. Third, in a high proportion of these studies, ALS patients were not stratified by important parameters such as age, nutritional state,
| Author (year) | Number of patients | Main findings |
|--------------|-------------------|---------------|
| Leads, Pollock, Robertson, Sutherland, and Allpress (1991) | — | Early axonal atrophy, increased remyelination and predominance of smaller fibre diameters. |
| Gregory, Mills, and Donaghy (1993) | 19 ALS | Axonal sensory nerve neuropathy. |
| Hammad et al. (2007) | 103 ALS | Sensory symptoms in 32% of patients. Abnormalities in sural sensory nerve conduction in 27% of patients. Histological abnormalities (loss of large-calibre myelinated fibres, axonal loss, and axonal regeneration) in 91% of patients. |
| Isaacs et al. (2007) | 5 ALS | Sensory neuropathy. Axonal degeneration in sural biopsy. |
| Pugdahl et al. (2007) | 88 sALS | Sensory neuropathy in 22.7% of patients. |
| Luigetti et al. (2012) | 17 ALS | Axonal loss in up to 2/3 of patients. |
| Truini et al. (2015) | 24 ALS (11 bulbar/13 spinal) | Abnormal thermal pain thresholds and reduced intra-epidermal nerve fibre density in spinal onset forms. |
| Isak, Tankisi, Johnsen, Pugdahl, Torvin, et al. (2016) | 18 ALS/31 control | Distal sensory nerve conduction tests evaluating antidromic dorsal sural nerve exhibit a higher sensitivity. |
| Dalla et al. (2016) | 57 ALS | Intra-epidermal nerve fibres reduction. No correlation between intra-epidermal nerve fibres and disease onset/course or disease severity. |
| Isak et al. (2017) | 32 ALS/32 control | No alteration in nerve conduction studies. Histological analysis with abnormal axonal swelling and fibres negative for GAP-43 in ALS. |
| Nolano et al. (2017) | 41 ALS/41 control | Intra-epidermal nerve fibre density reduction, loss of Meissner’s corpuscles, and loss of small blood vessels in ALS. |
| Ren et al. (2018) | 18 ALS/18 controls | Reduction of the intra-epidermal nerve fibre density and loss of Meissner’s corpuscles. TDP43 aggregates in nerve fibres. |
| Matamala et al. (2018) | 28 sALS/28 control | No significant differences in sensory nerve conduction studies. |
| Liu, Zhang, Ding, Song, and Sui (2019) | 150 ALS | Sensory nerve conduction alterations in up to 15% of patients. |
| Cosi, Poloni, Mazzini, and Callieco (1984) | 45 ALS | Pathological slowing along central sensory pathways. Altered amplitude of potentials in some ALS patients. |
| Radtke, Erwin, and Erwin (1986) | 17 ALS | Altered SEPs in 56% of ALS patients. |
| Theys, Peeters, and Robberecht (1999) | 50 ALS | SEP abnormalities in up to 60% of ALS patients. No progression of SEPs abnormalities over 6 months. |
| Simone et al. (2010) | 24 ALS/23 control | Altered LEPs in ALS patients. No correlation between LEP abnormalities, pain intensity, and clinical features. |
| Isak, Tankisi, Johnsen, Pugdahl, Finnerup, et al. (2016) | 18 ALS/31 control | LEP more sensitive to assess sensory disturbances in comparison to SEP (72% and 56%, respectively). |
or disease severity, conditions that could potentially influence the reported results.

With regard to nerve conduction studies, several investigators reported some degree of sensory nerve conduction impairment in ALS patients. One of the earliest studies, performed by Heads et al. (1991), provided evidence of early axonal atrophy, increased remyelination, and a predominance of the small diameter fibres. Importantly, these findings correlated with disease duration (Heads et al., 1991). Not long after, and consistent with these data, another study evaluated sensory nerve conduction in 19 ALS patients, finding significant falls in potential amplitudes with preserved nerve conduction velocities, in comparison to healthy controls (Gregory et al., 1993). Of high interest is the study performed by Hammad et al. (2007), which included 103 patients with a clinical diagnosis of ALS. In their investigation, up to 32% and 27% of ALS patients presented with sensory symptoms and abnormalities in sural sensory nerve conduction studies, respectively. In addition, sural nerve biopsy, which was performed in 22 patients, revealed histological abnormalities in 91% of patients. Such abnormalities included loss of predominantly large-calibre myelinated fibres, accompanied by axonal loss and axonal regeneration (Hammad et al., 2007). Other studies have reported similar rates of sensory nerve conduction disorders in ALS patients, presenting ALS as a multisystem neurodegenerative disorder that might occasionally include some degree of sensory neuropathy (Isaacs et al., 2007; Pugdahl et al., 2007). Interestingly, it has been suggested that distal sensory nerve conduction tests evaluating antidromic dorsal sural nerve and orthodromic medial plantar appear abnormal more often than conventional sensory nerve conduction evaluations (Isak, Tankisi, Johnsen, Pugdahl, Torvin, et al., 2016). More recently, a cohort of 150 Asian ALS patients, with a diagnosis of definite or probable ALS, were retrospectively assessed. Interestingly, the analysis of sensory nerve conduction studies revealed that they exhibited alterations in up to 15% of patients (Liu, Zhang, Ding, Song, & Sui, 2019).

However, published studies evaluating peripheral sensory disturbances are not fully concordant. Opposing results were reported by Matamala et al. (2018). In their investigation, they performed a case-control study involving 28 sALS patients and 28 age-matched controls and evaluated sensory nerve action potentials (Matamala et al., 2018). Another prospective study involving 32 sALS patients and 32 controls who were studied for nerve conduction and sural nerve biopsy did not find specific sensory abnormalities either. However, histological analysis demonstrated abnormal axonal swellings among all ALS patients, which were negative for growth-associated protein 43 (GAP-43), suggesting an insufficiency of regeneration in small sensory nerve fibres (Isak et al., 2017). Another retrospective study including 17 ALS patients who had undergone a sural nerve biopsy reported a significant axonal loss in more than two-thirds of the patients (Luigetti et al., 2012).

### Table 1 (Continued)

| Author (year) | Number of patients | Main findings |
|---------------|--------------------|---------------|
| Cohen-Adad et al. (2013) | 29 ALS/21 control | DTI and MT MRI sequences appeared altered in anterolateral and dorsal segments of spinal cord of ALS patients. |
| Iglesias et al. (2015) | 21 ALS/21 control | Combination of both DTI sequences and SEP identified subclinical sensory defects in up to 85% of ALS patients at early stages of the disease. |
| Somatosensory cortex | | |
| Hamada et al. (2007) | 26 ALS/15 control | Cortical SEPs amplitudes are associated with motor disturbances. Early cortical response appears enlarged in ALS patients at a moderate stage and markedly attenuated in patients with more advanced forms. |
| Mochizuki, Mizutani, Shimizu, and Kawata (2011) | — | Concomitant neuronal loss at primary motor cortex and somatosensory cortex in ALS patients. |
| Zhou et al. (2014) | 12 ALS/12 control | Sensory–motor network impairment is associated with more severe forms of the disease. |
| Shimizu et al. (2018) | 145 ALS/73 control | Larger somatosensory cortical amplitudes in SEPs are an independent factor for poor prognosis in ALS patients. |
| Nardone et al. (2020) | — | Marked disinhibition of somatosensory cortex in ALS patients from year 2 of disease evolution onwards. |

Abbreviations: DTI, diffusion tensor imaging; LEPs, laser evoked potentials; MT, magnetisation transfer; SEPs, sensory evoked potentials.
evaluated the involvement of both sensory and autonomic nervous systems by investigating the presence of TDP43 deposits in skin nerve fibres in patients and control subjects. Regarding sensory disorders, ALS patients showed a significant reduction in intraepidermal nerve fibre density as well as a significant loss in Meissner’s corpuscles (Ren et al., 2018). In addition, in comparison with controls, a large proportion of ALS patient biopsies demonstrated TDP43 deposits in nerve fibres, implying that such deposits could serve as a new biomarker (Ren et al., 2018). In our opinion, these intriguing results should be taken cautiously until replicated by other groups. Importantly, as previously discussed, ALS patients with sensory manifestations have characteristically been associated with mutations in SOD1, which typically do not exhibit TDP43 aggregates (Riancho et al., 2019). However, they are concordant with the results recently published by our group in which we reported abnormal TDP43 aggregates in dermic-derived fibroblasts from sALS patients (Riancho et al., 2020).

The loss of both intra-epidermal nerve fibres and Meissner’s corpuscles had also been reported in another study enrolling 41 sALS patients and 41 matched controls. Intriguingly, these findings were associated with a partial reduction in skin blood vessels and that those abnormalities correlated with disease progression (Nolano et al., 2017). Other authors have also reported intra-epidermal fibre loss in ALS patients but failed to correlate the severity of these findings with disease onset, clinical phenotype, as well as disease course and severity (Dalla et al., 2016). Another study including both spinal and bulbar onset ALS patients demonstrated that spinal, but not bulbar onset patients, exhibited distal small fibre neuropathy consisting of abnormal thermal pain thresholds as well as reduced intra-epidermal nerve fibre density (Truini et al., 2015).

In summary, although there is not full concordance among published reports, most of them agree on the presence of subtle sensory symptoms and signs of predominantly axonal sensory neuropathy in nerve conduction studies. These findings correlated with histological findings that frequently showed a loss of predominantly large-calibre myelinated fibres, as well as some degree of axonal degeneration. These histologically subtle alterations did not often manifest clinically or electrophysiologically. Regarding the assessment of peripheral sensory receptors and intra-epidermal nerve fibres at a dermic level, it seems clear that both are reduced in ALS patients, particularly in the spinal forms of the disease. In favour of its biological plausibility, abnormal TDP43 deposits have been documented in intra-epidermal nerve fibres of ALS patients.

2.2.2 Sensory ascending spinal tracts

Within the spinal cord, sensory tracts ascend through the dorsal (light touch, vibration, and proprioception) and anterolateral (pain and temperature) columns. Sensory evoked potentials (SEPs) constitute a widely used neurophysiological technique to evaluate the transmission of sensory impulses in dorsal spinal columns.

The first reported study assessing SEPs in ALS was performed almost 40 years ago and included 45 patients with the disease (Cosi et al., 1984). The authors reported a pathological slowing of conduction along the central sensory pathways that in some patients was also accompanied by a decreased amplitude response (Cosi et al., 1984). Subsequently, other investigators have reported a similar rate of SEP alterations in ALS patients, ranging from 50% to 60% of cases (Radtke et al., 1986; Theys et al., 1999). Interestingly, SEP differences did not significantly progress over the 180-day follow-up period, thus suggesting that, although frequent at diagnosis, sensory subclinical abnormalities are usually not as rapidly progressive as motor manifestations (Theys et al., 1999). Apart from the standard SEPs, components of late SEPs (N60, P100), which reflect on cortical pathways involved in cognitive–motor functions, were significantly depressed in ALS patients (Sangari, Giron, Marrelec, Pradat, & Marchand-Pauvert, 2018).

In recent years, laser evoked potentials (LEPs) have emerged as a complementary tool to SEPs to evaluate central conduction of the pain stimulus. Several authors have incorporated this technique for sensory assessment of ALS patients. A case–control study including 24 ALS patients and 23 controls concluded that the former exhibited abnormal delayed latencies when compared with healthy subjects, also supporting the presence of degeneration of sensory subcortical structures (Simone et al., 2010). One study combining both SEP and LEPs in 18 ALS patients and 31 controls obtained concordant findings with earlier results, suggesting an impairment of sensory tracts in more than half of the studied patients. Interestingly, LEPs appeared as a more sensitive tool than SEPs to evaluate sensory disturbances in patients with MN disease (72% and 56%, respectively) (Isäk, Tankisi, Johnsen, Pudgahl, Finnerup, et al., 2016).

MRI has also been used to assess spinal sensory tracts in ALS patients. Cohen-Adad et al. (2013) performed the first study in which diffusion tensor imaging (DTI) and magnetisation transfer (MT) were measured in the spinal cord of 29 patients and 21 healthy controls, respectively. Interestingly, in both lateral and dorsal segments of the spinal cord, significant differences between ALS patients and control subjects were detected in DTI and MT sequences, suggesting a subjacent degeneration of the two sensory dorsal and anterolateral tracts (Cohen-Adad et al., 2013). In line with these findings, a complementary investigation examined sensory spinal columns combining DTI sequences at dorsal columns and SEPs after median and ulnar nerve stimulation. Taken together, at early stages of the disease, DTI spinal imaging and SEPs were able to demonstrate that up to 85% of ALS patients had subclinical sensory impairment (Iglesias et al., 2015).

In conclusion, SEPs and LEPs appear as useful tools for evaluating ascending sensory tracts in the spinal cord. In comparison to healthy controls, an important proportion of ALS patients show prolonged nerve conduction latencies with these techniques, thus suggesting some degree of impairment at spinal levels. In this regard, LEPs seem to be a little more sensitive than SEPs in identifying such alterations. Likewise, DTI and MT MRI sequences have demonstrated spinal alterations at both dorsal and anterolateral tracts, reinforcing the concept that although asymptomatic in most cases, sensory ascending tracts frequently exhibit some degree of alteration in ALS patients.
2.2.3 | Somatosensory cortex

The somatosensory cortex constitutes the highest level in the sensory pathway. It comprises the primary somatosensory cortex and the secondary somatosensory cortex. In a simplistic representation, the former would be responsible for processing somatic sensations, while the latter would be responsible for the perception of that sensation. The primary somatosensory cortex is located in the parietal lobe at the postcentral gyrus. It is situated just posterior to the central sulcus adjacent to the primary motor cortex. Interestingly, the somatosensory cortex, particularly its secondary areas, is widely interconnected with other brain areas, including the motor cortex (Brazis, Masdeu, & Biller, 2011).

Based on their close anatomical and functional relationship, Mochizuki et al. (2011) evaluated the number of neurons in the primary motor and somatosensory cortex in ALS patients. Interestingly, the authors described a significant decrease of neurons and Betz cells in both locations, compared with control subjects. In addition, there was a positive correlation between the number of neurons at the motor and the somatosensory cortex, suggesting that interdependent mechanisms may exist between these areas, once neurodegeneration is initiated (Mochizuki et al., 2011). These findings are also supported by isolated clinical cases of ALS patients, in whom "unexplained" parietal lobe atrophy was seen by MRI with disease progression (Shimizu et al., 2020).

Recently, the concept of the "brain connectome" has modified our conception of brain functions. According to this concept, distinct cerebral areas are very extensively interconnected, resulting in different functional networks (Hodge et al., 2016). In this context, to investigate functional coherence within the sensory–motor network, 12 ALS patients were studied by resting state functional MRI (rsfMRI) analysis. After comparing ALS patients with healthy controls, a decreased functional coherence was found at distinct sensory–motor network areas. Intriguingly, sensory–motor network impairment in specific areas, such as right postcentral gyrus–precentral gyrus–superior frontal gyrus, was associated with lower Amyotrophic Lateral Sclerosis Functional Rating Scale Revised scores, suggesting a more severe disease evolution (Zhou et al., 2014).

Somatosensory cortex hyperexcitability is also being considered as a potential biomarker for shorter survival in patients with ALS. This is based on the hypothesis that at a particular point of the disease, somatosensory cortex hyperexcitability might reflect a compensatory mechanism of the sensory cortex for motor disturbances (Hamada et al., 2007). To test this hypothesis, Shimizu et al. (2018) studied a cohort of 145 ALS patients and 73 healthy controls and followed them until death or tracheotomy. Intriguingly, median survival was significantly shorter in patients who had larger somatosensory cortical amplitudes in SEPs. Subsequent multivariate analyses identified a more pronounced N20p–P25p amplitude as an independent prognostic factor (Shimizu et al., 2018). In line with this study, a marked disinhibition of somatosensory cortex in ALS patients from the second year of disease evolution has been recently reported (Nardone et al., 2020).

In addition to the sensory–motor integration at a cortical level, there are also relevant connections between sensory and motor systems at the spinal cord. The dorsal root ganglia (DRG) contain the cell bodies of neurons of the sensory pathway that transmit the somatosensory information from the periphery to the CNS through the dorsal and anterolateral tracts of the spinal cord (Haberberger, Barry, Dominguez, & Matusica, 2019). Apart from transmitting sensory information, proprioceptive sensory neurons are key in modulating motor behaviour by integrating the sensory and motor systems into the CNS. Thus, proprioceptive DRG neurons transmit peripheral information about muscle contractions to lower MNs as a feedback system to generate appropriate motor responses (Imai & Yoshida, 2018). Consequently, in addition to inducing somatosensory disorders, damage to proprioceptive neurons may secondarily contribute to the pathogenesis of motor disturbances in ALS. In contrast to the MNs at the anterior horn, each sensory neuron is wrapped by the cell bodies and laminar processes of several satellite glial cells (SGCs), forming a morphological and functional unit (sensory neuron–SGC units) (Haberberger et al., 2019). SGCs play an important regulatory role in sensory neuron function, particularly in controlling the neuronal microenvironment (Haberberger et al., 2019).

Recently, Sangari et al. (2016) reported an impaired spinal integration of these systems in ALS patients. In their study, transcranial magnetic stimulation (TMS) was applied over the motor cortex to induce motor evoked potential (MEP) in the contralateral triceps. Then, median and ulnar nerve stimulations at wrist level were combined with TMS to evaluate the resulting changes in MEPs. Although there were no differences in MEP recruitment curves between ALS and healthy subjects, MEP threshold was significantly higher in the latter. In addition, although nerve stimuli MEPs increased in both groups, facilitation was stronger in ALS patients. This led the authors to suggest that spinal network properties are likely to compensate for depression ofafferent inputs, thus leading to MN hyperexcitability, which may in turn contribute to excitotoxicity (Sangari et al., 2016).

In summary, an important number of studies support the involvement of somatosensory cortex and sensory–motor networks in ALS patients. Consequently, several studies have pointed to somatosensory hyperexcitability as an independent biomarker of shorter survival.

3 | PRECLINICAL EVIDENCE SUPPORTING THE INVOLVEMENT OF THE SENSORY SYSTEM IN ALS

Complementary to clinical studies, several preclinical studies support some degree of sensory system dysfunction in this disease (Table 2). Most of them have used the transgenic SOD1 mouse model. Up to 20% of fALS cases are due to SOD1 mutations. This gene encodes the SOD1 protein, which is involved in several cellular functions, including the oxidative stress response (Riancho et al., 2019). SOD1 mutations are also the basis of a commonly used transgenic mouse model expressing the human SOD1 gene with the G93A mutation
Gurney et al., 1994). High-copy SOD1G93A transgenic mice have been reported to replicate much of the pathophysiology of human ALS, including progressive MN degeneration, progressive neuromuscular function loss and reduced lifespan (Gurney et al., 1994). Despite the fact that this mouse model is based on a SOD1 familial form of ALS and consequently does not exhibit the cytoplasmic TDP43 aggregates, several authors have highlighted its translational usefulness for the study of sALS (Bosco et al., 2010).

Guo et al. (2009) first studied sensory disturbances in the transgenic SOD1G93A murine model. In their study, transgenic mice were used to explore the sensory system at several levels, including the dorsal roots, dorsal ganglia and posterior column tracts. Interestingly, they concluded that, from a histological perspective, transgenic SOD1 mice exhibited significant damage in the sensory system, which basically consisted of Wallerian-like degeneration in axons of both dorsal root and dorsal funiculus, as well as mitochondrial abnormalities in DRG sensory neurons (Guo et al., 2009). Subsequently, several investigations have focused on distinct levels of the sensory pathway to assess the presence or absence of pathology. On this basis, published studies can be divided into those evaluating pathology at (a) DRG sensory neurons and large sensory conduction fibres, (b) small intra-epidermal sensory fibres, and (c) sensory–motor networks.

### 3.1 DRG sensory neurons and large sensory conduction fibres

Several reports have tried to characterise sensory disturbances in sensory neurons at the DRG and in large sensory peripheral nerves (Figure 2). First, Vaughan et al. (2015) assessed two strains of transgenic mice harbouring mutations in SOD1 (G93A) and in the gene coding for TDP43, TARDBP (A315T), and evaluated retrograde...
axonal transport. Interestingly, the analysis of proprioceptive nerve endings in muscle revealed early disturbances at Ia/II proprioceptive nerve endings in muscle spindles before the motor symptomatic phase had initiated. Intriguingly, in TDP43 transgenic mice, clear sensory abnormalities were evident even in the absence of MN axon lesions (Vaughan et al., 2015). Also, sensory abnormalities have been evaluated in progressive motor neuronopathy (PMN) transgenic mice, characterised by a missense loss of function mutation in the tubulin-binding cofactor E (TBCE). These animals show an aggressive form of motor axon die-back and microtubule loss, similar to that observed in ALS patients associated with mutations in TUBA4A, the gene coding for \( \alpha \)-tubulin 4A, a major constituent of microtubules. Histological analysis showed evidence of sural sensory neuropathy with axonal discontinuities and bead-like spheroids. In addition, transgenic mice showed a marked impairment of microtubule polymerisation in DRG neurons, which were likely to result in a compromised microtubule-based transport in those neurons, thus providing a new potential explanation for the axonal pathology in sensory nerves (Schafer et al., 2017).

Coming back to the SOD1 transgenic mice model, it has been demonstrated that dorsal ganglion sensory neurons accumulate misfolded mutant SOD1 protein. However, this protein accumulation was not associated with endoplasmic reticulum stress, nor did it induce unfolded protein responses. If confirmed, these findings might indicate underlying differential vulnerability mechanisms between anterior horn MNs and sensory neurons in ALS (Taiana et al., 2016). In a related study, Vaughan et al. (2018) characterised mutant TDP43\(^{A315T}\) cultured sensory neurons and compared them with mutant SOD1\(^{G93A}\) and control cultured sensory neurons, respectively. Interestingly, both SOD1 and TDP43 mutant neurons were reported to have slower rates of neurite growth and lesser elaboration of neuritic branches. Mutation-bearing sensory neurons were also more sensitive to the microtubule inhibitor vincristine than control neurons. Interestingly, the analysis of several factors involved in stress responses, such as ATF3 or PERK, demonstrated important differences between SOD1 and TDP43 sensory neurons (Vaughan et al., 2018).

3.2 Small intra-epidermal sensory fibres

Sensory small nerve fibres have also been studied in SOD1 transgenic mice. It has been noted that these mice displayed small fibre pathology with loss of intra-epidermal nerve fibres, reduction of Meissner’s corpuscles and axonal degeneration, which characteristically preceded the disease onset and progressed over time (Rubio et al., 2016; Sassone et al., 2016). Complementarily, the culture of small diameter DRG neurons of mutant mice showed stress features and accumulation of peripherin 56 (a peripherin splice variant), which induced axonal damage because of its dis-assembled light and medium neurofilaments subunits. These important findings suggest a new potential mechanism for small fibre pathology in ALS and reinforce the role of peripherin in the pathogenesis of the disease (Sassone et al., 2016).
3.3 | Sensory–motor networks

Although motor manifestations are the key feature of ALS, several investigators have studied motor networks to elucidate whether degenerative mechanisms initiated at anterior horn MNs or in other cells of these motor circuits. In this context, Held et al. (2019) recently reported a Drosophila SOD1ΔG85R knock-in model. Their results showed that transgenic larvae at early stages exhibited a significant deterioration in motor function that was not associated with a clear degeneration of spinal MNs, thus suggesting that other components within the sensory–motor networks might be altered. Interestingly, a defect in the proprioceptive sensory neurons, which are necessary for the relay of the contractile status of muscles back to the central nerve cord, was identified. Mechanistic approaches suggested that this defect in sensory feedback might be related to the bone morphogenetic protein (BMP) pathway (Held et al., 2019).

Not long after, abnormalities in proprioceptive sensory neurons involved in jaw reflex were reported in SOD1 transgenic mice as another potential target for the disease. These included impaired action potential burst discharge related to sodium channels. Interestingly, other brainstem sensory neurons such as the mechanoreceptive and nociceptive trigeminal ganglion neurons did not exhibit pathological features (Seki et al., 2019).

4 | CONCLUDING REMARKS

Although ALS has been classically considered as a disease circumscribed to the motor system, there is an increasing amount of evidence that other neurological and probably non-neurological systems may also be involved. This also occurs in other neurodegenerative diseases such as Parkinson’s disease in which non-motor symptomatology has been proved to be highly relevant to the pathogenesis of the disease. In this regard, the sensory system has been widely reported to be affected in ALS, in both preclinical and clinical studies. Even though they are not usually described by patients, due to the high heterogeneity of the disease, subtle sensory alterations seem to be present in a subgroup of ALS patients.

Such evidence will probably have a double positive effect. On the one hand, a better understanding of the clinical spectrum of the disease will translate into better care of ALS patients. In contrast, the identification of new, “non-motor”, systems that might also be part of the degeneration should prompt the scientific community to consider ALS as a non-cell-autonomous disease. On this basis, more holistic approaches to research would, hopefully, translate into more successful results.

4.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Harding et al., 2018), and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20 (Alexander et al., 2019).

ACKNOWLEDGEMENT

This study was supported by the Institute of Research Valdecilla (IDIVAL) (Research grant NVAL 16/21).

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

REFERENCES

Abe, K., Aoki, M., Ikeda, M., Watanabe, M., Hira, S., & Itoyo, Y. (1996). Clinical characteristics of familial amyotrophic lateral sclerosis with Cu/Zn superoxide dismutase gene mutations. Journal of the Neurological Sciences, 136, 108–116. https://doi.org/10.1016/0022-510X(95)00314-R

Al Chalabi, A., & Hardiman, O. (2013). The epidemiology of ALS: A conspiracy of genes, environment and time. Nature Reviews Neurology, 9, 617–628. https://doi.org/10.1038/nrneurol.2013.203

Alexander, S. P. H., Cidlowski, J. A., Kelly, E., Mathie, A., Peters, J. A., Veale, E. L., … Davies, J. A. (2019). The Concise Guide to PHARMA- COLOGY 2019/20: Nuclear hormone receptors. British Journal of Pharmacology, 176(Suppl 1), S229–S524.

Besco, D. A., Morfini, G., Karabacak, N. M., Song, Y., Gros-Louis, F., Pasinelli, P., … Brown, R. H. Jr. (2010). Wild-type and mutant SOD1 share an aberrant conformation and a common pathogenic pathway in ALS. Nature Neuroscience, 13, 1396–1403. https://doi.org/10.1038/nn.2660

Bouvier, G., Laviolette, L., Kindler, F., et al. (1985). Dyspnea-pain counter-irritation induced by inspiratory threshold loading: a laser-evoked potentials study. Journal of Applied Physiology, 112, 1166–1173.

Brazis, P., Masdeu, J., & Biller, J. (2011). Localization in clinical neurology (6th ed.). Philadelphia: Lippincott Williams & Wilkins.

Caress, J. B., Ciaroni, S. L., Sullivan, E. A., Griffin L. P., & Cartwright, M.S. (2016). Natural history of muscle cramps in amyotrophic lateral sclerosis. Muscle & Nerve, 53, 513–517. https://doi.org/10.1002/mus.24892

Chio, A., Logroscino, G., Traynor, B. J., Collins, J., Simeone, J. C., Goldstein, L. A., & White, L. A. (2013). Global epidemiology of amyotrophic lateral sclerosis: A systematic review of the published literature. Neuroepidemiology, 41, 118–130. https://doi.org/10.1159/000351153

Chio, A., Moglia, C., Canosa, A., Manera, U., Vasta, R., Brunetti, M., … Calvo, A. (2019). Cognitive impairment across ALS clinical stages in a population-based cohort. Neurology, 93, e984–e994. https://doi.org/10.1212/WNL.0000000000008603

Chio, A., Mora, G., & Lauria, G. (2016). Pain in amyotrophic lateral sclerosis. Lancet Neurology, 16, 144–157.

Cohen-Adad, J., El Mendili, M. M., Morizot-Koutlidis, R., Lehericy, S., Meininger, V., Blanco, A., … Pradat, P. F. (2013). Involvement of spinal sensory pathway in ALS and specificity of cord atrophy to lower motor neuron degeneration. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 14, 30–38. https://doi.org/10.3109/17429968.2012.701308

Cosi, V., Poloni, M., Mazzini, L., & Callieco, R. (1984). Somatosensory evoked potentials in amyotrophic lateral sclerosis. Journal of Neurology, Neurosurgery, and Psychiatry, 47, 857–861. https://doi.org/10.1136/jnnp.47.8.857

Dalla, B. E., Lombardi, R., Porretta-Serapiglia, C., Ciano, C., Gellera, C., Pensato, V., … Lauria, G. (2016). Amyotrophic lateral sclerosis causes small fiber pathology, European Journal of Neurology, 23, 416–420. https://doi.org/10.1111/ene.12936
Journal of Biometeorology, 62, 1361–1374. https://doi.org/10.1007/s00484-018-1550-2
Riancho, J., Castanedo-Vázquez, D., Gil-Bea, F., Tapia, O., Arozamena, J., Durán-Vian, C., ... Lafarga, M. (2020). ALS-derived fibroblasts exhibit reduced proliferation rate, cytoplasmic TDP-43 aggregation and a higher susceptibility to DNA damage. Journal of Neurology, 267, 1291–1299. https://doi.org/10.1007/s00415-020-09704-8
Riancho, J., Gonzalez, I., Ruiz-Soto, M., & Berciano, J. (2019). Why do motor neurons degenerate? Actualization in the pathogenesis of amyotrophic lateral sclerosis. Neurology, 34, 27–37. https://doi.org/10.1016/j.ijnl.2015.12.001
Riancho, J., Lozano-Cuesta, P., Santurtun, A., Sanchez-Juan, P., Lopez-Vega, J. M., Berciano, J., & Polo, J. M. (2016). Amyotrophic lateral sclerosis in Northern Spain 40 years later: What has changed? Neurodegenerative Diseases, 16, 337–341. https://doi.org/10.1159/000445750
Ringholz, G. M., Appel, S. H., Bradshaw, M., Cooke, N. A., Mosnik, D. M., & Schulz, P. E. (2005). Prevalence and patterns of cognitive impairment in sporadic ALS. Neurology, 65, 586–590. https://doi.org/10.1212/01.wnl.0000172911.39167.b6
Rubio, M. A., Herrando-Grabulosa, M., Vilches, J. J., & Navarro, X. (2016). Involvement of sensory innervation in the skin of SOD1(G93A) ALS mice. Journal of the Peripheral Nervous System, 21, 88–95. https://doi.org/10.1111/j.12164
Sangari, S., Giron, A., Marrelec, G., Pradat, P. F., & Marchand-Pauvert, V. (2018). Abnormal cortical brain integration of somatosensory afferents in ALS. Clinical Neurophysiology, 129, 874–884. https://doi.org/10.1016/j.clinph.2017.12.008
Sangari, S., Iglesias, C., El Mendili, M. M., Benali, H., Pradat, P. F., & Marchand-Pauvert, V. (2016). Impairment of sensory–motor integration at spinal level in amyotrophic lateral sclerosis. Clinical Neurophysiology, 127, 1968–1977. https://doi.org/10.1016/j.clinph.2016.01.014
Sassone, J., Taiana, M., Lombardi, R., Porretta-Serapiglia, C., Freschi, M., Bonanno, S., ... Lauria, G. (2016). ALS mouse model SOD1G93A displays early pathology of sensory small fibers associated to accumulation of a neurotoxic splice variant of peripherin. Human Molecular Genetics, 25, 1588–1599. https://doi.org/10.1093/hmg/ddw035
Schafer, M. K., Belloue, S., Jacquier, A., Schaller, S., Richard, L., Mathis, S., ... Haase, G. (2017). Sensory neuropathy in progressive motor neuronopathy (pmn): mice is associated with defects in microtubule polymerization and axonal transport. Brain Pathology, 27, 459–471. https://doi.org/10.1111/bpa.12422
Seki, S., Yamamoto, T., Quinlin, K., Spigelman, I., Pantazis, A., Olcese, R., ... Venugopal, S. (2019). Circuit-specific early impairment of propriospinal sensory neurons in the SOD1(G93A) mouse model for ALS. The Journal of Neuroscience, 39, 8798–8815. https://doi.org/10.1523/JNEUROSCI.1214-19.2019
Shimizu, T., Bokuda, K., Kimura, H., Kamiyama, T., Nakayama, Y., Kawata, A., ... Uwaga, Y. (2018). Sensory cortex hyperexcitability predicts short survival in amyotrophic lateral sclerosis. Neurology, 90, e1578–e1587. https://doi.org/10.1212/WNL.0000000000005424
Shimizu, T., Kawata, A., Kato, S., Hayashi, M., Takamoto, K., Hayashi, H., ... Oda, M. (2000). Autonomic failure in ALS with a novel SOD1 gene mutation. Neurology, 54, 1534–1537. https://doi.org/10.1212/WNL.54.7.1534
Shimizu, T., Nakayama, Y., Funai, A., Morishima, R., Hayashi, K., Bokuda, K., ... Isozaki, E. (2020). Progressive deterioration of sensory cortex excitability in advanced amyotrophic lateral sclerosis with invasive ventilation. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 21, 147–149. https://doi.org/10.1080/21678421.2019.1704015
Simone, I. L., Tortelli, R., Samarelli, V., D’Errico, E., Sardaro, M., Difruscolo, O., ... de Tommaso, M. (2010). Laser evoked potentials in amyotrophic lateral sclerosis. Journal of the Neurological Sciences, 288, 106–111. https://doi.org/10.1016/j.jns.2009.09.023
Taiana, M., Sassone, J., & Lauria, G. (2016). Mutant SOD1 accumulation in sensory neurons does not associate with endoplasmic reticulum stress features: Implications for differential vulnerability of sensory and motor neurons to SOD1 toxicity. Neuroscience Letters, 627, 107–114. https://doi.org/10.1016/j.neulet.2016.05.057
Tao, Q. Q., Wei, Q., & Wu, Z. Y. (2018). Sensory nerve disturbance in amyotrophic lateral sclerosis. Life Sciences, 203, 242–245. https://doi.org/10.1016/j.lifes.2018.04.052
Theys, P. A., Peeters, E., & Robberecht, W. (1999). Evolution of motor and sensory deficits in amyotrophic lateral sclerosis estimated by neurophysiological techniques. Journal of Neurology, 246, 438–442. https://doi.org/10.1007/s004150050379
Trulli, A., Biasiotta, A., Onesti, E., Di Stefano, G., Ceccanti, M., La Cesa, S., ... Inghilleri, M. (2015). Small-fibre neuropathy related to bulbar and spinal-onset in patients with ALS. Journal of Neurology, 262, 1014–1018. https://doi.org/10.1007/s00415-015-7672-0
Van der Graaff, M. M., de Jong, J. M. B. V., Baas, F., & de Visscher, M. (2009). Upper motor neuron and extra-motor neuron involvement in amyotrophic lateral sclerosis: A clinical and brain imaging review. Neuro muscular Disorders, 19, 53–58. https://doi.org/10.1016/j.nmd.2008.10.002
van Es, M. A., Hardiman, O., Chio, A., Al Chalabi, A., Pasterkamp, R. J., Veldink, J. H., & van den Berg, L. H. (2017). Amyotrophic lateral sclerosis. Lancet, 390, 2084–2098. https://doi.org/10.1016/S0140-6736(17)31287-4
Vaughan, S. K., Kemp, Z., Hatzipetros, T., Vieira, F., & Valdez, G. (2015). Degeneration of proprioceptive sensory nerve endings in mice harboring amyotrophic lateral sclerosis-causing mutations. The Journal of Comparative Neurology, 523, 2477–2494. https://doi.org/10.1002/jcn.23848
Vaughan, S. K., Sutherland, N. M., Zhang, S., Hatzipetros, T., Vieira, F., & Valdez, G. (2018). The ALS-inducing factors, TDP43(A315T) and SOD1(G93A), directly affect and sensitize sensory neurons to stress. Scientific Reports, 8, 16582. https://doi.org/10.1038/s41598-018-34510-8
Wallace, V. C., Ellis, C. M., Burman, R., Knights, C., Shaw, C. E., & Al-Chalabi, A. (2014). The evaluation of pain in amyotrophic lateral sclerosis: A case controlled observational study. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 15, 520–527. https://doi.org/10.3109/21678421.2014.951944
Zhou, F., Xu, R., Dowd, E., Zang, Y., Gong, H., & Wang, Z. (2014). Alterations in regional functional coherence within the sensory–motor network in amyotrophic lateral sclerosis. Neuroscience Letters, 558, 192–196. https://doi.org/10.1016/j.neulet.2013.11.022
Zufiria, M., Gil-Bea, F. J., Fernandez-Torron, R., Poza, J. J., Munoz-Blanco, J. L., Rojas-Garcia, R., ... de Munain, A. L. (2016). ALS: A bucket of genes, environment, metabolism and unknown ingredients. Progress in Neurobiology, 142, 104–129. https://doi.org/10.1016/j.pneurobio.2016.05.004

How to cite this article: Riancho J, Paz-Fajardo L, López de Munain A. Clinical and preclinical evidence of somatosensory involvement in amyotrophic lateral sclerosis. Br J Pharmacol. 2021;178:1257–1268. https://doi.org/10.1111/bph.15202