Topical Review

Electrophysiological correlates of neurodegeneration in motor and non-motor brain regions in amyotrophic lateral sclerosis—implications for brain–computer interfacing

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Abstract

Objective. For patients with amyotrophic lateral sclerosis (ALS) who are suffering from severe communication or motor problems, brain–computer interfaces (BCIs) can improve the quality of life and patient autonomy. However, current BCI systems are not as widely used as their potential and patient demand would let assume. This underutilization is a result of technological as well as user-based limitations but also of the comparatively poor performance of currently existing BCIs in patients with late-stage ALS, particularly in the locked-in state.

Approach. Here we review a broad range of electrophysiological studies in ALS patients with the aim to identify electrophysiological correlates of ALS-related neurodegeneration in motor and non-motor brain regions in to better understand potential neurophysiological limitations of current BCI systems for ALS patients. To this end we analyze studies in ALS patients that investigated basic sensory evoked potentials, resting-state and task-based paradigms using electroencephalography or electrocorticography for basic research purposes as well as for brain-computer interfacing. Main results and significance. Our review underscores that,
Introduction

Brain–computer interfaces (BCIs) are an important class of assistive technology for severely paralyzed patients with motor and communication impairments. Through converging developments in microelectronic engineering (such as implantable microelectrode arrays), novel computational methods for decoding brain signals based on advanced machine learning, and advances in designing effectors for brain-based spelling or the control of robotic devices, BCI research has gained significant momentum in recent years.

In this interdisciplinary research program, obtaining viable neural control signals for decoding brain states, from basic sensory processing like visual evoked potentials (VEPs) to complex cognitive paradigms, is a crucial bottleneck for optimizing BCI modus (what paradigm or task) of neural signal acquisition to the disease dynamics (see box 1 for clinical staging of ALS).

Box 1. Clinical staging of ALS

From a clinical perspective, assessing ALS disease progression is still determined by the loss of motor functions and is most commonly assessed with the revised ALS Functional Rating scale (ALSFRS-R) [10]. While there is considerable uncertainty and debate about the precise dynamics of disease progression [11–13], it seems that the rate of ALSFRS-R change provides a reasonable predictive estimate [14, 15]. Because the ALSFRS-R scale reflects multimodal disease disability from a functional perspective, it does not map precisely on clinical milestones of disease progression and is thus not a reliable tool for staging. To overcome these limitations, two staging systems have been proposed recently: the ALS Milano-Torino Staging System (MITOS) [16] and a system by Roche and colleagues [17]. While both systems have merits and demerits, we will use the system by Roche et al to refer to clinical stages of ALS here. In the future, computational modelling, for example using crowd-based analysis and machine learning [18], might prove more effective in predicting disease progression in ALS.

Clinical stages of ALS according to Roche et al (2012)

| Stage | Description |
|-------|-------------|
| Stage 1: | Symptom onset (involvement of first region) |
| Stage 2A: | Diagnosis |
| Stage 2B: | Involvement of a second region |
| Stage 3: | Involvement of a third region |
| Stage 4A: | Need for gastrostomy |
| Stage 4B: | Need for respiratory support (non-invasive ventilation) |

Similarly to mounting evidence from neuroimaging and neuropathology, electrophysiological measures too indicate neurodegeneration in non-motor areas in ALS. Furthermore, we identify an unexpected gap of basic and advanced electrophysiological studies in late-stage ALS patients, particularly in the locked-in state. We propose a research strategy on how to fill this gap in order to improve the design and performance of future BCI systems for this patient group.

Keywords: electroencephalography, electrocorticography, brain–computer interfacing, event-related potentials, neurodegeneration, evoked potentials, amyotrophic lateral sclerosis
For late-stage ALS (4A and 4B), it remains unclear, precisely what structural and functional changes—driven by motor neuron degeneration and countered by adaptive plasticity—occur in non-motor brain regions. This, however, is an important and requisite information for developing BCI devices based on electrophysiological control signals of non-motor brain regions for ALS patients, as only cortex that produces vital and measurable electrophysiological activity is suitable for the continued use of a BCI system in later stages of ALS where the patients may need it most.

For BCI systems, electrophysiological control signals are a pivotal focus of research and development [19]. For optimal decoding performance, the control signal should be robust against artefacts, provide stable long-term measurements, and have a high information transfer rate. From the perspective of a severely paralyzed patient, the system should be usable in a home setting, be user-friendly, and controllable by non-experts [20]. Given the spatial and economic constraints, BCI systems based on functional magnetic resonance imaging (fMRI) may help patients for short-term training [21], but are not an economically viable nor user-friendly alternative in the long term.

Yet, non-invasive methods for obtaining electrophysiological control signals like extracranial electroencephalography (EEG) and magnetoencephalography (MEG, which is also impractical for mobile use), often have low spatial signal resolution, suboptimal signal-to-noise ratios and low sensitivity for higher cortical frequencies. Novel intracranial methods for measuring electrocortical activity like epi- or subdural electrocorticography (ECoG), specifically multi-channel Micro-ECoG, in contrast, offer a much better temporal-spatial resolution than extracranial EEG, less susceptibility to motion artefacts and a high signal-to-noise ratio [22–24].

The purpose of this review is to summarize studies on electrophysiological measurements in ALS patients with the aim to understand the changes in bioelectric cortical function that occur in ALS along with disease progression, particularly in the late-stage and locked-in state (see table T for an overview). We begin by reviewing studies that measured basic sensory evoked potentials like somatosensory evoked potentials (SEPs), VEPs, and brainstem auditory evoked potentials (BAEPs) in EEG and MEG. Then we examine ‘resting-state’ EEG, MEG and ECoG studies in ALS patients. Next, we analyze EEG- and ECoG-based studies that use event-related sensory and/or cognitive paradigms to assess perceptive and cognitive function in patients with ALS. Finally, we look at studies involving EEG- or ECoG-based BCIs in ALS patients. Overall, our review synthesizes qualitative and quantitative evidence from different electrophysiological measures in ALS. We identify important gaps in basic electrophysiological research in patients with late-stage ALS and in the locked-in state. Closing this research gap is important to obtain viable control signals for brain–computer interfacing, as well as improving the technical ability, usability, design, and real-life performance of BCI systems for ALS patients in the future.

Methods

Identification of studies

We searched the following databases without language restrictions: PubMed (1966, to 30 May 2017), Embase (1980, to 30 May 2017), Google Scholar (to 30 May 2017), the Cochrane Library (April 1996, to 30 May 2017). Search terms used were: amyotrophic lateral sclerosis, ALS, evoked potentials, SEP, VEP, AEP, BAEP, electroencephalography, EEG, electrocorticography, ECoG, brain–computer interface, BCI, brain–machine interface, BMI. Unpublished studies were located via contextual search, and relevant dissertations were located via NTLTD (Networked Digital Library of Theses and Dissertations). We also screened each retrieved paper for further relevant references.

Results

Sensory evoked potentials in ALS

In this section, we discuss basic electrophysiological measurements using sensory-evoked potentials (EPs) in patients with ALS. Clinical neurologists use evoked potentials routinely in the diagnostic work-up of neurological diseases. Depending on the sensory input modality, it is possible to localize pathologic changes to the peripheral nervous system, the spinal cord, subcortical or cortical regions.

Somatosensory evoked potentials (SEP)

Measuring SEP (mostly with scalp needle electrodes) from the electric stimulation of peripheral nerves (mostly the median or ulnar nerve) are often part of the clinical workup of patients with suspected ALS to investigate for concomitant peripheral or central sensory pathology. There are no specific abnormalities in scalp needle SEPs that are considered to be pathognomonic for ALS, however, because damage to peripheral or central sensory regions or pathways may occur in many different diseases such as peripheral neuropathy (peripheral) or multiple sclerosis (central). In total, we found ten studies that reported on such basic SEPs in ALS patients. Of these ten studies, only one did not describe any abnormalities in SEPs [25] in ALS patients. All other SEP studies reported abnormalities such as prolonged central conduction time or enlarged amplitude of the N20 in a proportion of ALS patients [26–34]. The patients investigated in these studies were in ALS stages 2A–3. We found no studies in which the researchers measured SEPs longitudinally in relation to disease progression and no systematic SEP measurements in ALS patients in the late-stage (4A and 4B) or locked-in stage.

Visual evoked potentials (VEP)

Eliciting VEPs is not a routine diagnostic test in ALS patients. This may explain why we found only very little studies that
measured VEPs in this patient population. With respect to BCI, however, the integrity of peripheral and central visual pathways, particularly in severely paralyzed patients, is important because many BCI systems rely on visual input like a computer screen.

Overall, we identified four studies that investigated VEPs in ALS patients. Two studies did not find abnormalities [25, 32] while the two others reported a significantly prolonged N100 in ALS patients when compared to controls, indicating damage to visual processing pathways, which the authors did not specify further [26, 35]. As with the other sensory evoked potentials, we found no studies that measured VEP in late-stage and/or locked-in ALS patients.

**Brainstem auditory evoked potentials (BAEP)**

As for VEP, measuring BAEPs is not a priority in the clinical work-up of suspected motor neuron disease. This may explain why also for BAEPs only a few studies in ALS patients are available. BAEPs allow for assessing the integrity of peripheral and central afferent auditory pathways. This makes them an important measure in patients in the locked-in state for deciding whether the auditory system may be a viable sensory input channel for a BCI system in a patient in the locked-in state [36].

We found five studies that measured BAEPs in ALS patients. While four reported no abnormalities [25, 27, 32, 35], one study found prolonged central conduction time, indicating damage to central auditory pathways, in 4 out of 19 early-stage ALS patients [26]. Again, we found no studies that investigated BAEP in later stages of ALS, particularly the locked-in state.

**Summary: basic sensory evoked potentials in ALS**

Given the routine availability, little cost, and lack of risks for subjects, we find it remarkable how little research is available on basic afferent sensory pathways particularly in late-stage ALS. The main reason for this gap, in our view, is that traditionally these measures had little relevance in the differential clinical work-up of suspected motor neuron diseases like ALS. Rather, the diagnostic focus in the pre-imaging era was on electromyography for investigating damage to spinal motor neurons and transcranial magnetic stimulation to assess central motor pathology. With the advent of magnetic resonance imaging (MRI) imaging, cervical spinal MRI (for excluding cervical spinal stenosis as a cause for muscular atrophy and/or central spinal motor pathway damage) and cerebral MRI were added as routine diagnostic tests in assessing suspected motor neuron disease. Thus, the basic electrophysiological methods like evoked potentials were side-lined and do not play a major role in the neurological work-up of ALS as of today.

Now, however, with the up-and-coming BCI technology for severely paralyzed patients, particularly the future prospect of providing reliable BCI communication for locked-in ALS patients, basic clinical neurophysiological research in ALS patients is important for several reasons:

(a) To assess the integrity of peripheral and central sensory input pathways (as potential input channels for BCI paradigms);
(b) To use electrophysiological measurements to assess the integrity of non-motor brain regions (and networks);
(c) To study disease progression in late stage ALS. In our opinion, the main research question in this respect is, if and to what degree late-stage ALS and particularly the locked-in state affects the integrity of afferent sensory pathways with regard as to their usefulness as input channels for BCI systems.

The available studies reviewed above yield very little consistent findings to this regard. The most significant result, cutting across this body of studies, is that these early studies from the 1980s and 1990s already show that a proportion of ALS patients in early to middle stages of the disease show abnormalities in basic sensory electrophysiological measures. This underrecognised common finding, from a time when non-motor system degeneration was not yet a widely recognised feature of ALS, could indicate that basic sensory evoked potentials may indeed be worth exploring more in late-stage ALS. Exemplified by the somatosensory domain, the idea that the enlarged amplitude of the N20 potential may reflect compensation of the somatosensory cortex for motor system degeneration rather than damage to sensory pathways [37] should also be explored further.

*Resting-state* electrographic studies in ALS

Here we give an overview about research studies measuring bioelectric activity of cortical areas in the so-called *resting-state* explored with extracranial (EEG, MEG). We did not find any intracranial EEG resting-state study in ALS patients. In the resting-state subjects are typically instructed to keep still and not do or think anything in particular and maintain a state of wakeful rest.

As for the basic evoked potentials studies, EEG is not a routine clinical test in the differential work-up of motor neuron disease and rarely plays a role in progressing stages of the disease. One clinical scenario, in which EEG may become relevant, is to assess global brain function in the event of impaired consciousness, for example as a result of hypoxia due to respiratory failure in late-stage ALS. Using EEG in that way, however, is an auxiliary method for the clinical neurologist in assessing the extent of hypoxic brain damage and not specific to ALS.

Thus, this section explicitly focuses on studies that used EEG, MEG or ECoG to investigate global brain activity and/or functional network organization in ALS patients independent of ancillary clinical questions.

*Resting-state electrographic studies (EEG and MEG)*

Historically, EEG recordings in patients with ALS were reported as early as 1943 [38]. This early study did not find consistent pathological changes in six ALS patients such that the authors could not relate the EEG to underlying cortical
pathology. Since then, only very few studies investigated EEG in ALS patients systematically. In the meantime, measuring brain activity in a state of wakeful relaxation, the so-called ‘resting-state’, has become an important research topic in neuroscience to investigate brain network activity and connectivity.

Resting-state EEG studies

Mai et al [39], recorded scalp EEG from 18 channels in resting ALS patients and controls. The ALS patients compared to controls had, on average, less alpha power (within a, generic rather than subject-specific, 8–12 Hz band as defined by the authors) over sensorimotor cortex, which the authors interpreted as a correlate of ALS-related pyramidal cell degeneration. Measuring resting-state EEG in twelve ALS patients, Santhosh et al [40] also found a power decrease in the alpha spectrum in ALS patients compared to controls, which the authors interpreted in relation to similar findings in normal aging and in patients with dementia.

Taking a network perspective, Iyer et al [41] investigated resting-state functional connectivity as a potential biomarker in ALS patients. Compared to controls, and in contrast to the two studies summarized above, ALS patients in this study on average had a higher alpha power and increased connectivity parameters (e.g. degree values of nodes and greater assortativity) over fronto-central regions. The authors suggested that this pattern of altered connectivity could be useful as a biomarker of early cortical changes in ALS.

Recording resting-state EEG in ALS patients and controls, Jayaram et al [42] found decreased spectral power in ALS patients over the central region in the theta-band, in contrast to previous findings cited above. Furthermore, increased spectral power in the gamma-band in non-motor regions in ALS patients could also be interpreted as electroencephalographic correlates of a more widespread system degeneration in ALS, similarly to gamma changes in other neurodegenerative diseases [43].

Resting-state MEG studies

We found only one MEG study of resting-state in ALS patients. Recording whole-head MEG from 148 channels, Boyajian et al [44] looked for local sources of slow wave (delta/theta) discharges in seven ALS patients without dementia. All patients showed localized slow wave discharges distributed all over the cortex, most prominently over the frontal cortex (and except occipital areas), whereas none of the controls did. The authors interpret the discharges as indication of widespread system degeneration despite no overt signs of dementia.

Summary: electrographic resting-state studies in ALS

Given the small body of extracranial electrographic (EEG, MEG) resting-state studies in ALS patients, we can only draw tentative conclusions. One observation that emerges from different studies is a global decrease of brain activity, specifically reduced power in the alpha-band, as well as an increase in slow wave power in the theta-band. Topographically, the regions most affected were the bilateral frontal cortex, specifically sensorimotor cortex. More recently developed measures like network connectivity and topography may be more promising as electrographic markers of ALS-specific pathological changes. Generally, the studies did not systematically assess non-motor symptoms like clinical signs of frontotemporal dementia in their patient populations. Therefore, we cannot know whether the global changes and alterations at the network level are features of natural disease progression in ‘pure-motor’ ALS or rather a possible proxy marker of the non-motor phenotype on the ALS-FTD clinical spectrum.

Another methodological problem in aggregating the evidence from this diverse body of studies concerns the precise definition of resting-state. In most of the studies, the researchers did not explicitly state whether the researchers instructed the subjects to remain in an unconstrained resting-state that allows mind wandering or to maintain a state of relaxed and focused attention. Conceivably, however, these different states of mind might modify global brain function, network topography and/or interconnectivity.

Finally, as was the case for the basic evoked potentials studies, we found no electrographic studies that used resting-state to investigate global brain function or network topography and function in late-stage ALS, particularly the locked-in state.

Electrographic studies in ALS using activation paradigms

In the following section, we review studies using ‘activation’ paradigms in EEG, MEG or ECoG, that is, experiments, in which subjects (ALS patients and controls) engage in particular tasks like self-paced movements or attending to ‘odd’ stimuli in an experiment using event-related sensory input. For systematic purposes, we divided this body of studies into three types of experimental paradigms: (a) experiments using event-related potentials (ERP) elicited by sensory input, (b) motor-related paradigms and (c) learned self-regulation of brain activity.

Ad (a) Measuring ERP in EEG examines the relationship between an experimental paradigm in a particular sensory domain (e.g. visual, auditory, tactile) and corresponding cortical potentials. The ERPs have specific temporal and polar properties. Temporally, early components and late components are distinguished which, together with the polarity of the signals, carry information about their neuronal source and correspond to particular stages of stimulus perception and cognitive processing. The early ERP components reflect basic sensory perception and the late components relate to higher order cognitive processing [45, 46].

In an oddball experiment, for instance, an otherwise regular sequence of stimuli is interspersed with irregular (or ‘odd’) stimuli. When participants engage in active detection of the deviant stimuli, a P300 response is elicited, whereas the so-called mismatch negativity (MMN) also occurs when
participants are not actively engaging in a particular task [47]. In healthy subjects, using ERP in different sensory domains, the function of brain networks in relation to different cognitive processing routines can thus be studied [45–48]. ERP measures have also been used to map cortical changes in aging and neurodegenerative diseases [43, 49–54] as well as in assessing cognitive function in disorders of consciousness [55–57].

The main methodological limitations of EEG-based ERP experiments are the low spatial resolution of the EEG signal, the problem of referencing, averaging and of source localization, and the dependence on sufficient arousal and awareness (which may be difficult to determine in non-communicative patients [57]).

Ad (b) Motor-related paradigms are experiments using variations of real or imagined motor tasks for eliciting cortical potentials in EEG. Commonly used tasks/paradigms are cued or self-paced movements (like fist clenching or finger tapping) and motor imagery (like imagined finger tapping). Common EEG correlates of these movement-related paradigms are slow cortical potentials (SCP) [58, 59] as the Bereitschaftspotential (or readiness potential) and the faster motor-related potential (MRP). In the oscillatory domain, cognitive motor activity like planning or motor imagery is related to a decrease of the mu-rhythm amplitude, often quantified as event-related desynchronisation (ERD) [60–63]. Moreover, eliciting motor imagery is often accompanied by ERD in the beta-range.

Ad (c) In contrast to classic ERP-based and motor-related paradigms, both of which mostly use external cues for eliciting EEG potentials, paradigms based on learned self-regulation use a different approach based on neurofeedback. For extensive background and review on learned self-regulation see the series of papers by Gruzelier [64–66]. SCP are an important electrophysiological control signal for such learned self-regulation neurofeedback based on cortical activation and inhibition. Neurophysiologically, SCPs are cortically and subcortically (reticular brain stem systems, thalamus and basal ganglia) generated potentials that oscillate between electrical positivity and negativity [67, 68]. Whereas the positive shift has been associated with disfacilitation of excitatory cortical thresholds, the negative shift is assumed to facilitate excitability and to be associated with attention and goal-directed behavior [66, 68]. It seems that cortico-thalamo-basal-reticular loops are the core network for procedural learning in neurofeedback [69].

Using reward feedback strategies based on operant conditioning, for example, a subject can implicitly learn strategies for the self-regulation of cortical signals and can use this strategy to operate a BCI [70].

**EEG, MEG and ECoG activation studies in ALS patients**

For a review of EEG activation studies in patients with ALS up to the year 2008, see Raggi et al [71]. This review summarized eleven studies from 1995 to 2008 [72–81] and the main conclusions of the authors were:

(a) A quantitative meta-analysis of particular EEG measures (like ERP latency or amplitude; ERD/ERS in motor-related paradigms) was not applicable because of the heterogeneity of activation paradigms

(b) All studies found abnormalities of ERP responses (early as well as late components) in ALS patients without major cognitive deficits, suggesting a possible role as a diagnostic tool to assess altered information processing in these patients

(c) Cognitive processes that were affected: executive functions, (e.g. novelty detection and discrimination, attentional processing), memory (recognition, context integration)

(d) Most authors linked the ERP abnormalities to putative pathophysiological changes like glutamatergic excitotoxicity (resulting in corticomotor hyperexcitability) as well as the remodelling of non-motor regions for compensation of neuronal loss

(e) In late- and end-stage ALS, particularly in the locked-in state, deafferentation and de-efferentation may have an additional effect on ERP processing and should be studied further (see below for more in-depth exploration of ERPs in the locked-in state).

Here, we supplement this review with ERP-based EEG activation studies from that period that were not included in the review by Raggi et al [71]. Moreover, we review and analyze activation studies in ALS patients from 2008 to 2017 that used P300-related, motor-related, and learned self-regulation paradigms. Below we also review results from two studies using MEG in ALS patients, patients with primary lateral sclerosis (PLS) and controls by Proudfoot et al [82] and in ALS patients and controls by Pekkonnen et al [83]. Because of limited comparability in terms of signal analysis, we have not included these studies in the batch of EEG studies detailed in supplementary table 1 (stacks.iop.org/JNE/15/041003/mmedia) and analyzed in supplementary figure 1.

In the supplementary material we provide a detailed list of the analyzed studies that used ERP-related and motor-related paradigms (supplementary Fehler! Verweisquelle konnte nicht gefunden werden.) as well as analyses of the demographic and clinical data (supplementary table 2 and supplementary Fehler! Verweisquelle konnte nicht gefunden werden.). Provides some statistics on demographic factors like number of subjects, age and clinical factors like disease duration and ALSFRS-R.

**MEG activation studies in ALS patients**

We also found two studies using an activation paradigm in ALS patients using MEG.

In a study using auditory ERP stimulation with tonal stimuli in MEG [83], the researchers measured auditory-evoked fields (AEF) elicited by tonal stimuli. Contrasting ALS patients with bulbar signs with healthy controls, they found increased amplitudes of the P50 and N100 response—most likely representing automatic auditory processing—and the MMN in the ALS group. They found no correlation between the increase in amplitude and clinical scores. They interpreted
the abnormalities as reflecting hyperexcitability of the non-motor cortical areas involved in ALS.

In a recent study involving ALS patients, patients with a PLS phenotype, asymptomatic carriers of gene mutations associated with ALS, and healthy controls, Proudfoot et al [82] used a visually cued Go-NoGo task to investigate magnetoencephalographic markers of neurodegeneration in relation to movement preparation and execution. They found that whole-brain MEG analysis of movement preparation showed increased beta desynchronization over bilateral sensorimotor cortex (particularly precentral gyrus) in ALS patients compared to controls. During movement execution, the asymptomatic carriers of ALS-related gene mutations showed excess beta desynchronization whereas all symptomatic patients (ALS and PLS) showed a slower beta power rebound than the gene mutation carriers and healthy controls. This elegant study demonstrates the feasibility of using (magneto-)electrographic markers for distinguishing different types of motor neuron diseases from asymptomatic gene carriers and healthy controls.

Due to concerns regarding the comparability between EEG and MEG studies, we did not include these MEG studies in the quantitative analysis (Fehler! Verweisquelle konnte nicht gefunden werden.). Next, we review the few studies that have used EEG and ECoG activation paradigms to investigate brain function in locked-in ALS patients.

EEG and ECoG activation studies in ALS patients in the locked-in state

We identified five studies (two of which are studies of the same patient) that measured ERP from activation paradigms with EEG- or ECoG in ALS patients in the locked-in state (see Fehler! Verweisquelle konnte nicht gefunden werden.). Importantly, four of these studies also used the task-based paradigms for brain-computer interfacing. Therefore, we will confine the analysis here to what the paradigms, specifically ERPs and motor-related paradigms, may reveal about sensory, cognitive and motor processing in the locked-in state in ALS. We will discuss the results of the studies in terms of brain-computer interfacing in ALS in the locked-in state in another section further below. A detailed list of the studies discussed is provided in the supplementary material in supplementary table 3.

To date no longitudinal extracranial EEG study with repeated ERP measurements, documenting the transition to the CLIS in ALS patients, is available. From the studies by Murguialday et al [97] and (with the same patient) Bensch et al [86], however, we have some ECoG data from activation paradigms in an ALS patient, documenting the transition from the partial to the complete locked-in state (supplementary table 3).

In these studies, the researchers used sensory stimulation and motor imagery (with and without passive movement of the hand or foot) and measured evoked responses from ECoG (for details see supplementary table 3). The patient, a 40 year-old male, had a ten-year history of ALS with artificial ventilation for the past seven years. Within the five months before implantation and the six months follow-up period after surgery, the patient progressed to the CLIS with no remaining volitional motor control. The ECoG grid had two electrode patches totaling 128 electrode contacts and the surgeons placed the grid over the left fronto-temporo-parietal cortex. At the time of the implantation, the patient could only communicate via vertical eye movements and progressed to the CLIS within three months after surgery. Importantly, the patient in this study did not seem to have severe upper motor neuron degeneration but suffered from lower motor neuron predominant ALS. With the peripheral vibrotactile stimulation, the researchers could not record evoked potentials over the somatosensory cortex, which they interpreted as either being due to damage to mechanico-sensory skin receptors or afferent central sensory pathways. With passive movement (with or without motor imagery), however, they were able to record evoked responses over somatosensory cortex, concluding that proprioceptive receptors andafferent proprioceptive processing seemed to be intact in the CLIS in this patient. Because of severe corneal damage in the patient in the CLIS, the scientists could not elicit visual ERPs reliably. Auditory stimuli also resulted in ERPs, which indicated the preservation of cortical areas for auditory processing. Motor imagery alone, however, did not result in a stable and reproducible ERP and the authors speculated that the apparent sensory deafferentation may have had a negative influence on the capacity for motor imagery—corroborating the ‘extinction of thought’ hypothesis (see box 2) [84].

Box 2. Cognition in the locked in state: the ‘extinction of thought’ hypothesis

In short, the ‘extinction of thought’ hypothesis posits that motor function is essential to maintain the ability for goal-directed and intentional thinking. It is grounded in internalist theories of volition and intention that can be traced as far back as Aristotle who already distinguished between volitional actions (hekousion) and intention (prohairesis). In the context of a BCI for locked-in patients, these historical concepts have been summarized under the term ‘extinction of thought’ [85]. He suggested that the CLIS provides a natural experiment for falsifying this hypothesis, for if communication can be established with these patients via a BCI it follows that the ability for motor action is not a necessary condition for goal-directed thinking.

In another study with the same patient, Bensch et al [86] measured further ERPs with ECoG. The ERP battery consisted of auditory stimuli with a MMN paradigm, a standard oddball paradigm, a priming test with semantically congruent and incongruent pairs of words, and a semantic oddball paradigm. The analysis yielded the highest effect sizes for the auditory oddball paradigm in superior temporal gyrus (STG) and inferior parietal lobule (IPL). As STG and IPL are also regions involved in semantic processing and in storing and phonological memory, respectively, the failure of the semantic ERP paradigm suggested that the STG/IPL
response for the auditory oddball paradigm may reflect more basic processing (like automatic speech recognition, phonological decoding or error/novelty detection). In the last measurement, when the patient was already in the CLIS, the MMN paradigm only elicited early ERP components (N100/P200). The authors offered different explanations for this failure in eliciting a cortical response via auditory stimuli based on semantic properties in the CLIS. First, fluctuations in vigilance, arousal, alertness and attention in the locked-in state may explain the failure of more subtle cognitive paradigms to elicit stable ERP responses [57, 87, 88]. In yet another study with the patient, the researchers also used the ECoG electrodes to measure oscillations related to sleep cycles and circadian rhythms in this patient [89]. These analyses demonstrate that ECoG measures may be useful to identify the level of arousal and relate these measures to circadian rhythmicity. Basic auditory processing or even error/novelty detection in oddball paradigms, in contrast, may also be measurable in phases of impaired wakefulness.

To summarize, the main result from the ERP paradigms in locked-in ALS patients (summarized in Fehler! Verweisquelle konnte nicht gefunden werden.) is that late ERP components are indeed measurable in the locked-in state. This suggests that higher-level cognitive processing, which is associated with late ERP components, may potentially be preserved in the locked-in state, though it is unclear to which degree. Important limitations of the studies are the sparsity of neuropsychological testing (NPT) in the patients before they entered the locked-in state. When NPT was performed, as in patient 2 in the study by Kotchoubey et al. [79], it indicated significant cognitive impairment of mostly frontal executive functions. This, however, can be a potentially confounding factor for interpreting the ERP results as the abnormalities or failure in measuring ERPs may be a result of concomitant cognitive impairment, including frontotemporal dementia [43, 90].

Furthermore, estimating the actual level of conscious awareness and higher cognitive abilities is complicated by the difficulty of applying independent methods for assessing these factors [89]. It could be the case, for example, that the ERP measurements only reflect necessary (perceptive and/or lower-level cognitive processes) but not sufficient conditions for higher-order cognitive processing. On the other hand, the technical and analytical limitations of the ERP method will more likely result in false negative than false positive results. Thus, it is worthwhile to pursue complementary methods for assessing cognitive function in the locked-in state such as imaging based on hemodynamic measures like fMRI and near-infrared spectroscopy (NIRS). An important advantage of the ERP method (over say fMRI) for assessing cognitive functions in patients with severe disability is of course the mobility of the measurement equipment, which allows for bedside testing in the patient’s home.

Summary: EEG, MEG and ECoG activation studies in ALS

As this overview shows, electrographic activation experiments can provide a valuable window for investigating basic perceptual as well as lower- and higher-level cognitive functions in ALS. However, one main caveat in interpreting this data, as with the EP and resting-state EEG studies reviewed above, is that the vast majority of the studies did not include patients in late-stage ALS, specifically the locked-in state.

Similar to the review by Raggi et al. [71], all ten (of the seventeen EEG-based studies) ERP-studies which we analyzed found ERP components in ALS patients, whether they had cognitive impairment or not. For early ERP components, which occur in more basic sensory processing, a repeated finding was the absence (in some cases) or the longer latencies (in most cases) of the N100, P100, and N200, whereas we found no consistent differences in amplitudes between patients and controls across studies. Regarding the late P300 and N400 components, which are more closely associated with cognitive processing, most studies also found longer latencies, and again no systematic pattern of amplitude changes of the late components.

Most studies performed correlational analysis between ERP components and neuropsychological data and/or clinical scores. These analyses mostly found a negative correlation between neuropsychological test performance or clinical factors (like disease severity, disease duration or bulbar onset) and the latency of late ERP components, particularly the P300.

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**Table 1.** Overview of electrographic recording methods and paradigms used in ALS patients.

| Recording method                        | Invasive? | Medical risks | Costs | Paradigm/task     | Used for BCI in ALS |
|-----------------------------------------|-----------|---------------|-------|-------------------|---------------------|
| Scalp needle electrodes                  | No        | No            | Low   | Evoked potentials | No                  |
| Electroencephalography (EEG)            | No        | No            | Low   | Resting-state     | No (yes) SSVEP      |
|                                         |           |               |       | Evoked potentials | P300 speller        |
|                                         |           |               |       | Event-related potentials (ERP) | Spelling systems |
|                                         |           |               |       | Learned self-regulation | Spelling system |
| Magnetoencephalography (MEG)            | No        | No            | High  | Resting-state     | No                  |
|                                         |           |               |       | ERP               | No                  |
| Electrocorticography (ECoG)             | Yes       | Infection, bleeding, seizure | High | ERP               | Yes                 |
|                                         |           |               |       | Motor-related     | Yes                 |
|                                         |           |               |       | Learned self-regulation | Yes              |

Topical Review
However, it should be noted that the late ERP components also correlate with factors like ageing and mild cognitive impairment [91, 92], which was rarely mentioned or investigated in the papers reviewed here, except in Volpato et al [93]. Some studies used less common ERP measures like the ‘late positive complex’ (LPC), ‘contralateral delay activity’ (CDA) or the ‘posterior switch positivity’ (PSP), the significance of which is difficult to determine. One interesting finding from these studies was higher ERP amplitudes with increased working memory load, an effect which was significantly smaller in ALS patients when compared with controls [94].

In total, we found seven studies that investigated EEG-based motor-related paradigm in ALS patients. As for ERP-related paradigms, the heterogeneity of the motor-related paradigms precludes a quantitative meta-analysis of these studies. The tasks most commonly used in the motor-related paradigms were self-paced movement (four of seven studies) and motor imagery (three of seven studies). The electrophysiological motor-related target signals most commonly analyzed were the Bereitschaftspotential (BP) (two of seven studies and event-related desynchronisation/synchronization (ERD/ERS) in the mu-frequency range (four of seven studies).

We interpret the results from studies using a self-paced movement paradigms in ALS patients as follows: (a) Changes in the Bereitschaftspotenzial (which is generated in SMA and premotor cortex) could be an indicator of neurodegeneration outside of the primary motor degeneration in M1; (b) Reduced MRPs in ALS patients in bilateral supplementary motor and caudal mesial areas area might be a useful indicator for upper-motor neuron burden; (c) Overall higher MRP amplitudes may reflect cortical hyperexcitability or compensatory recruitment of cortical motor neurons; (d) Reduction in pre-movement ERD and post-movement ERS could be a marker of cortical inhibition and pyramidal cell loss.

From the studies using motor imagery paradigms, we conclude that: (a) Patients with bulbar onset ALS and progressed disease performed worse in motor imagery paradigms than limb onset. It is unclear, whether changes in post-imagination ERD relate to bulbar or limb function; (b) The post-imagination ‘positive rebound rate (RR)’ may be a stronger predictor of effenter motor pathway damage than pre-imagination ERD or peak negativity during imagery.

Another more specific finding was a strong correlation between disease severity as well as site of onset (upper motor neuron dominant ALS) with reduced cortical activity in pre-motor and motor areas during movement preparation, execution, and termination [95]. Patients with upper motor neuron predominant ALS in this study also had smaller amplitudes in the movement- and respiratory-related potentials than patients with lower motor neuron predominance [96]. Disease progression in upper motor neuron ALS was also associated with an initial increase, possibly reflecting compensatory recruitment, and later decrease in MRPs, possibly as a correlate of progressive pyramidal cell degeneration. In a follow-up study on the same dataset, the alpha and beta frequency bands showed a decrease in spectral power density in the alpha- and smaller ERD in the beta-frequency band post-movement. Patients also generated only unilateral event-related synchronization in the alpha band whereas controls showed bilateral synchronization. This could be a correlate of cortical cell degeneration and a possible involvement of the corpus callosum.

To summarize, the few available EEG and ECoG activation studies in ALS patients in the locked-in state show that, in principle, late components of ERPs—as proxy markers for higher-level cognitive processing—are detectable. Motor-related paradigms, specifically motor imagery, however, could not be reliably used in ALS patients in the locked-in state. This failure to elicit cortical potentials via motor imagery in the CLIS [84, 85, 97] could be an important factor in failed BCI communication in these patients.

The third category of activation paradigms, learned self-regulation of SCP or oscillations for neurofeedback, similarly to ERPs, are measurable in locked-in ALS patients and have played an important role in developing BCIs for this patient population. Thus, we now turn to reviewing and discussing different approaches to brain–computer interfacing in ALS patients.

### EEG/ECoG-based BCIs for ALS patients

In recent years, several systems for EEG/ECoG-based BCIs have been developed, many of used by patients with ALS [85, 88, 98–121]. Similar to the electrographic research studies using activation paradigms reviewed above, these BCI systems employ either an ERP-based targeting system (mostly a P300 speller system), motor-related paradigms (like motor imagery, or self-paced movement) or learned self-regulation of brain activity (e.g., SCP, oscillations, beta- or µ-rhythm).

Before discussing the different control paradigms in depth, we want to highlight some basic design principles and common features. The type of activation paradigm, for instance, mainly relates to the expected capabilities of the target user population. To take obvious examples, a BCI system based on visual ERPs would be as useless for visually impaired users as a system based on self-paced movement would be for paralyzed persons. From a control-theoretic perspective, the action possibilities of the BCI system should match the integrity of the afferent sensory and efferent motor system of users. This implies that the direction of BCI research and development should be in close contact with the intended users, as well as their relatives, caregivers, and doctors. Furthermore, a particular control paradigm like ERPs can be more effective for operating one particular effector, like a spelling system, than another like a robotic arm. Thus, the control paradigm should both match the user’s capabilities and be effective in operating a particular external device.

From a user perspective, specifically regarding ALS patients, studies using questionnaires and structured interviews show that ALS patients priorities BCI systems for communication (like spelling systems) and mobility (like a wheelchair) over robotic devices [8, 122]. In in-depth interviews with ALS patients that had used BCIs, the users expressed an interest in flexible and adaptive systems and reported frequent frustrations because of slow spelling [9].
**Using EP- and ERP-related paradigms for BCI control in ALS patients**

Here, we review different EP- and ERP-based systems for brain–computer interfacing and highlight important advantages and disadvantages.

**SSVEPs for brain–computer interfacing.** The few EP-based BCIs that we identified are using steady-state VEPs (SSVEPs) in ALS patients. SSVEPs are evoked responses to visual stimulation at specific frequencies. When a visual stimulus in the frequency range of 3.5 Hz to up to 75 Hz excites the retina, the evoked activity is generated at the same frequency (or multiples of it) in the brain. While SSVEP is a common BCI-paradigm for research with healthy subjects, we have found only few studies describing the use of a SSVEP-based BCI in ALS patients.

Using a selective attention to a visual stimulus Lim et al [123] used an SSVEP approach—which was developed with healthy subjects—in one ALS patient and report reaching a classification accuracy of 80%. Using a similar approach, they used SSVEPs for ALS patients in the (most likely partial) locked-in state to operate a ‘brain switch’ [124]. The three severely paralyzed patients learned to use the system for an ‘emergency call system’ to call a care provider to their bedside, one of the patients for up to four weeks.

While SSVEPs are usually measured over occipital cortex, the evoked responses can also be measured over frontal electrodes. In a study using such frontal SSVEPs in healthy subjects and seven ALS patients, the four less severely affected ALS patients reached an average classification accuracy of 81.2% in a two choice task (with low information transfer rate of 1.51 bits min⁻¹ however) [125].

These studies show that while SSVEP can be used for simple BCI control, they achieve only low information transfer rates and are not practical for operating more advanced spelling systems.

**ERP-based BCIs in ALS.** Most ERP-based BCI systems use auditorily or visually presented stimuli, whereas systems based on somatosensory or vibrotactile input are a rare exception. The vast majority of ERP-based BCI systems for ALS patients use visual input. One main reason is that, from the user perspective, auditory paradigms based on detecting ‘oddball’ tonal stimuli are particularly monotonous and tiresome [9, 126].

Furthermore, the few comparative studies available show that healthy subjects perform better in visual compared to auditory ERP-based BCI systems [127, 128]. Due to frequent visual deficits, however, this may be different for ALS patients, particularly in later disease stages. Interestingly, the salience of the visual input stimuli seems to influence the performance of a visual P300 BCI for spelling. Superimposing pictures with faces of well-known persons onto the flashing characters for spelling, Kaufmann and colleagues were able to boost BCI spelling performance in patients with ALS [129].

Despite of their tediousness, auditory ERPs can still be useful for BCI development in ALS patients, because they are very reliable, robust, and they can be elicited even in late-stage ALS in the partially locked-in state [104]. Moreover, studying healthy subjects [130] as well as ALS patients [117] researchers showed that a standard ‘oddball’ auditory ERPs can predict BCI user performance. Because of its simplicity, auditory ‘oddball’ ERPs could therefore be a useful tool in predicting BCI user aptitude and avoid unpromising training.

Visual paradigms for ERP-based BCI control offer many advantages over auditory paradigms. Given the potential richness and variability of the stimulus material, visual paradigms can avoid monotony and tedium much more easily than in the auditory domain. In surveying the landscape of current visual BCI systems, the two most widely used visual ERP-based BCI system is the ‘P300-BCI’ and the ‘BCI2000’ the most popular decoding toolbox.

The ‘P300-BCI’ is an early row-and-column speller based on a visual ERP paradigm that was developed in the late 1980s [131, 132]. Adapting the system for ALS patients, two of three patients reached similar aptitude as healthy controls [101].

Another early row-and-column speller based on visual ERPs with the BCI2000 system was developed by Schalk et al [133, 134]. Using a modified version of the system, researchers re-established communication with a severely paralyzed and ventilated ALS patient and demonstrated the feasibility of long-term use over two and a half years by training caregivers in operating the system at the patient’s home [106]. By changing the visual paradigm from a row-and-column to a checkerboard speller, other researchers could improve the classification accuracy in ALS patients from 77% to 92% and achieve a higher information transfer rate [107]. Apart from improving performance by adapting the paradigm, researchers have also made advances in boosting the decoding algorithms of this BCI system for ALS patients [109].

Beyond these two ‘classic’ systems, different groups have recently developed new BCI systems based on visual ERPs. The system by Pires and colleagues [112], for example, targets single characters and reached a high accuracy (89% on average) as well as a better signal-to-noise ratio in ALS patients than the standard row-and-column spellers. To further improve performance of visual P300 spellers, Ikegami et al [135] compared a conventional row/column spelling paradigm with a two-step speller in seven ALS patients. They found that using the two-step speller improved online classification accuracy.

In terms of performance, researchers have shown that ALS patients, even in late stages and the locked-in state, can use BCI systems based on visual ERPs with high classification accuracy, information transfer rate and can maintain levels of BCI control for many months [103, 106, 119, 136–138].

Whereas increasing age seems to negatively influence BCI performance, disease severity from early stages to a time before tracheostomy does not significantly affect user aptitude [119, 139]. In another study, ALS patients with more severe motor impairment showed a more widespread cortical activation pattern [140]. This could indicate that superficial stability of performance with disease progression may nevertheless be accompanied by underlying cortical reorganization.
As in the EEG activation studies, some studies using ERPs for BCI controls registered differences in location and amplitude of late ERP components when compared to healthy BCI users as a possible marker for changes in cortical organization. In the study by McCane et al. [119], for instance, the latency of the visual P300, the amplitude of the N200, and the latency of the late negativity was prolonged in ALS patients from controls.

Others have used a visual ERP-based system to investigate EEG measures of connectivity like functional coherence in ALS patients. In one study, researchers looked at directed fronto-parietal and parieto-frontal functional connectivity and showed that feedback connectivity (frontal → parietal) was not different between ALS patients and controls, whereas feedforward connectivity (parietal → frontal) was significantly higher in ALS patients [141]. This indicates that EEG-based connectivity analyses may be useful to map adaptive changes to the neurodegeneration in ALS.

In the auditory domain, researchers have worked towards moving from often monotonous, tone-based, auditory stimuli (such as beeps) towards BCI systems using more natural, speech-based, stimuli. Using a binary auditory streaming paradigm, Hill et al. [118] showed that ALS patients could use the speech stimuli just as well as the tone stimuli to answer simple ‘yes’/’no’ questions.

Some research groups have explored other sensory input routes for ERP-based brain–computer interfacing, for example using vibrotactile [120] or proprioceptive [97] ERPs. However, these systems could only provide very rudimentary and unstable communication of yes/no answers thus far.

One particular challenge for assistive BCIs for paralyzed individuals is making the system work in the patient’s home environment. In a pioneering study, using a P300/EEG-based BCI in six ALS patients, Nijboer and colleagues could demonstrate that such a system can indeed be successfully established in the patient’s home environment [136]. They also showed that the patients could use the system over 40 weeks with a stable amplitude and latency of the P300, with a mean online spelling accuracy of 79%.

In terms of the types of hardware- and/or software-based effectors that can be controlled by P300-based BCIs, some studies have explored solutions that go beyond spelling text for communication. One study, for example, used an asynchronous P300 paradigm to control various domestic items/appliances (such as curtains, lights, and others) in a virtual environment [142] and another study demonstrated the effective use of a P300-based speller to browse the internet [143].

**Using motor-related paradigms for BCI control in ALS patients**

Compared to ERP-based BCI-systems, there are much fewer systems using motor-related paradigm for BCI control in ALS patients. One reason might be that paradigms based on active movements are of course more difficult and sometimes even impossible for ALS patients. In a study by Kübler et al. [144], four ALS patients with severe impairment (two of four had mechanical ventilation and only minimal residual motor function) were trained to control a cursor on a screen by reducing the amplitude of sensorimotor rhythms (µ- and beta-rhythm) via motor imagery of the hands or feet. All four patients achieved sufficient BCI control (>70% correct selection) despite clinical signs of cortical motor involvement indicating, in principle, the feasibility of this BCI system. As mentioned above, the failure to successfully get ALS patients in the CLIS to operate a BCI system, however, has led to the ‘extinction of thought’ hypothesis [85].

Most recently, researchers at the University of Utrecht have presented a fully implantable BCI system in a pilot clinical study with an ALS patient [121]. One paradigm described in the study was based on attempted movement (Vansteensel et al. [121]: ‘[…] trying to move her right hand […]’, p. 2063; which might strictly speaking be distinct from motor imagery in which subjects are instructed to imagine moving their hand, rather than actively attempting to). This paradigm was used for selecting items in a row and column matrix in such a way that attempted movement of 1s generated a ‘brain click’. The navigation across rows and columns was realized by a learned self-regulation paradigm (see next section).

**Using learned self-regulation of brain rhythms for BCI control in ALS patients**

EEG-based systems using learned self-regulation, or neurofeedback, were amongst the first successful BCI systems developed. One example is the original ‘Thought Translation Device’, which used SCPs in pioneering BCI studies in ALS patients [98, 99, 145].

Much like motor-related paradigms, however, BCI systems based on learned self-regulation of brain activity are less common than P300-based speller systems. One reason for this could be that subjects require many training sessions to learn sufficient BCI control. In the study by Kübler et al. [99], for example, two late-stage ALS patients needed three and eight weeks, respectively, to attain sufficient control over the spelling system with one patient progressively achieving a spelling accuracy rate of 80%–90% and the other patients ceiling at 65%.

In a recent paper from the group of author MG-W, the researchers reported results from an experiment using successful learned self-regulation of band power in the gamma range recorded from parietal cortex in two ALS patients with moderate disease severity [146]. Whereas source localization revealed the gamma power modulation to be non-localized, they could localize power in the theta range to the precuneus. This result suggested that self-regulation of parietal gamma oscillations is implemented through networks for high-level cognitive processing, whereas theta power modulation in the precuneus may indicate the involvement of ‘Default Mode Network’ nodes for maintaining conscious awareness.

In the study by Vansteensel et al. [121] the paradigm that the ALS patient used for navigating the row and column matrix in the BCI spelling system was based on learned self-regulation (cp. supplementary table 3). Essentially, the patient learned to regulate the magnitude and timing of her brain signals over sensorimotor cortex by moving the image of a ball up...
and down the computer screen. This control signal was then used to navigate the row and column matrix. The actual selection of the items was then achieved by the motor paradigm described above (attempted movement of the right hand) in which attempted movement of 1s generated a ‘brain click’ for selecting an item on the screen.

**Using BCIs in ALS patients in the locked-in state**

While the studies with the locked-in ALS patients detailed in supplementary table 3 show some success in measuring sensory-evoked potentials and task-based ERPs in these patients, stable use of a BCI proved much more challenging.

**Prima facie,** by their nature, motor-related paradigms based on active movements are not useful in the CLIS and very limited in the partial locked-in state as oculomotor movement capability often fluctuates and tires quickly. In and of themselves, paradigms based on motor imagery, though, could conceivably still work in the locked-in state. Yet, in reality, no reliable and stable BCI system based on motor-imagery could thus far be established in completely locked-in ALS patients. This poses interesting questions on the integrity of cognitive motor networks for goal-directed behavior in the CLIS—captions of the ‘extinction of thought’ hypothesis. This leaves learned self-regulation and ERP-based paradigms as the most promising approaches to brain–computer interfacing in ALS patients.

In the pioneering studies by the research group at the University of Tübingen [98, 145], the researchers used learned self-regulation of SCPs to operate a spelling device in two ALS patients in the partially locked-in state. Both patients were able to achieve a spelling accuracy of at least 75% after 327 and 288 sessions, respectively. Later, in a study by Iversen et al [147], two partially locked-in ALS patients were trained to use SCP to direct 2D cursor movement to choose between two targets to differentiate stimuli according to certain properties (e.g. odd versus even numbers). After several training sessions, the patients were able to operate the cursor and complete the simple two-choice tasks with nearly 90% accuracy but had difficulties with more complicated tasks like mental calculation.

In a study measuring an unusual physiological target parameter—changes in saliva pH via food imagery—in an ALS patient in the locked-in state, Wilhelm et al [148] showed that this paradigm can be used for communication via simple yes/no answers. The affiliated neurosurgeons then implanted the patient with a subdural ECoG grid (unfortunately the anatomical location of the implant is not specified in the article) in order to establish communication with ECoG-based ERPs. After successful implantation, the researchers did not succeed in establishing sustained communication with the patient, with neither EEG or pH regulation.

Some of the studies detailed in supplementary table 3 used the task-based paradigms to establish a BCI for communication with ALS patients in the locked-in state. Both the earlier studies by Murgualday et al [97] and Bensch et al [86], and the recent study by Vansteensel et al [121] demonstrated, that brain signals from somatosensory cortex generated by motor imagery and learned self-regulation can be successfully leveraged for operating a BCI communication system in the partially locked-in state. In the one patient which was longitudinally examined in the studies by Murgualday et al [97] and Bensch et al [86], however, no successful communication could be established once the patient had transitioned into the CLIS.

The study by Vansteensel et al [121] with a partially locked-in female ALS patient also demonstrated the effectiveness of leveraging brain activity elicited by different paradigms for BCI control by combining a motor-related paradigm (for row and column navigation) and learned self-regulation (for item selection). A crucial innovative aspect of that study was the fact that the brain signals were recorded intracranially from four implanted subdural electrodes, further supporting the safety and feasibility of an intracranial BCI system in ALS patients.

In another recent study by [149], a partially locked-in ALS patient was able to operate a BCI based on extracranial EEG with 62.5% decoding accuracy (above chance level of 50%) using gamma-oscillations recorded with EEG from parietal cortex for learned self-regulation. The subject was a fifty-three year old woman who developed ALS fifteen years ago and was now in a partially locked-in state with only intermittently remaining oculomotor control that enabled her to answer yes/no questions. This shows that viable control signals can also be obtained from areas outside of the primary sensorimotor cortex.

As for ERP-based BCI systems, contrary to the proportion of studies for non-locked in patients, auditory ERPs also seem to be reliable for establishing BCI control for communication in locked-in ALS patients. With a BCI system using an auditory oddball as well as on operant semantic conditioning paradigm in three patients with advanced ALS (one completely locked-in), De Massari et al [88] showed that basic attentional processing was preserved. The completely locked-in patient did not achieve a stable and reliable level of BCI performance over thirty-seven sessions, which the authors attributed mainly to fluctuating levels of vigilance and attention.

A promising trend in the studies reviewed here is that different tasks and paradigms can be combined effectively for BCI control. For example, using an EEG-based P300 auditory oddball paradigm for multiple choice answers and SCPs for neurofeedback in a fifty-eight year old ALS patient in the CLIS, Hinterberger et al [150] were able to achieve 62% correct responses after only three training sessions.

**Summary:** EEG- or ECoG-based BCI systems using activation paradigms

For ALS patients, paradigms for BCI control based on active movements are not useful for later disease stages given the progressive paralysis. For ERP-based paradigms, we found that visual paradigms were more widely used in ALS patients than auditory paradigms in all disease stages but the locked-in state, in which more studies used auditory ERPs successfully. One reason for this could be that the locked-in state often results in corneal damage which can significantly impair the input quality of a visual paradigm [7, 97, 151].
Paradigms based on motor imagery and learned self-regulation in BCI systems with EEG or ECoG, however, have been used successfully in severely paralyzed (including partially locked-in) but not in completely locked-in ALS patients thus far. A major limitation of all the studies reviewed here is that, while they demonstrate in principle that partially locked-in ALS patients can operate a BCI system for communication, they do not show this for an extended period and we found no clear documentation on whether ALS patients were trained prior to entering the locked-in state.

Overall summary, discussion and conclusions

For a quick overview of the main findings and implications for future BCI research with ALS patients from our review, see box 3.

Box 3. Key findings and implications for future BCI research with ALS patients

1) Finding: There is a substantial lack of research on basic electrophysiological measurements, such as evoked potentials, resting-state, and task-based EEG particularly in late-stage / locked-in ALS patients. Implications: More basic electrophysiological research, particularly longitudinal and into late stages of ALS, could help to (a) evaluate the integrity of basic efferent sensory pathways with disease progression; (b) investigate resting-state networks, connectivity patterns and high gamma activity in EEG as potential biomarkers for degeneration in non-motor cortical regions in ALS.

2) Finding: Across studies, ALS patients with bulbar onset show more ERP abnormalities than limb onset ALS patients, possibly related to higher comorbidity with frontotemporal dementia in this subgroup. Implications: This finding should be replicated in a group of ALS patients with bulbar onset but without clinical, neuropsychological, genetic or imaging evidence for FTD. If ALS patients with bulbar onset (and without FTD) have more ERP abnormalities, perhaps motor-related or cognitive paradigms should be considered as viable alternatives for BCI control.

3) Finding: The most common paradigms for non-invasive BCI systems in ALS patients are currently based on ERPs and learned self-regulation of SCPs, but these may have limits in terms of user-friendliness and assistive performance. Implications: More research in ALS patients should be performed with motor-related (particularly motor imagery) and cognitive tasks such as high-level goal-directed tasks to explore their potential for BCI control and broaden the range of applicable solutions. On the decoding side, new machine learning methods with potentially superior performance, such as artificial neural networks for ‘deep learning’, should also be explored to optimize the performance of future BCI systems in ALS patients [152].

In the following discussion, we first address the role of basic diagnostic electrophysiological measures in late-stage ALS. Then we summarize the findings from the studies using ERP-related, motor-related or learned self-regulation activation paradigms for EEG/ECoG-based research and/or BCI systems. We then integrate these findings to the natural disease ecology of ALS with particular focus on late-stage and the locked-in state. Along the way, we also consider the interweaving implications for current models of neurodegeneration in ALS and discuss the ‘extinction of thought’ hypothesis in locked-in ALS patients.

Measuring sensory evoked potentials and ‘resting-state’ EEG in ALS patients

In summary, we found no studies that systematically measured sensory evoked potentials or ‘resting-state’ EEG, MEG or ECoG in late-stage/locked-in ALS patients. This lack of basic electrophysiological research is worrying, given that studies reviewed above demonstrated alterations of SEPs in ALS patients in the early and middle stages of the disease, which could indicate damage to central sensory pathways as is suggested by recent models of neurodegeneration in later stages [5]. In our view, more basic electrophysiological research is crucial in order to map the longitudinal changes from early to late-stage ALS, particularly in the locked-in state.

The same is true, in our view, for ‘resting-state’ EEG studies in late-stage ALS. Non-motor involvement in ALS is by now well documented, particularly in the disease spectrum of ALS and frontotemporal dementia [90]. New methods of multichannel EEG analyses are available for investigating network connectivity with measures like phase coherence in the high-gamma band [153]. High-gamma band activity may also be a useful control signal for operating a BCI system via self-learned regulation, which makes this line of research particularly salient for tailoring BCI systems to the specific needs of locked-in ALS patients [149]. Research from intracranial and lately also extracranial EEG suggests that Gamma band is an important direct marker for neuronal activity, for example in the context of error processing in the brain [154].

Moreover, the studies either did not report whether patients with a family history of ALS were included—leaving open the possibility that the study sample could be influenced by pathological cortical changes related to an ALS-FTD overlap—or explicitly excluded patients with familial (genetic) ALS (in earlier studies based on family history, lately also by screening for C9orf72 mutation). Therefore, we would recommend to study evoked potential and resting-state EEG in a large patient sample that includes both patients with sporadic and familial ALS types to investigate the influence of ALS-FTD overlap on cortical electrophysiology.

Furthermore, since the ‘extinction of thought’ hypothesis, discussed below, hinges on the idea of a lockdown of crucial brain circuits for higher cortical functions (like mental imagery or goal-directed thinking) as a result of the de-efferentation in the locked-in state, investigating oscillatory networks with
multichannel EEG may also shed light on changes in network topography in late-stage ALS.

Therefore, we think it is important to investigate basic multimodal sensory ERPs as well as multichannel ‘resting-state’ EEG in a cohort of ALS patients longitudinally, documenting the electrophysiological changes during the disease progression to the locked-in state.

**EEG/ECoG-based activation paradigms for research and BCI systems**

Unfortunately, the heterogeneity of the studies—due to different activation paradigms (ERP, self-regulation, motor-related), the different analysis methods used within any specific paradigm (e.g. visual P300), and the fact that some studies used extracranial and others intracranial EEG—does not allow for a quantitative meta-analysis of EEG parameters across the studies identified here. However, all studies reported abnormalities of ERPs (early as well as late components) in ALS patients even in patients without major cognitive deficits, suggesting a possible role as a diagnostic tool to assess basic perceptual as well as cognitive brain function in ALS patients. These measures, if explored more systematically, could also inform the optimal site of recording for future intracranial BCI systems.

The ERP abnormalities can be related to frontal and prefrontal regions involved in executive functions like attentional processing and memory deficits (recognition, context integration), as well reticulo-thalamo-cortical networks involved in novelty detection and discrimination. These findings tie in to converging evidence from NPT, neuroimaging, as well as clinical and genetic data. Studies using NPT in ALS patients also demonstrated deficits in executive functions and memory associated with prefrontal regions [155, 156]. Morphometric neuroimaging studies show atrophy in non-motor regions, particularly in the prefrontal cortex [157, 158]. Clinically and genetically, increasing evidence points to an overlap of some types of ALS with frontotemporal dementia in ALS-FTD, for example as result of the C9orf72 hexanucleotide repeat expansion [159–161]. Mapping these motor and non-motor changes across different methods has led to the notion that neurodegeneration in ALS is essentially an ‘anterior brain disorder’ [4]. Yet, we do not know whether this is also the case in later disease stages, particularly in the locked-in state or whether widespread ‘posterior’ non-motor degeneration occurs. For future invasive intracranial BCI systems, like the BrainGate system [162] or systems based on micro-electrocorticography (micro-ECoG), identifying the brain region that promises the most stable neural recordings for long-term use in the locked-in state is a crucial challenge.

In the studies reviewed here, P300 spellers are the most common BCI system for communication in ALS patients. In these ERP-based BCI control paradigms, visual ERPs (thirteen studies) are more often used than auditory ERPs (five studies), most likely because of the tediousness of an auditory oddball paradigm for subjects.

In the auditory domain, researchers have also suggested to go beyond simple oddball discrimination tasks by leveraging the spatial hearing capabilities of the human auditory system for BCI control. In a study with healthy subjects using spatially distributed auditory cues [163] Schreuder and colleagues demonstrated high selection scores (mostly >90%) and information transfer rates (mean approx. 17 bits min⁻¹). With a single speaker, the selection score fell to <70% in most subjects.

Using an auditory paradigm involving natural sounds and spatial information (via directional cues) in patients with ALS [164], Halder and colleagues have shown, that such more complex auditory stimuli may indeed be successfully used for BCI control with high selection accuracies (depending on the stimulus ranging from approx. 55% to approx. 67%), although with a lower information transfer rate (mean approx. 5 bits min⁻¹) than healthy subjects usually attain.

These studies suggest that, over and above the classical auditory ‘oddball’ ERP tasks, the capacity to process complex auditory stimuli, particularly involving cues for spatial hearing, may improve BCIs based on auditory ERPs.

There is some evidence from research on healthy subjects, that the performance of these original P300 spelling systems can be improved in classification accuracy and information transfer rate, for example by the online use of error-related potentials [114]. To which degree such auxiliary methods for improving P300 spellers also translates into improving BCI performance in ALS patients is not explored sufficiently yet.

Because BCI aptitude varies considerably in healthy as well as severely paralyzed users, an auditory oddball task may be useful to screen for BCI ‘illiteracy’ (which might, however, be paradigm-specific) before embarking on months of possibly frustrating BCI training for the patient [130]. Whether and to what degree this BCI illiteracy is specific to control paradigms (in healthy subjects and patients) and which ALS-specific factors contribute to the inability to learn any specific BCI paradigm, however, has thus far not been studied extensively.

For example, irrespective of the sensory input domain, it seems reasonable to assume that BCI performance will also be influenced by cognitive processes, such as attention or memory. So far, this question has received relatively little attention within the BCI community. In a study using two behavioral paradigms in patients with ALS [165], researchers found the temporal filtering capacity in a rapid serial visual presentation (RSVP) task predicted BCI spelling accuracy (and the P300 amplitude). Now, given the possible degeneration of frontal areas involved in executive attention networks in ALS, we do not know whether (and to what degree) attentional attentional processing might have been impaired in the ALS patients in this study. Nevertheless, the study points to the importance of studying the role of ‘higher-order’ cognitive processes—such as attention, language, or memory—for BCI performance, particularly in patients with disorders (such as ALS) that might affect large-scale brain networks maintaining these processes.

The review by Marchetti and Priftis [166] posits that ‘[…] there is not as yet clear evidence of BCI effectiveness with ALS patients, and the studies with ALS in CLIS have been unsuccessful […].’ We concur with this assessment to some degree, particularly as the three general categories of paradigms (ERPs, learned-self regulation of SCPs and motor-related)
have essentially remained the main strategies for BCI control in ALS patients and have clear limits. We expect and hope, however, that future research will also explore novel strategies. At the task level, using higher-level cognitive tasks, such as planning-related brain activity, that are already used in BCIs in healthy subjects [152], should be translated to clinical research with ALS patients. A user-centered approach in developing BCI solutions for ALS patients would therefore include the empirical study of BCI aptitude of various control paradigms and across tasks in ALS patients to find the optimal system for each patient.

At the decoding level, emerging machine learning methods based on artificial neural networks have recently shown promising results in decoding and visualizing brain activity [167] and could also be used in BCIs for ALS patients.

Importantly, with respect to mapping cognitive changes in ALS, EEG-based measurements have important advantages over imaging methods and extensive neuropsychological workup in terms of mobility, adaptability to the patient’s home environment and applicability in later disease stages, particularly the locked-in state [168]. Therefore, they could be an important longitudinal biomarker for charting cognitive changes throughout the disease progression in individual ALS patients, even in the locked-in stage. Furthermore, the ERP-based BCI systems’ usability seems to be to some degree independent of the disease severity [119, 139]. However, it is also important to recognize that, while no clear relationship between disease severity and BCI aptitude exists, bulbar onset ALS is associated with a higher likelihood of developing frontotemporal dementia and has an overall worse prognosis. This makes finding a satisfactory BCI solution for this subgroup of patients on the ALS-FTD spectrum particularly challenging [169, 170].

For the future, we suggest, it is important to move beyond the currently existing variety of activation paradigms and investigate ‘internal’ cognitive and meta-cognitive processes like mind-wandering or self-referential thinking (for a recent example see [171]) as potential electrographic markers (and BCI control signal) in ALS.

There are also other medical factors to consider that may negatively influence BCI use. For example, due to insufficient lacrimation with subsequent abrasive corneal damage, ALS patients in the late-stage and locked-in state often have visual problems, which may limit the use of visually guided BCI systems. Extra-medical factors that should be considered in developing of a BCI system are computational design issues (like user-friendliness, redundancy and computational efficacy) and psychological factors like emotional adjustment to the disease, coping strategies, as well as quality of life [9, 20, 172–175].

Importantly, considering the different activation paradigms for electrographic BCIs, we want to point out that not every BCI system is equally useful for ALS patients in the partial or complete locked-in state. As many of the studies show, different control paradigms are not mutually exclusive either and may be combined effectively for BCI control.

Neurodegeneration in late-stage ALS evidence from electrophysiology, neuroimaging and neuropathology

Overall, very little in vivo data on the structural and functional integrity of brain regions in late-stage ALS, particularly the locked-in state, are available. In particular, our review shows that very few studies have systematically tested basic or advanced electrophysiological brain measures in late-stage ALS.

With regard to the dynamics and anatomy of system degeneration, ALS is now considered to be an ‘anterior brain disorder’ with involvement of brain regions outside of primary sensorimotor cortex, such as prefrontal and temporal cortex [4, 5]. While it seems that posterior brain regions like parietal and occipital cortex are much less affected, a caveat is that we do not yet know whether that is also true also in patients in the locked-in state with long disease duration as very little data from neuropathology and neuroimaging in this subpopulation of ALS patients is available.

This makes visual and auditory ERP-based paradigms, in theory, particularly attractive for BCI control because they tap brain regions that may be less affected than in paradigms relying on sensorimotor cortex like motor-related paradigms.

However, as the cortical degeneration in later disease stages, particularly in ALS-FTD overlaps, spreads to prefrontal areas, all BCI paradigms that rely on intact attentional processing and fronto-parietal attention networks could be limited in their applicability. Therefore, exploring other BCI control signals that are less reliant on attention networks, e.g. based on lower-level emotional processing might help in such circumstances.

Notably, some studies have shown prolonged latencies and reduced amplitudes in late ERP components in visual and auditory paradigms between ALS patients and healthy controls in ERP-based studies. This finding suggests that these late components may indeed be markers of dynamical cortical changes—either representing neurodegeneration or adaptive plasticity. Importantly, these differences in the temporal and local properties of late ERP components could be useful to assess cortical progression in ALS. This may also have implications for the selection of channels in non-invasive and the placement of electrode grids in invasive BCI applications in the future.

Despite enormous development in modern neuroimaging protocols, no studies are available that have mapped changes in structural or functional MRI or PET in individual patients from early to late-disease stages. Currently, only the neuropathology literature provides evidence on the patterns of neurodegeneration in ALS. Analyzing pTDP-43 deposits in the brain of 76 deceased ALS patients, researchers were able to identify distinct patterns of neurodegeneration in relation to the disease stage [5]. In stage 1, neurodegeneration was mostly found in bulbar and spinal somatomotor neurons. In stage 2, the pathologists found additional pTDP-43 deposits in the pontine reticular formation and precerebellar motor nuclei. The prefrontal cortex and the basal ganglia become
involved in stage 3. Stage 4 is characterized by the spread of neurodegeneration to anteromedial parts of the temporal and hippocampal cortex. One important limitation of this study is, in our opinion, that though many different clinical parameters (like site of onset, disease duration and ALSFRS-R) were recorded, it is not clear from the paper what the exact criteria were for assigning the patients to the particular stages.

Additionally, it is an unsettled issue whether pTDP-43 deposits are specific and reliable neuropathological marker of ALS at all. The family of TDP-43 proteins are essentially DNA-binding proteins that are an important component of ubiquitin-positive and tau-negative cytoplasmic inclusions which have been found in a variety of neurodegenerative diseases including ALS, frontotemporal lobar degeneration, Alzheimer’s dementia and Lewy body dementia [176, 177]. To complicate matters further, a recent neuropathological study of 286 autopsy cases has found an increased TDP-43 deposition in the anterior hippocampus with normal aging without marked neuropsychological impairment [178]. Furthermore, we know very little about the mechanisms and extent of adaptive processes like synaptic plasticity that may counter, modulate, or perhaps even worsen (‘maladaptive plasticity’) the relentless neurodegeneration in ALS. Given that various hypotheses postulate the coexistence of pyramidal cell degeneration and non-motor degeneration with mechanisms of adaptive plasticity and/or compensatory cortical changes, this issue should be studied in more detail [179].

Nevertheless, given the lack of other biomarkers for the non-motor extent of neurodegeneration, these neuropathological findings allow the best approximation yet. For the time being, we take these aggregated findings as evidence that posterior brain regions, like the superior and IPL or the occipital lobe, do not seem to be markedly affected in late-stage ALS.

Cognition in the CLIS in ALS: beyond the ‘extinction of thought’ hypothesis

The main goal of brain-computer interfacing in ALS patients at present is to preserve communicative abilities. One aspect that has emerged from the various studies reviewed here is that motor-related paradigms based on movements or motor imagery do not seem to be very promising for BCI control in ALS patients. As mentioned, the total loss of voluntary motor control in the CLIS makes paradigms based on active movements impossible. Importantly, the locked-in state in ALS patients, in our experience, is not a binary state but rather a continuum of declining motor functionality over time. Initially remaining motor abilities fluctuate depending on a patient’s level of alertness, wakefulness and overall condition. As the disease progresses we notice that the periods in which yes/no communication can be maintained with oculomotor movements become less frequent until at some point some patients transition to the CLIS. While early BCI training for communication as well as continued and frequent BCI use throughout later ALS stages may prolong the period in which communication is maintained, it may still turn out that BCIs do not work indefinitely in ALS patients in the CLIS.

Accordingly, rather than asking ‘Can ALS patients in the CLIS use BCIs at all?’ it might be a more meaningful research program to ask ‘How much longer can late-stage ALS patients communicate with BCIs in comparison to other assistive communication devices?’.

There are important limitations to interpreting the results from the studies reviewed here. First, only a small number of ALS patients in the locked-in state have been equipped with a BCI system so far and no longitudinal electrophysiological, neuropsychological, or neuroimaging data for these patients are available. Importantly, the fluctuations of attention, awareness and vigilance in locked-in patients is an important factor for successful brain-computer interfacing [88] and should be explored more systematically in future studies. Furthermore, no adequate neurological controls were used in any of the BCI experiments with ALS patients to date. While some studies compared the BCI ability, decoding accuracy and performance of ALS patients and healthy controls, no study used neurological controls—like locked-in stroke patients—to compare BCI performance. Overall, these limiting factors make it difficult to determine the crucial factors for problems or in some cases complete failure in using a BCI system in each case.

At the heart of the ‘extinction of thought’ hypothesis lies the idea that the complete cessation of motor function results in a functional down-regulation of cortical networks for maintaining higher-order cognition, specifically goal-directed and intentional thinking, in the locked-in state. This view, which we may call ‘motor essentialism’, presupposes that effective motor function is a necessary condition for higher-order cognitive capacities. In terms of theoretical legacy, this view is grounded in theories of the inter-linkage between perception, motor and action systems in the brain [180, 181]. In this family of theories, Gentsch et al [180] distinguish three main branches: (a) theories of ‘common coding’, (b) theories relying on ‘internal models’, and (c) ‘simulation theories’. Building on this account, theories of ideomotor integration posit a bidirectional link between sensory and motor representations in which percepts automatically activate associated motor representations. This idea would belong to the ‘common coding’ class and the concept of ‘motor imagery’, i.e. the idea that covert motor action relies on the simulation of motor ‘images’ in premotor centers, would belong in the class of ‘simulation theories’.

Crucially, while the ‘ideomotor integration’ account is dependent on a physically intact cortical motor system, the concept of ‘motor imagery’ is to some degree independent of the integrity of sensorimotor cortex. This is supported by observations in patients with brain lesions which supports an anatomical dissociation between motor imagery and concrete motor action [182]. Whereas damage to left prefrontal [183] and parietal [184, 185] cortex can lead to impaired capacity for motor imagery while preserving motor function, damage to sensorimotor cortex does not necessarily result in deficits of motor imagery [186, 187]. Based on the available neuroimaging and electrophysiological data reviewed here, it seems that the principal locus of neurodegeneration in ALS—as an ‘anterior brain disorder’—lies in the frontal cortex and largely spares posterior parietal areas [157, 188]. However, we do not presently know, whether the neurodegeneration in late-stage...
ALS routinely spreads to more posterior non-motor regions and if so, what the determining factors in terms of genetic susceptibility (other than the known factors like SOD1 and C9orf72) are or for which subtypes within the ALS disease spectrum this may be the case [90]. For example, neuroimaging and neuropsychological studies in bvFTD, show that apathy as a key feature in bvFTD—and thus in patients with ALS-bvFTD overlap—may lead to impaired goal-directed behavior which may seriously affect BCI performance in those patients [189].

With the disintegration of crucial regions for sensorimotor processing in ALS, particularly in the motor cortex and prefrontal cortex, as the disease progresses, several large-scale networks for maintaining cognitive motor loops (for example for motor imagery, pantomime and others) may also become impaired. Conceivably then, establishing a stable BCI for effective cognitive motor interaction could help to preserve these functions even in later stages of the disease. Thus, perhaps the capacity for motor imagery in the locked-in state could be preserved if patients are trained early with feedback-based BCI paradigms using posterior parietal activity.

Apart from motor imagery paradigms, ALS patients in the CLIS, in our experience, also have difficulties in modulating motor-related mu-rhythms. Thus, ERD signals are unlikely to be useful for motor-related BCI use. Thus, it may be the case that motor imagery and/or motor-related BCI paradigms are particularly challenging for ALS patients in the late stage.

The current literature on motor imagery for EEG-based BCI control, however, does not allow for much conclusion with respect to its general usefulness as a paradigm in ALS patients. The work from studies with intracortical electrode arrays (‘Utah array’, Braingate trials), however, does suggest that activity recorded from the Gyrus praecentrals during motor imagery can be used to control a BCI in ALS patients [162] and it would therefore be important to further study whether intra- or even extracranial EEG measures during motor imagery could be harnessed for BCI control with similar effectiveness.

Crucially, a recent study using a BCI-System based on NIRS as control signal reported to have established above-chance level communication with a patient in the CLIS [190]. In the study, the patient was presented with sentences with known and unknown answers and instructed to think ‘yes’ or ‘no’ after each sentence. Whether or not this study conclusively falsifies the ‘extinction of thought’ hypothesis is certainly debatable, depending on whether one considers the task (thinking ‘yes’ or ‘no’) as particularly representative for goal-directed behavior or not. However, if replicable with other paradigms (and other recording methods) the study might well be the first indication that ‘extinction of thought’ in the CLIS is by no means a necessary outcome in late-stage ALS.

For the future (see box 3), we therefore advocate for more in-depth research on cortical function in late-stage ALS, particularly the locked-in state, using the full range of available (and ethically feasible) in vivo measurement tools, particularly electrophysiological and neuroimaging methods.

Gathering and integrating further data on the structural (MRI, neuropathology) and functional (fMRI, NIRS, EEG/ECoG) changes across brain regions and networks in late-stages of ALS would be an integrative and comprehensive translational research program for finding suitable and sustainable BCI solutions for this patient group.

Furthermore, the thorough investigation of the quality and stability of electrophysiological cortical signals over motor and non-motor cortical regions may help researchers to move towards a more individualized and user-centered design of BCI systems that takes the capabilities and needs of ALS patients into account [191, 192].

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Conflicts of interest

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