Motor imagery in amyotrophic lateral Sclerosis: An fMRI study of postural control

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ABSTRACT

Background: The functional reorganization of brain networks sustaining gait is poorly characterized in amyotrophic lateral sclerosis (ALS) despite ample evidence of progressive disconnection between brain regions. The main objective of this fMRI study is to assess gait imagery-specific networks in ALS patients using dynamic causal modeling (DCM) complemented by parametric empirical Bayes (PEB) framework.

Method: Seventeen lower motor neuron predominant (LMNp) ALS patients, fourteen upper motor neuron predominant (UMNp) ALS patients and fourteen healthy controls participated in this study. Each subject performed a dual motor imagery task: normal and precision gait. The Movement Imagery Questionnaire (MIQ-rs) and imagery time (IT) were used to evaluate gait imagery in each participant. In a neurobiological computational model, the circuits involved in imagined gait and postural control were investigated by modelling the relationship between normal/precision gait and connection strengths.

Results: Behavioral results showed significant increase in IT in UMNp patients compared to healthy controls (P_corrected < 0.05) and LMNp (P_corrected < 0.05). During precision gait, healthy controls activate the model’s circuits involved in the imagined gait and postural control. In UMNp, decreased connectivity (inhibition) from basal ganglia (BG) to supplementary motor area (SMA) and from SMA to posterior parietal cortex (PPC) is observed. Contrary to healthy controls, DCM detects no cerebellar-PPC connectivity in neither UMNp nor LMNp ALS. During precision gait, bilateral connectivity (excitability) between SMA and BG is observed in the LMNp group contrary to UMNp and healthy controls.

Conclusions: Our findings demonstrate the utility of implementing both DCM and PEB to characterize connectivity patterns in specific patient phenotypes. Our approach enables the identification of specific circuits involved in postural deficits, and our findings suggest a putative excitatory–inhibitory imbalance. More broadly, our data demonstrate how clinical manifestations are underpinned by network-specific disconnection phenomena in ALS.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive and fatal neuromuscular disease. The motor clinical picture of ALS is characterized by increasing spasticity, weakness, postural instability, backward falls, impaired postural reflexes, retropulsion, bradykinesia, and rigidity (Feron et al., 2018; Pradat et al., 2009). Numerous studies have investigated the neuronal substrate of motor and gait impairment in amyotrophic lateral sclerosis (ALS) and it is thought to be driven by multi-network degeneration affecting motor, extra-pyramidal and cerebellar circuits (Feron et al., 2018). Based on longitudinal functional studies, it had been postulated that despite relentless cerebral and spinal degenerative changes compensatory processes may occur during the course of ALS (Proudfoot et al., 2019). The study and characterization of
adaptive functional processes may help to develop effective rehabilita-
tion strategies and potentially slow functional decline. One of the key
facets of clinical heterogeneity in ALS is the relative involvement of
upper and lower motor neurons which defines the clinical phenotype,
determines the disability profile of patients and ultimately their care
needs.

The neuronal underpinnings of physiological gait and postural con-
trol have been successfully studied by functional magnetic resonance
imaging (fMRI) and positron emission tomography (PET) using a motor
imagery task (Jahn et al., 2008; Fougère et al., 2010) which confirmed
the pivotal role of the supraspinal locomotor network encompassing
the supplementary motor area (SMA), the posterior parietal cortex (PPC),
the basal ganglia (BG), and cerebellum. There is compelling evidence
that imagined movements are largely analogous to executed movements
with regard to intention, motor planning, and motor control (Marc
Jeanne, 2001) and both tasks result in similar activation patterns (M.
Jeannerod, 1995). This analogy is crucial to study populations with
considerable motor disability (Lalet et al., 2007).

The majority of motor imagery studies have focused on the extent of
brain activation, and interaction within the motor system is poorly
characterized. Several fMRI studies have used functional connectivity
methods to investigate correlations between time series across the brain.
They found functional alterations and large-scale brain networks
disconnection. However, these correlational methods do not reveal the
causal influence of one neural system on another (Friston, 2011). In
order to overcome this methodological limitation, some authors have
advocated for alternative approaches, such as the assessment of ‘effective
connectivity’ which is defined as the directed (causal) influence of
one (neuronal) system on another, which is inferred by modeling the
neuronal interactions that generate BOLD time series (Friston et al.,
1997). This generative approach, called dynamic causal modelling
(DCM), is strongly hypothesis driven. Among all known effective con-
nectivity methods such as structural equation modeling (SEM), multi-
variate autoregressive modeling (MAR) and Granger causality (GC),
DCM is a well-established determinist method permitting the modeling
of causal influences among different brain regions (Friston et al., 2003).
By modeling time-varying hidden parameters that affect the trans-
formation of neuronal activity into a hemodynamic response, DCM es-
imates the temporal precedence of one neuronal system over another
and assesses how changes in one system linearly and nonlinearly influ-
ence another, how changes in multiple systems influence each other
across time and how those neural interactions are influenced by external
perturbations.

In this fMRI study, we aimed to investigate neural interactions in
the motor system during imagery to characterize hemodynamic responses
in a cohort of clinically stratified ALS patients. We hypothesized that
implementing state-of-the-art models such as DCM, we will succeed in
describing effective connectivity patterns within a large-scale brain
network, including the gait circuits. This is in sharp contrast with the
method of the psychophysiological interactions (PPI), which operates at
the level of the measured BOLD signal and focuses on a single source
region. The evaluation of a single seed region limits the extent to which
one can infer causal relationships in the brain, making the interpretat-
ion of the interactions ambiguous. Furthermore, the absence of a forward
model linking neuronal activity to the measured haemodynamic BOLD
signals makes analyses of inter-regional connectivity by PPI problematic.

The advantage of DCM is that the coupling between models of neural
dynamics and biophysical forward models is a mandatory component
(Friston et al., 2011). Moreover, this causal method offers new insights
into the pathophysiology of neurological disease and potentially into
pharmacodynamics (Rowe et al., 2010). Accordingly, our objective is
to investigate the effective connectivity with DCM, among four key motor
regions: the supplementary motor area, the posterior parietal cortex, the
cerebellum and the basal ganglia, which are known to closely interact
during motor-imagery of gait (Abidi et al., 2021; Bakker et al., 2008; la
Fougère et al., 2010). Using a plausible neurobiological model of
imagined gait, our study aims to capture phenotype-specific connec-
tivity patterns within the gait control and postural control circuits in
ALS. Our overarching objective is the demonstration of differential
network degeneration in clinical phenotypes and showcase the utility of
imagery based paradigms in studying patient cohorts with significant
motor disability.

2. Materials and methods

2.1. Subjects

This study was approved by the institutional research board of the
CPP Ile-de-France Paris VI. Thirty-one patients with ALS and 14 age-
and gender-matched healthy controls gave informed consent to participate
in this study. Based on standardized clinical evaluation (Simon et al.,
2015), ALS patients were divided into two subgroups: a UMNp cohort (n
= 14) and an LMNp group (n = 17) (Table 1). Clinically, UMNp patients
exhibited frank UMN predominance based on established UMN signs,
such as marked spasticity, Hoffmann sign, Babinski sign, clonus etc.
UMN burden was estimated based on the revalidated Penn UMN score
(Quinn et al., 2020). LMNp patients showed obvious clinical signs of
LMN pathology predominance such as decreased tone, muscle atrophy,
fasciculations etc. Inclusion criteria included ‘definite’ or ‘probable’ ALS
according to the revised El Escorial criteria (Brooks et al., 2000), age
between 18 and 70 years, right-handedness. Exclusion criteria included
frank frontotemporal dementia based on the Bascovsky criteria, co-
morbid musculoskeletal conditions that would have interfered with
functional evaluation, and contraindications to MRI.

All participants underwent a standardized clinical examination on
the day of imaging. Functional impairment was evaluated by the revised
ALS Functional Rating Scale (ALSFRS-r). Disease progression rate was
calculated as ((48-ALSFRS-r)/disease duration in months). All partici-
pants also underwent a comprehensive neuropsychological evaluation
including tests for memory, executive, language and visio-spatial do-
 mains (Table 1).

2.2. Motor imagery paradigm

The paradigm consisted of two tasks: a motor imagery (MI) task and
a visual imagery (VI) task. Both tasks were tested with normal loco-
motion (broad path) and with complex locomotion (narrow path).
A total of four photographs were used for the experimental procedure (i.e.,
two start pads × two path widths). Subjects were asked to observe the
photograph for 3 s and then they were asked to imagine performing the
task while keeping their eyes closed.

Participants were given written instructions before the training ses-
sions and the fMRI experiment. On the day of the scan, the instructions
were explained again, and a practice session was organized outside the
scanner to simulate the procedure before data acquisition commenced
inside the scanner.

During the MI task, subjects were asked to imagine walking along the
path in an egocentric perspective called “first person.” However, during
the VI task participants had to imagine observing a black disc moving
along the trajectory. The VI was used as a control condition (Fig. 1).

2.3. Motor imagery scores: The visual and kinesthetic scales

Computation of mean scores (average, standard deviation [SD]) was
carried out for each scale VI and KI in each group. The resultant values
may vary from 1 to 7, with a score of 7 constituting maximal motor
imagery ability. The 2 × 3 repeated-measures ANOVA compared VI and
KI scores between groups and were carried out using Statistica 13.0
software. P < 0.05 was considered significant.
imagery (MI), visual imagery (VI) and path width (narrow, wide) on agery time (IT) was recorded. Furthermore, the effects of task (motor -
- For each trial, the time between the two button presses that marked errors (matrix B) representing changes in endogenous connection strength due to external perturbations and (c) direct influence of an external input (driving input) to a region (matrix C) (Friston et al., 2003; Pool et al., 2013). In addition to interactions between regions, DCM allows for external stimuli to influence regions, either directly or by modifying the connections between regions.

We hypothesized that the average strengths of endogenous and

2.5. MRI data acquisition

MRI data were acquired with a 3 T Siemens (Erlangen, Germany) Prisma platform using a 32-channel head coil. T1-weighted structural images were acquired with a magnetization-prepared rapid acquisition-gradient echo (MP-RAGE) sequence with a repetition time (TR) / echo time (TE) = 2300/4.2 ms, inversion time (TI) = 900 ms, and isotropic 1 × 1 × 1 mm voxel size. Functional images were obtained using a single-shot gradient echo (GE-EPI) sequence. A total of 700 EPI volumes were acquired with TR/TE = 2020/27 ms; flip angle = 78°; field of view (FOV) = 198 × 198 mm2 for the motor paradigm using 3 mm slice thickness.

### Table 1

The demographic and clinical profile of study participants.

|                          | Healthy controls (n = 14) | UMN predominant ALS patients (n = 14) | LMN predominant ALS patients (n = 17) | p value |
|--------------------------|---------------------------|---------------------------------------|---------------------------------------|---------|
| Age (years)              | 63.0 (57.0–66.0)          | 59.0 (20.0–71.0)                      | 62.0 (31.0–74.0)                      | 0.39    |
| Sex (female/male)        | 5/9                       | 3/10                                  | 6/11                                  | 0.29    |
| Height (cm)              | 170 (168–175)             | 171 (157–187)                         | 176 (154–186)                         | 0.34    |
| Weight (kg)              | 74.5 (66.0–83.7)          | 67.2 (53.0–90.0)                      | 66.0 (54.0–86.0)                      | 0.45    |
| Disease Onset            |                           |                                       |                                       |         |
| Upper limb               | NA                        | 3                                     | 3                                     | 0.37    |
| Lower limb               | 7                         | 10                                    | 10                                    | 0.58    |
| Bulbar                   | 4                         | 4                                     | 4                                     | 0.81    |
| ALSFRS-r (max. 48)       | NA                        | 37.5 (35.2–41.0)                      | 40.0                                  | 0.07    |
| Disease duration (months)| NA                        | 23.5 (14.7–37.2)                      | 15.0                                  | 0.73    |
| Disease progression rate | NA                        | 0.58 (0.12–1.1)                       | 0.46                                  | 0.13    |
| Cognitive assessment     |                           |                                       |                                       |         |
| California verbal learning test II CVLT II |                      |                                       |                                       |         |
| Immediate recall         | NA                        | 07.0 (04.0–13.0)                      | 06.0                                  | 0.16    |
| total trial recall       | 57.0 (35.0–68.0)          | 52.0                                  | 52.0                                  | 0.32    |
| (1–5)                    |                           |                                       |                                       |         |
| Short delay free recall  | 12.0 (09.0–16.0)          | 12.0                                  | 12.0                                  | 0.21    |
| Short delay cued recall  | 01.0 (0–13.0)             | 02.0 (0–16.0)                         | 02.0 (0–16.0)                         | 0.48    |
| Long delay free recall   | 14.0 (11.0–16.0)          | 14.0                                  | 14.0                                  | 0.41    |
| Long delay cued recall   | 01.0 (0–13.0)             | 01.0 (0–16.0)                         | 01.0 (0–16.0)                         | 0.25    |
| Total recognition        | 16.0 (13.0–16.0)          | 16.0 (0–16.0)                         | 16.0 (0–16.0)                         | 0.27    |
| discrimination           |                           |                                       |                                       |         |
| Stroop test              |                           |                                       |                                       |         |
| Reading                  | NA                        | 99.5 (46.0–117)                       | 92.0                                  | 0.23    |
| Naming                   | 73.5 (34.0–84.0)          | 64.0                                  | 64.0                                  | 0.13    |
| Double task              | 38.5 (24.0–53.0)          | 37.0                                  | 37.0                                  | 0.33    |
| Verbal fluency test      | NA                        | 25.0 (03.0–40.0)                      | 18.0                                  | 0.46    |
| Phonemic                 |                           |                                       |                                       |         |
| Semantic                 | 31.0 (16.0–51.0)          | 32.0                                  | 32.0                                  | 0.44    |
| Wisconsin card sorting   |                           |                                       |                                       |         |
| test Categories achieved | NA                        | 06.0 (01.0–06.0)                      | 06.0                                  | 0.36    |
| Perseverative errors     | 07.0 (0–31.0)             | 99.5                                  | 99.5                                  | 0.22    |
|                        | 03.0 (0–11.0)             | 04.0                                  | 04.0                                  | 0.38    |
|                        |                           |                                       |                                       |         |
| Digits span              |                           |                                       |                                       |         |
| Forward                  | 08.0 (04.0–11.0)          | 07.0                                  | 07.0                                  | 0.49    |
| Backwards                | 05.0 (04.0–08.0)          | 04.0                                  | 04.0                                  | 0.34    |

2.4. Acquisition of behavioral data

For each trial, the time between the two button presses that marked the start and the end of the imagined visual or motor conditions (imagery time [IT]) was recorded. Furthermore, the effects of task (motor imagery [MI], visual imagery [VI]) and path width (narrow, wide) on the response time in each group were also assessed.

2.6. fMRI data preprocessing and experimental conditions

Functional MRI analyses were performed using the Statistical Parametric Mapping SPM12 (https://www.fil.ion.ucl.ac.uk/spm/). In each dataset, for T1 equilibrium, the first four volumes were discarded. All EPI volumes were corrected to adjust for within-volume time differences and then realigned with the last volume to correct for head movements. The fMRI data were coregistered with the T1 anatomical images of the same subject and then spatially normalized into the MNI space. Spatial smoothing was performed with an 8-mm full width half-maximum Gaussian kernel. A whole-brain analysis was performed using the motor imagery broad (MI-Broad) condition to identify the brain regions involved in imagined locomotion of normal gait. A complementary analysis measuring the specific effects of the trajectory constraints was also carried out using the motor imagery-narrow (MI-Narrow) condition. This condition aimed to identify brain areas more specifically involved in postural control and balance during complex imagined locomotion.

2.7. Region of interest selection for DCM

Four regions of interest (supplementary motor area, cerebellum, basal ganglia and posterior parietal cortex) were defined on the basis of prior knowledge of their functional interaction in motor imagery and on the basis of their activation in the second-level random-effect SPM analysis. Anatomical masks of the SMA, cerebellum, basal ganglia and PPC were created using the Automated Anatomical Labeling (AAL) atlas of the SPM Wake Forest University (WFU) PickAtlas toolbox and placed in each subject. The cerebellar mask included lobule VI and crus I/II of the cerebellum, and the basal ganglia mask included putamen and caudate. Time series were extracted, pre-processed and summarized within each ROI by their first principal component.

2.8. DCM approach

Effective connectivity analysis was performed using dynamic causal modelling (Friston et al., 2003), as implemented in SPM12, to link all these regions in the same model by considering different commonalities of connectivity. The underlying principle behind DCM is that it considers the brain as a non-linear dynamical system where inputs are known along with experimental perturbations (Friston et al., 2003). DCM is a framework for specifying, estimating and comparing generative models of time series. It incorporates known effects of interest and assesses task-dependent modulations among a group of interconnected regions through a set of matrices, known as: (a) task independent endogenous connectivity (matrix A) among the regions representing influence without any external perturbation, (b) task dependent modulation effects (matrix B) representing changes in endogenous connection strength due to external perturbations and (c) direct influence of an external input (driving input) to a region (matrix C) (Friston et al., 2003; Pool et al., 2013). In addition to interactions between regions, DCM allows for external stimuli to influence regions, either directly or by modifying the connections between regions.
modulatory connectivity would be unique to the study-groups and change according to width path conditions. Our neural model was specified with bidirectional connections between all regions (SMA, basal ganglia, PPC and cerebellum, except the PPC-basal ganglia circuit as this connection doesn’t play a crucial role in imagined gait. This base model was then modified systematically to produce ten plausible alternative models’ variants determined after Bayesian Model reduction described below.

2.9. Parametric empirical Bayes (PEB) analysis

To enable the quantification of commonalities and differences across subjects (inter-subject variability) in neural circuitry, DCM is supplemented with a hierarchical model over parameters, called the Parametric Empirical Bayes (PEB) framework (Friston et al., 2016). The PEB approach estimates the effect of each covariate on each connection (both the group mean and any group differences), as well as determining between-subject variability. The parameters of the PEB model were computed using a standard variational Laplace procedure. After having fitted each subject’s DCM to their data, we subsequently performed PEB analysis to estimate the group mean and the effect of path width (broad versus narrow) on each connection within each group.

2.10. Bayesian model comparison (BMC)

To evaluate how the connectivity in broad band condition differs from that in narrow band condition, we used Bayesian model comparison to explore the space of possible models, where each model assumes that a different combination of the connections could exist across participants. It refers to the process of comparing the evidence of the full GLM model with multiple reduced GLM models that have certain combinations of connectivity parameters switched off, by fixing the prior expectation at zero (Zeidman et al., 2019). Such comparisons are very efficient since the evidence and parameters of reduced PEB models can be derived analytically from the full model using Bayesian Model Reduction (Friston et al., 2016). Lastly, to confirm the Bayesian Model Comparison results, we applied Bayesian Model Reduction to automatically remove redundant effective connectivity links from the full PEB model that did not contribute to the model evidence. Specifically, the algorithm implemented a greedy searching over all the permutations of a small set of parameters (i.e., twenty four parameters in our case) whose removal produces the smallest reduction (i.e., greatest increase) in model fitting (Friston et al., 2003). The procedure was repeated until discarding any parameter starts to decrease model evidence or there were no more new parameters to add. After Bayesian Model Reduction, the best ten reduced models were combined using Bayesian Model Averaging to account for uncertainty about the underlying model.

In summary the main steps of PEB analysis include 1) specifying a DCM for each subject 2) fitting it to their data, providing estimates of the connectivity parameters (expected values and covariance) 3) subject-specific estimates are taken to group-level and modeled using a Bayesian approach of the GLM (PEB model) 4) the parameters of the GLM represent the group average of each connectivity parameter and group differences 5) using a Bayesian model reduction to search over the reduced PEB models with different combinations of connections 6) the best models from this search were combined using Bayesian model averaging.
averaging whose results are reported below.

3. Results

3.1. Behavioral results

The UMNp and LMNp groups were matched in age, ALSFRS-r subscores, disease duration, progression rates, and cognitive performance. No significant inter-group difference were detected in the MIQ-RS F(2, 42) = 1.13, P = 0.33. Visual and kinesthetic scores were high (KI: mean = 5.04, SD = 1.23; VI: mean = 5.71, SD = 0.96) indicating a good imagery ability in each group.

A significant main effect of path width on imagery time (IT) was observed in the MI task (F(1, 42) = 67.76, P < 0.05; effect size: partial η² = 0.61). The IT systematically increased with decreasing path width. On the other hand, path width had no significant effect on the IT of visual imagery F(1, 42) = 0.13, P = 0.71. A Group–Band interaction was also observed (F(2, 42) = 13.50, P = <0.05; effect size: partial η² = 0.38). After Bonferroni correction (tests post-hoc), UMNp patients had longer IT on the narrow path compared to control subjects (P < 0.05) and LMNp patients (P < 0.05). No significant difference was observed between the control subjects and LMNp patients on the narrow path.

3.2. Effective connectivity results

3.2.1. Healthy control group

Endogenous connection strengths in controls revealed significant connectivity between all the nodes of the model (Fig. 2). In contrast, for the broad path condition, LMN patients present significant positive connectivity between BG → SMA and similar negative bilateral effective connectivity between BG and cerebellum. The bilateral inhibition of BG and cerebellum connectivity suggests a lesser involvement of this circuitry in broad path condition (Table 2, Fig. 3). During narrow path condition, LMN patients present different pattern of connectivity as healthy controls. Significant effective connectivity between SMA → PPC and positive bilateral connectivity between BG and Cerebellum was recorded. However, significant bilateral SMA-basal ganglia interaction and suppression of cerebellum → PPC connectivity was observed (Table 2, Fig. 4).

3.2.2. LMN group

Endogenous connection strengths in LMN patients revealed significant connectivity between BG → SMA and similar negative bilateral effective connectivity between BG and cerebellum. The bilateral inhibition of BG and cerebellum connectivity suggests a lesser involvement of this circuitry during broad path condition (Table 2, Fig. 3). During narrow path condition, LMN patients present different pattern of connectivity as healthy controls. Significant effective connectivity between SMA → PPC and positive bilateral connectivity between BG and Cerebellum was recorded. However, significant bilateral SMA-basal ganglia interaction and suppression of cerebellum → PPC connectivity was observed (Table 2, Fig. 4).

3.2.3. UMN group

Endogenous connection strengths in UMN patients revealed significant connectivity between all the nodes of the model (Fig. 2). In contrast, for the broad path condition, BG → SMA and SMA → PPC effective connectivity were negatively modulated by broad path condition. Negative effective connectivity between these regions was detected suggesting an inhibition of these connections during broad path condition (Table 2, Fig. 3). Different pattern of activations/connections were demonstrated in UMN patients during narrow path condition. Only a positive bilateral effective connectivity between BG and Cerebellum was recorded (Table 2, Fig. 4).

4. Discussion

This study investigated the effective integrity of the motor network during motor imagery of locomotion in ALS. We have successfully applied DCM to fMRI data on imagined gait and were able to
characterize distinct patterns of effective connectivity during normal and precision gait tasks in both UMNp and LMNp ALS patients.

There is ample imaging evidence of structural disconnection between cortical and sub-cortical regions in ALS (Bede et al., 2018, 2021; Meier et al., 2020; Tu et al., 2018), but the functional interplay between these structures has not been characterized in sufficient detail. Our results revealed increased effective connectivity between basal ganglia and cerebellum and decreased connectivity between basal ganglia-SMA and SMA-PPC in UMNp patients during imagined gait. This reported increase between basal ganglia and cerebellum may be driven by the increased inhibitory influences from SMA to PPC and basal ganglia to SMA. This finding provides a possible novel explanation for the
commonly observed increased connectivity in sub-cortical areas in ALS patients (Abidi et al., 2020; Abidi et al., 2021; Tessitore et al., 2006). PPC is known to store representations of movement and predict conscious motor intentions (Assal et al., 2007), whereas SMA will reflect the imminence of a motor response (Desmurget et al., 2009). The PPC is known to store representations of movement and predict conscious motor intentions (Assal et al., 2007), whereas SMA will reflect the imminence of a motor response (Desmurget et al., 2009). The PPC has been proposed to generate a body schema that would be responsible for integrating limb movement, and their movements relative to the body, integrating information about the surrounding environment (Takakusaki et al., 2008). The activation of the PPC for sensory integration, body schema, error monitoring and adjusting movement to environmental constraints would allow the PPC to assist the SMA in selecting subsequent locomotor regions and are conveyed by the basal ganglia to brainstem locomotor centers (Bostan et al., 2010). The cerebellum contains neural representations reproducing the dynamic properties of the body and to exploit them to create sensorimotor predictions; this allows performing accurate motor forecasts linked to environmental stimuli/constraints and to body kinematics (Manto & Hausman, 2018). The wide neural network in which the cerebellum communicates with the basal ganglia allows not only movement prediction, coordination and timing but also the definition of spatiotemporal and visuospatial sequences of body segment movements and the generation of appropriate patterns of limb movements and in modulating their activation duration during locomotion (Martinot et al., 2014).

Our study managed also to show an absence of cerebellum-PPC connection in UMNp patients during narrow path condition compared to controls. Both regions are thought to be critically involved in postural adjustments, balance control, and motor coordination (Goel et al., 2019), as well as the prediction of sensory consequences of action (Blakemore et al., 2003). These predictions contribute to limb positioning and negotiating environmental constraints (Bakker et al., 2008). During locomotion, cerebellar climbing fibers increase their activity, coding for predicted error severity during the stance portion of the perturbed leg and the swing phase of the next step and allowing for planning of the next foot placement (Yanagihara & Udo, 1994). The activation of PPC would then complement feedback from cerebellum to inform updates to the locomotor plan and allow an associative workload need to integrate visual and proprioceptive stimuli (Hinton et al., 2019). Reciprocal connection between cerebellum and PPC is then critically involved in encoding internal postural model in space and self-motion (Shaikh et al., 2004). Such a bodily information can be utilized to maintain upright posture during standing and to achieve anticipatory postural adjustment (Takakusaki, 2017). Therefore, damage observed in UMNp within the cerebellar—PPC connection makes gait adaptation to environment constraints impossible.

More interestingly, this damage was also recorded in LMNp patients, however, these latter, compared to healthy controls and UMNp patients, present additional connectivity between SMA and basal ganglia to probably compensate the suppression of cerebellum-PPC connection. Previous researches highlight the crucial role of the SMA-basal ganglia connection in locomotion especially in motor imagery task. Cortical commands for locomotion originate in the supplementary motor cortices and are conveyed by the basal ganglia to brainstem locomotor centers (Bakker et al., 2008; Jahn et al., 2008; la Fougère et al., 2010). In addition, it has been shown that the SMA was highly activated when the task involved walking over obstacles rather than walking normally.

| Broad path condition | SMA | PPC | BG | Cerebellum | Narrow path condition | SMA | PPC | BG | Cerebellum |
|----------------------|-----|-----|----|-----------|----------------------|-----|-----|----|-----------|
| Healthy controls     | SMA | 0.008 | 0.007 | 0.028 | 0.010 | SMA | 0.027 | 0.014 | 0.010 | -0.030 |
| PPC                  | 0.008 | -0.015 | -0.037 | -0.040 | 0.053 | PPC | 0.017 | 0.032 | 0.009 | 0.049 |
| BG                   | 0.004 | 0.007 | 0.008 | 0.003 | 0.014 | BG | 0.050 | 0.007 | 0.007 | 0.047 |
| Cerebellum           | 0.012 | -0.008 | -0.040 | -0.016 | -0.004 | Cerebellum | -0.010 | 0.008 | 0.004 | 0.046 |
| LMN                  | SMA | 0.006 | -0.0007 | 0.020 | 0.007 | SMA | 0.030 | 0.007 | 0.007 | 0.007 |
| PPC                  | 0.003 | -0.020 | 0.050 | 0.002 | 0.017 | PPC | 0.008 | 0.0024 | 0.0092 | 0.0001 |
| BG                   | -0.0237 | -0.0699 | -0.028 | -0.0092 | -0.008 | BG | 0.028 | 0.0160 | 0.0007 | 0.0607 |
| Cerebellum           | 0.0073 | -0.0015 | -0.015 | -0.0079 | 0.0099 | Cerebellum | -0.0079 | 0.0099 | 0.0425 | -0.0079 |

SMA; Supplementary Motor Area, PPC; Posterior Parietal Cortex, BG; Basal Ganglia.
(Malouin et al., 2003). This implies that this premotor region plays an important role in demanding balance tasks. Similarly, the basal ganglia are known to play an important role in balance and postural control for instance, they enable postural flexibility and sensorimotor integration (Visser & Bloem, 2005), in particular during complex gait task. These data highlight the role of the basal ganglia-SMA circuit in adapting the locomotor pattern in complex gait situations, and their probable dysfunction in pathological conditions could affect the ability to freely walk in complex environments (Maidan et al., 2016). Since previous research usually didn’t capture any differences between LMNp patients and healthy controls (Abidi et al., 2020; Abidi et al., 2021; Tessitore et al., 2006), further researches are needed.

The nuanced characterization of the functional interplay between the cortex, basal ganglia and cerebellum has practical relevance to our understanding of gait impairment, fall risk and extrapyramidal features in ALS. While ALS is primarily associated with UMN and LMN degeneration, extrapyramidal involvement is a likely contributor to the heterogeneity of motor manifestations observed clinically. Beyond their contribution to motor disability, functional alterations between subcortical structures, the cerebellum and cortex are likely to drive ALS-associated cognitive and behavioral symptoms (Bürke et al., 2016; Christidi et al., 2019).

This study is not without limitations. Although differences were detected in the locomotion network in ALS patients, future studies need to replicate and validate these findings in a larger sample of patients. Moreover, additional structural connectivity analyses would have complemented our functional connectivity findings to provide a more comprehensive and multifaceted characterization of network disintegration in ALS.

5. Conclusions

Our data provide evidence of functional reorganization and neural circuitry disconnection in UMN-predominant ALS patients and indicate that loss of network integrity is a key determinant of clinical manifestations. UMN-predominant ALS patients exhibit increased effective connectivity between cerebellum and basal ganglia and diminished BG-SMA and SMA-PPC connectivity during motor imagery of gait; which impacts on locomotor, balance and postural control processing. Enhanced basal ganglia-cerebellar connectivity may represent functional adaptation. We have identified a unique connectivity pattern in LMNp patients with enhanced SMA-BG connectivity which may counterbalance the lack of cerebellum-PPC connectivity during precision gait paradigms.

CRediT authorship contribution statement

Malek Abidi: Conceptualization, Methodology, Software, Data curation, Writing – original draft, Investigation, Formal analysis, Writing – review & editing. Pierre-François Pradat: Writing – review & editing. Nicolas Terzom: Writing – review & editing. Annabelle Couillandre: Writing – review & editing. Peter Bede: Writing – review & editing. Giovanni de Marco: Conceptualization, Methodology, Software, Data curation, Writing – original draft, Supervision, Validation, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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