IMG-01: Abnormal EEG Connectivity during Resting State, Motor Planning, and Motor Execution in Amyotrophic Lateral Sclerosis

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Background:
Functional connectivity (FC) in the brain networks have been shown to be different across resting-state (RS), motor planning (MP), and motor execution (ME) in healthy individuals. However, it remains unclear how the cortical motor networks are disrupted in the patients with amyotrophic lateral sclerosis (ALS). The aim of this study is to find the abnormal changes in FC during RS, MP, and ME in ALS suited to the development of targeted biomarkers of network disruption.

Method:
Eleven healthy controls (HC) and 22 ALS patients performed isometric-pinch-grip between thumb and index finger of right hand to maintain 10% of maximum-voluntary-contraction upon presentation of visual cue, while 128-channel electroencephalography (EEG) was recorded. Sensor-level FC between electrodes (surface Laplacian filtered) over primary motor (M1), pre-motor (PM), primary somatosensory (S1), dorsolateral prefrontal (DLPF), dorsomedial prefrontal (DMPF), and superior parietal lobule (SPL) cortices were estimated using spectral coherence for 8 frequency bands between 1-100 Hz and statistically compared across 3 stages of the task. P-values were corrected for multiple comparison using adaptive-false-discovery-rate at q=0.05. A machine-learning method, Linear support vector machines (LSVM), was used to compare the levels of discrimination provided by the abnormal connectivity patterns during RS, MP and ME.

Results:
Significantly higher pair-wise functional connectivity was found in ALS versus HC with the distinct patterns: Resting state: (a) ipsilateral M1-PM FC at theta band (p=0.038), (b) contralateral DLPF-DMPF FCs at lower-beta (p=0.009), higher-beta (p=0.009), and lower-gamma (p=0.047) bands. Motor planning: (c) contralateral M1-S1 FC at lower-alpha band (p=0.030), (d) contralateral DLPF-DMPF FCs at higher-alpha (p=0.032) and higher-beta (p=0.005) bands, (e) contralateral DLPF-SPL FC at lower-gamma band (p=0.019). Motor execution: (f) contralateral M1-S1 FC at theta-band (p=0.038), (g) contralateral M1-SPL FC at higher-beta band (p=0.004), (h) contralateral DLPF-DMPF FCs at higher-alpha (p=0.021), higher-beta (p=0.008), and lower-gamma (p=0.005) bands.
The combination of these abnormal FC measures in the 3 states provided higher discrimination between ALS and HC (90.91% accuracy, 5-fold cross-validation) than the measures in each stage in isolation (RS=69.70%, MP=75.76%, ME=84.85%). Amongst these abnormal FCs observed in ALS, contralateral DLPF-DMPF at lower-beta band during RS and contralateral M1-SPL at higher-beta band during ME were negatively correlated (r=-0.596, p=0.007 and r=-0.505, p=0.041 respectively) to ALSFRS-R scores.

Discussion and Conclusion:
The abnormal frontal RS network and parietal ME network at beta band indicate a pathology in ALS, likely due to compensatory mechanisms.
Amalgamation of the abnormal FC during different stages of functional activity (RS, MP and ME) can reliably discriminate ALS from controls, pointing to the potential of network disruption as a diagnostic and prognostic biomarker.

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IMG-02: Age at symptom onset influences cortical thinning distribution in ALS

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Background:
There is a wide range of age at symptom onset in ALS, despite a mean age of 65 years has been reported in previous population-based studies (1). Older age at symptom onset has been previously identified as a risk factor for the development of frontotemporal dementia (FTD) in ALS (2) and, more recently, as a negative prognostic factor in ALS (3), but the underlying neurobiological mechanisms are still poorly investigated. We hypothesized that older age at symptom onset would have determined more widespread extra-motor cortical degeneration in ALS. Objective. To explore the relationship between age at symptom onset and regional cortical thinning distribution in ALS.

Methods:
We included 26 ALS patients without cognitive impairment and 37 age-matched healthy controls (HC) with T1-weighted Magnetic Resonance Imaging (MRI) sequences acquired on a 1.5 T GE scanner. Freesurfer 6.0 was used to identify regions of cortical atrophy in ALS patients, and to relate age at symptom onset with regional cortical thinning distribution. All the MRI results were corrected for multiple comparisons using the Monte Carlo Simulation method ($P < 0.01$), and regression analyses were further corrected for disease duration at the time of the MRI exam.

Results:
Relative to HC, ALS patients exhibited significant cortical atrophy mainly encompassing motor regions (precentral and paracentral cortex bilaterally), but also involving the superior parietal cortex bilaterally and right lateral occipital cortex. Conversely, older age at symptom onset was selectively associated with greater extra-motor cortical thinning (including pars opercularis bilaterally, as well as left middle temporal and parahippocampal cortices).

Discussion:
We observed greater frontotemporal cortical thinning associated with older age at symptom onset in ALS, suggesting that the interaction between aging and symptom onset timing mainly influences extra-motor, rather than disease-specific (motor), vulnerability to cortical neurodegeneration in ALS. These findings have potential to improve our knowledge on the neurobiological mechanisms contributing to worse prognosis in ALS patients with older age at onset.

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IMG-03: Applications of surface EMG arrays for identification and tracking of motor units in amyotrophic lateral sclerosis

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Background:
Recording the electrical activity of motor units (EMG) within a muscle using invasive needle electrodes is an important step in the diagnosis of amyotrophic lateral sclerosis (ALS). Recent advancements in EMG technology have enabled individual motor units to be detected from non-invasive recordings from the skin surface using high-density surface EMG arrays. The potential applications of this new technology to study changes in brain-muscle communication in ALS, however, have yet to be fully realised.

Objectives:
The aim of this study is to highlight how information on motor unit populations, obtained using surface EMG arrays, could be used to interrogate motor unit networks in ALS.

Methods:
We have evaluated two novel methods for analysing motor unit data from surface EMG arrays: 1) multi-variate coherence estimation, and 2) motor unit tracking in multi-dimensional space. The multi-variate coherence method provides an accurate assessment of rhythmic patterns present in the motor unit firing activity. The synchronous discharge of motor units, particularly in the beta-band frequency range (15-30 Hz), has been linked to oscillatory cortical and sub-cortical processes. The collective synchrony of the motor unit population can thus provide insight into changes in the communication between brain and muscle. The second method is a technique that can be used to reliably track the same motor unit across different experimental sessions. The action potential waveform of each motor unit is characterised in multi-dimensional space, incorporating information from all channels of the surface EMG array. This technique opens up the possibility of tracking motor units longitudinally in ALS patient groups, whereby changes in the activity of individual motor units over time could be directly assessed.

Results:
In young, healthy subjects (N=18) the multi-variate coherence method detected a decrease in beta-band and a novel increase in gamma-band motor unit coherence at higher muscle contraction forces. When applied to simulated datasets, the motor unit tracking method identified action potentials from the same motor unit with 100% accuracy (compared with cross-correlation methods which yield high rates of false positives, 40-60%).

Discussion:
The ability to accurately assess collective motor unit synchrony and reliably track the same motor unit over time could offer new insights into brain-muscle connectivity in ALS patient groups, and be used to explore how this communication is altered as the disease progresses. The information gained from high-density surface EMG recordings is a potential non-invasive biomarker of disease progression in ALS.

IMG-04: Brain architecture changes across the FTLD spectrum

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Objective:
Motor neuron disease (MND) and the behavioral variant of frontotemporal dementia (bvFTD) lie on the same pathologic/genetic continuum. The aim of this study was to unravel distinct and shared structural MRI connectomic features of these syndromes.
Materials. 115 MND (83 with amyotrophic lateral sclerosis [ALS] and 32 with primary lateral sclerosis), 35 bvFTD patients and 61 healthy controls underwent clinical, cognitive and MRI evaluations. According to neuropsychological testing, MND patients were classified in 79 pure-motor (MNDpm) and 36 cognitive and/or behavioral impaired (MNDci/bi – including 8 ALS-FTD). A sub-analysis was performed considering ALS patients only, classified in 54 ALSpm, 21 ALSci/bi and 8 ALS-FTD.

Methods:
Graph analysis and connectomics assessed global and local structural and functional topological network properties and regional structural and functional connectivity (FC).

Results:
bvFTD showed altered structural and functional global network properties compared to all other groups. At the lobar level, bvFTD showed altered structural network properties within the frontotemporal and basal ganglia areas relative to all groups. Noteworthy, structural alterations in the parietal lobe discriminated bvFTD from controls and MNDpm. MND groups showed altered graph metrics within the sensorimotor and basal ganglia areas relative to controls. Focusing on ALS, structural alterations were confirmed within the same areas. Functionally, bvFTD showed altered metrics relative to controls and MND groups within frontotemporal, sensorimotor and basal ganglia areas. Regional analysis showed that widespread structural changes were observed in bvFTD relative to controls, while structural alterations within frontotemporal areas and among frontal and motor areas differentiated bvFTD from MND groups. The structural alterations in all MND subgroups encompassed connections within and among frontotemporal and sensorimotor networks and basal ganglia area, with a more widespread pattern of differences against controls. Results were confirmed in the ALS sub-analysis. Furthermore, bvFTD were characterized by reduced FC within the frontotemporal and sensorimotor networks relative to controls and all MND groups. ALS sub-analysis highlighted that ALSci/bi showed an increased FC relative to ALS-FTD within the same areas.

Discussion and Conclusions:
The disruption of the structural architecture in MND phenotypes worsens in relation with the progression of cognitive deficits. Functional changes are characterized by an increase of FC in presence of exclusive motor impairment that intensifies with the occurrence of cognitive impairment in MND. The condition of comorbidity of ALS and FTD leads to a decrease in FC similar to bvFTD.

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IMG-05: Brain bioenergetics in ALS: a phosphorus-31 magnetic resonance spectroscopy study

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Background:
Evidence from in vitro and animal studies indicates that mitochondrial bioenergetic dysfunction in the brain represents an important pathophysiological mechanism in ALS (1), but has not yet been directly measured in people living with ALS in vivo.

Objectives:
To characterise brain energy metabolism in vivo in ALS patients using phosphorus-31 magnetic resonance spectroscopy (31P-MRS), and assess associations with measures of disability, respiratory function, and upper motor neuron burden.

Methods:
Twenty patients and ten age and gender-matched healthy controls were scanned at 3 Tesla with a two-dimensional chemical shift imaging sequence employing image-selected in vivo spectroscopy for volume localisation to obtain spectra from brain motor regions. T1-weighted volumetric images were acquired to correct for partial volume effects. Amplitudes of relevant spectroscopic parameters were estimated employing the AMARES non-linear least square algorithm and expressed as a proportion of total phosphorus signal. Disability, respiratory function, and upper motor neuron burden were assessed using the Revised ALS Functional Rating Scale (ALSFRS-R), slow vital capacity (SVC), and upper motor neuron score (UMNS), respectively.

Results:
PCr was reduced in the pons in patients compared to controls (p=0.002) and retained significance after adjusting for voxel partial brain fraction (p=0.008) and age (p=0.012). Lower PCr was associated with greater disability on ALSFRS-R (R=0.54, CI=0.11 to 0.80, p=0.017) and lower SVC (R=0.59, CI=0.18 to 0.82, p=0.008), but not with UMNS (R=0.31, CI=-0.20 to 0.68, p=0.223). No differences were found in motor cortex or deep white matter. No difference in total phosphorus signal were detected in any of the analysed voxels.

Discussion and conclusion:
Decreased PCr is a hallmark of bioenergetic dysfunction in mitochondrial cytopathies (2) and acts as a buffer to maintain stable levels of ATP at times of elevated energy demand unmet by mitochondrial capacity. Correlations with ALSFRS-R and SVC suggest clinical relevance. This study is the first to illustrate the presence of cranial bioenergetic dysfunction in vivo in ALS patients, and illustrates the potential of 31P-MRS as a biomarker of mitochondrial dysfunction for future clinical trials.

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IMG-06: Brain MRI signatures of atrophy in genetic frontotemporal lobar degeneration

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Objectives:
Genetic heterogeneity underlying different clinical presentations of the frontotemporal lobar degeneration (FTLD) spectrum hampers the identification of useful biomarkers that may be able to monitor disease progression and/or facilitate the enrolment in clinical trials. The aim of this study was to assess cortical, subcortical and cerebellar grey matter (GM) atrophy using magnetic resonance imaging (MRI) in patients affected by disorders of the FTLD spectrum with known genetic mutations.

Materials and methods:
362 patients with disorders of the FTLD spectrum referred between 2007 and 2019 were screened for known pathogenic mutations. 66 patients carrying mutations in the C9ORF72, GRN, TARDBP, SOD1, TBK1, MAPT, TREM2 or FUS genes were identified, including 44 with pure motor neuron disease (MND) and 22 with frontotemporal dementia (FTD). Patients carrying a C9ORF72 expansion were divided into two groups of C9-MND and C9-FTD. 61 patients with sporadic FTLD matched for age, sex and disease severity with genetic FTLD were also included, as well as 52 healthy controls (HC). Comprehensive clinical and neuropsychological assessments and three-dimensional T1-weighted MRI sequences on a 3 Tesla scanner were obtained. First, a whole-brain voxel-based morphometry (VBM) analysis was performed. Subsequently, GM volumes of the basal ganglia, hippocampus, amygdala and cerebellar volumes were also obtained.

Results:
Compared with HC, GM volume loss on VBM was generally greater and more diffuse in genetic FTD (gFTD) cases, followed by sporadic FTD (sFTD) cases and genetic MND (gMND) cases, whereas sporadic MND (sMND) showed very focal atrophy of the motor cortex. Patients carrying GRN and C9ORF72 mutations showed the most widespread cortical volume loss, whereas SOD1 and TARDBP patients were the least atrophic. Greater atrophy of the parietal cortices and thalami was found, globally, in genetic FTLD patients compared with sporadic FTLD and, particularly, in C9-MND patients compared with sMND. When assessing deep GM volumes, genetic FTLD patients showed significant volume loss compared with sporadic FTLD in the caudate nuclei and thalami. In particular, greater atrophy of the left caudate and right thalamus was found in C9MND compared with sMND. At the cerebellar level, greater atrophy of the right lobule VIIb could discriminate genetic FTLD from sporadic FTLD patients.

Discussion and conclusions:
Our data suggest that measures of deep GM and cerebellar involvement might be useful markers of genetic FTLD, particularly C9ORF72-related disorders, regardless of the clinical presentation within the FTLD spectrum.

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IMG-07: Cerebellar degeneration in adult spinal muscular atrophy patients

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Background:
Spinal Muscular Atrophy (SMA) is a genetic motor neuron disease related to SMN1 gene deletions. There is growing evidence that the disease is not confined to motor neurons. In this study we aimed to investigate cerebellar damage in patients diagnosed with adult SMA that had not been treated with disease-modifying-therapies.

Method:
Twenty-five molecularly confirmed patients with SMA type III or IV and 25
healthy controls underwent MRI with cerebellar focused structural analysis by the CERES automated pipeline. Volumetry (total and gray matter – GM) as well as cortical thickness of the cerebellar lobules were compared in both groups. Clinical and demographic data were then evaluated for correlations with cerebellar imaging findings.

Results:
The volumes of cerebellum lobules VIIIB (right), IX and X were significantly reduced in SMA patients. Lobule IX also had GM atrophy compared to controls. We found no correlations between cerebellar damage and clinical findings.

Conclusion:
Neuroimaging identifies cerebellar structural changes in adult SMA patients, which suggests that neurodegeneration is not limited to lower motor neurons in the disease.

IMG-08: Circulating CD4+ lymphocytes relate to changes in fractional anisotropy within the corpus callosum in amyotrophic lateral sclerosis

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Background:
Involvement of the immune system is increasingly recognised as an integral component of the neurodegenerative process in amyotrophic lateral sclerosis (ALS). Animal models of disease implicate a subpopulation of CD4+ CD25+ FoxP3+ 'regulatory' T lymphocytes (Tregs) in redirecting the inflammatory response towards neural protection and repair. The rate of disease progression in patients with ALS has correlated negatively with the absolute Treg count or the Tregs:total CD4+ ratio. The Modifying Immune Response and Outcomes in ALS Trial (MIROCALS: www.mirocals.eu) is currently investigating the safety and efficacy of boosting blood-borne Tregs using low dose subcutaneous Interleukin-2. A subgroup of patients in MIROCALS have undergone multimodal brain MRI at baseline and after treatment, including diffusion MRI. Diffusion tensor imaging has consistently demonstrated reduced fractional anisotropy (FA) within the corticospinal tracts (CSTs) and corpus callosum (CC) in ALS.

Aim:
to explore the relationship between FA at baseline and pre-treatment levels of patients' blood-borne Tregs, total CD4+ count and the Tregs:total CD4+ ratio.

Methods:
Interim analysis was performed on 23 patients and 24 age-matched controls using brain MRI scans at 1.5T. FA maps generated using FSL DTIFIT were non-linearly warped into the MNI152 standard space using Advanced Normalisation Tools. A customised FSL Tract Based Spatial Statistics (TBSS) processing pipeline was used to identify FA values associated with white matter tracts. CD4+ cells and Tregs were enumerated by flow cytometric analysis of whole blood. Group comparisons white matter tract FA between patients and controls, and associations between patients' FA and immune cell levels, were performed using randomise_parallel applying threshold-free cluster enhancement in two dimensions and $p<0.05$ accepted as statistically significant. Age and rate of progression were used as covariates.

Results:
Compared to controls, patients with ALS showed reduced FA within the CC and CSTs ($p=0.04$). FA within the CC demonstrated a weak negative relationship with total blood CD4+ T cell count ($p=0.04$).

Conclusion:
This interim analysis has reproduced the finding of reduced FA within the motor pathways in patients with ALS. Although further investigation is awaited on the full cohort, these findings provide evidence for immunological crosstalk between the blood and central nervous system relevant to mechanisms of disease in ALS.

IMG-09: Cognitive and Auditory Cortical Network Oscillations are Abnormal in ALS

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Background:
Executive dysfunction is the most common cognitive impairment in ALS, identified in approximately 25% of patients by psychological tasks [1]. However early/pre-symptomatic cognitive network pathology, and abnormalities in other cortical and subcortical networks, such as sensory afferent pathways, may occur in the absence of detectable clinical symptoms. By recording EEG during engagement of these networks by sensory stimulation or executive tasks, abnormalities in the activated neural networks can be directly quantified by event related potential (ERP) waveforms, as we have previously shown in ALS [2]. In addition to eliciting ERPs, sensory input and cognitive tasks alter cortical network communication, captured as changes in cortical oscillations at characteristic frequencies. This may be observed as an increase (event-related synchronisation, ERS) or decrease (event-related desynchronisation, ERD) in oscillation intensities during task performance or following stimulation [3]. Such oscillations can inform of disturbances to intracortical and corticothalamic communication in ALS and have been found to provide better diagnostic utility than ERP measures in mild cognitive impairment and Alzheimer's disease [4]. While motor network oscillation abnormalities are well established in ALS [5], the effect of ALS on communication of sensory and cognitive networks has yet to be examined via these measures.

Objectives:
To investigate if cortical oscillations associated with performance of the sustained attention to response task (SART) and the auditory oddball paradigm are disrupted in ALS.

Methods:
A randomised SART was undertaken by 24 ALS patients and 33 controls, and an auditory oddball paradigm was undertaken by 94 ALS patients and 62 controls during 128-channel EEG. Complex Morlet wavelet transform was used to quantify non-phase-locked oscillatory activity in ERD/ERS associated with sensory stimulation and task performance. Electrical source imaging (ESI) was used to identify the sources of these oscillations. The relationships between these perturbations and task performance, and motor and cognitive changes in ALS was also investigated.

Results:
ALS patients exhibited similar reaction times and accuracy to controls in the SART; however, prefrontal (AUROC=0.8) and parietal (AUROC=0.82) beta-band ERD was significantly lower. ALS patients with higher ECAS ALS-specific scores demonstrated greater ERS in beta (rho=0.72) and theta rhythms (rho=0.78) upon successful withholding. ALS patients also showed auditory sensory-associated alpha oscillation hypersynchrony predominant in the medial and lateral temporal cortex, including the hippocampus as well as the right insula, but also present in the thalamus and basal ganglia.

Discussion:
EEG cortical oscillations can capture cognitive and sensory cortical and subcortical network pathophysiology in the absence of task performance decline, which may facilitate development of sensitive, early ALS biomarkers.

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IMG-10: Cortical atrophy patterns in asymmetrical symptom onset ALS.

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Background:
Asymmetrical symptom onset is a well-established clinical feature in the early stages of ALS. However, investigating brain structural correlates of lateralized disease onset
is particularly challenging due to the common presence of demographic and clinical differences between right and left limb-onset patients.

Objective:
To explore cortical atrophy patterns in two clinically homogeneous samples of patients with lateralized ALS onset.

Methods:
This retrospective study included 13 right limb-onset ALS patients, 8 demographically and clinically matched left limb-onset cases, and 37 age-matched healthy controls (HC) with T1-weighted Magnetic Resonance Imaging (MRI). The two ALS samples were matched for disease duration, severity of motor impairment, rate of disease progression, clinical phenotype, absence of cognitive impairment and initial presentation (upper motor neuron vs lower motor neuron onset). Cortical thickness comparisons between ALS
subgroups and HC were performed using Freesurfer 6.0. All the MRI results were corrected for multiple comparisons using the Monte Carlo Simulation method (P < 0.05).

Results:
Compared to HC, left limb-onset ALS patients showed widespread bilateral atrophy encompassing the left pericalcarine cortex, left precentral gyrus, left postcentral gyrus, right lateral occipital cortex, right superior temporal gyrus and right postcentral and paracentral gyri. Conversely, right limb-onset ALS cases exhibited selective atrophy of the left superior parietal cortex.

Discussion:
Our findings are in line with previous MRI studies reporting unilateral dominant grey matter (GM) losses in patients with right limb-onset ALS, and more extensive cortical damage in left limb-onset ALS. Intriguingly, while previous studies have argued that greater generalized cortical atrophy in left limb-onset ALS patients might represent a cortical signature of more severe disease, our MRI findings in clinically matched patients rather suggest that this phenomenon might underlie a greater pathological burden possibly associated with more aggressive longitudinal decline. Future longitudinal studies in larger samples are warranted to further explore this hypothesis.

Acknowledgements:
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IMG-11: Dentate nucleus structural and functional connectivity changes in Amyotrophic lateral sclerosis: A multi-center and multi-modal neuroimaging study

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Background:
Amyotrophic lateral sclerosis (ALS) is characterized primarily by motor neuron but also frontotemporal lobar degeneration. Although the cerebellum is involved in both motor and cognitive functions, little is known of its role in ALS. The cerebellar dentate nucleus (DN) plays a critical role in connecting the cerebellum to the cerebral cortex. We hypothesized that the DN is implicated in the pathophysiology of ALS. We aimed to investigate the cerebellar structural and functional connectivity patterns connecting the DN to the rest of the brain using multimodal imaging techniques in ALS patients.

Methods:
A cohort of 127 participants (56 healthy controls (HC); 71 ALS patients) were recruited across Canada through the Canadian ALS Neuroimaging Consortium (CALSNIC). Resting state functional MRI (rsFMRI), diffusion tensor imaging (DTI), and 3D weighted T1 structural images were acquired on a 3-tesla scanner from 5 sites of CALSNIC using a harmonized protocol. For rsFMRI, the DN in the cerebellum was used as a seed to evaluate the whole brain cerebral functional connectivity (FC) using FSL. With DTI, the superior cerebellar peduncle (SCP), middle cerebellar peduncle (MCP) and inferior cerebellar peduncle (ICP) were used as regions of interest to evaluate the structural integrity of the white matter connecting the DN with the cortex and brain stem using FSL. Further, DN grey matter (GM) volumetric changes were assessed using SUIT software. Lastly, an association between DN FC and structural alterations was explored using Spearman's rank correlation in SPSS.

Results:
DN FC was reduced with the cerebrum (supplementary motor area, precentral gyrus, frontal, posterior parietal, temporal), lobule IV of the cerebellum, and brain stem, and increased with the parieto-occipital region. Lower fractional anisotropy (FA) was present at the SCP and ICP. Moreover, higher axial and radial diffusivity was reported at the SCP and MCP. The group comparisons were reported after correcting for multiple comparisons at family-wise error (FWE) of $p<0.05$. Furthermore, DN FC and white matter (WM) diffusivity alterations at the SCP, MCP, and ICP were accompanied by correlations with ALSFRS-R. The FC correlation results were reported after correcting for multiple comparisons at FWE of $p<0.05$ and DTI correlations results did not survive FWE corrections, thus reported after correcting for multiple comparison at false discovery rate (FDR) of $p<0.05$. There were no DN volumetric changes. Interestingly, altered patterns of DN FC revealed a strong association with WM abnormalities at the SCP.

Conclusion:
This study demonstrates altered cerebellar FC with motor and extra-motor regions in ALS. Impaired FC is likely due to the observed impaired cerebellar peduncular WM integrity. The correlation between the altered DN connectivity, and the clinical data support the hypothesis that the DN plays a pathophysiological role in ALS.

IMG-12: Differences in axonal excitability between ALS and Controls: a systematic review and meta-analysis

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Background:
Consensus guidelines were recently published that highlight the potential for axonal excitability outcome measures to be used as biomarkers to monitor progression and treatment response in ALS [1]. Primary studies have indicated that pathophysiological changes in sodium and potassium channels distinguish individuals with ALS from controls. However, only narrative reviews with qualitative synthesis are currently available.

Objective:
To quantitatively measure the heterogeneity and pooled results of axonal excitability studies comparing individuals with ALS to healthy controls. Secondly, to establish the effect sizes for specific excitability indices that demonstrate diagnostic potential and propose cut-offs for accuracy studies.

Methods:
Potential studies were identified by searching the following databases: MEDLINE, PubMed Central, CINAHL Plus, EMBASE, HealthSTAR, Scopus, and Web of Science. Screening, full-text review, quality assessment and data extraction were done by two independent authors (with conflicts resolved by a third author) using Covidence. Data were exported to RevMan 5 for Forest Plot analysis. Only studies assessing median motor axons were included.

Results:
After removal of duplicates, 2866 records were screened, 43 full-text assessed, and 26 studies reporting axon excitability indices were included. Not all >30 indices generated by an axonal excitability test were fully reported; a bias was to report indices that demonstrated significant differences. In thirteen well reported indices there was no relationship between the meta-analysis outcomes of heterogeneity (I^2) and pooled effect (Z, $r^2 = 0.0026$). Seven indices had significant pooled effect (Z ranging from 9.29 to 2.97): Superexcitability, SDTC, max CMAP, TEd 90-100 ms, 50% Depolarizing, Late subnormality, and TEd 10-30 ms (descending rank ordered). Heterogeneity was low for six measures (0 to 42%, mean 24.5%) indicating similarity across reporting studies, but maximum CMAP had a heterogeneity of 92%. The six indices that did not discriminate between ALS and Controls had similar heterogeneity (0 to 67%, mean 34%) indicating consistency across studies finding no significant difference in these indices: TEh 90-100 ms, Rheobase, Hyperpolarizing I/V slope, Refractoriness, 100% Hyperpolarizing, and Relative refractory period.

Conclusion:
High quality diagnostic test accuracy studies are warranted to firmly establish the utility of using the six homogeneous and significant indices for routine clinical evaluation in individuals suspected of an ALS diagnosis.

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IMG-13: Motor task evoked brain network function in ALS and PLS

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Background:
The cortical hyperexcitability demonstrated in amyotrophic lateral sclerosis (ALS) is associated with a wider network dysfunction. The precise topology and nature of these functional alterations remains controversial, as does the generalisability of observations in ALS to primary lateral sclerosis (PLS).

Methods:
Study participants comprised 44 ALS, 9 PLS, and 18 age matched healthy individuals. Each individual underwent motor task functional MRI (fMRI) at 3T (Siemens Magnetom). Voxelwise statistics were performed using the FSL (FMRIB software library) neuroimaging analysis toolkit.

Results:
Spatial maps of statistically significant activation in response to finger movement differed between groups, with ALS patients showing widened activation compared to controls, notably including marked hemispheric activation ipsilateral to the finger moved, not noted in controls. In PLS, activation was not as widespread, but a similar pattern of abnormal ipsilateral activation was noted. Exploratory analysis performed using network connectivity analysis based on functional parcellation demonstrated alterations in connectivity profiles between motor and somatosensory cortical regions.

Discussion and conclusions:
Unilateral motor task evoked activation in ALS and PLS is characterised by a shared pattern of loss of physiological asymmetry, and a wider regional spread of activation in ALS. Recruitment of ipsilateral structures may reflect changes in local circuit function, which in turn may underpin observed changes in cortical excitability. Longitudinal and presymptomatic studies may help to untangle the relative contribution of primary pathological loss of local circuit architecture versus compensatory recruitment of intact pathways.

IMG-14: The preferential involvement of thalamic nuclei in ALS: a multimodal neuroimaging study

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Background:
The thalamus mediates a multitude of sensory, extrapyramidal motor, cognitive and behavioural functions, through corticoefferent and corticoafferent connections. Previous imaging studies in ALS have evaluated the thalamus as a single structure and described global changes even though it consists of cytologically and functionally distinct nuclei.

Methods:
A prospective imaging study was undertaken with 100 patients with ALS and 117 healthy controls to determine the integrity of individual thalamic nuclei. ALS patients were stratified into those with the GGGGCC hexanucleotide repeat expansions in C9orf72 and those without. The volumetric profile of individual thalamic nuclei, overall thalamic shape deformations and focal density alterations were evaluated based on high-resolution MRI data.

Results:
Our data indicate that C9orf72 negative ALS patients exhibit ventral anterior and ventral lateral involvement, corresponding to the 'motor' thalamus. Both C9orf72 positive and negative ALS patients show focal changes in the mediodorsal-paratenial-reuniens nuclei, which is involved in executive and memory functions. On vertex analyses, symmetric patterns of superior-inferior and posterior involvement atrophy were noted in association with C9orf72.

Discussion:
Our data indicate that thalamic pathology is not homogenous, but it preferentially affects nuclei mediating motor and cognitive functions. Our results support the emerging literature of extrapyramidal dysfunction in ALS. The preferential involvement of thalamic nuclei highlights that future studies should no longer evaluate the thalamus as a single structure because of the risk of averaging changes across affected and unaffected regions.

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IMG-15: Converging longitudinal patterns of atrophy in clinical variants of frontotemporal lobar degeneration

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Objectives:
To assess longitudinal patterns of atrophy shown by magnetic resonance imaging (MRI) in the cortical and subcortical GM of patients affected by different clinical variants of the FTLD spectrum.

Methods:
Fifty-nine patients, including 26 with behavioral variant of frontotemporal dementia (bvFTD), 10 non-fluent/agrammatic variant of primary progressive aphasia (nfvPPA), 12 semantic variant of PPA (svPPA), and 11 MND, in the absence of known pathogenic mutations, underwent MRI on a 3T scanner at 6-month intervals for one year. Thirty-three healthy controls underwent the same protocol. 3D T1-weighted MRI sequences were analyzed using voxel-based morphometry to assess the longitudinal evolution of GM atrophy in patients, compared with HC.

Results:
At baseline, severe diffuse atrophy of frontotemporal cortical regions and basal ganglia was found in bvFTD, nfvPPA and svPPA groups, whereas MND did not show significant GM atrophy. At 6-month follow-up, bvFTD and PPA groups showed significant progression of atrophy in the insular (bvFTD, nfvPPA and svPPA) and anterior cingulate cortex (bvFTD and nfvPPA), bilaterally, as well as in the left caudate nucleus and middle temporal cortex (svPPA). At 12-month follow-up, similar patterns of atrophy progression were found, with the additional involvement of the superior frontal cortical gyri in nfvPPA, bilaterally, and the right hippocampus in svPPA. No significant progression of atrophy was found in MND patients.

Conclusions:
Our data suggest that atrophy of insular and anterior cingulate cortical regions closely reflects the progression of neurodegeneration across the behavioral and linguistic presentations of frontotemporal dementia (FTD), in contrast with a substantial sparing of GM in MND.

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IMG-16: Cortical inexcitability defines an adverse clinical profile in amyotrophic lateral sclerosis

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Background:
The critical role of corticomotoneuronal dysfunction in the onset and evolution of amyotrophic lateral sclerosis (ALS) has been highlighted across a wide range of studies (1). In particular, threshold-tracking transcranial magnetic stimulation (TMS) studies have shown that inhibitory processes at the cortical level are depressed (2,3), which is linked to survival in early disease (4). Some patients, however, display no motor cortical response even at maximal TMS intensities, termed as an 'inexcitable' motor cortex. The extent to which this cortical finding impacts clinical outcomes remains unclear.

Objectives:
To determine the clinical and prognostic profile of ALS patients who present with 'inexcitability' to TMS at initial assessment.

Methods:
TMS was undertaken across all four limbs in 133 patients with ALS to determine cortical excitability regionally across the motor cortex. Patients in whom a motor evoked potential (MEP) could not be recorded in one or more limbs at maximal TMS intensities were classified as 4-limb or partially 'inexcitable'. The 'excitable' cohort represented patients in whom MEPs could be recorded in all limbs. Where resting motor thresholds (RMT) could be calculated, short interval intracortical inhibition (SICI, %) was measured. Demographic information, clinical variables and survival data were additionally analysed.

Results:
40 ALS patients were identified with inexcitability, with 4-limb involvement being the most common pattern (n=14). 93 patients formed the 'excitable' cohort. Patients with 4-limb inexcitability were younger ($p=0.03$) and had lower-limb disease onset (64%), greater functional disability ($p<0.001$) and faster disease progression ($p=0.02$), particularly if inexcitability developed within one year of symptoms ($p<0.01$). These differences were not found in patients with partial inexcitability, indicating that changes were restricted to 4-limb involvement. CMAP amplitude did not differ between inexcitable and excitable ALS groups. RMT was significantly higher for partially inexcitable patients compared to the excitable cohort ($p<0.01$), but averaged SICI was comparable ($p=0.5$). Mean survival was reduced if inexcitability involved all 4-limbs within 12 months of symptom onset ($p=0.04$).

Discussion and conclusion:
The presence of cortical inexcitability in all 4-limbs appears to define a unique clinical and prognostic profile in ALS patients, marked by faster progression, greater functional disability, and reduced survival when occurring early in disease. This cohort is typically younger with a lower-limb predominant phenotype. This measure identifies a distinct subgroup of patients with a more malignant disease trajectory, and may provide an important prognostic marker in ALS.

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IMG-17: Developing an automated tool to detect fasciculations from ultrasound recordings

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Background:
The presence of fasciculations is one of the diagnostic criteria for amyotrophic lateral sclerosis (ALS). Fasciculations are conventionally scored with EMG and visually. However, observer studies reported a higher sensitivity compared to EMG when using ultrasound (US) to grade fasciculations by their spatial and temporal nature (1, 2). Reliably quantifying fasciculation patterns from US requires automated protocols. Thus far, such protocols predominantly focus on producing a temporal measure of fasciculations (3-5). Additional automatic quantification of the spatial nature of fasciculations may further improve diagnostic sensitivity and monitoring in ALS, while mitigating operator bias.

Objectives:
To expand established automatic fasciculation detection protocols for US sequences with a spatial component, in congruence with clinical practice.

Methods:
US recordings were obtained from 8 patients with ALS recruited through our outpatient clinic. US sequences of 30 seconds were transversally recorded from the abductor pollicis brevis and biceps brachii (n = 16). Each sequence received a score from an experienced US rater and our fasciculation detection algorithm that included clustering based on co-occurrence rates and spatial distribution. Scores were defined as a combination of a) focal, multifocal, diffuse (distribution of fasciculations), b) sporadic, intermittent, continuous (fasciculation frequency). The clinician's score was compared to the algorithm's proposed score.

Results:
Fasciculations were detected in 11 sequences by the algorithm and 14 by the clinicians. Scores by the experienced US rater were focal-sporadic (n = 6); multifocal-intermittent (n = 2), and diffuse-continuous (n = 6). The algorithm scored the fasciculations by focal-sporadic (n = 2), diffuse-sporadic (n = 2), diffuse-intermittent (n = 1), and diffuse-continuous (n = 6). Discrepancy between the algorithm and the manual scoring mostly occurred due to probe motion or due to low contrast in the region containing fasciculations.

Discussion:
Using our initially implemented algorithm, we successfully quantified the distribution of fasciculations and their frequency to define a fasciculation score. Further development of the algorithm is required to more reliably detect fasciculation specific movement patterns. The use of the algorithm may eventually support the diagnostic phase by objective fasciculation scoring.

Acknowledgments:
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IMG-18: Developing Biomarkers of Focal Network Disruptions in ALS Using Threshold-Tracking Transcranial Magnetic Stimulation

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Background:
Threshold-Tracking Transcranial Magnetic Stimulation (TT-TMS) refers to the variation of magnetic pulse intensity to achieve an MEP of target amplitude. TT-TMS measures exhibit a high degree of reproducibility relative to the traditional approach of fixing pulse intensity and measuring variation in MEP amplitude [1]. Lower TT-TMS-measured posteroanterior short intracortical inhibition (SICI, a measure of interneuronal, GABA-Aergic inhibition of the corticospinal tract), compared to mimic disease and healthy populations has been proposed as a diagnostic ALS biomarker [2]. Abnormalities in SICI in ALS now requires replication in samples from other patient populations.
Furthermore, use of a circular coil, as in previous TT-TMS implementations, involves stimulation of large cortical areas [3] which can result in simultaneous interrogation of multiple upper motor neuron-regulating circuits. For example, both intracortical facilitation (ICF), attributed to intra-motor cortical glutamatergic circuits, and short interhemispheric inhibition (IHI) of the corticospinal tract via the corpus callosum, can be elicited by suprathreshold conditioning pulse delivery 10ms before upper motor neurone stimulation. These measures of two different cortical circuits are deciphered by conditioning stimulation location, requiring more focal pulse delivery.

Objectives: To take advantage of the sensitivity and reproducibility of TT-TMS, in conjunction with the use of focal TMS stimulation, to determine if ALS-associated cortical network disruption is expressed via specific measures of intra- and inter-hemispheric inhibition and facilitation.

Methods:
EMG was recorded from dominant-hand APB muscle while fully-automated TT-TMS protocols [4] were applied over the contralateral motor cortex using a 50mm figure-of-eight coil with posteroanterior and anteroposterior directions of induced current flow. SICI, ICF, long intracortical inhibition (LICI) and short and long IHI were measured for a range of interstimulus intervals (ISIs). Data from 12 patient and 19 controls has been recorded to date.

Results:
With use of anteroposterior current flow, patients show significantly lower short IHI (p=0.029) and SICI (p=0.0022, 3ms ISI) than controls. Although tendencies toward higher ICF and lower SICI in ALS patients were observed when ("traditional") posteroanterior current flow was used, in neither case was the trend reliable. Level of posteroanterior SICI (1ms ISI) positively correlated with ALSFRS-R (p=0.017, rho=0.94).

Discussion:
These results suggest that measurement of posteroanterior SICI is more suitable for the quantification of ALS progression than for diagnosis. The use of alternative coil orientations which stimulate other motor cortical neurons may capture additional aspects of ALS pathology that are pertinent to diagnostic biomarker development. Our findings of lower short IHI also implicate functional decline in the corpus callosum as a contributor to motor cortex hyperexcitability in ALS.

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IMG-19: Disease burden in early primary lateral sclerosis: a neuroimaging study of 'probable' PLS

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Primary lateral sclerosis (PLS) is a low-incidence neurodegenerative disorder of the upper motor neurons. The majority of patients with PLS face a long diagnostic journey and often fear conversion to ALS in the years following symptom manifestation. The new consensus diagnostic criteria for PLS introduced the category of 'probable PLS' for patients with a symptom duration of 2-4 years.

The objective of this study is to evaluate disease burden in this new diagnostic category based on clinical and imaging metrics.

A total of thirty-nine patients were stratified by the new diagnostic criteria into 'probable' or 'definite PLS'. Patients were systematically evaluated by a standardised battery of clinical instruments including ALSFRS-r, the modified Ashworth spasticity scale and the Penn upper motor neuron score. All patients and 100 healthy controls underwent high-resolution structural and diffusion MRI.

Despite their shorter symptom duration, the 'probable PLS' group already exhibited motor cortex atrophy, but their white matter metrics in the corticospinal tracts and corpus callosum were relatively well preserved. The clinical profile of 'probable PLS' patients revealed considerable functional disability and widespread upper motor neuron dysfunction.

Our clinical and imaging data support the introduction on this new diagnostic category which may curtail the diagnostic journey and facilitate an earlier inclusion into research studies and pharmaceutical trials.

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IMG-20: Effect of genotype on cerebral 18F FDG uptake in patients with Amyotrophic lateral sclerosis

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Background:
The multifaceted clinical syndrome of Amyotrophic lateral sclerosis (ALS) is a rapidly progressing neurodegenerative disorder that is usually fatal in 2-5 years. Most patients with ALS will have cytoplasmic aggregation of TDP-43. Even though the majority of patients with ALS have a form of the condition that is described as sporadic (sALS), an estimated 5 to 10 percent of ALS is familial and caused by a mutation in the C9orf72, SOD1, TARDBP, FUS, TBK1, or other genes.

Objectives:
In this study, we studied the impact of genotype on cerebral 18F-FDG uptake in patients with ALS.

Methods:
A large cohort of 789 patients was consecutively included in the neuromuscular reference center of Leuven, between January 2010 and June 2020. In 717 patients with ALS, genetic screening was performed for mutations with a strong evidence of causality (C9orf72, SOD1, TARDBP, or FUS). Static Fluorine 18 fluorodeoxyglucose positron emission tomography ([18F]FDG PET) were acquired 30 min after injection in 453 patients with ALS and 20 healthy controls (HC). All [18F]FDG PET images were analyzed using a voxel-based and volume-of-interest (VOI)-based approach to study the relation between genotype and regional glucose metabolic changes. Voxel-based analyses were thresholded at $P_{height,uncorr.} < 0.001$ and $P_{cluster,FWE-corr.} < 0.05$, kE = 150 voxels at cluster level, while a one-sided P_{corr}-value < .05 was considered significant for all VOI-based analyses.

Results:
Of the 453 patients that were considered for this study, we included 39 patients carrying a mutation in the C9orf72 gene, 17 patients carrying a mutation in the SOD1 gene (SOD1-ALS), 50 age- and gender-matched sporadic ALS patients (sALS) and 20 HC in our analyses.

We did not identify significant clusters of relative hypo- or hypermetabolism in SOD1-ALS, when compared to sALS. C9orf72 repeat expansion carriers did present with significant clusters of relative hypometabolism in the peri-rolandic region, when compared to sALS and SOD1-ALS. We also found a significant cluster of relative hypometabolism bilaterally in the thalami of C9orf72 repeat expansion carriers, in relation to sALS.

In addition, we identified a significant cluster of relative hypermetabolism in the posterior lobe of the cerebellum of C9orf72 repeat expansion carriers, when compared to sALS and SOD1-ALS. We also identified a significant cluster of relative hypermetabolism in the brainstem of C9orf72 repeat expansion carriers when compared to sALS. VOI-based analyses confirmed these findings.

Conclusion:
This study suggests that, unlike C9orf72 repeat expansion carriers, SOD1 mutation carriers do not appear to present with a significantly different glucose metabolic signature from sporadic ALS patients. C9orf72 repeat expansion carriers on the other hand display a more widespread central nervous system involvement than sporadic ALS patients and SOD1 mutation carriers.

IMG-21: Electromyography in Amyotrophic Lateral Sclerosis: a staging indicator and a marker of prognosis

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Aims:
ALS is a neurodegenerative disease, involving upper and lower motor neurons. The diagnosis of ALS is based on clinical criteria supported by EMG, which investigates spontaneous activity, motor unit potential and the voluntary maximum recruitment pattern. The first aim of this paper is to assess, at diagnosis, some of the main ALS electromyographic findings and compare them to King's staging system, MiToS and NBRI. The second aim is to stratify patients' prognosis on the basis of electromyographic findings.

Methods:
Electromyographic data of 7 muscle districts in 394 patients, belonging to PARALS register (2012-2018) were recorded. We selected the EMG examination performed at diagnosis and we compared it with the nearest ALSFRS-r scale.

Results:
The increase of MiToS, King's and NBRI systems stage is correlated with a higher percentage of muscle districts with alterated voluntary maximum recruitment pattern. Fib/PSW are predominant in distal muscle districts; fasciculations are mostly recorded in upper limbs rather than lower limbs (chi-squared test p<0,001). Fasciculations in the upper limbs has been used to stratify patients, belonging to the same clinical stage, in groups characterized by different prognosis.

Discussion:
The level of disability at the time of EMG examination is correlated to the alteration of voluntary maximum recruitment pattern, rather than spontaneous activity. Different features of EMG spontaneous activity (Fib/PSW vs fasciculations) have distinct distribution in muscle districts, maybe underlying different neuropathological mechanisms. Fib/PSW are frequently found in distal muscle districts: this may be explained by early distal denervation in ALS onset. Fasciculations are often observed in upper limbs, possibly correlating to wider cortical projection of upper limb muscles (De Carvalho et al., 2017). Fasciculations has been correlated not only to a lower motor neuron disease, but also to an increased cortical excitability (Kleine et al., 2008). Frequent fasciculations in specific muscle districts are correlated, in patients in the same disease stage, with poorer prognosis. The presence of spontaneous activity in the proximal districts of upper limbs could be linked to a faster involvement of the respiratory muscles. This hypothesis is consistent with previous data (Zhang et al., 2016).

Conclusion:
Needle EMG is a useful tool in motor neuron diseases, as it can be used to highlight different neuropathological characteristics in ALS patients cohorts with different prognosis.

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IMG-22: Elucidating the optimal HDSEMG recording duration for fasciculation parameters in Amyotrophic Lateral Sclerosis and Benign Fasciculation Syndrome

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Background:
Fasciculations are random spontaneous muscle twitches, a hallmark of both Amyotrophic Lateral Sclerosis (ALS) and Benign Fasciculation Syndrome (BFS). Fasciculations can be detected using high-density surface electromyography (HDSEMG). Surface Potential Quantification Engine (SPIQE) is an automated toolkit developed to analyse the raw HDSEMG data and produce an interpretable fasciculation frequency and fasciculation amplitude output.

Objectives:
SPiQE was validated using 30-minute HDEMG recordings. A shorter duration of recording would improve patient convenience and reduce processing time. Therefore, we set out to calculate the shortest recording duration that accurately reports the fasciculation parameters.

Methods:
392 (196 biceps brachii and 196 gastrocnemii), 30-minute recordings from 20 ALS patients and 114 (58 biceps and 56 gastrocnemii), 30-minute recordings from 5 BFS patients were collected. From each raw 30-minute recordings, five test durations were derived: 5, 10, 15, 20 and 25-minute recordings. SPiQE was then utilised to process these recordings using its noise-responsive algorithm and its Active Voluntary IDentification (AVID) system to detect and characterize fasciculations. This produces an output containing the fasciculation frequency (number of fasciculations per minute) and median/IQR fasciculation amplitude (μV) of the recording. Agreement between the test durations and the 30-minute recording (the validated duration length) was assessed using a Bland-Altman plot. The mean difference (bias) and the 95% limits of agreement (LOA) were calculated.

Results:
The fasciculation frequency bias and limits of agreement were smaller the longer the duration of recording, for both the biceps and the gastrocnemius. However, they were narrower in the BFS group compared to the ALS group at all test durations.
For the gastrocnemius median fasciculation amplitude, the bias and LOA were largely consistent at the different test durations in both the BFS and ALS data. In contrast, the bicep median fasciculation amplitude was sensitive to a reduction in recording duration demonstrated by the wider bias and LOA.
The bicep IQR fasciculation amplitude for the ALS and BFS group had a wide LOA at the 5, 10, 15, 20 and 25-minute recordings. This was also the case for the ALS gastrocnemius data but it also demonstrated proportional bias.

Conclusions:
For the fasciculation frequency parameter, reducing future recording durations from 30 minutes to 15 minutes would add significant practical convenience without compromising on the accuracy of the outputs. However, factors that mediate the discrepancy between the test durations and 30-minute recording in the fasciculation amplitude parameter need to be investigated.

IMG-23: Exploring High Density Surface Electromyography (HDsEMG) Correlates of Upper and Lower Motor Neuron Impairment in Amyotrophic Lateral Sclerosis

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Live Poster Session C, December 11, 2020, 12:05 PM - 12:50 PM

Background:
Electrophysiology is an important method in reaching diagnostic certainty in ALS, as exemplified by the Awaji Criteria that assigns equal weightage to electrophysiological evidence (e.g. fasciculation potentials) as clinical signs and symptoms. High density surface electromyography (HDsEMG) is a non-invasive technique of recording fasciculation potentials over long durations. Bashford and colleagues (2019) developed the Surface Potential Quantification Engine (SPiQE) as an automated analytical tool to detect and quantify fasciculation potentials in HDsEMG recordings. Subsequently, they introduced Active Voluntary IDentification (AVID) as a semi-automated strategy to exclude voluntary potentials from the main fasciculation analysis.

Objective:
The two objectives of this project are i) to analyse voluntary parameters that were excluded from HDsEMG analysis using the AVID strategy; and ii) to identify potential pathophysiological signatures of high-frequency motor unit activity from HDsEMG recordings in ALS patients.

Methods:
30-minute HDsEMG data recordings taken from 20 ALS patients in a previous longitudinal study were analysed in MATLAB across two domains. In the time domain, voluntary parameters were generated, which allowed for comparisons with fasciculation parameters, clinical examination parameters, and riluzole intake. In the frequency domain, specifically designed scripts were utilised in looking for pathophysiological signatures (e.g. myokymic and neuromyotonic discharges) of high-frequency motor unit activity.

Results:
Statistical analysis showed that the voluntary and fasciculation parameters were significantly different ($p < 0.001$), with muscle parameters showing different trends across time ($p = 0.001$). Utilising exploratory manual analysis, fasciculation doublets and triplets both in and out of the range of myokymic discharges were detected.

Discussion:
The significant difference between the voluntary and fasciculation parameters validates the AVID strategy as a complement for SPiQE fasciculation analysis. The quantification of voluntary parameters and the multiple comparisons with other parameters over time provide a framework for future hypotheses to be generated and tested. The successful discovery of high-frequency motor unit activity demonstrates the feasibility of expanding this novel approach to detect abnormal electrophysiological patterns in a variety of diseases other than ALS.

IMG-24: Global brain and tongue atrophy in ALS via deformation-based voxel analysis from T2-weighted structural MRI

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Live Poster Session B, December 10, 2020, 5:10 PM - 5:50 PM

Background:
Whole-body magnetic resonance imaging (MRI) plays an important role in visualizing and quantifying anatomical structures of the body under different pathological conditions. In amyotrophic lateral sclerosis (ALS), patients suffer from symptoms due to degeneration of motor neurons, which yields atrophy in the brain and the tongue. Two onset conditions are commonly observed in ALS cases: bulbar onset and limb onset. When compared with other imaging modalities, T2-weighted MRI offers better anatomical information to measure muscle volumes, providing invaluable information regarding status of the disease.

Objectives:
It has been difficult to objectively compare ALS measurements due to large variability (e.g., size, shape, tissue property, etc.) of a study population. Deformation-based voxel analysis is a widely used technique to identify global anatomical differences via an image atlas and image registration.

Methods:
We created a head and neck image atlas using 20 normal control subjects using group-wise diffeomorphic registration. Diffeomorphic registration between ALS patient subjects and the atlas were then performed for further deformation-based voxel analysis. The patient population consisted of three subjects with bulbar onset and twenty-three subjects with limb onset. The output of diffeomorphic registration provided not only the aligned patient image in the atlas space but also the relation between the atlas space and each subject space in the form of a three-dimensional deformation field. Computing the Jacobian determinant of each deformation field yielded a score showing the volume change of each subject when being deformed to align with the atlas. Therefore, any expansion or contraction of a specific organ of interest comparing to the atlas image as common standard was learned. Specifically, a manual segmentation of the brain and the tongue in the atlas space was performed, which was used as a mask to limit the computation of volume change in these regions of interest.

Results:
Results showed that for the bulbar onset patients, the average ratio of their brain volume to the standard brain atlas volume was 0.964, while the average ratio of their tongue volume to the standard tongue atlas volume was 0.991. On the other hand, for the limb onset patients, the average ratio of their brain volume to the standard brain atlas volume was 1.061, while the average ratio of their tongue volume to the standard tongue atlas volume was 1.168.

Discussion:
Patients with bulbar onset have smaller gross volume for both the brain and the tongue, and patients with limb onset have bigger gross volume for both the brain and the tongue. The proposed method was able to show detailed information on the change of muscle and brain volumes in an ALS population, while it sidesteps laborious segmentation tasks and automates quantitative study in the research of ALS.

IMG-25: Impaired functional connectivity of the primary motor cortex is associated with underlying structural and neurochemical deficits: A multicentre-multimodal imaging approach to investigating ALS pathology

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Background:
Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease that affects cortical and spinal motor neurons (MNs). Impaired MN activation is reported in electrophysiological and transcranial magnetic stimulation (TMS) studies as a feature of ALS pathophysiology. Magnetic resonance spectroscopy (MRS) evidence of reduced gamma amino butyric acid (GABA) levels, an inhibitory neurotransmitter, and NAA[1], a neuronal marker, has been useful in explaining impaired activation. Increased glial activation in the primary motor cortex (PMC) is shown to correlate with reduced cortical thickness and decreased fractional anisotropy (FA, a marker of white matter integrity) in the PMC[2]. However, these independent observations do not address the contributions of structural and neurochemical alterations on activation of cortical MNs. Therefore, we hypothesized that FC between the PMC and other brain regions at rest is explained by their underlying structural and neurochemical properties.

Methods:
Fifty-nine ALS patients and forty-six healthy controls from four Canadian centers participated in the Canadian ALS Neuroimaging Consortium study. All patients met El Escorial criteria for clinically possible, probable, or definite ALS. MRS, diffusion tensor imaging, and resting-state functional magnetic resonance imaging data were used to respectively quantify neurochemical levels (NAA), FA, and FC alterations of the PMC and to examine whether FA or NAA alterations related to the FC differences.

Results:
The PMC showed a significant increase in functional connectivity (FC) with the left superior parietal lobule (SPL: T = 3.76) and left secondary visual cortex (T = 3.71), and a significant decrease in FC with the right middle frontal gyrus (MFG: T = -3.98). The levels of NAA positively correlated with FC in the right MFG (T = 3.85) and negatively with FC in the bilateral SPL (T = -4.13). FA of the PMC negatively correlated with FC in the left inferior parietal lobule (T = -4.67), bilateral inferior frontal (T = -3.79) and left anterior cingulate gyri (T = -3.57).

Conclusion:
In accordance with previous literature, our study shows that functional impairment occurs in-part because of underlying structural deficits. An advantage of this study is a localized, hypothesis-driven, and multimodal approach to examining the structural and neurochemical correlates underlying impaired function of the PMC in ALS. Future studies are important to combine imaging and electrophysiological methods longitudinally to characterize the temporal and spatial dynamics of cerebral functional changes in ALS.

Acknowledgement:
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IMG-26: Improving the diagnostic utility of EMG measures as biomarkers of Motor Neuron Disease using multivariate discriminant analysis

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Background:
Novel biomarkers are urgently needed to allow early diagnosis and accurate tracking of disease progression in MND/ALS patients.

Objectives:
To determine whether multivariate data analytics, e.g. Fisher's Linear Discriminant Analysis (FLDA), could be used to enhance the utility of existing biomarkers by providing improved discrimination between patients and controls (1).

Methods:
Data used in this study consisted of Compound Muscle Action Potential (CMAP), Motor Unit Number Index (MUNIX), and Motor Unit Size Index (MUSIX) taken from 6 muscles, abductor pollicis brevis (APB), abductor digiti minimi (ADM), biceps brachii (BB), tibialis anterior (TA), extensor digitorum brevis (EDB), abductor hallucis (AH), in a cohort of 43 MND patients and 40 healthy controls (2). Informative measurements were selected through an automated procedure and combined into a single score using FLDA.

Results:
The new combined score provided cross-validated Area Under the Curve (AUC) values as high as 0.965(±0.01), while the maximum cross-validated AUC for any individual measure was 0.887(±0.095). Similarly, by combining measures, cross-validated classification accuracies of 87.8±6.4% could be reached, while the maximum accuracy for any single muscle was 81.9±9.9%. Inspection of the most informative contributing measures showed that APB CMAP, TA CMAP, EDB CMAP were among the most important variables in achieving this discrimination.

Discussion:
A combination of measures using multivariate methods such as FLDA can exploit discriminating information which could not be found in any one of the original univariate measures in isolation. This can shed light on the underlying pathophysiology by identifying the maximally-contributing measurements and muscles for diagnosis and prognosis. Such multivariate approaches could be useful in clinical settings by improving diagnostic accuracy.

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IMG-27: Mathematical modeling reveals the correlates of cognitive impairment across the FTLD spectrum

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Objective:
Patients with amyotrophic lateral sclerosis (ALS), characterized by motor system degeneration, can also develop cognitive and/or behavioural symptoms that lie on a continuum with the behavioral variant of frontotemporal dementia (bvFTD). The aim of this study was to apply mathematical modeling to unravel MRI connectomic signatures of cognitive and/or behavioral impairment in ALS patients.

Materials:
Eighty-three ALS, 35 bvFTD and 61 controls underwent clinical/cognitive evaluations and MRI scan. Neuropsychological testing identified 54 ALS pure motor (ALSpm), 21 ALS with mild cognitive and/or behavioral impairment (ALSci/bi) and 8 ALS with bvFTD (ALS-FTD).

Methods:
The structural macroscale connectome of each subject was constructed. Connections linking cerebral lobes to each other were considered. The structural value of each connection for each patient was normalized relative to controls. The percentage of patients showing intra- and inter-lobe alterations was calculated considering those patients with normalized structural values below the reference value, i.e., zero. A statistical distribution analysis, intra- and inter-lobes, was performed to identify different structural patterns between bvFTD and ALSpm and to assess where ALSci/bi and ALS-FTD showed an ALS-like or a bvFTD-like pattern.

Results:
Compared to ALSpm, bvFTD showed greater structural involvement of the connections within and between frontal, temporal and parietal lobes, which were altered in most bvFTD patients (92%). On the other hand, 80% of ALSpm patients showed greater involvement of the connections between sensorimotor and basal ganglia areas, compared with bvFTD (66%). Similar to ALSpm, ALSci/bi was characterized by a relative preservation of the connections within frontal lobe and between frontal, temporal and basal ganglia areas. Noteworthy, ALSci/bi showed an ALS-like pattern within motor areas and a bvFTD-like pattern within the parietotemporal connections. Indeed, the percentage of ALSci/bi with structural alterations in the parietotemporal areas (57%-71%) was increased compared to that of ALSpm (54%-57%). Finally, ALS-FTD showed a pattern similar to bvFTD within frontal and between frontal and sensorimotor areas, while they showed an ALSpm-like pattern within sensorimotor and basal ganglia areas.

Discussion and Conclusions:
This study showed a widespread structural damage in bvFTD, particularly in the connections within frontotemporal areas and between frontal and other lobes, and a more focal structural damage within sensorimotor-basal ganglia areas in ALSpm. ALSci/bi and ALS-FTD showed an ALS-like pattern with the exception of a greater damage within the frontal and parietotemporal areas, signature of the occurrence of cognitive impairment.

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IMG-28: Brain MRI white matter graph theory network analysis shows degeneration in patients with ALS vs ALS-FTD is not on a continuum

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Background:
Clinical assessment and routine neuroimaging has identified 4 subgroups of ALS patients, including those showing (1) classic ALS (cALS) with upper motor neuron (UMN) and lower motor neuron (LMN) signs, (2) upper motor neuron-(UMN-) predominant ALS with hyperintensity of the corticospinal tract (ALS-CST+), (3) UMN-predominant ALS without CST hyperintensity (ALS-CST–), and (4) ALS with frontotemporal lobe dementia (ALS-FTD). While some studies have shown ALS and ALS-FTD to be a continuum [1, 2], others have not [3, 4].

Objectives:
To determine (1) which, if any of the cALS, ALS-CST+, ALS-CST–, or ALS-FTD patient subgroups share regions of WM abnormalities, and (2) whether ALS and ALS-FTD are on a continuum.

Methods:
An exploratory whole brain white matter (WM) network analysis was performed using graph theory approach. Diffusion tensor MRI data were obtained for 83 ALS patients (cALS n=25, ALS-CST+ n=19, ALS-CST– n=24, ALS-FTD n=15) and 14 neurologic controls.

Results:
Significant differences in degree (WM network) measures were observed between ALS patients with or without FTD and neurologic controls in prefrontal, motor, extra motor, subcortical and cerebellar regions. WM networks affected by ALS degeneration were noticeably different between cALS, ALS-CST+, ALS-CST–, and ALS-FTD groups, although with some overlaps, particularly in ALS-CST+ and ALS-FTD groups.

Discussion and Conclusion :
Of the few brain regions sharing WM abnormalities between patient groups: (1) more were found in the cerebellum than in the forebrain of those with cALS, ALS-CST+, or ALS-CST–; (2) only three occurred in all four groups, including ALS-FTD patients. Despite some overlap, distinct regional involvement in cALS, ALS-CST+, ALS-CST–, and ALS-FTD patients does not support a continuum between the subgroups and suggests differential patterns of WM neurodegeneration between these ALS phenotypes.

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IMG-29: Circulating CD4+ lymphocytes relate to thickness of the primary motor cortex in amyotrophic lateral sclerosis.

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Background:
Immune system involvement is increasingly recognised as an integral component of the neurodegenerative process in amyotrophic lateral sclerosis (ALS), with animal models of disease implicating a subpopulation of CD4+ CD25+ FoxP3+ 'regulatory' T lymphocytes (Tregs) in beneficially tempering these inflammatory responses. Elevated Treg:total CD4+ ratio, or the absolute Treg count, has correlated negatively with rates of disease progression in patients with ALS. The Modifying Immune Response and Outcomes in ALS Trial (MIROCALS: www.mirocals.eu) is currently investigating safety and efficacy of boosting circulating Tregs with low dose Interleukin-2. A subgroup of patients in MIROCALS have undergone multimodal brain MRI at baseline and after treatment, including structural T1 sequences which have previously demonstrated reduced thickness of the primary motor cortex in ALS. Aim: to explore the relationship between thickness of the primary motor cortex at baseline and pre-treatment levels of patients' blood-borne Tregs, total CD4+ count and the Tregs:total CD4+ ratio.

Methods:
An interim analysis was performed on 23 patients and 24 age-matched controls using brain MRI scans at 1.5T. Cortical reconstruction and volumetric segmentation was performed within the FreeSurfer image analysis suite using the T1 MPRAGE files in order to calculate average thickness of the precentral cortex for each participant. CD4+ cells and Tregs were enumerated by flow cytometric analysis of whole blood. Group comparisons between patients and controls, and associations between patients' cortical thickness and immune cell levels, were performed in IBM SPSS where $p<0.05$ was accepted as statistically significant.

Results:
Compared to controls, patients with ALS were found to have reduced thickness of the right precentral gyrus cortex ($p=0.022$). Cortical thickness demonstrated a weak negative relationship with total blood CD4+ T cell count ($p=0.04$).

Conclusion:
This interim analysis has reproduced the finding of reduced primary motor cortex thickness in patients with ALS. Although further investigation is awaited on the full cohort, these findings provide evidence for immunological crosstalk between the blood and central nervous system relevant to mechanisms of disease in ALS.

IMG-30: Exploring the electro-mechanical properties of fasciculations in amyotrophic lateral sclerosis

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Live Poster Session C, December 11, 2020, 12:05 PM - 12:50 PM

Background and aim:
Amyotrophic lateral sclerosis (ALS) is characterised by hyperexcitability of motor neurones resulting in spontaneous electrical discharges. These translate into involuntary muscle twitches, also known as fasciculations. Two non-invasive techniques allow to detect fasciculations: high density surface electromyography (HDSEMG) and muscle ultrasonography (MUS). HDSEMG and MUS were simultaneously used to detect fasciculations, ultimately exploring the electro-mechanical characteristics of these. It was also sought to identify a potential biomarker of disease based on the differential characteristics of fasciculations in ALS versus healthy participants.

Methods:
Six 50-seconds simultaneous HDSEMG and MUS recordings were taken from five ALS patients and six healthy controls. The recordings were made from the right biceps brachii and gastrocnemius medialis from both groups. Two novel analytical methodologies were utilised to identify fasciculations, namely Surface Potential Quantification Engine for HDSEMG and Gaussian mixture model for MUS. Fasciculations simultaneously detected from both HDSEMG and MUS were identified as electrical peaks on HDSEMG followed by mechanical peaks on MUS within 500 milliseconds.

Results:
For 33.4% (402/1,204) of all fasciculations detected by MUS, across both groups, muscles and two orientations of the ultrasound probe, a corresponding fasciculation potential was detected in HDSEMG. By contrast, only for 8.5% (402/4,704) of fasciculations detected by HDSEMG there was a MUS correlation. The median depth of the correlated fasciculations, when the MUS probe was used transversally across the muscle, was 15.8 mm (IQR 9.5 - 23.5), while for uncorrelated events was 27.9 mm (IQR 20.2 -39.3). Similarly, when the MUS probe was positioned longitudinally to the muscle, the median depth of correlated events was 17.1 mm (IQR 10.7 - 26.0) and 28.2 mm (IQR 17.6 - 45.4). The electro-mechanical delay, across muscles and MUS orientations, was significantly different between the ALS group and the healthy controls showing respectively: 71.5 ms (IQR 55 – 220, n = 217) and 64 (IQR 55 -84, n = 188), p = 0.028 as per Mann Whitney testing.

Conclusions:
The practical feasibility of utilising HDSEMG and MUS to detect fasciculations simultaneously by both was successfully demonstrated with this study. The number of fasciculations found to be correlated between the two modalities were lower than expected. This could be partly due to the 2-dimensional nature of MUS compared to the 3-dimensionality of HDSEMG. It was also shown that HDSEMG detected fasciculations as deep as 35mm, highlighting its spatial sensitivity. Notably, a significantly different electromechanical delay was identified in the ALS group's fasciculations compared to healthy controls, opening new avenues for a novel biomarker of disease.

IMG-31: Feasibility and future role of high-density transcranial magnetic stimulation in ALS: A pilot study in healthy volunteers

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Live Poster Session C, December 11, 2020, 12:05 PM - 12:50 PM

Background:
The development of valid diagnostic and reliable progression biomarkers for Amyotrophic Lateral Sclerosis (ALS) is urgently needed to accelerate the search for effective therapies. Transcranial magnetic stimulation (TMS) and high-density surface EMG (HDSEMG) are non-invasive tests that have shown potential as electro-diagnostic markers of ALS. These techniques have demonstrated that cortical (upper motor neuron) and spinal (lower motor neurons) hyperexcitability are early pathogenic mechanisms preceding the relentless and irreversible muscular atrophy and weakness seen in ALS(1,2).

Objectives:
Our aim was to validate the combination of TMS and HDSEMG, for the first time. Specifically, the motor cortex of healthy volunteers was stimulated with TMS and motor-evoked responses at the contralateral hand area were recorded with 64-channel HDSEMG. We hypothesised that high-density TMS (HD-TMS), compared to the conventional single channel EMG recording, can provide an enriched dataset to study cortico-spinal hyperexcitability in ALS, building upon previously recorded abnormalities of TMS parameters that have been proposed as early hallmarks of motor neuron degeneration.

Methods:
Well-known TMS protocols probing inhibition through the duration of the cortical silent period (CSP) and the magnitude of short interval intracortical inhibition (SICI) and intracortical facilitation (ICF), were measured during simultaneous HDSEMG registration from the first dorsal interosseous (FDI) muscle of the dominant hand in 5 healthy volunteers (1 male, 4 females, mean age 35.2 years). Analysis was performed in MATLAB using customised scripts.

Preliminary results:
Preliminary data indicated high data quality and methodological validity of our novel electrophysiological approach. Although the sample size is small, this study allowed the development of a new analytical pipeline for data visualisation and analysis. By capitalising on the improved spatial resolution allowed by the HDSMEG array, we have incorporated the different TMS indices of cortico-spinal excitability into a more detailed 3D anatomical map of the FDI firing.

Discussion and Conclusions:
To the best of our knowledge, HDSEMG has never been combined with TMS to investigate motor cortical neurophysiological mechanisms. The future application of this pilot study to the ALS population has the potential to improve our understanding of the topographical distribution of disinhibition (as measured by CSP and SICI) or excess facilitation (as measured by ICF) that has been postulated to underlie cortical hyperexcitability in ALS. To conclude, we predict that HD-TMS could help us determining more precisely how excitability abnormalities evolve and spread over time, enabling the progression of a detailed anatomical map of the disease trajectory. We also expect that this strategic combination may help us to better discriminate between the contribution of LMN versus UMN to our TMS findings in ALS patients.

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IMG-32: Longitudinal changes of functional networks disruption in ALS: a resting-state EEG study

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Background:
The use of electrophysiological data, mostly recorded from muscles and peripheral nervous system, has been of utility to improve clinical diagnosis, phenotyping, and to track disease progression in ALS [1]. More recently, neurophysiological recordings that reflect cortical activity have been shown to have ALS-specific patterns. More specifically, resting-state spectral electroencephalography (EEG) measures that pertain to motor and non-motor brain regions have shown great promise as potential biomarkers of network dysfunction in ALS [2]. However, the longitudinal changes of these measures need further investigation.
Objectives:
To assess the longitudinal changes of the previously observed resting-state spectral EEG patterns of dysfunction in ALS as potential prognostic biomarkers.
Methods:
Resting-state EEG data (125 patients; 81 healthy controls) were collected up to 5 times, with an interval of approximately 3 to 7 months between sessions. Neural activity (spectral power) and functional connectivity (amplitude envelope correlation and imaginary coherence) measures were estimated across 90 brain regions and 6 frequency bands. These were analysed for longitudinal trends using pairwise statistical comparisons and linear mixed-effect (LME) models. Permutation-based False Discovery Rate analyses ($\alpha = 0.05$, 5/10 subsamples, 1000/5000 permutations) were used to correct for multiple comparisons. Furthermore, correlations were evaluated between significant slopes of EEG measures and the disease progression (estimated for each patient using an LME model of ALSFRS-R scores).
Results:
The θ-band normalised spectral power in a temporal region showed a significant decrease over time of 2‰ per month [95% Confidence Intervals: -0.00033 to -0.000048]. The mean slope was significantly different from zero ($p = 0.009$) but varied considerably across patients (standard deviation: 0.0002) indicating weaker or stronger progression in different individuals. These patient-specific slopes also showed correlation with ALSFRS-R slopes ($\rho = -0.26$, $p = 0.0043$).
The δ-band AEC between two occipital regions showed a significant increase over time ($p = 0.002$), of 2‰ per month [95% CI: 0.0006 to 0.003] and a patient-specific random-effect with 0.0005 standard deviation.
Discussion:
This study demonstrated the presence of longitudinal changes in resting-state EEG measures in specific brain regions in ALS. Moreover, these longitudinal changes are functionally relevant as they correlated with ALSFRS-R. The study confirms the potential of spectral resting-state EEG measures, as reliable, consistent and quantitative functional biomarkers that can track the abnormal network patterns in ALS longitudinally, and can be instrumental as new tool for future clinical trials.

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IMG-33: Monitoring disease progression with electrophysiological markers obtained from compound muscle action potential scans in amyotrophic lateral sclerosis

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Background:
The compound muscle action potential (CMAP) scan is an emerging electrophysiological tool from which clinically relevant markers on motor unit (MU) number, MU sizes and axonal excitability can be obtained. Several studies have shown the ability to quantify disease progression in muscles affected by ALS. It remains, however, to be established which of the electrophysiological markers are most sensitive to monitor disease progression and whether they can serve as surrogate endpoint in clinical trials.

Objectives:
To select optimal electrophysiological markers for monitoring ALS disease progression and evaluate their sensitivity as compared to the ALSFRS-R.

Methods:
A multicenter collaboration was initiated between MND centers in Utrecht, Aarhus, Istanbul and Brisbane to retrospectively assess longitudinal electrophysiological and ALSFRS-R patterns. For each patient we determined the change over time in maximum CMAP amplitude (CMAPmax), D50 (number of largest discontinuities within CMAP scans), returners (number of increased CMAPs with decreasing stimulus currents), stimulus currents required to elicit 5%, 50%, and 95% of CMAPmax, a motor unit number estimate (MUNE) and MU size properties (e.g. mean, median and largest MU size, number of large-sized MUs). Linear mixed models were used to estimate variance components and population averages. Outcomes were compared in their required sample size to detect a 50% change in progression rate after 6 months with 80% power.

Results:
In total, 57 patients diagnosed with MND were included in this study with a total follow-up time of 327 months (average of 6 months per patient). The ALSFRS-R total score decreased on average by 0.91 points per month (95% CI -1.18 to -0.64). MUNE, number of large-sized MUs, CMAPmax and D50 showed the largest change over time with standardized progression rates of -0.092, -0.081, -0.055 and -0.061 standard deviations per month, respectively. In terms of sample size, a composite of MUNE and number of large-sized MUs required 132 patients, whereas the ALSFRS-R required 146 patients (+10.6%).

Discussion:
There is a wide variety in the ability of electrophysiological markers to monitor disease progression in patients with ALS. Endpoints based on MUNE or MU sizes may exhibit the most favorable longitudinal pattern for use in clinical trials. A composite of electrophysiological markers obtained from the CMAP scan may further increase its sensitivity to monitor disease progression in ALS and maximize its utility for clinical trials.

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IMG-34: Quadratic association between hypothalamic volume and BMI in non-neurodegenerative control participants and patients with MND

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Background:
The loss of appetite in MND resulting in decreased energy intake is associated with greater weight loss and loss of fat-free mass (1), both of which are linked to faster disease progression and earlier death (2). The cause for loss of appetite in MND is multifactorial (3). A positive association between body mass index (BMI) and hypothalamic volume in MND (4) suggests that impaired hypothalamic function could contribute to weight loss in patients.

Objectives:
To determine the relationship between BMI and hypothalamic volume in patients with MND who have intact or loss of appetite.

Methods:
Thirty-three patients with probable or definite MND (11 with loss of appetite; identified using the Council on Nutrition Appetite Questionnaire (CNAQ) (5)) and 17 non-neurodegenerative disease (NND) healthy controls participated in imaging studies at 3-Tesla using a T1-weighted MP2RAGE sequence (6), and a T2-weighted FLAIR sequence (7). Hypothalamic volumes were extracted and corrected for intracranial volume using a bimodal delineation procedure (8) coupled with Joint Label Fusion (9). Adjusted hypothalamic volumes were contrasted to measures of BMI, fat mass and fat-free mass.

Results:
We found a quadratic association between hypothalamic volume and BMI in all participants ($p<5e-4$). The interaction effect between control participants and patients with MND was not significant ($p=0.98$). There was no significant interaction when patients with MND were subdivided into those with an intact appetite or a loss of appetite ($p=0.73$). There was no relationship between hypothalamic volume and fat mass or fat-free mass in controls or patients with MND.

Discussion and conclusions:
These observations challenge existing literature that show a linear association between hypothalamic volume and BMI. Observations suggest that deviations in BMI might be associated with structural changes within the hypothalamus resulting in lower hypothalamic volume. The non-significant interaction effect between those with intact and loss of appetite suggests that associations between hypothalamic volume and BMI alone cannot explain the loss of appetite in MND; this is undergoing validation in a larger cohort of patients.
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IMG-35: Pathological EEG-EMG Coherence Patterns in Spinal Muscular Atrophy

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Background:
Spinal Muscular Atrophy is a pure lower motor neuron disorder with onset occurring usually in infancy or childhood. Breakthroughs in the treatment of SMA with anti-sense oligonucleotide has been shown to be effective in infants. However, the benefit of this therapy in adults remains unclear.
Recent MRI studies[1] in adult SMA patients have provided convincing evidence of re-organization of the motor cortex, raising the possibility that loss of anterior horn cells in childhood leads to upstream changes in neuronal structure and function.

Objective:
To test the hypothesis that functional cortico-muscular connectivity reflects the network-level alteration of neural communication in cortical and spinal circuits in spinal muscular atrophy (SMA).

Methods:
13 patients with SMA, comprising over 50% of the Irish adult SMA population, and 13 healthy controls were recruited and studied during the performance of isometric precision grip tasks tailored for patients with minimal hand muscle function. Simultaneous recordings of high-density 128-channel EEG and 8 bipolar surface EMG recordings from extrinsic and intrinsic hand muscles were taken. Time-series analyses quantified the neural communication between cortical brain regions and the muscles, that represent the oscillatory motor drives to muscles during the adapted pincer grip motor tasks.

Results:
Analysis of the SMA patient group showed pathological presence of cortico-muscular coherence (CMC) between EMG and EEG signals recorded from frontal and parietal brain regions in abnormal frequency bands. This included alpha-band increases over the parietal (Pz) region which extend to other frequency bands in the frontal (Fz) and central (Cz) regions.

Discussion:
EEG-EMG coherence during functional motor tasks shows pathological changes in the central-peripheral communication in SMA Patients. Pathological locations of CMC suggest compensatory changes in the motor cortex, which involves broader cortical regions with synchronous activity to muscles, in those affected with SMA. This study provides a proof of concept demonstrating that interrogation of CMC patterns could be developed as a marker of therapeutic efficacy at a network level in LMN conditions such SMA, where current quantitative clinical outcome measurements are limited by severe motor disability.

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IMG-36: Progression of brain functional connectivity and frontal cognitive dysfunction in ALS

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Background:
In amyotrophic lateral sclerosis (ALS) cognitive symptoms can occur in the 50% of cases (1) and have been shown to hold significant prognostic implications (2). Longitudinal studies in ALS are particularly relevant in order to identify novel biomarkers of motor and cognitive decline and to better define the patient's prognosis. Up to date, only few studies have investigated resting-state functional connectivity (rs-FC) changes over time in ALS (3-6).

Objectives:
To investigate the progression of rs-FC changes in patients with ALS and their relationship with frontal cognitive alterations.

Methods:
This is a multicentre, observational and longitudinal study. At baseline and after six months, 25 ALS patients underwent 3D T1-weighted MRI, rs functional MRI (rs-fMRI), and the computerized Test of Attentional Performance (TAP). Using independent component analysis, rs-FC changes of frontal brain networks and their relationship with baseline cognitive scores and cognitive changes over time were assessed. With a seed-based approach, rs-FC longitudinal changes of the middle frontal gyrus (MFG) were also explored.

Results:
After six months, ALS patients showed an increased rs-FC of the left anterior cingulate, left middle frontal gyrus (MFG) and left superior frontal gyrus within the frontostriatal network, and of the left MFG, left supramarginal gyrus and right angular gyrus within the left frontoparietal network. A worse baseline performance at TAP divided attention task was associated with an increased rs-FC over time in the left MFG within the frontostriatal network. A seed-based rs-FC analysis of the MFG with the whole brain showed decreased rs-FC of the right MFG with frontoparietal regions over time.

Discussion:
Rs-FC changes in ALS patients progressed over time within the frontal networks and are related to frontal-executive dysfunction. The MFG emerges as a core region in the framework of a frontoparietal functional disconnection, which is typical of frontotemporal lobar degeneration. These findings offer new potential markers for monitoring extra-motor progression in ALS.

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IMG-37: Psychosis risk-states in motor neurone disease

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Psychosis is a challenging feature of motor neurone disease (MND), frontotemporal dementia (FTD) and their overlap (FTD-MND). Clinically evident psychosis is not common, except in those with C9orf72+ expansions. However, sub-threshold psychosis and pro-psychotic processes are common and provide the opportunity to study the mechanisms of psychosis in MND and FTD-MND.

In the COGENT study, we aimed to identify the cognitive and neural correlates of psychosis and risk-states for psychosis in MND. We measured candidate pro-psychotic cognitive features in a cross-sectional cohort of MND patients, combined with structural and functional brain imaging. 150 patient participants were screened in the NHS specialist MND clinic, using the Edinburgh Cognitive and Behavioural ALS Screen. In 60 patients and 30 controls we then tested three key neurocognitive mechanisms, proposed to underlie risk for psychosis in other clinical groups, using: (i) a jumping to conclusions decision-making task, (ii) the CANTAB: intra/extra dimensional set shift, (iii) a visual perceptual processing task and (iv) psychiatric questionnaires (Cambridge Behavioural Inventory, CBI-R; Neuropsychiatric Inventory, NPI; Brief Psychiatric Screen, BRPS).

20-41% of patients manifested abnormal behaviours, on psychiatric questionnaires, with 12-16% showing psychosis-specific symptoms (CBI-R and NPI psychosis index scores). In the jumping-to-conclusions task, patients made decisions based on less evidence than controls and were insensitive to the cost of sampling information. Carer ratings of patient behaviour correlated with performance on the jumping to conclusions task when decisions were rewarded or costs fixed. Attentional shifting and predictive perceptual processing were normal in MND.
MRI analyses focused on the correlates of jumping-to-conclusions and insensitivity to cost, as a potential risk profile for psychosis, with exploratory analyses of the correlates of the CBI-R psychosis index, and carer's ratings of patient behaviour. Using a Freesurfer regions-of-interest approach, grey matter volume correlated inversely with CBI-R psychosis index in the caudate, amygdala, cingulate and hippocampus. Using tract-based spatial statistics, reduced fractional anisotropy (FA) and increased mean diffusivity (MD) of diffusion weighted imaging correlated with the CBI-R psychosis responses in superior longitudinal fasciculus, and uncinate fasciculus. The carer's ratings of patient behaviour correlated with white matter change adjacent to the ventral temporal cortex. Cost sensitivity correlated with cingulate and cerebellar grey matter volumes. White matter correlates of cost sensitivity included reduced FA with increasing cost sensitivity in white matter connecting the inferior frontal lobe in controls and patients.

Although overt psychosis is uncommon in MND, many patients displayed abnormal behaviour or cognitive symptoms, including suboptimal reasoning biases and inferential impulsivity. Degeneration of cerebellar, cingulate and striatal grey matter, and adjacent major white matter tracts, may underlie these cognitive impairments. Compromised reasoning and inference have implications for clinical management, including decisions around treatment options and management of psychiatric well-being in MND.

IMG-38: Quantifying the variability of precision force in Amyotrophic Lateral Sclerosis as a signature of motor system output

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Background:
An under-appreciated yet essential aspect in the coordination of movement is the desired end state of a given motor task in an environmental context. The precision with which an individual matches a target force provides the necessary context for, and a window to understanding and determining the severity of functional deficits in motor coordination in ageing and disease. Although the loss of force is an early symptom in ALS and is well characterised, less attention is given to the fluctuations or variability in force generation, i.e. the precision of force matching, and how it might be affected in ALS. This can help to understand the mechanisms of the disease and disease progression by detecting abnormal subtle signatures in the motor system output and the underlying motor circuits affected in different stages of the disease and in different phenotypes of the disease.

Objective:
To quantify the signatures of force variability in ALS patients with reference to healthy individuals in time and frequency domains.

Methods:
11 healthy controls and 11 ALS patients performed a precision force matching task across thirty trials, each consisting of a five-second period of sustained contraction. The task was guided by a visual cue and visual force feedback indicating the target and exerted force levels in real-time. The coefficient of variation (SD/Mean) and root mean square error (RMSE) were calculated as measures of variability. Power spectral estimates were calculated using the Welch method.

Results:
The coefficient of variation was significantly higher in ALS patients (median=78.3) compared to controls (median=12.64), U=83, p=0.01, effect size=0.37. RMSE was not significantly different between ALS patients (median=0.2236), and controls (median=0.2809), U=60, p=0.48. Preliminary inspection of the fluctuation patterns in force indicates potential differences in the frequencies that contribute to force variability in ALS patients and healthy individuals.

Discussion/Conclusion:
Further inspection of force variability patterns in ALS can inform of potential biomarkers that can amend neurophysiological measures for screening and for phenotyping and stratification of patients. These variability patterns and their frequencies originate from active motor control and its deficits and can therefore be indicators of dysfunction in specific motor circuits with feedback and/or feedforward processes, such as peripheral sensorimotor loops or other cortical and subcortical sensorimotor pathways.

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IMG-39: Test-Retest Reliability of EEG Markers of Cognition

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Background:
Research into cross-sectional and longitudinal changes in cognition (and motor function) in MND depends on the identification of biomarkers that are reliable and stable over repeat testing in the absence of cognitive change. EEG is safe, well-tolerated, and cost-effective, making it well-suited to longitudinal research. This study aims to evaluate the reliability of EEG-based markers of cognition to facilitate research into cognitive changes in MND.

Methods:
A total of 10 healthy young adults are currently undergoing a complete battery of EEG tests on two consecutive days. Time of day and experimenters are kept consistent for both days. Participants will complete a frequency oddball passive listening task, the Sustained Attention to Response Task (SART), blocks of resting-state EEG with eyes open and closed, and a series of pincer grip motor tasks in combination with surface EMG of the arm. The mismatch negativity (MMN) and P300 waveforms will be identified from the auditory oddball and SART tasks, respectively. The two-way random effects absolute agreement intraclass correlation coefficient (ICC) will be calculated for the amplitudes and latencies of the MMN and P300 obtained on day 1 and day 2.

Expected results:
Earlier work suggests that the P300 and MMN should be stable over time in people without MND[1]. Visual results to date confirm the similarity of the P300 and MMN on repeat testing.

Current status:
This work is in progress. Data has been collected from 6 healthy young adults to date. Qualitative results indicate the consistency of cognitive EEG markers on two consecutive days. Quantitative ICC results will be obtained for the test-retest reliability of the MMN and P300 (waveform peaks, amplitudes, and delays). Future analyses will assess the degree of test-retest reliability for measures derived from the MMN, SART, motor, and resting-state experiments.

Discussion:
High ICC values for P300 and MMN peak amplitudes and delays indicate stability of these measures over time in healthy individuals. Good test-retest reliability justifies the use of EEG biomarkers of cognition in cross-sectional and longitudinal studies. Longitudinal EEG has the potential to be a reliable method of tracking changes to cognition (and motor function) in MND. An improved ability to track impairment in brain networks throughout the MND disease course will facilitate new clinical trials, better treatments and eventually a better prognosis for those living with MND.

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IMG-40: The characterisation of amygdala pathology in ALS: a multimodal imaging study

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Background:
Temporal lobe pathology is a recognised feature of the ALS, but existing imaging studies have predominantly focused on cortical changes, white matter alterations and hippocampal atrophy. As a key structure of the limbic system mediating several cognitive and behavioural functions, the amygdala has been strikingly understudied in ALS. It is typically evaluated as a single structure despite consisting of several functionally and cytologically distinct nuclei.

Objective:
To characterise patterns of amygdala involvement in ALS.

Methods:
100 genetically-stratified ALS patients and 117 healthy individuals were recruited in a prospective, single-centred neuroimaging study. Patients were clinically evaluated using standardised validated clinical tools, underwent genetic screening and structural MRI. The structure was segmented using a Bayesian parcellation algorithm based on a probabilistic atlas. In addition the volumetric analysis of individual nuclei, complementary vertex analyses were also undertaken to assess overall atrophy patterns.

Results:
Compared to controls, the accessory basal nucleus (p=.021) and the cortical nucleus (p=.022) volumes were significantly reduced in C9orf72 negative ALS patients. The lateral nucleus (p=.043) and the cortico-amygdaloid transition area (p=.024) were preferentially affected in C9orf72 positive patients. A trend of lower total amygdala volume was detected in C9orf72 mutation carrying ALS patients (p= .055) which also manifested in inferior-medial shape deformations on vertex analyses.

Conclusion:
Our results highlight the selective degeneration of amygdalar nuclei as opposed to global amygdala pathology. Our finding of distinct, C9orf72-associated, patterns of amygdala pathology is consistent with previous post mortem reports and the clinical profile of the genotype. Mesial temporal lobe pathology in ALS is not limited to hippocampal pathology but, as a key hub of the limbic system, the amygdala is also affected in ALS.

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IMG-41: The prognostic value of neurophysiological parameters in ALS

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Introduction:
The application of neurophysiological indices [1] in amyotrophic lateral sclerosis (ALS), such neurophysiological index (NI), split-hand index (SI) and split-leg index (SLI), has been emerged in the last twenty years as potential tools not only in the diagnostic pathway, but also as end-points in clinical trials of potential therapies. In the present study we analyzed these main neurophysiological indices (NI, SI and SLI) in a cohort of ALS patients to evaluate their association with clinical outcome measures, respiratory assessments, disease progression and survival.

Methods:
All patients underwent nerve conduction study (NCS) to analyze the NI, SI and SLI indices. Of all patients we collected a set of demographic and clinical evaluations including Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R), the Disease Progression Index (DPI), the Milano-Torino (MiToS) functional staging, the King's clinical staging systems, the Forced Vital Capacity (% FVC), and survival data.

Results:
Eighty-two ALS patients were enrolled (median age: 60.0 years [52.0 – 70.0], male/female ratio: 40/42, bulbar/spinal site of onset: 19/63). Considering the multivariable models adjusted for the potential confounding effect of age at evaluation, sex, disease duration and site of onset, the SLI index resulted to be associated only with the respiratory subscore of the ALSFRS-R. However, both the NI and SI indices were significantly associated with the ALSFRS-R total and subscores, the MiToS and King's staging system and the % FVC (the lower the indices, the worse the functional and respiratory status, and the higher the stage). Moreover, slow progressors' patients in accordance with the Kimura et al. classification [2] reported a significantly higher NI and SI values in comparison with normal and fast progressors' patients. After dichotomizing patients in slow progressors' (SP) patients (DPI < 0.5) and not-slow progressors' (NSP) patients (DPI ≥ 0.5), a post-hoc stepwise multiple-regression analysis to drive relationships between the indices, demographic data and disease progression was investigated, reporting a combination of SI index value and disease duration as the best predictive model to discriminate patients in accordance with their disease progression (c-index: 0.92).

Conclusion:
The present study confirm that SI, NI and SLI have a good correlation with functional measures such as the ALSFRS-R, MiToS and King's, and with FVC. SI is strongly correlated with disease progression rate, so it seems represent the more sensitive neurophysiological biomarker in monitoring disease course. Future longitudinal studies are needed to confirm the role of these neurophysiological biomarkers to predict and monitor disease progression in ALS.

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