

Cortical Neurophysiology of ALS

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Abstract

The experiments described in this thesis aimed to investigate the neurophysiological consequences, at the cortical level, of the neurodegenerative condition, amyotrophic lateral sclerosis (ALS). A principle tenet of this study was that ALS is, first and foremost, a disorder of the cortical motor system, the precise pathological mechanisms of which remain incompletely understood. Furthermore, the degree to which neurodegeneration can be evidenced before the onset of symptoms is thus far uncertain, and the optimal means by which to measure therapeutic response has yet to be determined.

Chapter 1 introduces relevant key concepts in ALS and briefly summarises three studies completed in the early phases of pursuit for the above degree. These studies respectively considered presymptomatic cellular ALS pathology, quantitation of disease progression and eyetracking assessment of cognitive dysfunction. Chapter 2 describes magnetoencephalography, the investigative technology utilised in the subsequent experimental chapter. In chapter 3, the effects of ALS on movement related modulation of neuronal oscillations are determined. An excessive peri-movement desynchronisation and delayed post-movement rebound was described. Functional connectivity between cortical regions at rest is appraised in chapter 4. ALS appeared to result in quite striking increases in functional connectivity, in keeping with the fMRI literature and in support of diminished intracortical inhibitory influences. The functional communication from the motor cortices is directly considered during active motor performance in chapter 5. ALS related reductions in beta-band coherence were noted in both corticospinal and inter-hemispheric communication.

In conclusion, the results demonstrated considerable support for proposed excitotoxic disease mechanisms and were in alignment with reported findings in other neurodegenerative diseases. Finally, a pilot study by which the neural mechanisms for cognitive impairment in ALS are explored via antisaccade performance is described. While underpowered, the experimental design showed promise for future application.

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Publications

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Abbreviations

ACC	Anterior Cingulate Cortex	MNI	Montreal Neurological Institute
ALS	Amyotrophic Lateral Sclerosis	MPRAGE	Magnetization-Prepared RAPid Gradient-Echo
AGC	Asymptomatic Gene Carrier	MRCP	Movement Related Cortical Potential
APB	Abductor Pollicis Brevis	MRI	Magnetic Resonance Imaging
AUN	Auditory Network	MSR	Magnetically Shielded Room
BOLD	Blood Oxygen Level Dependent	MVN	Medial Visual Network
CHD	Coronary Heart Disease	NfL	Neurofilament Light Chain
CMCT	Central Motor Conduction Time	OCMR	Oxford Centre for Magnetic Resonance
CST	Corticospinal Tract	OHBA	Oxford Centre for Human Brain Activity
cTBS	continuous Theta Burst Stimulation	OSL	OHBA Software Library
DCM	Dynamic Causal Modeling	PAC	Phase-Amplitude Coupling
DMN	Default Mode Network	PDC	Parkinsonism Dementia Complex
DoL	Degree of Lateralisation	PET	Positron Emission Tomography
DPR	Dipeptide Repeats	PLS	Primary Lateral Sclerosis
ECN	Executive Control Network	PMBR	Post Movement Beta Rebound
EEG	Electroencephalogram	PMA	Progressive Muscular Atrophy
ERD	Event Related Desynchronisation	RFP	Right Fronto-Parietal Network
FC	Functional Connectivity	ROC	Receiver Operating Characteristic
FSL	FMRIB Software Library	RSN	Resting State Network
GLM	General Linear Model	RT	Response Time
HC	Healthy Control	SBMA	Spino-Bulbar Muscular Atrophy
HPI	Head Position Indicator	SICI	Short Interval Intracortical Inhibition
LFP	Left Fronto-Parietal Network	SMA	Supplementary Motor Area
IFC	Inferior Frontal Cortex	SMN	Sensori-Motor Network
IFG	Inferior Frontal Gyrus	SPM12	Statistical Parametric Mapping v12
ISI	Inter Stimulus Interval	TDCS	Transcranial Direct Current Stimulation
MEG	Magnetoencephalography	TFCE	Threshold-Free Cluster Enhancement
MEP	Motor Evoked Potential	TFR	Time Frequency Representation
MMN	Multifocal Motor Neuropathy	TMS	Transcranial Magnetic Stimulation
MND	Motor Neuron Disease	UMN	Upper Motor Neuron

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Chapter 1 An Introduction to ALS

In this introductory chapter I will consider ALS in terms of clinical features, epidemiology, genetics and patho-mechanisms. Three particular aspects are emphasised in summaries of my recently published work: measuring progression in ALS, assessing cognition in ALS with an eyetracker, and pathological evidence of presymptomatic ALS.

1.1 The Clinical Definition of ALS

1.1.1 The Motor Neuron Diseases

Unique among the adult-onset neurodegenerative diseases, amyotrophic lateral sclerosis (ALS) is distinguished by relentless accumulation of physical disability and typically marked curtailment of life expectancy as ventilatory failure encroaches [Kiernan et al., 2011]. Diagnosis today continues to depend on the clinical syndrome accurately described by Charcot almost 150 years ago [Charcot and Joffroy, 1869]: a gradual spread of weakness from a focal site of symptom onset while sensation remains typically intact. The resulting physical limitation is accompanied by clinical signs suggestive of concomitant impairment in upper motor neuron (UMN) and lower motor neuron (LMN) function [Talbot, 2009]. Both sets of signs appear maximal in the region of symptom onset [Ravits et al., 2007b]. Progression through contiguous regions is a cardinal feature of the illness [Fujimura-Kiyono et al., 2011] and pathological distribution of LMN loss correspondingly peaks quantitatively at the rostro-caudal level of onset with graded decline across sequential regions [Ravits et al., 2007a].

The term ‘motor neuron disease’ (MND) is now almost synonymous with ALS, but MND remains a useful collective label for a group of related conditions, numerically dominated by ALS. Other MND sub-types include primary lateral sclerosis (PLS, a form of MND with pure UMN involvement [Pringle et al., 1992; Younger et al., 1988]) and progressive muscular atrophy (PMA, MND with pure LMN involvement [Maragakis, 2010]). The

discriminatory boundaries between ALS and these syndromes have never been well demarcated [Mackay, 1963]. PLS is typically more slowly progressive than ALS [Zhai et al., 2003], but late transformation into ALS has been described [Bruyn et al., 1995; Gordon et al., 2006] and PLS cases often share histopathological abnormalities with ALS [Hudson et al., 1993; Tan et al., 2003] including muscle biopsy evidence of denervation [Le Forestier et al., 2001]. Furthermore, *in vivo* evidence of reliably distinguishing features is lacking; white matter abnormalities with the corticospinal tracts (CST) and corpus callosum (CC) are present (if not identical) within both ALS and PLS [Agosta et al., 2014b; Ciccarelli et al., 2009; Müller et al., 2012] and cognitive profiles reveal a comparable range of executive deficits [Grace et al., 2011]. PMA is similarly less rapid than ALS although progression rate is still predicted by shared prognostic factors such as age and forced vital capacity at diagnosis [Kim et al., 2009]. Extension of pathology beyond the LMN [Brownell et al., 1970; Ince et al., 2003] is further evidenced by detectable cognitive impairment in 17% of cases [Raaphorst et al., 2011] accompanied by reduced activation of the left inferior frontal gyrus (IFG) during verbal fluency testing [Raaphorst et al., 2014]. The prognostic benefit of PMA may largely be driven by MND variants with clinical features initially restricted to either upper or lower limbs (so-called ‘flail arm’ or ‘flail-leg’) who on average survive approximately twice as long as the approximately 30 months expected from ALS symptom onset [Wijesekera et al., 2009].

1.1.2 Diagnostic Considerations

A majority of ALS patients (63% in an Israeli population-based study [Gubbay et al., 1985]) present with limb weakness as the first symptom, while most of the remainder (34% in an Italian population-based study [Chiò et al., 2011]) present with bulbar dysfunction. Bulbar symptoms (foremost dysarthria [Chen and Garrett, 2005; Devine et al., 2013; Traynor et al., 2000]) as an initial and isolated complaint may be more common among older females [Li et al., 1990], underlining the complex and poorly understood

interplay between aging and developmental vulnerability [Eisen, 2009]. An unusual and ominous first symptom is respiratory weakness [Czaplinski et al., 2003], reported in 2.7 % of a Canadian clinic database [Shoesmith et al., 2007]. Acute respiratory presentations may, however, stabilise with ventilatory support and importantly are more often associated with upper limb rather than bulbar progression [de Carvalho et al., 1996].

The characteristic distribution of muscles most susceptible to the downstream effects of ALS, even within affected body regions, often serves as a diagnostic prompt and may reflect the relatively recent evolutionary expansion of monosynaptic corticomotoneurons [Eisen et al., 1992]. A striking example pertains to the small hand muscles within overlapping myotomes. The marked atrophy affecting the median-innervated thenar muscles, in contrast to the ulnar-innervated hypothenar eminence, has long warranted the ‘split-hand’ appellation [Wilbourn, 2000], but equally specific to ALS is denervation of the ulnar-innervated first dorsal interosseous [Kuwabara et al., 2008]. The aetiological implications raised by these simple observations were investigated by direct comparison of central and peripheral neurostimulation. Cortical motor evoked potentials (MEPs) were disproportionately *reduced* in ALS patients, specifically for thenar target muscles, thereby supporting primacy of corticomotoneuronal failure [Weber et al., 2000]. Furthermore, although peripheral axon abnormalities in both sodium and potassium conductance may contribute to disease progression [Kanai et al., 2011], the more homogenous distribution across the hand muscles of ALS-induced axonal excitability reaffirms cortical pathomechanisms [Menon et al., 2014]. Further refinement was achieved in considering the relative preservation of flexor pollicis longus in the face of weakened abductor pollicis brevis (APB). A simple strength ratio encapsulating this ‘split-hand plus’ phenomenon was shown to have reasonable diagnostic accuracy (particularly for limb-onset ALS) [Menon et al., 2013]. A predominantly cortical explanation for this

phenomenology was suggested by *increased* MEPs and reduced cortical silent period to the APB target only [Bae et al., 2014]. The divergent alterations to MEPs relative to healthy controls in these two studies, both attributed to cortical ALS pathology, are a pertinent reminder of the diagnostic limitations commonly (albeit not exclusively) experienced by both peripheral and central neurophysiology studies in ALS [Eisen et al., 1990; Menon et al., 2015; Simon et al., 2014a].

In general, therefore, current diagnostic frameworks place more emphasis on bedside clinical features than specific investigations, the role of which is largely limited to the exclusion of rare diagnostic mimics [Turner and Talbot, 2013]. Certain symptoms may still be under-appreciated; muscle cramps are a feature in 95% of patients at some stage in the disease (more commonly in younger limb-onset patients) [Caress et al., 2015] while neck weakness was shown to be an important independent prognostic predictor [Nakamura et al., 2013], reflecting shared segmental innervation with the diaphragm [Pinto and de Carvalho, 2008]. Diagnostic delays remain a concern. When evaluated over a 20-year period, despite implementation of a ‘fast-track’ referral process, diagnostic latency was found to persist at around 12 months from symptom onset [Mitchell et al., 2010]. Delayed referral to a neurologist has been reported as the most significant hurdle [Nzwalo et al., 2014]. Inappropriate referrals to other specialties may also contribute, particularly concerning as an apparent acceleration of ALS progression was described in the 3-month period after (often unnecessary) surgical procedures [Kraemer et al., 2010; Pinto et al., 2013].

Overall, neurologists are better able to detect the clinical signs associated with LMN compared to UMN pathology. This may reflect the unreliable emergence of UMN signs from behind co-existing LMN damage and additional confounding factors such as spinal interneuron loss [Swash, 2012]. Furthermore, the current arsenal of biomarker

investigations (UMN targeted and otherwise) remain diagnostically imprecise at the individual level, although relative to disease monitoring, this aspect is arguably not the highest priority for immediate development [Turner and Benatar, 2015]. By contrast however, a wealth of peripheral neurophysiology techniques impart reasonable sensitivity in the detection of LMN dysfunction (summarised in [de Carvalho and Swash, 2016]), which is reflected in their formal incorporation as an ancillary test in the more recent iterations of World Federation of Neurology ‘El Escorial’ ALS diagnostic criteria (**Table 1.1**, [Brooks et al., 1994; Brooks et al., 2000; Ludolph et al., 2015]).

Clinically definite

- Evidence of UMN *plus* LMN signs in the bulbar region *and* in at least two spinal regions, *or*
- The presence of UMN signs in two spinal regions *and* LMN signs in three spinal regions

Clinically probable

- Evidence of UMN *plus* LMN signs in at least two regions with some UMN signs rostral to LMN signs

Probable laboratory supported

- Clinical evidence of UMN *and* LMN signs in only one region, *or*
- UMN signs alone in one region *and* LMN signs defined by EMG criteria in at least two muscles of different root and nerve origin, in two limbs

Possible

- UMN plus LMN in only one region, *or*
- UMN signs alone in two or more regions, *or*
- LMN signs found rostral to UMN

Table 1.1 Diagnostic Criteria for ALS

Modified El-Escorial Criteria for the diagnosis of ALS.

The ‘Awaji’ revisions to these criteria [de Carvalho et al., 2008] expanded the acceptable range of neurogenic abnormalities to include fasciculation potentials, which in the context of ALS can take on complex and slow-firing morphologies [Hirota et al., 2000]. **Table 1.2** demonstrates that neurophysiological findings are now proposed as equivalent to clinically recognisable LMN dysfunction, thus negating the requirement for a ‘probable laboratory supported’ category (no UMN substitute for clinical signs is included).

Clinically definite

- Clinical or electrophysiological evidence of LMN *and* UMN signs in the bulbar region *and* at least two spinal regions *or* the presence of LMN and UMN signs in three spinal regions

Clinically probable

- Clinical or electrophysiological evidence of LMN *and* UMN signs in at least two regions *with* some UMN signs necessarily rostral to the LMN signs

Clinically possible

- Clinical or electrophysiological evidence of UMN *and* LMN dysfunction in only one region *or*
- UMN signs are found alone in two or more regions *or*
- LMN signs are found rostral to UMN signs.

Table 1.2 Awaji Update to Diagnostic Criteria

Neurophysiology takes equal precedence to clinical signs.

The broadening range of neurophysiological abnormalities acceptable as evidence of LMN involvement was reported to improve the diagnostic sensitivity both for bulbar-onset [Carvalho and Swash, 2009] and in a meta-analysis of 881 patient records, limb-onset cases [Geevasinga et al., 2016a], particularly if a re-instatement of the ‘probable laboratory supported’ category was simulated. The performance of these criteria, regardless of how cumbersome they might appear for routine clinical practice [Belsh, 2000], remains highly relevant for clinical trial enrolment whereby inclusion of patients early in the course of disease is widely held to be desirable to maximise the possible success of disease modification [Berry et al., 2014]. Further criteria modifications should therefore be anticipated if the development of ancillary tests for UMN dysfunction progresses to individual-level capability [Geevasinga et al., 2014]. The need is clear when 10% of patients die with pathological ALS, while remaining ‘trial ineligible’ [Traynor et al., 2000].

1.2 Life, Genes, the Environment & ALS

1.2.1 Aging Demographics

In the UK, the lifetime risk of death from MND is estimated at approximately 1 in 400 with a relative risk (age-adjusted) for males of 1.54 [Alonso et al., 2009]. US prevalence is comparable [Harper et al., 2015] and incidence rates (at least in developed nations) have furthermore remained stable in recent decades. To put this in some perspective, the lifetime risk for Alzheimer's disease, estimated from 65-year-olds followed for a further 29 years in the Framingham Study, is 1 in 6 [Seshadri et al., 2006]. Secondly and in apparent contrast to ALS, the risk of developing Parkinson's disease was shown to increase with age through to a lifetime risk of 1 in 15 [Driver et al., 2009] (although this may plateau in the 10th decade of life, neurodegeneration is not an inevitable consequence of aging [den Dunnen et al., 2008]). The peak age for ALS onset is considerably younger than both of these neurodegenerative comparators; a stable estimate of 65 years for men and 67 years for women was generated from a capture recapture of the Scottish population across the 1990s [Forbes et al., 2007]. Although ALS incidence rates were held to decline rapidly from 80 [Logroscino et al., 2010] or perhaps 85 years of age [Marin et al., 2009], a recent 10-year study within a geographically restricted region outside Barcelona found incidence rates to increase markedly in the eighth decade and beyond [Aragones et al., 2016]. This disparity may reflect under-ascertainment of very elderly cases or even misdiagnosis of late-life presentations.

1.2.2 Global Epidemiology

High-quality worldwide epidemiological data are still lacking, but ALS appears to be globally, if not evenly distributed (lower rates are, for example, reported in Hong Kong [Fong et al., 2005]). Geographical variation is driven in part by genetic founder effects resulting in disproportionate frequencies of certain familial ALS subgroups [Byrne et al., 2011; Chiò, 2011; Ishiura et al., 2012; Pliner et al., 2014] which are typically more common

in Finland and other Northern European populations. Curiously, the ethnically mixed ‘mulatto’ population of Cuba was shown to be relatively protected from ALS in comparison to both white and black local populations [Zaldivar et al., 2009], in keeping with a dilution of multiple ‘risk’ genes that would otherwise interact with environmental factors in a still poorly understood, complex and age-dependent manner (discussed in [Al-Chalabi and Hardiman, 2013]).

1.2.3 Environmental Triggers

Geographical variations in ALS incidence rates and phenotypes have conversely been largely unsuccessful in generating enduring hypotheses regarding environmental risk factors [Marin et al., 2015]. Perhaps one notable exception is a historical cluster of cases on the South Pacific island of Guam (summarised in [Lee, 2011]). High rates of ALS were reported by US Navy physicians stationed on the island. Incidence was estimated at perhaps 100-fold of that expected [Kurland and Mulder, 1954], accompanied by obvious familial clustering. Native Chamorros were additionally susceptible to a unique and ill-defined neurodegenerative syndrome termed parkinsonism dementia complex (PDC [Elizan et al., 1966], pathologically and clinically on a spectrum with ALS). As Guam became thoroughly Westernized, both ALS and PDC steadily declined in incidence through the 1980s, accompanied by marked cultural, dietary and economic shifts [Plato et al., 2003]. Although genome-wide studies highlighted linkage with regions on chromosome 12 and the *MAPT* gene [Sieh et al., 2009], such marked changes in incidence were more in keeping with removal of some environmental trigger(s). Without conclusive evidence, the culprit neurotoxin for Guam ALS/PDC is held to be β -N-methylamino-L-alanine (BMAA) from cycad seeds traditionally crushed into flour [Borenstein et al., 2007]. BMAA produced by cyanobacteria continues to be suspected as an environmental risk factor for ALS elsewhere in the world [Bradley et al., 2013]. Compromised water quality is therefore one ongoing line of epidemiological investigation [Torbick et al., 2014],

further implicated by variations in ALS mortality contingent on well water use [Schwartz and Klug, 2016]. As yet however, systematic attempts to identify environmental links between oft-reported geographical clusters of ALS remain unrewarding [Henry et al., 2015; Rooney et al., 2015].

1.2.4 Is ALS a Lifestyle Disease?

Less striking perhaps are the handful of ‘lifestyle’ factors associated with altered ALS risk, all of which may contribute alongside genetic predisposition and stochastic events, to a modelled ‘multi-step’ process that culminates in disease expression later in life [Al-Chalabi et al., 2014]. Potentially modifiable risk factors may include pesticide exposure [Su et al., 2016] or heavy metal poisoning but retrospective questionnaire studies are highly susceptible to recall bias [Sutedja et al., 2009]. Even smoking’s impact on ALS is not beyond doubt; previously considered an ‘established’ risk factor by a systematic review [Armon, 2009] that relied heavily on the findings of increased ALS death risk in both current (two-fold) and former (50 % higher) smokers in a large pan-European prospective cohort [Gallo et al., 2009]. Risk also declined with increasing years since quitting. A subsequent even larger cohort, with many more ALS deaths, confirmed a relative risk of 1.44 in former and 1.42 in current smokers [Wang et al., 2011] but correlations with smoking ‘doses’ were not universally consistent and a UK case-control study failed to concur [Alonso et al., 2010].

The most high-profile occupational risk factor for ALS, military service, may well be conflated with another common exposure long suspected to contribute, that of exercise [Felmus et al., 1976]. ALS rates among First Gulf War veterans were reported to be increased in two US studies, firstly comparing the total number of military cases identified through Department-of-Defence records to expected rates in the age-matched population [Haley, 2003] and secondly proactively ascertaining cases from the veterans community

which revealed a hazard ratio of 1.92 for deployment to the Gulf versus military service *without* deployment [Horner et al., 2003] (ALS rates among the non-deployed veterans matched the US civilian population). Concerns regarding widespread neural injury from oil-well fires or chemical weapons are not however supported by long term mortality data [Barth et al., 2009]. ALS risk calculated from a national US cohort study of older individuals was also elevated among veterans of earlier wars (HR 2.03 for WW2 service) [Weisskopf et al., 2015].

Intense interest in the relationship between physical exercise and subsequent ALS development was rekindled by Italian reports of marked ALS risk to professional footballers [Chiò et al., 2005]. Definitive conclusions are confounded by a number of factors, not least recall bias in case-control studies [Gotkine et al., 2014; Harwood et al., 2016; Huisman et al., 2013], although recent prospective studies do re-affirm the link [Eaglehouse et al., 2016; Fang et al., 2016; Gallo et al., 2016; Mattsson et al., 2012]. Further complicating inference, exercise typically exerts a protective effect against other more common causes of mid-life mortality. In particular, death from coronary heart disease (CHD) might well pre-empt ALS onset, thus exercise effects on ALS incidence may be mediated through reduction CHD risk, unmasking cases that might otherwise not reach the age of ALS onset. This effect is further reflected in the modestly elevated risk of ALS among people unaffected by CHD [Turner et al., 2012a] and benign CHD risk profiles among patients with ALS [Mariosa et al., 2015; Seelen et al., 2014; Sutedja et al., 2011]. There is also potential for reverse causation if lean body habitus is used as a proxy measure of exercise, since even at onset, ALS can be associated with marked cachexia, implying profound changes to energy metabolism [Dupuis et al., 2011]. Patients however still report ‘always being slim’ 2.2 times more often [Scarmeas et al., 2002] and premorbid Body Mass Index (BMI) differences were confirmed by longitudinal study [O’Reilly et al.,

2013]. Causation is far from certain however. The mechanisms proposed for exercise induced neural injury are speculative [Harwood et al., 2009] and propensity to enjoy exercise could equally reflect developmental advantages to the ALS risk phenotype [Chiò and Mora, 2012; Turner, 2013]. This endophenotype might be reflected in subtly altered connectivity in neural networks in much the same way that handedness can influence both cerebral structure [Amunts et al., 1996; Herve et al., 2009; Seizeur et al., 2014; Westerhausen et al., 2007] and the laterality of focal ALS symptom onset [Devine et al., 2014; Turner et al., 2011].

1.2.5 The Genetic Substrate of ALS

Across multiple European studies, cases with a clear familial (typically autosomal dominant) pattern of inheritance accounted for approximately 5% of the total ALS population [Byrne et al., 2011]. However, given that the heritability of ALS was estimated at 0.61 by twin study [Al-Chalabi et al., 2010], the overall contribution of genetics to ALS expression is considerably more extensive and the distinction between sporadic and familial ALS is blurred. Accordingly, 10.7% of an Italian ALS population [Chiò et al., 2012c] tested positive for one or other ALS-related gene, 9.7% in an Irish study [Kenna et al., 2013] and 8% of a Dutch *sporadic* ALS population [van Blitterswijk et al., 2012]. Positive genetic testing without a family history is readily accounted for by any of incomplete penetrance, premature deaths of mutation-carrying relatives, non-paternity, adoption, incomplete family histories and even *de novo* mutations [Al-Chalabi and Lewis, 2011]. Mutations within at least 10 genes are now shown to cause ALS while a number of other *loci* contribute indeterminate risk. The result is that, in the majority of familial cases at least, the relevant mutation can now be readily identified (succinct review in [Renton et al., 2014]).

The description and interruption of the processes by which each genetic mutation finally translates into the varied phenotypes of ALS continue to be the subject of intense research efforts worldwide [Poppe et al., 2014]. *SOD-1* mutations were described over 20 years ago [Rosen et al., 1993] but the complexity by which over 100 distinct and variably penetrant mutations in the gene [Andersen et al., 2003; Robberecht et al., 1996] could engender such diverse phenotypes as the common and aggressive A4V substitution (death within one year of symptom onset) or the indolent homozygous *D90A* (survival beyond 10 years) [Bali et al., 2016] suggests diverse pathological mechanisms at play. Nevertheless, the physiological anti-oxidant cellular function of SOD protein, and the phenotypic overlap between sporadic and *SOD1* ALS, engendered plausible hypotheses that oxidative stress was a key initiator of pathology [Barber and Shaw, 2010]. Rescue of abnormal Cu^{2+} and Zn^{2+} binding to mutant SOD was demonstrated *in vitro* [Estevez et al., 1999; Wiedau-Pazos et al., 1995] and further optimism followed demonstration of toxic *SOD1* protein aggregates in both neurons and astrocytes of symptomatic overexpressed transgenic mice [Bruijn et al., 1998; Johnston et al., 2000]. The greatest disappointment in ALS research has, however, been the failure of therapies seemingly capable of disease modification within the *SOD1* mouse model to translate into meaningful clinical benefits for human ALS patients [Ludolph et al., 2007]. In part this reflects the near impossibility of faithfully representing human neurodegenerative diseases within a less complex neural macro-architecture, mitigated only partially by the sole ALS model in a non-human primate that was limited to spinal cord delivery of an adenovirus vector [Uchida et al., 2012]. A naturally existing canine model of *SOD1* has recently been described and deserves further consideration [Crisp et al., 2013].

The key discovery in ALS pathogenesis was the identification of ubiquitinated TDP-43 within the characteristic intra-cellular protein deposits [Neumann et al., 2006]. Shared

mechanistic pathways between sporadic and familial ALS were then further reinforced by the recognition that mutations within *TARDBP* [Sreedharan et al., 2008], the gene encoding TDP-43, are also a (rare) cause of ALS. *SOD1* mutation carriers (~2% of all ALS cases) however do not show TDP-43 accumulation [Mackenzie et al., 2007]. Thus ALS to an extent remains a pathologically heterogeneous syndrome against which any single therapy may not be universally effective. TDP-43, alongside the translated product of *FUS* (another gene implicated in ALS), plays a key functional role in messenger RNA processing which may be compromised by cytoplasmic mislocalisation in ALS [Colombrita et al., 2012; Lagier-Tourenne et al., 2012]. Mouse models over-expressing wild-type and mutated human TDP-43 suggest that a toxic gain of function is equally plausible [Huang et al., 2012a; Xu et al., 2010], although this may in turn be mediated by nuclear dysfunction and TDP-43 knockout also results in an age-dependent motor phenotype [Iguchi et al., 2013].

In 2011, a dominant GGGGCC hexanucleotide-repeat expansion in *C9orf72* was not only the first intronic mutation to be associated with ALS [Dejesus-hernandez et al., 2011; Renton et al., 2011], but also was responsible for up to 40% of familial cases and (with some variation by population) up to 7% of sporadic ALS in Western populations, though significantly less common in Asian/Far Eastern nations [Chen et al., 2015; Majounie et al., 2012]. In the UK therefore, *C9orf72* far outweighs *SOD1* in numerical importance [Beck et al., 2013]. Entirely new mechanistic considerations and therapeutic avenues opened up, not least the possibility to use antisense oligonucleotides as a targeted therapy [Lagier-Tourenne et al., 2013]. Although familiar evidence of TDP-43 deposition was again found in human pathology [Mackenzie et al., 2014] and a mouse model [Chew et al., 2015], speculation regarding the definitive upstream mechanism of toxicity continues [Gendron et al., 2014]. Progress is hindered by an incomplete understanding of the

physiological function of this highly conserved and widely expressed region's physiological function, although it may include coordination of vesicle trafficking during autophagy [Levine et al., 2013]. Three distinct classes of pathomechanism have emerged. The first is simple haploinsufficiency, although *C9orf72* knockdown was well tolerated in an initial mouse model [Koppers et al., 2015], a marked systemic alteration to cellular immune function was subsequently noted [Burberry et al., 2016; O'Rourke et al., 2016]. The second is interference with RNA biology [Kwon et al., 2014] as evidenced by the characteristic foci that may sequester RNA binding proteins [Cooper-Knock et al., 2014b; Mizielinska et al., 2013]. The third is non-ATG dependent translation of the repeat sequences, in both sense and anti-sense directions, which was shown to generate dipeptide repeat proteins which are detectable at autopsy in multiple brain regions (including the cerebellum) [Mackenzie et al., 2013; Mann et al., 2013; Mori et al., 2013] and in a *C9orf72* mouse model [Peters et al., 2015], albeit without any evidence of behavioural phenotype or neuronal degeneration. To what extent these discoveries will guide future therapies for sporadic ALS remains to be seen, but as is discussed below, *C9orf72* certainly reaffirms the multi-domain overlap between ALS and frontotemporal dementia (FTD) [Hodges, 2012].

1.3 The Brain and Cognition in ALS

1.3.1 Pathological Overlap with Frontotemporal Dementia

The last 30 years have established a clinical, histopathological, and most recently also genetic overlap between ALS and frontotemporal dementia. In addition to the high frequency with which *C9orf72* causes ALS, the mutation is also responsible for up to 30 % of principally behavioural variant FTD (bvFTD), particularly in the presence of a family history [Benussi et al., 2013; Devenney et al., 2014; Majounie et al., 2012; van der Zee et al., 2013]. Co-occurrence of ALS and bvFTD within the same individual or kindred is frequent [Boeve et al., 2012; Chiò et al., 2012b] and is also reported for the *VCP* mutation

[Kazamel et al., 2015], while significant cognitive deficits accompanying *TARDBP* are only occasionally reported [Borghero et al., 2011; Borroni et al., 2009; Kovacs et al., 2009]. Caution should be exercised given the reported co-occurrence of *C9orf72* with other potentially pathogenic mutations including *TARDBP* [Kaivorinne et al., 2012; Restagno et al., 2012], which could be coincidental or perhaps suggestive of an oligogenic basis for these diseases [van Blitterswijk et al., 2012]. Dementia associated with *SOD1* mutation is exceptional [Nakamura et al., 2015; Wicks et al., 2009a].

Cytoplasmic accumulation of TDP-43 in cortical neurons is further shared evidence of a common underlying pathological process to 98% of ALS cases *and* a significant proportion of FTD (tau is however a more common proteinopathy to cause FTD, the ‘FET’ fusion oncogene family of proteins are a third subgroup) [Arai et al., 2006; Mackenzie and Neumann, 2016; Scotter et al., 2015]. The extent to which TDP-43 is distributed between different cerebral regions appears to correlate with clinical symptomatology and may be useful as a pathological staging tool for both conditions [Brettschneider et al., 2013; Brettschneider et al., 2014]. In particular, the anterior cingulate is rarely affected in pure ALS while the hypoglossal nuclei are commonly involved; the reverse pattern was shown in bvFTD. Other regions, such as the primary motor cortex frequently stained for TDP-43 in both conditions [Tan et al., 2015]. No convincing explanation yet exists for the variable individual predilection with which certain cerebral regions are affected clinically and pathologically while sparing others. In the context of *C9orf72*, somatic heterogeneity in repeat expansion length has been suggested [Cooper-Knock et al., 2014a] but investigations thus far are inconclusive (repeat size in the frontal cortex did correlate with FTD age of onset [van Blitterswijk et al., 2013]). Multiple genetic modifiers, environmental and developmental factors may therefore contribute.

Since 2011, clinical studies have also swiftly attempted to delineate *in vivo* the distinguishing characteristics of *C9orf72* in both ALS and FTD, but with more modest success. Firstly, in FTD, patterns of atrophy were most prominent in frontal and anterior temporal regions in *C9orf72* cases, plus there was evidence of cerebellar degeneration. Overall classification from sporadic FTD, *MAPT* or *GRN* was possible but this study failed to take account of disease duration [Whitwell et al., 2012]. Similarly, in ALS, extra-motor involvement was more prominent in a magnetic resonance imaging (MRI) study of *C9orf72* versus sporadic cases, but again participant groups were not otherwise well matched [Bede et al., 2013]. The concern expressed by the authors that extra-motor cortical atrophy and white matter damage previously widely reported in the ALS neuroimaging literature may have been solely driven by unwitting inclusion of *C9orf72* patients, does not appear to be borne out by two more recent studies that specifically sought and failed to demonstrate this confound [Agosta et al., 2016; Walhout et al., 2014]. In neuroanatomical terms therefore, ALS is a multi-system brain disorder [Geser et al., 2008], the cognitive impact of which is discussed below.

1.3.2 The Cognitive Phenotype of ALS

Beyond the core motor features of ALS that have retained diagnostic primacy since the earliest descriptions, extends a more recent appreciation of a significant burden of cognitive dysfunction (comprehensive reviews in [Goldstein and Abrahams, 2013; Phukan et al., 2007]). Initial systematic enquiries suggested cognitive impairment to feature in approximately one third of ALS patients [Gallassi et al., 1985; Massman et al., 1996]. These findings have remained relatively consistent in more recent studies [Rippon et al., 2006], depending on the defined threshold for cognitive impairment [Murphy et al., 2007; Ringholz et al., 2005] and the epidemiological context from which the sample is drawn [Gordon et al., 2011]. Population-based studies suggest similar rates within ALS

patients from both Ireland [Phukan et al., 2012] and Italy [Montuschi et al., 2014], despite differing genetic substrates.

In addition to the genetic and pathological commonalities between FTD and ALS, there is significant overlap in their neuro-psychometric profiles and behavioural features [Witgert et al., 2010]. Consensus criteria to formalise the recognition of these deficits in ALS have been developed [Strong et al., 2009] alongside a range of different psychometric tools including a validated bedside screening questionnaire, the Edinburgh Cognitive and Behavioural ALS Screen (*ECAS*) [Abrahams et al., 2013; Niven et al., 2015]. Formal cognitive testing has been complemented by behavioural indices [Mioshi et al., 2014]. Several reports indicate a particularly high prevalence of apathy in ALS (up to 80% showed a degree of reduced motivation [Lillo et al., 2011]) even at symptom onset [Grossman et al., 2007] and independent of physical disability [Radakovic et al., 2016; Terada et al., 2011].

Cognitive and behavioural impairment may have serious implications for an ALS patient beyond daily activities. Adherence to therapies (and participation in clinical trials) may be compromised [Chiò et al., 2012a; Olney et al., 2005], care-giver relationships may degrade [Bock et al., 2015; Tremolizzo et al., 2016; Watermeyer et al., 2015] and executive dysfunction may independently contribute to poor prognosis [Hu et al., 2013]. Both the presence of apathy [Caga et al., 2016] and executive dysfunction [Elamin et al., 2011] were associated with reduced survival and faster functional decline (even in the absence of *C9orf72* mutation [Elamin et al., 2013]). These prognostic implications, associated with certain clinical characteristics such as bulbar onset [Abrahams et al., 1997] (not consistently replicated [Zaloni et al., 2012]) or UMN signs [Iwasaki et al., 1990] and reports of longitudinally stable cognitive performance [Schreiber et al., 2005] beg the question whether ALS with cognitive/behavioural impairment represents a

distinguishable phenotypic category. Such stability in the context of devastating neurodegeneration is perhaps counter-intuitive and also to an extent disputed [Robinson et al., 2006], but seems reliable in those patients with normal cognition at diagnosis [Elamin et al., 2013]). Recent research efforts have therefore attempted to reveal *in vivo* the biological substrate that contributes simultaneously to ALS and cognitive impairment, spurred on by the identification of *C9orf72* repeat expansions. As might be expected, structural abnormalities were more pronounced amongst ALS patients with cognitive involvement [Agosta et al., 2016; Frank et al., 1997] and furthermore MR spectroscopy NAA/Cr ratios were lower in the dorsolateral prefrontal cortex and correlated with letter fluency [Quinn et al., 2012]. In further detail, atrophy of subcortical structures such as the thalamus and hippocampus [Machts et al., 2015] was more pronounced and certain prefrontal white matter tract DTI metrics correlated with particular executive sub-functions [Pettit et al., 2013].

Moving to measures of cortical function, early positron-emission tomography (PET) studies revealed localised reductions in cerebral blood flow to correlate variably with executive dysfunction [Ludolph et al., 1992; Tanaka et al., 1993] while regional activation of the anterior cingulate during a free-selection task was also reduced [Kew et al., 1993]. Abnormal findings in ALS patients were extended in the functional MRI (fMRI) era to include differential activation (despite comparable task performance) of frontal, prefrontal, cingulate and temporal regions during tasks probing language [Abrahams et al., 2004], attention and inhibitory executive function [Goldstein et al., 2011]. Neurophysiological methods have also contributed in demonstrating decreased event-related potential (ERP) responses to a Stroop task (accompanying higher error rates by ALS patients) [Amato et al., 2013] and abnormally heightened responses to irrelevant

auditory stimuli [Pinkhardt et al., 2008]; both studies suggest impairment of attention control mechanisms.

1.3.3 Does ALS Begin in the Cerebral Cortex?

In the face of the above evidence, the enduring consideration of whether ALS first and foremost comprises a cerebral neurodegenerative disease might seem increasingly moot. However, end-stage pathological summaries and static cross-sectional neuroimaging snapshots struggle to depict the progressive spread of the disease [Baker, 2014; Schuster et al., 2015], the mechanism of which seems likely to involve existing synaptic connections [Fatima et al., 2015], perhaps operating via ‘prion-like’ spread of culprit RNA binding proteins [Kanouchi et al., 2012; Kim et al., 2013; Polymenidou and Cleveland, 2011].

Proponents of the ‘dying back’ hypothesis [Chou and Norris, 1993; Dadon-Nachum et al., 2011] argue that, since some of the earliest detectable abnormalities in ALS patients [de Carvalho and Swash, 2013] and animal models [Bendotti et al., 2001; Hayworth and Gonzalez-Lima, 2009; Kennel et al., 1996] are to be found at distal nerve terminals and the neuro-muscular junction, neuronal death could then result, perhaps from failure of retrograde transport along the axon [Fischer et al., 2004]. The evidence draws heavily upon the compromised *SOD1* mouse model [Gould et al., 2006; Pun et al., 2006] and fails to account for any of the described cognitive manifestations of ALS.

By contrast the ‘dying forward’ hypothesis, of which Eisen was the earliest protagonist, focused investigations on monosynaptic corticomotoneuronal cells [Eisen et al., 1992]. This theory emphasised the lack of evidence for pathological retrograde transmission above the anterior horn cell (not even for polio virus) and proposed instead that downstream effects could easily result in disproportionately high numbers of anterior horn cells lost. Beyond the above described ‘split hand’ phenomenon and the lack of monosynaptic connections to the (typically spared by ALS) oculomotor and Onuf’s

nuclei, evidential underpinnings rested on abnormal motor cortex transcranial magnetic stimulation (TMS) responses that were subsequently replicated in PLS [Weber et al., 2002] and symptomatic *SOD1* patients [Stewart et al., 2006].

1.3.4 Evidence for Cortical Hyperexcitability

A further diverse array of aetiological hypotheses considers ALS at the sub-cellular level, each with varying amounts of experimental evidence [Robberecht and Philips, 2013]. Implicated molecular processes are as diverse as protein misfolding [Basso et al., 2006] with impaired degradation and autophagy [Chen et al., 2012], endoplasmic reticulum stress [Saxena et al., 2009], mitochondrial failure [Bannwarth et al., 2014; Xu et al., 2010], RNA processing [Bäumer et al., 2010] and nucleocytoplasmic shuttling [Xiao et al., 2015], axon failure [Volkening et al., 2009; Wu et al., 2012], and selective cell vulnerability [Talbot, 2014] either innately or due to the influence of activated glial cells [Philips and Robberecht, 2011; Re et al., 2014; Turner et al., 2004].

Perhaps the most consistent molecular narrative concerns glutamatergic excitotoxicity in ALS, potentially responsible for both dysfunction of corticomotoneurons (which may be selectively vulnerable to the resultant calcium influx and downstream transmission of aberrant neurophysiology [King et al., 2016; Turner et al., 2013]. Although not unique to ALS [Di Lazzaro et al., 2004], converging experimental modalities suggest hyperexcitability as a key mechanism, possibly accompanied by a relative failure of inhibitory cortical interneuronal function [Turner and Kiernan, 2012]. Pathology studies have demonstrated a particular vulnerability of cortical parvalbumin-positive interneurons [Maekawa et al., 2004; Nihei et al., 1993] while the relative proportions of GABA_A receptor subunits were also altered [Petri et al., 2003]. Interneuron loss in the spinal cord has also been reported [Ince et al., 1993; Stephens et al., 2006]. This seemingly selective

neurodegeneration was a contributing factor to reduced inhibitory GABAergic tone in animal models [McGown et al., 2013; Nieto-Gonzalez et al., 2011].

Evidence in support of glutamate's role in perpetuating ALS pathology includes elevated levels of glutamate in the CSF of some patients (40% in one large study, correlating with limb onset and rapid weakness [Spreux-Varoquaux et al., 2002]) but free concentrations in *post mortem* tissue were reduced, particularly in the spinal cord, perhaps suggesting redistribution of neurotransmitter pools [Plaitakis et al., 1988]. Animal studies implicate non-neuronal cells in the excitotoxic framework since knockout of glutamate transporters on glial cells resulted in a neurodegenerative phenotype [Rothstein et al., 1996]. Further investigations used the *SOD1* mouse to demonstrate loss of a specific spinal cord astroglial glutamate transporter, EAAT2 [Howland et al., 2002]. Over-expression of EAAT2 was protective against excitotoxicity and crossing this transgenic mouse with *SOD1* mice partially ameliorated disease onset [Guo et al., 2003], but successful overexpression in spinal cord astrocytes transduced with an adenovirus vector failed to improve survival [Li et al., 2015]. EAAT2 distribution appears to be altered in human pathological samples; surfaces of degenerated anterior horn cells stained densely for EAAT2, suggesting an abnormal (perhaps compensatory) local clustering of these channels [Sasaki et al., 2000].

Neuroimaging studies across multiple modalities have broadly supported the concept of reduced cortical inhibition. Initial observations were of a “boundary shift” in regional cerebral blood flow measured using positron emission tomography (PET) in ALS patients during a joystick task [Kew et al., 1993]. Further support stems from the observation of widened cortical blood oxygenation level-dependent (BOLD) activation in ALS patients during fMRI motor tasks [Mohammadi et al., 2011; Stanton et al., 2007a]. Also demonstrated was reduced binding of the PET GABA_A ligand [¹¹C]-flumazenil [Lloyd et

al., 2000; Turner et al., 2005a], reduced GABA MR spectroscopy peak in the motor cortex [Foerster et al., 2012], and elevated Glx (glutamate and glutamine) peak in the medulla [Pioro et al., 1999].

Direct evidence of disrupted cortical inhibition (inconsistent early reductions both of motor threshold and of the silent period – held to represent GABA_B dysfunction) in ALS has been provided by TMS [Mills and Nithi, 1997; Prout and Eisen, 1994; Siciliano et al., 1999; Yokota et al., 1996]. These abnormalities may occur alongside disruption to peripheral axonal membranes that might explain two common ALS symptoms: cramps and fasciculations [Mogyoros et al., 1998; Vucic and Kiernan, 2006a]. The peripheral findings may also have more than symptomatic relevance since motoneuron excitability assessed early in the disease course was predictive of patient survival [Kanai et al., 2011], although in contrast, a study of mSOD1 mice found that only degeneration *resistant* ‘S-type’ motoneurons are hyperexcitable, questioning therefore (at least in the SOD1 model) the aetiological importance of peripheral hyperexcitability [Leroy et al., 2014].

TMS using conditioning-pulse protocols has more reliably demonstrated reduced intracortical inhibition as a characteristic feature of ALS [Menon et al., 2015; Yokota et al., 1996; Ziemann et al., 1997], particularly 3 ms short-interval inhibition - more suggestive of synaptic GABA_A dysfunction [Vucic and Kiernan, 2006b]. The degree of abnormality may vary over the course of the illness [Mills, 2003; Zanette et al., 2002b] and be partially ameliorated by reducing glutamatergic influence through administration of riluzole – the only licensed disease-modifying therapy in ALS [Desiato et al., 1999; Geevasinga et al., 2016b; Stefan et al., 2001; Vucic et al., 2013a]. Riluzole has a complex set of dose-varying CNS actions [Bellingham, 2011; Doble, 1996] that include inhibition of persistent Na⁺ channels demonstrated to underlie cortical hyperexcitability [Pieri et al., 2009]. Multiple clinical trials of other anti-glutamatergic drugs have been performed in

ALS, but despite evidence that such agents reduce excitotoxicity in model systems [Yin and Weiss, 2012], results in patients have been disappointing [Blasco et al., 2014]. Meticulous clinical trial design is however a prerequisite to successful appraisal of novel therapies [Mitumoto et al., 2014]; pertinent issues concerning participant stratification and outcome measure expectations are considered below.

1.4 Measuring ALS: Why and How

1.4.1 Prognostication

A crucial aspect of ALS to be considered in the design of future clinical trials is the heterogeneity of the disorder, which, as discussed above, encompasses genetics, pathology (although TDP-43 is almost pathognomonic), perhaps also mechanisms, and certainly clinical phenotypes [Gordon and Meininger, 2011; Kenna et al., 2013; Marin et al., 2015; Murray et al., 2011; Ravits et al., 2009]. Smaller phase-2 trials of novel therapies may therefore choose to narrow recruitment within well-defined sub-groups of patients, while the scale of large multi-centre phase-3 clinical trials typically overcomes these limitations and permits generalizable inference. Nevertheless, for most trial designs, stratification of patient participants by their anticipated prognosis will aid effective randomisation and could potentially improve statistical power [de Carvalho and Swash, 2006].

A considerable array of longitudinal studies, within diverse epidemiological contexts, have been able to identify baseline demographic, clinical and simple lab-measured factors that correlate with subsequent disease progression – both in terms of mortality (reviewed in [Chiò et al., 2009]) and disability (reviewed in [Creemers et al., 2014]). Consistently reported adverse prognostic factors reflect underlying personal biological substrates including age [del Aguila et al., 2003; Czaplinski et al., 2006; Kihira et al., 2008; Kondo and Hemmi, 1984; Pastula et al., 2009; Stambler et al., 1998; Watanabe et al., 2015] and perhaps female sex [del Aguila et al., 2003; Watanabe et al., 2015], although sex differences

are unconfirmed [Kollewe et al., 2008; Zoccolella et al., 2008] and even reversed in other studies [Kihira et al., 2008]. Clinical characteristics with adverse prognostic implications are frequently reported to include bulbar onset [Chiò et al., 2011; Ganesalingam et al., 2009; Magnus et al., 2002] or early respiratory symptoms [Leonardis et al., 2012], while others such as pronounced UMN signs are reported as protective [Sorarù et al., 2010; Zoccolella et al., 2008].

The most recent investigations of prognosis in ALS have attempted to incorporate multiple baseline variables simultaneously in order to assemble predictive tools that might ultimately become useful for individual consultations [Elamin et al., 2015; Knibb et al., 2016]. In doing so these models must be updated to take account of current (and hopefully future) beneficial therapeutic interventions [Qureshi et al., 2009; Traynor et al., 2003a] including the patient's decision to start riluzole (repeatedly confirmed outside of clinical trials to slow disease progression [Traynor et al., 2003b; Turner et al., 2002]) or the initiation of non-invasive ventilation [Berlowitz et al., 2015; Gordon et al., 2012] while also adjusting for repeatable measures such as remaining respiratory muscle strength [Capozzo et al., 2014]. The current limitations in part reflect a trade-off between the number and complexity of inputted baseline measurements against the precision (and thus utility) of prognostic information returned [Wolf et al., 2015].

Finally, these longitudinal studies have served to highlight substantial inter-individual variation in disease progression over time, as seen in my analysis of a recently released open-access database (PRO-ACT [Atassi et al., 2014]) comprising 4752 individual patient records compiled from 17 negative therapeutic trials [Proudfoot et al., 2016]. **Figure 1.1** graphically demonstrates diverse individual timelines of disability accumulation as measured by the revised ALS Function Rating Scale (ALSFRS-r).

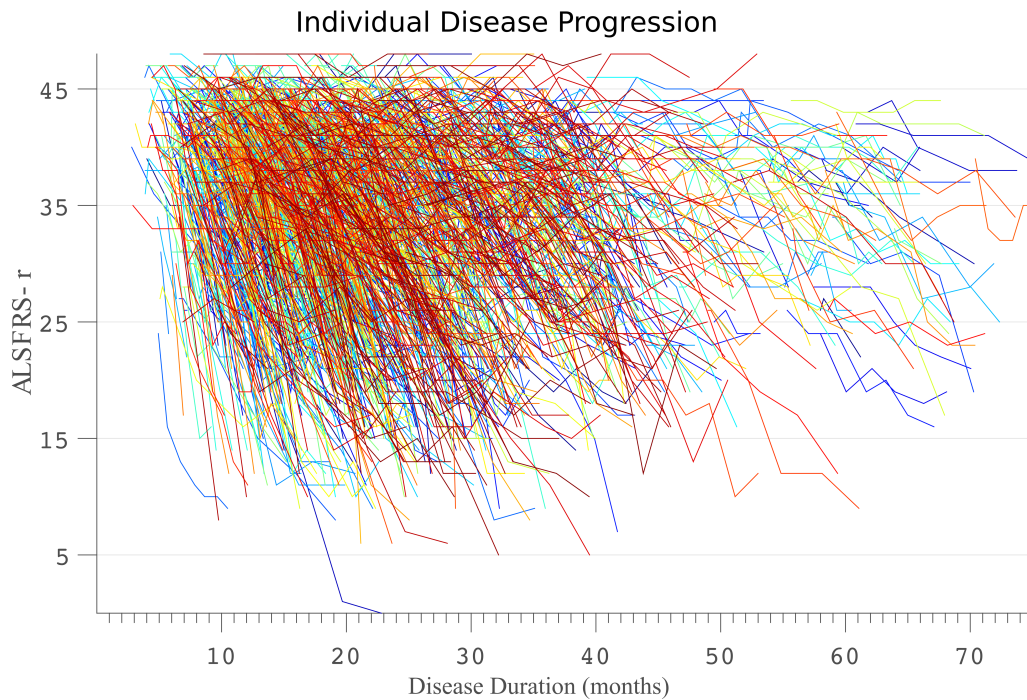


Figure 1.1: Individual ALSFRS trajectories.

Disability accumulation within individuals over time (ALSFRS-r, max score 48 = no significant disability).

The PRO-ACT database was conceived to encourage the development of large-scale multivariate predictive models in support of future clinical trial stratification. In open competition, the winning random forest machine-learning algorithm was shown to predict ALSFRS-r outcomes better than experienced clinicians ($R^2 = 0.87$ [Küffner et al., 2015; Zach et al., 2015]). This high-profile competition also underlined the longstanding reliance of clinical trials on the ALSFRS-r, often as a primary outcome measure alongside or in combination with mortality [Berry et al., 2013]. An individual's rate of change in ALSFRS-r can therefore also serve as a summary measure of disease severity (**Figure 1.2**) that can furthermore be calculated at first presentation using time from symptom onset $((48 - \text{current ALSFRS-r}) / \text{months})$ and has successfully been applied as a prognostic marker in itself [Gomeni and Fava, 2014; Kollewe et al., 2008; Labra et al., 2015; Mandrioli et al., 2015].

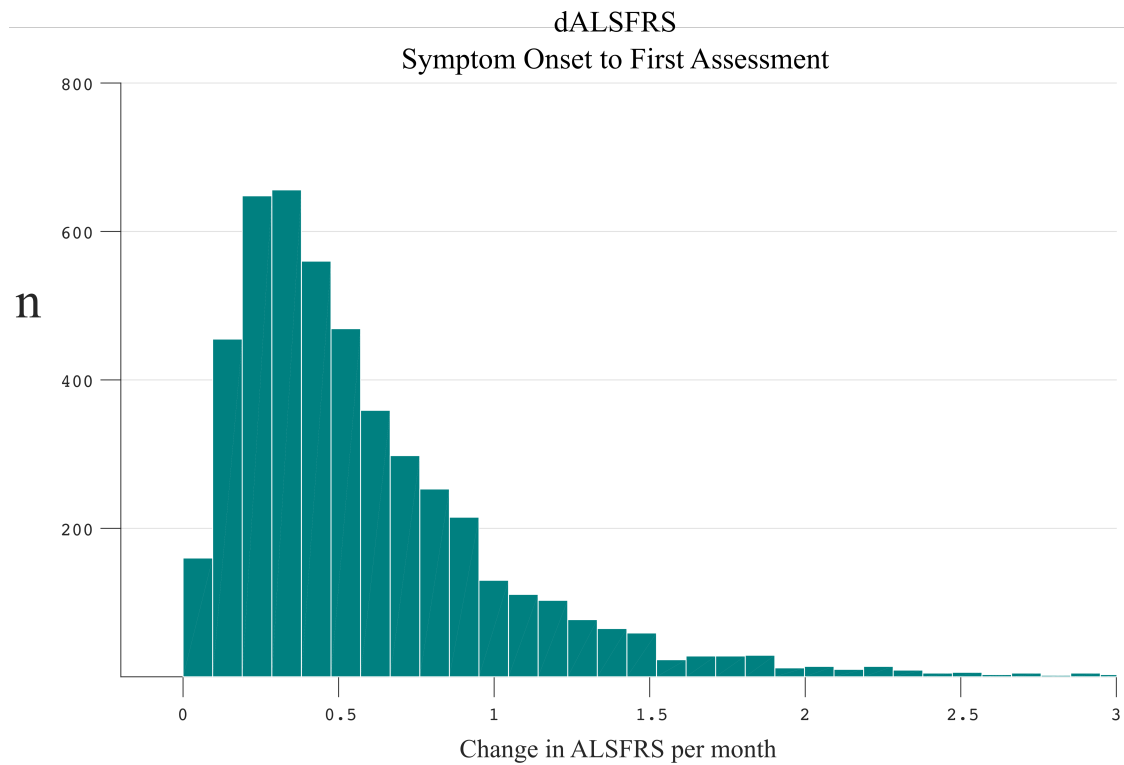


Figure 1.2: Distribution of delta ALSFRS.

Range of initial rates of disease progression in the PRO-ACT database.

Given the central role that this summed ordinal scale plays in ALS clinical trials, aspects of its longitudinal performance are considered below, alongside alternative and complimentary strategies to measure progressive neurodegeneration – the discovery of which is the principle aim of this thesis.

1.4.2 Longitudinal Measurement

The ALSFRS was originally designed as a simple and fast questionnaire to evaluate physical function in activities of daily living (Cedarbaum et al., 1996). The scale considered bulbar, fine motor, gross motor and respiratory domains and was revised to ensure equal weighting between these 4 components [Cedarbaum et al., 1999]. Early appraisals of the ALSFRS_r suggested fair inter-user reliability and linear decline over time [Traynor et al., 2004], but subsequent studies identified a lack of sensitivity to milder functional deficits and possible floor effects in advanced disease [Wicks et al., 2009b]. The scale has also been considered in terms of its latent components [Bacci et al., 2015]. Rasch analysis

suggested redundancy and poor fit to some domains, for instance ‘fine’ and ‘gross’ motor could be rationalised together [Franchignoni et al., 2015].

In light of these concerns I sought to consider longitudinal changes in the PRO-ACT database and was able to reaffirm overall linearity to ALSFRS decline, at least within the timeframe of the contributing clinical trials (**Figure 1.3**).

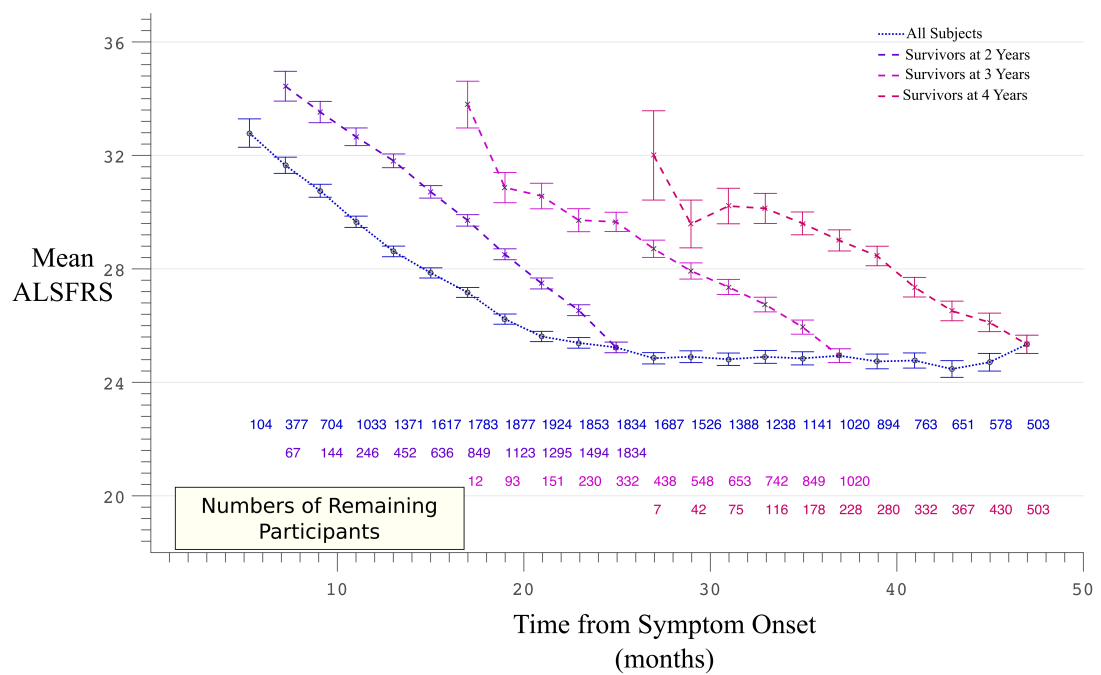


Figure 1.3: Clinical Progression in ALS.

Disability accumulation is tracked over time in linearly declining ALSFRS scores. ‘All subjects’ curve flattens due to selective drop out or death of most rapidly progressing individuals.

Recent comparable studies had suggested a curvilinear slope to better fit ALSFRS decline [Gordon et al., 2010], but by restricting analysis to predefined cohorts of survivors, we demonstrated selective trial drop-out (and death) of more rapidly progressing individuals to artificially create such an appearance. The PRO-ACT database has inspired several other analyses including a demonstration of (rare) non-progressive individuals and even (transient) reversals of disability [Bedlack et al., 2015]. This study did not however consider measures of respiratory function also recorded within PRO-ACT, which was demonstrated to decline linearly with time.

In all likelihood therefore, the ALSFRS_r, or a close approximation, will continue to find application in the next generation of clinical trials. This pragmatic and reliable choice should be accompanied by measures of quality of life, shown to correlate rather poorly with ALSFRS_r [McElhiney et al., 2014; Yates and Rafiq, 2016], and perhaps also measures directly appraising the impact on underlying biology (rather than downstream functional consequences) [Shefner and Mihaila, 2014]. The latter is particularly pertinent to phase-2 trials, which typically are under-powered to detect changes in either mortality or ALSFRS. Therefore, biomarkers responsive to the impact of a new therapeutic on its proposed (typically neural) target could be instrumental in guiding the decision to initiate costly and time-consuming phase-3 studies [Bowser et al., 2011; Simon et al., 2014b; Turner and Benatar, 2015]. At present however, the most consistent neuroimaging marker, diffusion tensor imaging (DTI), lacks sensitivity to change when compared to the ALSFRS_r [Cardenas-Blanco et al., 2016]. Markers of neural function, perhaps within the context of a multi-modal event-based model of disease progression [Fontein et al., 2012], therefore deserve close consideration.

One further key component of ALS as a clinical syndrome, widely ignored by previous clinical trials, is the impact on cognition [Abrahams et al., 2005]. Cognitive performance has thus far typically been applied as an exclusion criterion rather than an outcome measure, but in the following paragraph and associated publication, we consider an alternative strategy for reliable, longitudinally repeatable, assessment of cognition.

1.4.3 Assessing Cognitive Impairment with Eyetracking Devices

Given the relentless and irreversible accumulation of physical impairments as ALS progresses and the extent to which this can interfere with conventional communication, assessment of cognitive abilities in late-stage disease while avoiding confounding influence of weakness (particularly if measures are dependent on reaction times) is a

distinctive challenge. Encouraging use of alternative communication strategies, including eyetracking devices, is now commonplace in the holistic care of ALS patients [Spataro et al., 2013]. With some success therefore, cognitive tests making use of this modality may circumvent limb and speech disability [Cipresso et al., 2011; Hicks et al., 2013]. Cognitive capacity assessment is particularly relevant in the context of advanced disease given the need for patients to make informed decisions about potentially life-prolonging interventions. No firm expectations are held regarding cognition in this situation, *enhanced* performance on learning tasks has even been demonstrated using a binary response paradigm in 11 severely impaired individuals [Lakerveld et al., 2008].

However, some caution is required in the application of eyetracking cognitive tests however, given the potential impact of ALS pathology on oculomotor function (reviewed in [Sharma et al., 2011]), which might eventually be unavoidable after prolonged ventilator dependence [Mizutani et al., 1990]. Earlier in the disease however, oculomotor abnormalities may still correlate with measures of executive dysfunction [Donaghy et al., 2011; Shaunak et al., 1995] and overlap with other atypical clinical phenotypes such as ALS with parkinsonism [Gizzi et al., 1992]. Anti-saccade errors [Evdokimidis et al., 2002; Shaunak et al., 1995], variably accompanied by an increased proportion of inappropriately early saccades [Burrell et al., 2013], were reported without clear correlation to the overall burden of physical impairment, and therefore serve to widen the extra-motor spectrum of ALS manifestations. Indeed anti-saccade performance is a popular method to infer executive function in diverse conditions, not limited to healthy aging [Mirsky et al., 2011; Peltsch et al., 2011], Alzheimer's disease [Kaufman et al., 2012], and miscellaneous neurological conditions [Hellmuth et al., 2012], including presymptomatic Huntington's disease [Blekher et al., 2006].

Our group's first investigation of ALS using eyetracking devices utilised three separate tasks to assess overlapping cognitive domains. Sixty-one patients with ALS were compared against 39 age-matched healthy controls and 7 patients with PLS. When feasible ALS patients were assessed longitudinally for up to two years [Proudfoot et al., 2015]. The results demonstrated ALS and PLS patients to be impaired on the executive components of the tasks despite preserved basic (pro) saccadic function (**Figure 1.4**).

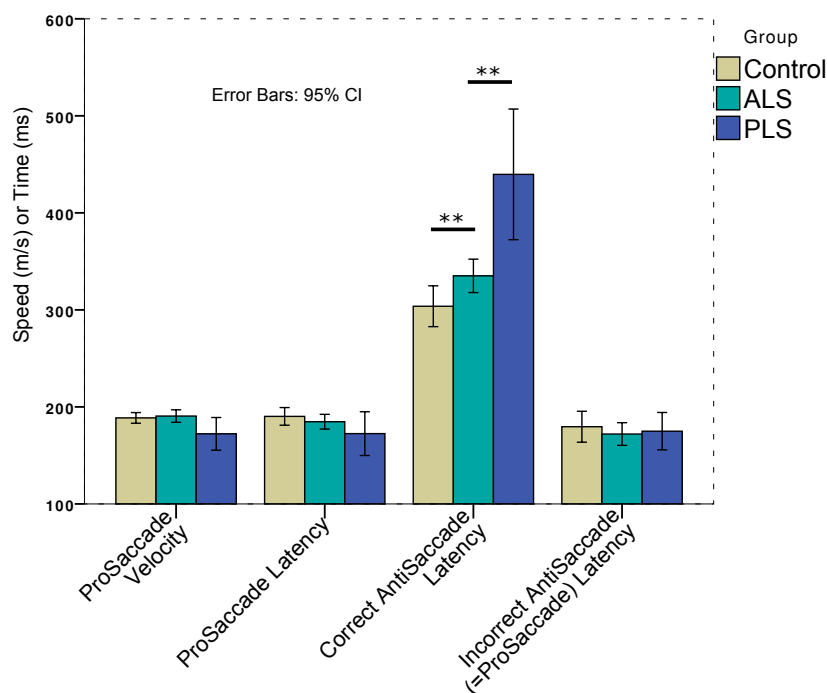


Figure 1.4: Pro and Antisaccade Performance in ALS & PLS.

Even at first assessment point patients are shown to have slowed correct antisaccade latencies but preserved prosaccades.

The longitudinal data directly compared the first visit with the final available assessment point and confirmed stable differences between the groups. Within six ALS patients assessed on 4 separate occasions (a mean total time interval of 20 months), there was no effect of time other than a slight practice-driven improvement on one measure (part A of an eyetracking trail-making-test (TMT), of note 25% of ALS patients could not complete the written TMT even at first visit). In summary therefore, higher-level oculomotor tasks are sensitive indicators of extra-motor ALS pathology while basic saccadic function is

most commonly spared, in keeping with the described sparing of extra-ocular motoneurons in neurodegenerative models [Liu et al., 2013; Mosier et al., 2000].

The results of this study re-affirm that antisaccade performance is a readily obtained barometer of executive control capability, concordant with recent studies in FTD [Boxer et al., 2012] and in healthy older adults that noted correlation with other executive measures and cortical thickness in the left IFG and right SEF [Mirsky et al., 2011]. An unanswered question concerns the ability of portable eyetracking to detect *sub-clinical* frontotemporal neurodegeneration. Other easily accessible techniques may be more powerful, for example near infrared spectroscopy, which was used to show altered prefrontal activation during a working memory task in patients with ALS [Kuruvilla et al., 2013]. The rationale behind detection of abnormalities in neural function prior to the onset of overt ALS symptoms is discussed in the final part of this introduction.

1.5 When does ALS begin?

1.5.1 The Pre-Diagnostic Landscape

The ever-closer prospect of targeted interventions aiming to prevent otherwise irreversible neurodegeneration is greeted with both excitement and uncertainty by researchers and relatives alike. Characterisation of the pre-symptomatic phase is a pre-requisite [Benatar and Wu, 2012] and appears increasingly feasible given the encouraging results of such investigations in other dementias [Chandra et al., 2014; Rolinski et al., 2016; Sperling et al., 2011]. The best established example remains florbetapir PET positivity that may precede symptoms of Alzheimer's disease by 20 years [Caselli et al., 2010; Reiman et al., 2009]. However, an over-emphasis of the amyloid cascade pathway (and neglect of tau's role) has exposed many trial participants to the risks of immunotherapy [Sperling et al., 2012]; progress towards effective dementia therapies is slow [Gauthier et al., 2016].

It remains an open question to what extent symptoms of ALS are preceded by temporally remote cellular abnormalities [Eisen et al., 2014]. Although animal models of ALS demonstrate abnormal neural architecture and function during embryonic stages [Martin et al., 2013; Vinsant et al., 2013], epidemiological links to human neurodevelopmental disorders are sparse [Byrne et al., 2013; Schoder et al., 2010]. Suggestions that ALS (or FTD) pathology might manifest in a behavioural prodrome long before diagnostic symptoms remain speculative [Eisen et al., 2014; Lule et al., 2008]. Within model systems at least, pathological changes including interneuron loss are demonstrable in advance of motor phenotypic expression [McGown et al., 2013], and furthermore early neuronal abnormalities in keeping with hyper-excitability [Saba et al., 2016] have proven amenable to pharmaceutical modification [Wainger et al., 2014]. Pending further characterisation of the first models of *C9orf72* [Jiang et al., 2016; Liu et al., 2016], mechanistic inference for this major cause of ALS remains dependent on post-mortem tissue examination. The rare circumstance of premature death of a young adult with a *C9orf72* expansion, summarised below and fully reported in the attached publication [Proudfoot et al., 2014a], therefore allows crucial insight into the sequential ordering of pathological developments.

1.5.2 A Case Study of Emergent Pathology in *C9orf72*

A central and as yet incompletely resolved question is the primacy of the various neuropathological features shown to co-exist in *C9orf72* ALS, in particular the protein species most characteristic of sporadic ALS, TDP-43 [Al-Sarraj et al., 2011; Mackenzie et al., 2014; Murray et al., 2011], and the translated products specific to the *C9orf72* hexanucleotide expansion, referred to as ‘dipeptide repeats’ (DPR) [Ash et al., 2013; Zu et al., 2011]. A small kindred were identified with seemingly autosomal dominant transmission of either FTD or development intellectual delay. The index case died at 53y following quite typical FTD that evolved from diagnostically unstable psychiatric symptoms. Her son was known to have language delay in early childhood and developed severe obsessive compulsive

symptoms from the age of 17 years. While a teenager, he had been able to assist on the family farm, but he subsequently declined functionally to the extent that he required residential placement. Prior to his death, aged 26 years from pulmonary embolus, he had become violent and withdrawn, and he also exhibited altered food preference. *C9orf72* repeat expansions were confirmed from stored DNA and pathological examination performed. The mother's neocortical pathology revealed widespread ubiquitin/p62 staining intracellular inclusions with only occasional TDP-43 positivity. The son's pathology confirmed ubiquitin/p62 inclusions, albeit less widespread, but no TDP-43. Evidence of DPRs was demonstrated in both: the mother had widespread and abundant DPR in neocortex, hippocampus, and cerebellum; while the son demonstrated DPR particularly in neocortex and cerebellum (**Figure 1.5**).

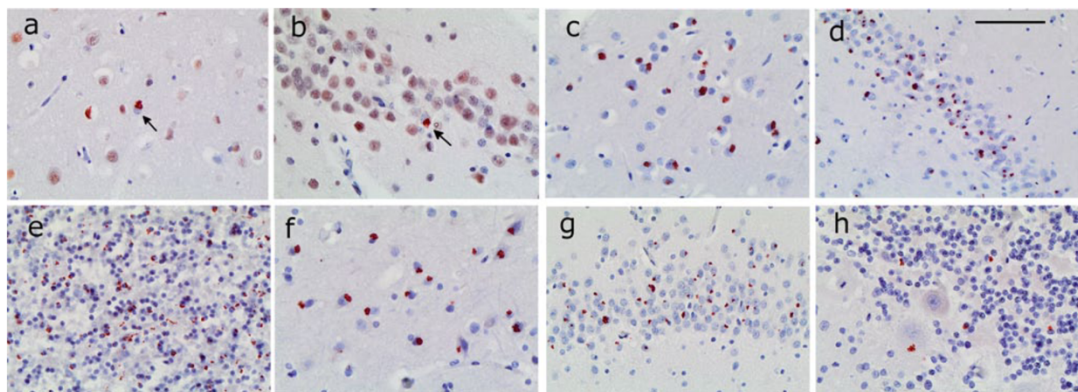


Figure 1.5: Pathological Consequences of *C9orf72* Repeat Expansion.

Immunohistochemical findings mother (a–e) and son (f–h). The mother had very rare TDP-43-immunoreactive neuronal cytoplasmic inclusions (NCI) in the frontal neocortex (arrow, a) and hippocampal dentate granule layer (arrow, b). In contrast, immunohistochemistry using an antibody against GA dipeptide repeats (DPR) demonstrated much more abundant DPR-immunoreactive NCI in the frontal cortex (c), hippocampus (d) and cerebellar granular layer (e). No TDP-43-immunoreactive pathology was found in case 2; however, abundant DPR-immunoreactive NCI were present in the frontal cortex (f), hippocampus (g) and cerebellum (h). Scale bar 50 microns.

The pathology of this kindred therefore reinforces the pathogenic role of DPR inclusions upstream of TDP-43, even if TDP-43 distribution typically correlates better with clinical symptomatology [Mackenzie et al., 2013]. The association with developmental intellectual delay, also noted in a younger son untested for *C9orf72*, was novel but subsequently

replicated in an independent case series [Hensman Moss et al., 2013]. Whether the DPR changes in the son were truly presymptomatic is uncertain, given the absence of alternative explanation for his early cognitive decline.

1.5.3 *In vivo* evidence in ALS

There are inconsistent reports of structural MRI abnormalities prior to symptom onset in those at high genetic risk of ALS [Ng et al., 2008; Vucic et al., 2008; Walhout et al., 2015] and un-replicated findings of altered neuro-metabolites on MR spectroscopy of the spinal cord in asymptomatic *SOD1* carriers [Carew et al., 2011]. Evidence of cortical hyperexcitability in asymptomatic carriers of genetic mutations who are ‘at risk’ of ALS is restricted to a very limited finding of reduced ligand [^{11}C]-flumazenil binding in two individuals with the D90A *SOD1* mutation [Turner et al., 2005a], and three *SOD1* mutation carriers who demonstrated reduced or absent intra-cortical inhibition within three months of symptom onset [Vucic et al., 2008]. Further TMS studies on seven asymptomatic *SOD1* mutation carriers (mean age 33 years) and 11 *C9orf72* carriers (mean age 49 years) failed to differentiate them from controls by intracortical inhibition measures [Geevasinga et al., 2015b; Vucic et al., 2010]. The implication of the latter studies is therefore that although cortical hyper-excitability may drive disease progression peri-diagnosis, it may still represent a relatively late event in the stochastic sequence culminating in manifest disease. No preventative clinical trials have yet been performed in asymptomatic ALS gene carriers; the lack of evidence for cortical hyper-excitability perhaps discourages the investigation or compassionate use of riluzole in this context.

Functional modalities may have higher sensitivity in the presymptomatic period [Kloppel et al., 2009; Kunz et al., 2015]. Our resting-state fMRI study of a mixed group of gene carriers revealed subtle differences in functional connectivity (further discussed in

Chapter 4) [Menke et al., 2016]. Non-invasive exploration of cortical function in ALS using magnetoencephalography (MEG) is the core ambition of this thesis.

Chapter 2 Introduction to MEG Methodology

The experimental chapters that follow in this thesis all use MEG to investigate the neural signature of ALS. This methods chapter therefore summarises MEG technology, acquisition techniques and analysis strategies.

2.1 Detecting Neural Signals in the Brain's Magnetic Field

2.1.1 Neuroanatomical Considerations

The great majority of neuroimaging experiments performed thus far in ALS clinical studies have relied on either fMRI or PET modalities [Turner et al., 2012b] to gain insight into the functional consequences of, and compensation for, progressive neurodegeneration. In contrast to these modalities MEG (and electroencephalography (EEG)) directly measures neural activity and can do so with millisecond temporal precision. Not only do electrophysiological methods therefore bypass the (as yet incompletely characterised) intermediary metabolic steps that link neural events to blood oxygenation and perfusion changes, but these techniques obviate several seconds of temporal dispersion that occurs through the haemodynamic response function [Proudfoot et al., 2014b]. This is advantageous both in the ability to specify a discrete time period of interest relevant to a particular cognitive and motor operation and the potential to spectrally decompose the neural signal into constituent oscillatory components [Lopes da Silva, 2013]. Unlike invasive studies, restricted to animal experiments and opportunistic acquisitions from patients undergoing functional neurosurgery, M/EEG recording resists microscopic anatomical localisation but instead benefits from dynamic recording across dispersed cortical sources that better represents complex cognitive processes (for example [Hunt et al., 2012]). MEG offers additional spatial precision over EEG since the magnetic flux induced by pooled neural activity does not suffer from the same degree of physical dispersion during transmission through skull and scalp [Leahy et al., 1998].

The neural signal detected by MEG is not held to represent axonal action potentials, but is instead generated by unidirectional intracellular currents arising at apical dendrites, referred to as post-synaptic potentials. Action potential contributions are largely discounted given signal attenuation with distance and their short time duration (~ 1 ms) that would prevent temporally synchronous firing in many neurons from summing together without jitter [Ioannides, 2005; Murakami and Okada, 2006]. Each neuron receives many hundreds of afferent glutamatergic and GABAergic synaptic connections, summed to locally modulate the resting membrane potential and consequently the neuron's firing probability. The generation of an externally detectable current-dipole probably requires concurrent activity in around 50,000 neurons [Hämäläinen et al., 1993] and therefore mandates brief consideration of cortical micro-architecture. Pyramidal neurons are arranged parallel to their neighbours in a palisade formation with apical dendrites radially aligned relative to the cortical surface. An 'open' electrical field (**Figure 2.1**) is therefore generated by each cortical 'column' [Mountcastle, 1997], sets of which function cooperatively in a dynamic fashion to sub-serve cerebral processes.

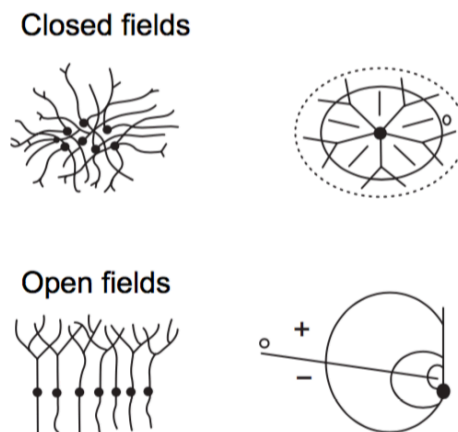


Figure 2.1: Palisadal configurations of neurons

This cellular organisation supports generation of externally detectable electrical fields (adapted from [Hansen et al., 2010])

The macroscopic structure of the cortex also impacts on the detectability of neuronal sources; cortical folding is such that dendritic orientation will vary with transition from

gyral crown, at which location the current dipole lies at a radial orientation with respect to the skull, to the sulcal bank where dipoles lie tangentially oriented. Unlike EEG recordings, radially oriented sources (from either gyral crown or sulcal fundus) are less likely to influence the magnetic field outside the head (**Figure 2.2**). The extent of this insensitivity may be overstated however [Hillebrand and Barnes, 2002]) and is also likely to be dependent on individual (perhaps also pathological) variation in both cortical gyrification and macro-anatomy.

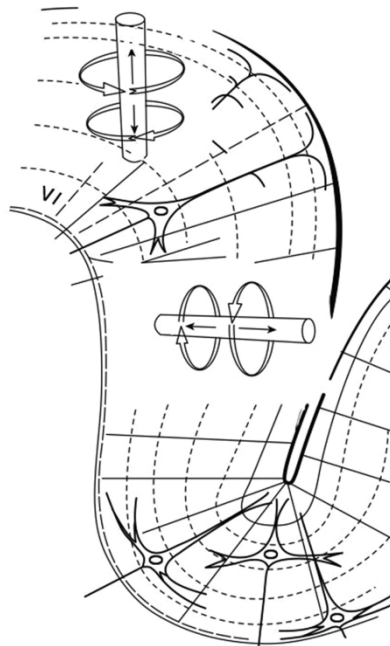


Figure 2.2: Dipoles generated by cortical microcolumns.

Cortical microcolumns within the sulcal bank generate dipoles tangentially orientated to the skull. Their induced magnetic fields will project beyond the skull surface and can be detected with MEG. Conversely, apical dendrites orientated perpendicularly to the skull, as found at the gyral crown, are better detected by EEG (adapted from [Hansen et al., 2010])

2.1.2 Technical Solutions

The detection of neural signals by MEG requires a sensor of extreme sensitivity, given that the alterations to magnetic fields outside the head are in the order of 10 femtotesla. This technological leap forward involved the isolation of the superconducting quantum interference device (SQUID) within a magnetically shielded-environment to eliminate the

otherwise overwhelming environmental sources of magnetic interference (**Figure 2.3**) [Cohen, 1968].

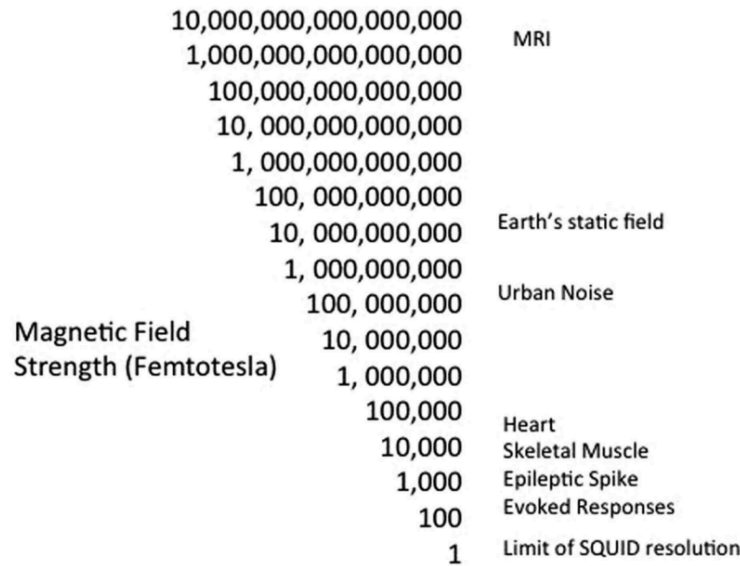


Figure 2.3: Sensitivity of MEG sensors.

Magnetic field strength density measured in femtotesla (fT), highlighting the exquisite sensitivity of the SQUIDS used in magnetoencephalography.

SQUIDS comprise an interrupted ring of superconducting material (properties only acquired at temperatures close to absolute zero) that, on exposure to an external magnetic field, induces a proportional strength current measured via the amount of flux and hence electrical resistance across a Josephson junction (a type of electronic circuit capable of switching at very high speeds when operated at temperatures approaching absolute zero). While SQUIDS themselves are necessarily tiny (~ 1 mm), coupled pick-up coils are sensitive to magnetic flux across a larger surface area and transmit this to the SQUID. Modern whole-head MEG systems, such as the Elekta Neuromag installed in Oxford, often incorporate multiple pick-up coils within each sensor. In our case, 102 such sensor triplets were distributed within a helmet to provide global coverage (**Figure 2.4**).

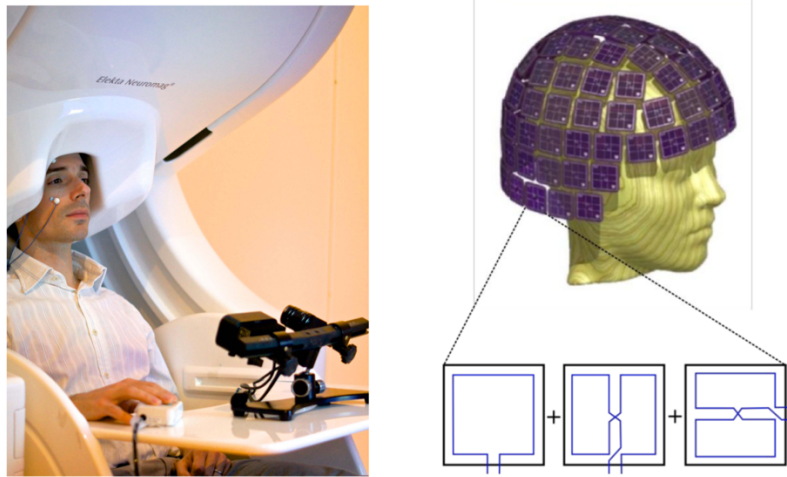


Figure 2.4: The Neuromag MEG scanner.

An MEG recording at the Oxford Centre for Human Brain Activity (left). The sensor configuration for the Elekta Neuromag system (right).

Each sensor in the Neuromag system comprises of two pick-up coil designs, deliberately arranged for complementary spatial sensitivity, analogous to lens choices for particular photographic purposes. A single ‘magnetometer’ coil measures any orthogonal magnetic field. Pairs of coils placed closed together and wound in opposite directions are also used to measure gradients in the magnetic field over space. These ‘gradiometers’ are typically arranged in one of two configurations (axial or planar) and measure a gradient in magnetism between two coils. Planar gradiometers, as in the Neuromag, are best placed to detect cortical surface sources directly beneath them while the magnetometers are better able to detect deep sources; recording is made from both sensor types simultaneously and combined to aid source localisation throughout the head.

The corollary of the SQUID’s sensitivity is an extreme susceptibility to artefactual noise interfering with neural signal recoding (**Figure 2.5**). The magnetically shielded room (MSR) serves the purpose of isolation from almost all external magnetic noise by using permeable mu-metal and aluminium to provide low-reluctance paths for magnetism around the MSR walls. Feed-forward compensation from large pickup coils in the MSR can also be used to detect and compensate for far-field disturbances that remain fairly

constant; given the low levels of ambient magnetic noise these were inactivated in the OHBA setup during the described experiments.

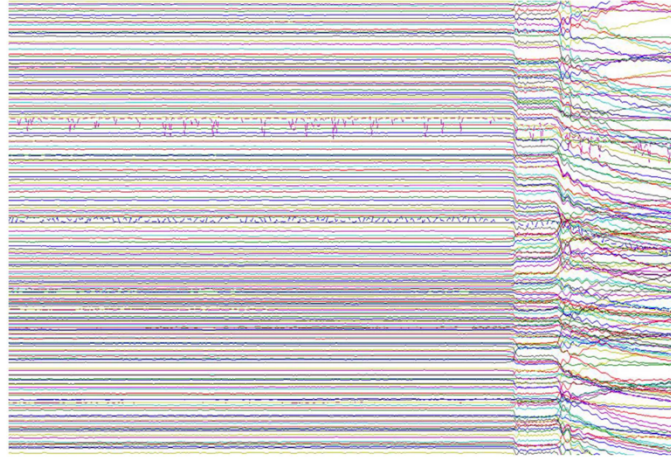


Figure 2.5: Raw MEG data from the Neuromag

After 4 s of raw magnetoencephalography data (two channels contain obvious artefacts), the door to the magnetically shielded room is opened during recording. The interference caused by external magnetic fields highlights why effective room shielding is essential.

Other recording and stimulus presentation devices (including the infrared eyetracker pictured in **Figure 2.4**), necessarily located within the MSR, are optimised to ensure electro-magnetic silence. Sensible recording from many subjects is precluded by dental amalgam, cardiac pacemakers, or other ferromagnetic implants, somewhat offsetting the major safety advantages MEG claims over fMRI acquisitions.

2.2 Best Practice in MEG Data Acquisition

Given the particular properties of MEG sensors and their susceptibility to artefact, considerable care must be taken by experimenters during data acquisition to maximise the useful interpretability of the resulting complex data set. While consensus guidelines have been developed to foster good practice across the international MEG community [Gross et al., 2013], local acquisition conduct is also herein recorded for future reference and are relevant to the subsequent experimental chapters.

Prior to attending MEG recording sessions, participants were verbally screened for potential metallic sources of artefact. If significant doubt remained, participants were asked to attend for an artefact measurement session in advance of the experimental session, during which they were seated in the MSR, MEG data were acquired and inspected in real time. Certain movements were requested, to bring out sources of artefact, such as deep breaths or mouth opening and closure. If the participant was of high value (ie an asymptomatic gene carrier) and doubt remained over the MEG signal usability, provisional preprocessing using Maxfilter software was performed prior to the full experimental recording and the results subjectively inspected.

Preparation of the participant for MEG scanning took place after behavioural task training and familiarisation with the scanner environment. Surface electromyography (EMG) electrodes were applied to each arm in positions appropriate to the capture of relevant motor responses. Surface electrooculography (EOG) recordings were made in both vertical and horizontal planes, with electrodes above and below the left eye to detect blinks, and to the right and left of respective orbits in order to detect lateral saccades. Electrodes were applied to each wrist for recording of the electrocardiogram (ECG). Continuous adjustment was made for head position within the MEG helmet using four emitting head-position indicator (HPI) coils secured to the participant's scalp. A Polhemus 3D tracking system recorded coil positions relative to nasion and preauricular fiducial landmarks, alongside distributed points covering the scalp surface (**Figure 2.6**). Points covering the distributed surface of the nose were added in most recent acquisitions to improve anatomical coregistration (see below).



Figure 2.6: Determining head position in the MEG scanner.

Using the Polhemus pen to record anatomical fiducials and head shape points.

Participants were seated comfortably in the MEG scanning chair which was then raised until light contact was made between vertex and helmet. Efforts were made to ensure that the participant was symmetrically seated within the helmet along both right-left and anterior-posterior axis, HPI position was re-checked prior to each session and recording not initiated until stable measurements were demonstrated.

Eye movements were also recorded using an infrared eyetracking camera (SR Research Eyelink 1000). Calibration was performed prior to each recording block using 9 distributed saccadic targets. Eye position was recorded bilaterally if possible, saved in a separate data file and also added as x,y and pupil diameter channels into the MEG data file.

MEG data were digitised at 1000 Hz with a high-pass filter of 0.03 Hz to allow online visualisation throughout the acquisition. The Neuromag system requires tuning prior to each acquisition to ensure sensitivity falls within a dynamic range appropriate to neural activity. Individual channels were also heated and reset if artefact detected. Residual bad

channels were exceptional and marked for subsequent removal. Temporally precise event markers were added by the stimulus computer and response devices.

2.3 Data Preprocessing & Source Localisation

2.3.1 Artefact Identification & Rejection

A locally developed analysis pipeline, OHBA Software Library (OSL), was used for analysis, incorporating Matlab toolboxes from SPM12 (UCL, London, UK), FSL (FMRIB, Oxford, UK) and FieldTrip (Donders, Nijmegen, NL). Continuous MEG data were initially inspected to identify noise-corrupted channels and segments contaminated by brief artefact (**Figure 2.7**).

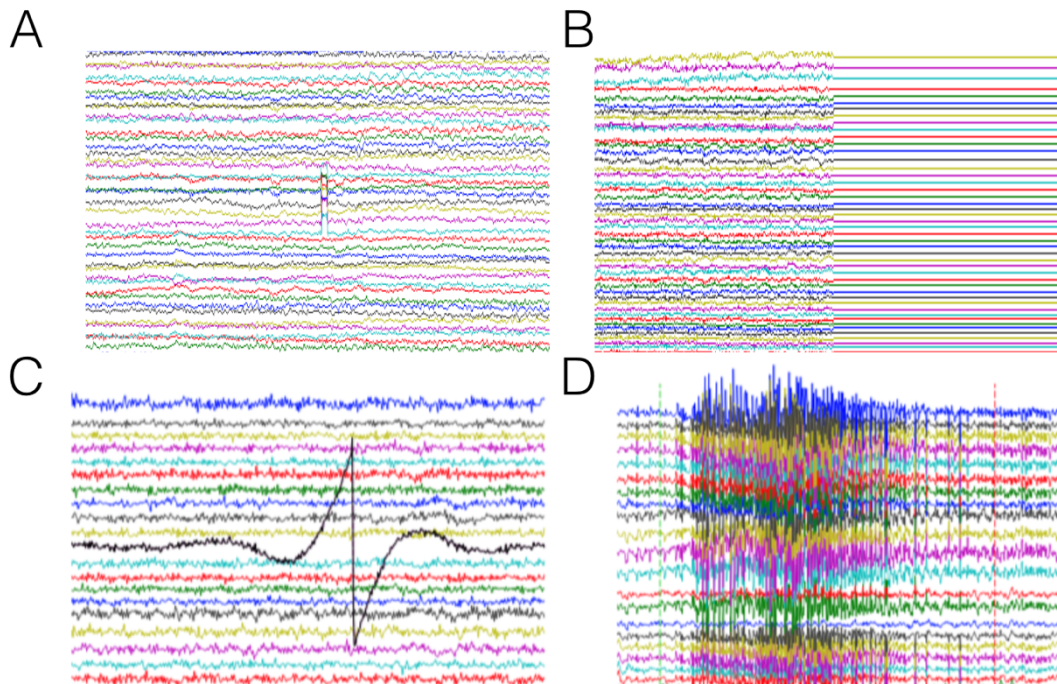


Figure 2.7: Examples of MEG sensor hardware artefacts.

Artefact, either brief bad segments in multiple channels (A) or one bad channel over longer time periods (C) require exclusion prior to application of Maxfilter that otherwise propagates the artefact across channels (D) or zeros data (B). Visual inspection of Maxfilter outputs is therefore mandatory.

Maxfilter software (Version 2.2, Elekta) was then applied to the remaining channels for Signal Source Separation and head position adjustment, transforming the data into a set

of virtual sensors. Maxfilter, using proprietary algorithms, aims to reject data identified as originating from outside the head and corrects for head movement within a session [Taulu et al., 2004]. The remaining de-noised components are re-projected onto the MEG sensors, with a resulting loss of dimensionality. Source-space analyses (discussed below) further account for head position in forward model calculations; differences in head position between sessions and subjects are therefore better accounted for than the corresponding sensor level analyses.

Data were then downsampled to 250 Hz, and physiological artefacts were identified and removed using an independent component analysis classification tool based on visual inspection of stereotypical component spatial topography and timecourse [Baker et al., 2014; Mantini et al., 2011]. Exactly two temporal independent components pertaining to 1) cardiac pulse and 2) eye-blink were removed from each data set (**Figure 2.8**), these components typically correlated highly over time with the relevant external signal channel (ECG or vertical EOG).

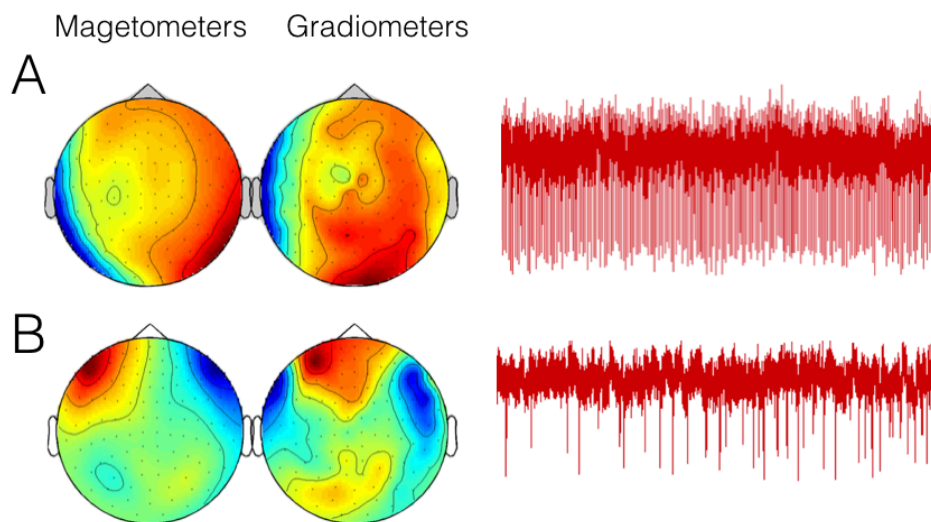


Figure 2.8: Removing physiological artefacts

ICA components pertaining to ECG (A) and blinks (B) were identified on the basis of typical topography and time-course.

Data were then epoched according to the time period of interest, including a (typically one second) pre-cue baseline period, for subsequent analysis. Alongside behaviourally incorrect trials and those with premature responses identified by surface EMG, epochs contaminated by artefact were identified either by a semi-automated approach within FieldTrip or an automated rejection tool with OSL, and removed from the analysis. The automated tool used a robust bisquare linear regression to fit for the mean standard deviation in the data over trials. Trials that were down weighted by more than 99 percentage points during the regression were classed as outliers. The FieldTrip tool visually identifies outlier trials on the basis of variance, kurtosis or maxima/minima, either in the MEG channels or a specified external channel.

2.3.2 Source-Space MEG Data

While interpretation of experimentally acquired data at the sensor level is for some scientific questions both adequate and computationally frugal, analytic sensitivity is typically improved by transforming data to the estimated intra-cerebral sources and functional localisation conclusions can then also be made more confidently. The means by which these anatomical sources are inferred from MEG data continues to be developed (see chapters 5-8 in [Hansen et al., 2010]). In essence, there exists an ‘ill-posed’ mathematical problem whereby many different possible configurations of neural sources can give rise to any given sensor-level configuration of MEG data. The configuration of neural sources therefore requires constraint either in the form of a focal simplistic model such as a small number of ‘equivalent current dipoles’, or only accepting the distributed neural solution that accounts for sensor measurements with a minimum overall electrical current (which tend to disproportionally favour superficial sources), or lastly (widely used, including in this thesis) the constraining of activity to anatomical priors defined by cortical structure.

The initial step to source localisation is the definition of a ‘forward model’, which entails a solution at the sensor level for a known cerebral source. The calculation therefore depends on a (simplified, but still adequate) model of magnetic conductance through the cranial anatomy. While a simple sphere can be used as the anatomical model, magnetic fields are also generated by return currents as electrical activity is volume conducted. This conductivity is not homogenous between the cranial tissue layers, therefore these layers can parsimoniously be modelled as concentric spheres, but without much impact on the overall performance of the forward model [Sarvas, 1987]. The head is of course not a perfect sphere; more advanced models attempt to reflect anatomical realities but inevitably contribute to a computationally more intensive analysis [Baillet et al., 2001].

The forward model in essence returns a set of ‘lead fields’ for each sensor, a weighted matrix transformation that defines the activity detected at each sensor for the given activity at each source. Two spatial relationships must be defined before the lead fields can be estimated: the position of the head in relation to the sensors within the helmet and the location of the cortical anatomy with respect to the head surface. The head position is localised by the HPI coils that must be reliably fixed to the participant’s scalp prior to entering the MSR. Periodic electrical impulses through the HPI coils during the recording allow their 3D position to be ascertained relative to an MEG coordinate system. The locations of the HPI coils are recorded using a spatial digitiser ‘pen’ (Polhemus Isotrack) alongside anatomical landmarks that are reliably and automatically identified on the participant’s structural MRI, acquired after the MEG session on a Siemens Trio 3T scanner (OCMR). Surface head-shape points also contribute to this process. MRI space, organised within Montreal Neurological Institute (MNI) coordinates, is therefore spatially coupled to the MEG sensors. During data preprocessing the co-registration accuracy was checked for each individual and errors corrected where possible. Collection of surface

points around the nose facilitated this using a recently developed OSL tool (**Figure 2.9**), which also enabled manual removal of errant headshape points. Future coregistration gains may be made by photographic records being made of the pen fiducial points onto which MR opaque markers (such as cod liver oil capsules) can then be fixed during the structural acquisition.

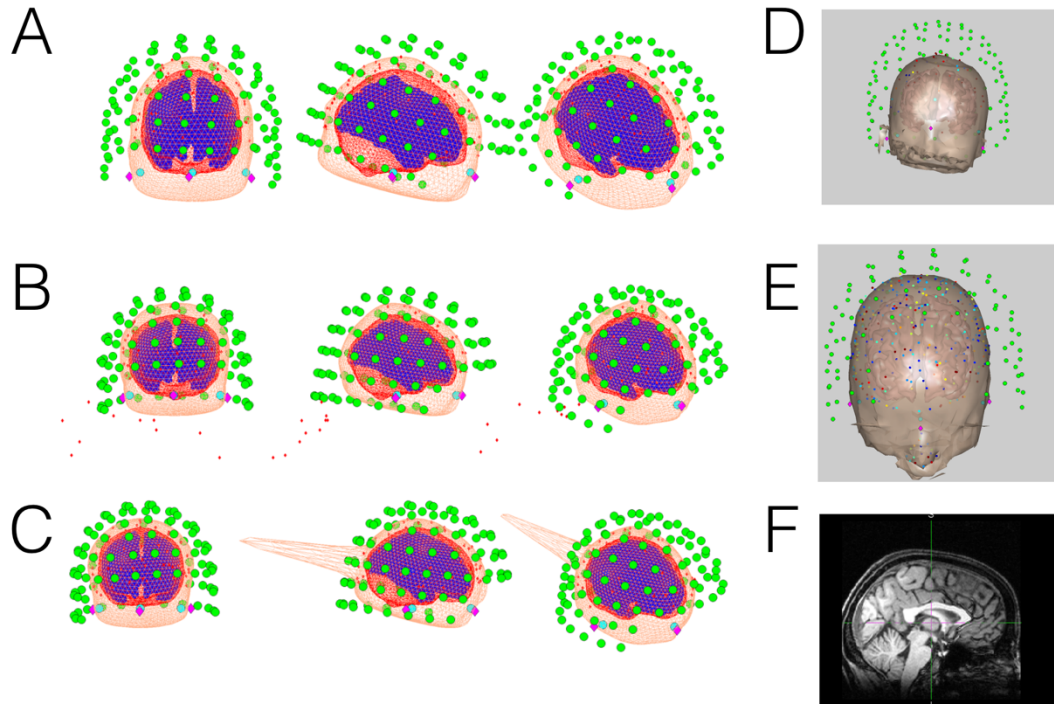


Figure 2.9: Coregistration of MEG data to cortical sources.

Coregistration examples, green = sensors, blue circles and purple diamond = anatomical locations and pen placement for fiducial markers. (A) good fit using unmodified SPM tool. (B) errant head shape points (red dots). (C) cortical surface warped due to sub-optimal field of view of occiput on structural MRI (F). (D) OSL's RHINO tool used to display poor co-registration example, head rotated with respect to sensors. (E) coregistration accuracy much improved when nose surface points included.

The source reconstruction method applied throughout this thesis is *beamforming*. This tool enables the estimation of activity at each location of interest (for example evenly spaced points on a 3D grid) by constructing spatial filters, in much the same way that sonar operates to estimate the location of an enemy submarine. A set of beamformer weights describes the transformation from sensor data to the beamformed locations. These weights freely pass signal components estimated to arise from the spatial location, but

attenuate components from other locations. The estimation of the weights is that which minimises the output variance while still allowing unit gain at each specified location in turn [Hillebrand et al., 2005]. This method has the additional benefit of inherently suppressing sources of signal that principally originate from beyond the brain's 3D grid, ie artefact. It is a data-driven approach that does not assume activity to be restricted to a limited number of sources and it has been shown to be sensitive to both superficial and deep sources (including for example the hippocampus [Engels et al., 2016]). This method, known as *linearly constrained minimum variance* beamforming is known to underperform in specific circumstances such as highly correlated distant sources that may either be cancelled or be merged; the latter effect is strikingly demonstrated with cyclic binaural acoustic stimuli, erroneously localising auditory cortex to the midline [Brookes et al., 2007]. Activity at each source is commonly represented as a scalar (rather than a 3D vector) result; the orientation of the scalar can be constrained by the pattern of cortical folding, or decomposed into maximum eigenvalues and eigenvectors. Beamformer reconstructions are commonly used prior to connectivity analyses across spatially remote cortical regions; enduring close correlation between cortical sources might therefore be underestimated by the beamformer but in practice such communication is transient enough not to have an impact [Hadjipapas et al., 2005].

A final consideration in relation to beamforming concerns the user-defined sampling parameters in spatial, temporal and spectral dimensions. The input for a beamformer transformation is the data covariance matrix at the sensor level. As this is likely to differ significantly between different frequency bands, the beamformer operation was specifically performed to cover a frequency range appropriate to the experimental paradigm – typically inducing power changes with the beta band range in the following experiments. The temporal window was generally defined by the epoched structure of the

experimental tasks or across the entire data-set during resting-state analysis. Spatial sampling is a trade-off between resolution, computational expense and smoothing of results; through most of the brain, MEG data have been demonstrated to have a smoothness of < 8 mm [Barnes et al., 2004]; 3D grid-steps between 6 and 8 mm were variably chosen in the following experiments.

2.4 Statistical Analysis of MEG Signals

MEG experiments, particularly after reconstruction to source-level, generate a wealth of multi-dimensional data that can sustain many complimentary analytic techniques (that may in itself contribute to selective reporting and the risk of type I errors in neuroimaging [Eklund et al., 2016]). The corollary of such rich datasets is that probability estimates for any particular MEG data feature often warrant severe multiple comparison correction and therefore, without *a priori* restriction of inference to a given sub-set of the feature space, null results may also be common-place [Bender and Lange, 2001].

One solution to this dilemma is to use multivariate statistical techniques. Cluster-based permutation testing is an appropriate means by which to control the false-positive technique [Maris and Oostenveld, 2007], comparing acquired data to Monte Carlo generated random permutations of the data, either in temporal or frequency dimensions (or both). The spatial distribution of an effect measured by MEG can also be permuted in space, making use of established MRI tools such as FSL's *Randomise*, but this application was computationally limited to 3D space only (ie averaged within a specific time period of interest or across the whole temporal series, for a specific frequency band of interest). Where possible, threshold-free cluster enhancement (TFCE) was preferentially used as this provides a more unbiased estimate of null probabilities that is equally applicable to electrophysiological data [Frehlich et al., 2016] as to fMRI [Smith and Nichols, 2009].

Chapter 3 Altered Cortical Beta-Band Oscillations Reflect Motor System Degeneration

The experiment described in this chapter investigates the effect of ALS on fundamental neural mechanisms that sub-serve movement – modulation of cortical oscillations within the beta-band.

3.1 Background

3.1.1 Movement-Related Cortical Oscillations

Direct non-invasive recording of cortical neurophysiology supplements existing functional MRI findings by harnessing millisecond temporal precision at the expense of reduced spatial resolution, although MEG does allow neural signal analysis from anatomically relatively precise cortical structures. Movement preparation and execution are consistently associated with modulations to motor and premotor neuronal oscillation power, particularly within the beta-band (15 - 30 Hz) [Pfurtscheller and Lopes Da Silva, 1999]. Beta-band limited power is initially reduced (alternatively described as desynchronisation), but after movement termination a relative increase (or synchronisation) in power follows, accompanied by fluctuation in corticospinal excitability [Chen et al., 1998; Fry et al., 2016; Kilavik et al., 2013]. As well as their potential as biomarkers, such signals are of heightened relevance in ALS given their proposed use as a user input to brain-computer interfaces in the advanced stages of disability [Grosse-Wentrup and Schölkopf, 2014; Huang et al., 2012b; Kasahara et al., 2012].

However, precise physiological functions of beta oscillations and their task-related modulations remain uncertain. More intense beta desynchronisation is induced as movements require more force [Stančák et al., 1997], speed [Toma et al., 2002] or complexity [Hummel et al., 2003; Manganotti et al., 1998]. Conversely, exaggerated and overly consistent beta synchrony is anti-kinetic, whether driven by Parkinson's disease

pathology [Little et al., 2012] or direct stimulation [Pogosyan et al., 2009]. Physiological beta synchrony is promoted in expectation of impending perturbation to a desired posture [Androulidakis et al., 2007] but is also sensitive to the uncertainty of motor outcome estimation [Tan et al., 2016]. Beta oscillations may also contribute to long-range communication across cortical regions [Engel and Fries, 2010; Kopell et al., 2000] and can facilitate modulation of selective attention in support of action selection [Grent-'t-Jong et al., 2013; Grent-'t-Jong et al., 2014; Tzagarakis et al., 2010], beyond simple correlation with reaction times [van Ede et al., 2012].

3.1.2 Cortical Neurophysiology in ALS & PLS

Previous EEG investigations in ALS largely focused on evoked movement-related cortical potentials (MRCPs), time-locked to movement onset and averaged over many trials. The impact on these measures appears most prominent in patients with a high burden of UMN dysfunction [Bizovičar et al., 2013; Inuggi et al., 2011; Westphal et al., 1998], with MRCPs particularly reduced in patients with PLS [Bai et al., 2006]. Event-related potentials (ERPs) have also revealed abnormal neural correlates of attention control [Pinkhardt et al., 2008], particularly within a bulbar-onset sub-group [Mannarelli et al., 2013]. The experimental design detailed in the current chapter permitted assessment of neuronal function during a period of motor preparation, independent of and temporally distinct to subsequent motor performance, thus minimising the potentially significant confound of group differences in motoric activity.

Two EEG studies have directly considered the effect of ALS on movement related modulation of beta oscillations. Reduction in cortical post-movement synchronisation (termed post-movement beta rebound, PMBR) was identified in both studies, but conflicting conclusions drawn regarding the integrity of peri-movement event-related desynchronisation (ERD) [Bizovičar et al., 2014; Riva et al., 2012]. The present study

applied the combined temporal and spatial resolution uniquely afforded by MEG to a group of both typical ALS and PLS patients. The central hypothesis was that alterations to cortical beta-band oscillations may reflect pathological cortical hyperexcitability, which is an early and distinguishing feature of ALS and related phenotypes (Geevasinga *et al.*, 2015). A group of asymptomatic ALS gene mutation carriers (AGCs) was included to appraise the sensitivity of MEG in the detection of cortical pathology prior to the development of overt symptoms.

3.2 Methods

3.2.1 Participants

Apparently sporadic ALS and PLS patients (ie without a family history of ALS or FTD), both prevalent and incident cases, were recruited from a tertiary referral clinic as a component of the Oxford Study for Biomarkers in Motor Neurone Disease ('BioMOx'). Diagnosis was confirmed by one of two experienced neurologists according to consensus criteria [Brooks *et al.*, 2000; Gordon *et al.*, 2006]. Six of the ALS patients were taking riluzole at the time of study. Healthy controls, typically spouses of patients, were similar in age, handedness and level of education. AGCs included were recruited locally, and through collaboration with the Pre-symptomatic Familial ALS (Pre-FALS) study [Benatar and Wu, 2012]. Participants from the Pre-FLAS study travelled to Oxford for both MEG and MRI. Demographics for all participant groups are detailed in **Table 3.1**. Twelve ALS and 10 PLS patients underwent MEG acquisition. One ALS participant was excluded from analysis after failing to recognise the laterality of the cue. MEG source-space variance maps for one PLS participant revealed heavy artefact contamination. Therefore, MEG data from the remaining 11 ALS patients (9 male, mean age 63.5 ± 7.6 years) were contrasted against nine patients with PLS (2 male, 59.6 ± 8.0 years) and 10 age-matched healthy controls (4 male, 61.7 ± 9.3 years). Twelve asymptomatic gene carriers (AGCs) (2 male, 51.7 ± 9.9 years, 10 *SOD1*, 2 *C9orf72*) were contrasted against another age-matched

selection of 10 healthy controls (3 male, 51.0 ± 9.5 years). Six of the healthy controls were included in both age comparators.

$\pm SD$ (range)	ALS (n = 11)	PLS (n = 10)	Asymptomatic GC (n = 12)	Controls Old (n = 10)	Controls Young (n = 10)
Age (years)	63.5 $\pm$ 7.6 (48:74)	60.4 $\pm$ 8.0 (44:70)	51.7 $\pm$ 9.9 (36:66)	61.7 $\pm$ 9.3 (45:75)	51.0 $\pm$ 9.5 (37:64)
Gender	9 M : 2 F	3 M : 7 F	2 M : 10 F	4 M : 6 F	3 M : 7 F
Handedness	11 R	10 R	12 R	9 R : 1 L	8 R : 2 L
Site of Onset or Genetics	1 bulbar 2 respiratory 1 RUL, 3 LUL 2 RLL, 2 LLL	1 bulbar 2 both legs 2 RLL, 5 LLL	9 SOD-1 2 C9orf72	N/A	N/A
ALSFRS-r	34.8 $\pm$ 8.8 (21:48)	33.4 $\pm$ 8.4 (18:43)	N/A	N/A	N/A
Disease Duration from Symptom Onset (months)	23.7 $\pm$ 18.9 (5 :72)	113.7 $\pm$ 78.6 (47:283)	N/A	N/A	N/A
Progression Rate (48 – ALSFRS-R / duration in months)	0.79 $\pm$ 0.69 (0 : 2.4)	0.13 $\pm$ 0.11 (0.02 : 0.4)	N/A	N/A	N/A
Cognition %	84.8 $\pm$ 8.5 (69:95) (10 ECAS, 2 ACE-r)	84.4 $\pm$ 10.3 (73:98) (8 ECAS, 2 ACE-r)	91 $\pm$ 4.5 (80:97) (11 ACE-r)	96.1 $\pm$ 3.1 (91:100) (9 ACE-r)	96.3 $\pm$ 2.4 (92:99) (8 ACE-r)

Table 3.1: Demographic and clinical details.

Clinical and cognitive assessments were performed on the same day as MEG acquisition. Contemporaneous T1-weighted structural MRI scans were acquired for co-registration with the MEG data (3T Siemens Trio, MPRAGE sequence). Three ALS patients were unable to tolerate MRI, and a standard MNI template was instead used for MEG co-registration. An additional healthy control was excluded due to incidental white-matter changes. Disability was assessed using the ALSFRS_r, and cognitive function was predominantly assessed using the ECAS [Abrahams et al., 2013], or the revised Addenbrooke's Cognitive Examination (ACE-R) [Mioshi et al., 2006] for those cases studied prior to development of the ECAS. Rate of disability progression (Δ ALSFRS_r) was calculated as the decrease in ALSFRS_r from a presumed baseline score of 48, divided by the disease duration in months from reported symptom onset. A measure of the burden of clinical UMN signs was based upon a pathological reflex sum score [Menke et al., 2014; Turner et al., 2004]

All participants provided written informed consent. All aspects of the studies described in the current and following chapters were approved by the National Research Ethics Service South Central Oxford Research Ethics Committee B (08/H0605/85), and South Central Berkshire Committee (14/SC/0083).

3.2.2 Experimental Design and Acquisition

A Go-NoGo task was designed to investigate neural activity related to spatially selective motor preparation. Monochromatic visual cues, with one side shaded indicating the hand to be moved, were presented foveally for 200 ms, followed by an inter-stimulus interval (ISI) of either 1 or 2 seconds, during which a central fixation cross remained. After the variable time period of lateralised motor preparation, the fixation cross was replaced by either a green 'Go' circular target in 80% of trials, or a red 'NoGo' target in 20% (randomly distributed) (**Figure 3.1**).

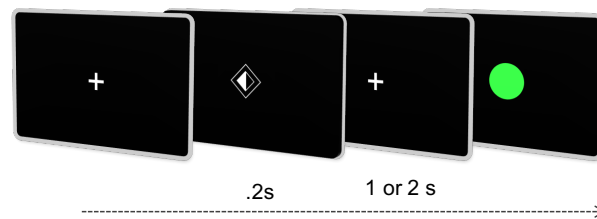


Figure 3.1: On-screen visual cues for the go/noGo task.

The figure demonstrates a single trial in which the left hand is cued for a short interval (inside of diamond is filled) followed by a Go target (noGo targets coloured red).

Participants were instructed to make rapid responses to just the ‘Go’ targets by lifting and replacing the index finger of only the prepared hand. Trials were randomly distributed in laterality and ISI duration. A maximum of three blocks of 100 trials (median inter-trial interval 6.25 s) were acquired per participant. Fatigue limited acquisition to two blocks in one PLS patient. Each block lasted ~12 min. Stimuli were created in Matlab and presented via the Psychtoolbox package [Brainard, 1997].

Participants were seated comfortably in the MEG scanner, 90 cm away from a back-projected screen (Panasonic PT D77OOE). Behavioural responses were measured using a fibre-optic sensing device, and confirmed by off-line inspection of surface electromyography (EMG) traces recorded from the extensor digitorum communis. To ensure that participants were engaged in motor preparation, only those trials in which correct responses were confirmed were included in subsequent analyses.

3.2.3 Preprocessing & Source Analysis

Data were then epoched according to the time period of interest (including a one second pre-cue baseline period) for subsequent analysis. Alongside behaviourally incorrect trials and those with premature responses identified by surface EMG, epochs contaminated by artefact were identified by an automated rejection tool, and removed from the analysis. This comprised 1.3 % of trials, on average, over subjects. Epochs were centred on either (1) the preparatory cue, to investigate neural correlates of motor preparation, (2) response

time, to investigate motor execution while accounting for differences in reaction time, (3) movement termination time, to investigate PMBR or (4) target appearance, to investigate successfully withheld ‘NoGo’ trials.

A LCMV scalar beamformer [Robinson and Vrba, 1999; Van Veen et al., 1997] was used via a single-shell forward model [Sarvas, 1987] to project pre-processed MEG data, bandpass filtered between 15-30 Hz, onto a regular 3D grid spanning the entire brain. Estimates of the data covariance matrix were regularized by removing the weakest PCA components [Woolrich et al., 2011] to leave only 61 (the approximate rank of the data after the use of Maxfilter and removal of two ICA components pertaining to a) ECG and b) eye-movement artefacts). Cue, response and movement termination locked epochs were then inspected across 8-mm whole-brain grids to locate subject specific, functionally defined regions of interest (ROIs) corresponding to cortical motor regions: for each subject, the MNI coordinates pertaining to the maximal preparatory ERD, response ERD or PMBR were selected for each hemisphere (locations depicted in **Figure 3.2**).

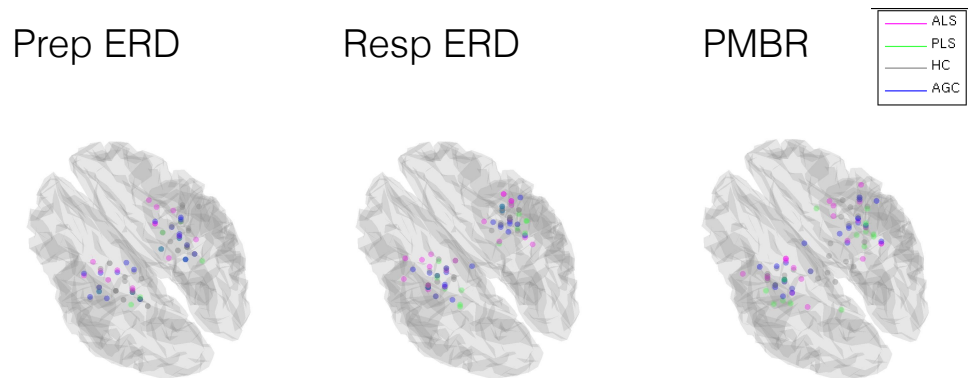


Figure 3.2: Functionally defined ROI locations
Separate per participant ROIs were defined for each epoch of interest.

Neural signals from these pairs of voxels were carried forward from each subject for comparison of timecourse dynamics. Note that an alternative analysis using the first

principal component of the signals from the surrounding voxels within an 8 mm radius, yielded similar results (data not shown).

Time-frequency transformations as implemented in the FieldTrip toolbox were then applied. Hanning tapers of length 300 ms at 50 ms intervals within a frequency range 4–45 Hz were used to reveal the spectral distribution of ERD/S, and multitapers centred at 21.5 Hz with 8.5-Hz frequency smoothing were used to display the timecourse of beta-band power. Summary values for preparatory beta ERD (baselined mean value over 0 – 1.2 s post-cue), response ERD (± 200 ms around response), baselined PMBR (0.15 to 1.5 s from response completion) and PMBR laterality (1 to 2.5 s from response completion) were generated per participant from the voxel ROI data for subsequent clinical correlation (response ERD ROI used for PMBR laterality). Cluster-based permutation statistics as implemented in FieldTrip [Maris and Oostenveld, 2007] were used to compare the main task effects between participant groups. For exploration of non-normal outcome measures, Kendall's Tau was chosen to assess the (uncorrected) 2-tailed significance of correlations (SPSS, IBM Inc.).

Whole-brain source-space data (beta-band, 15–30 Hz) were also compared across groups using a mass univariate trial-wise general linear model (GLM) approach [Hunt et al., 2012; Woolrich et al., 2009]. The trial-wise GLM consisted of different regressors that picked out the trials that corresponded to left and right lateralisation, and 'NoGo' and 'Go' conditions. First-level (within-subject) contrasts of parameter estimates (COPEs), were then calculated comparing either left or right lateralised effect against baseline, or successfully withheld 'NoGo' effect either against baseline or against 'Go' effect. The first-level COPEs were averaged over repeated sessions to compute subject-level means, which were in turn passed into the group-level subject-wise GLM. Group-level regressors were set to model the group means and group contrasts set to detect group differences

using unpaired t-tests. Prior to passing subject-level COPEs to the group-level analysis, they were transformed such that only left-hand preparation/response source-space COPEs were flipped around the medial surface (ie around the x-axis in MNI coordinates). This enabled merging of both response lateralities into contralateral and ipsilateral hemispheres, relative to the effector limb. 4D spatiotemporal maps were averaged across selected time windows of interest, corresponding to the all-subjects combined group's maximal ERD following appearance of cue/target, or corresponding to (individual trial specific) response onset/offset. The resulting 3D maps were compared between groups using cluster-based permutation statistics (Randomise, FSL), with a pre-defined cluster-forming threshold ($t\text{-stat} = 2.4$) and 10,000 permutations with 100-mm of spatial smoothing applied to the variance of the COPE to improve the effective degrees of freedom. Given the strong *a priori* expectation that group differences would be prominent within the motor cortices, group comparison was restricted to an anatomically confined binary mask encompassing bilateral motor areas.

The extent to which PMBR was confined to the contralateral motor cortex was investigated using three independent measures of 'degree of lateralisation' (DoL). Firstly, dynamic beta power timecourses from each subject's motor ROI were contrasted as a percentage $((\text{contra-ipsi}) / (\text{contra+ipsi}))$ prior to group comparison over time. Secondly, a 3D voxel-wise lateralisation effect was calculated over the time-averaged period of maximal PMBR (1:2.5 s post movement). The resultant subject specific DoL spatial map was contrasted between groups using cluster-permutation tests as above. Lastly, the correlations between fluctuations of beta power in the same PMBR time period were assessed. Using anatomical parcels (from the Harvard-Oxford cortical structural atlas), time-courses for each motor cortex were extracted by taking the first principal component over the enclosed voxels, using an orthogonalisation procedure to correct for spatial

leakage from surrounding anatomical parcels [Colclough et al., 2015]. Correlations were taken between the Hilbert power envelopes of these corrected signals and converted to normal variates with Fisher's transformation. These correlations were averaged within subjects and contrasted between groups, performing inference with 5000 permutations of the subject labels.

The expected oscillatory signature of response inhibition has been shown to involve an augmentation of beta power relative to unsuccessful inhibition [Huster et al., 2013]. The parcellation, orthogonalisation and correlation method was additionally applied to an exploratory analysis of 'NoGo' trial epochs, assessing the functional connectivity between the motor cortices and two anatomical regions commonly implicated in response inhibition: the supplementary motor area (SMA) and right inferior frontal cortex (rIFC) [Aron et al., 2014].

3.3 Results

Data from 47 individual participants were available for analysis.

3.3.1 Behavioural

ALS patients tended to complete fewer correct 'Go' responses than other groups, but this did not distinguish the groups in ANOVA statistics (mean number of responses per ALS participant $196 \pm$ standard deviation 66) from a maximum possible 240 (healthy controls 228 ± 18 , $p = 0.14$). An effect of group membership was noted on response times (RT), $F(4,42) = 5.44$, $p = 0.001$, **Figure 3.3A**. PLS patients responded the slowest (623 ms, significantly slower than older controls, 440 ms, $t(18) = -2.98$, $p = 0.016$) and AGCs the

fastest (377 ms, not significantly faster than younger controls, 434 ms, $p = 0.17$).

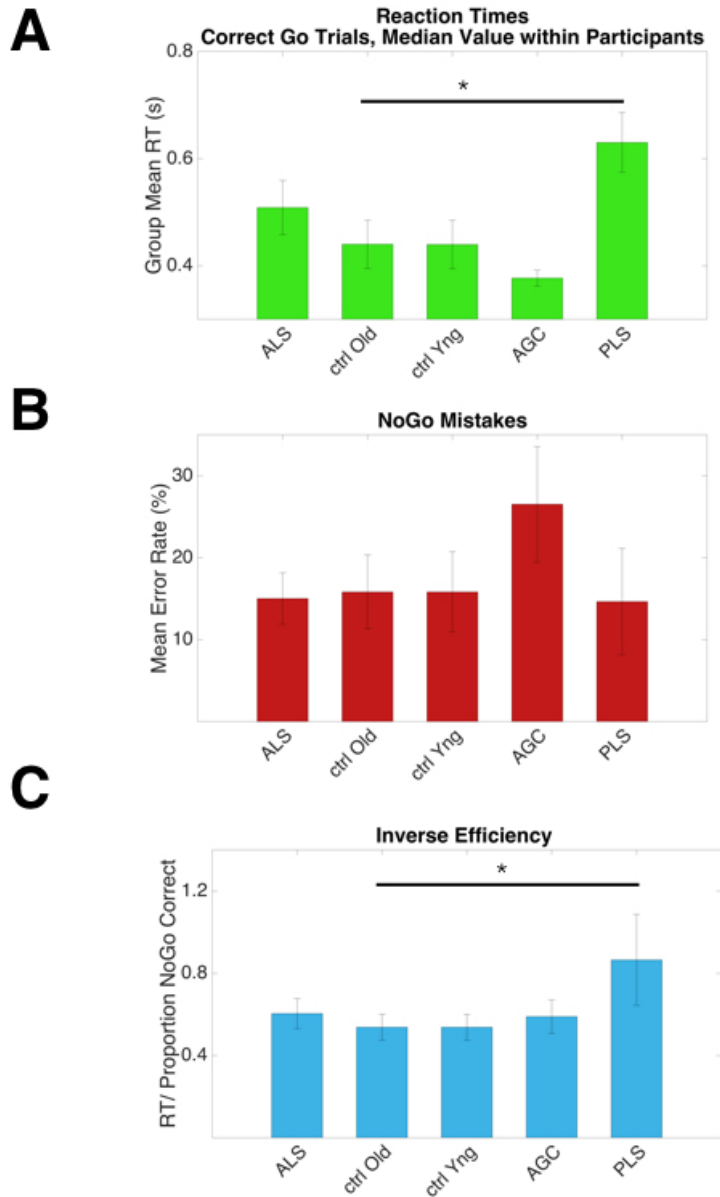


Figure 3.3: Behavioural data

Summary of task performance across groups. A) PLS patients responded slower than older controls, $p = 0.016$ B) A trend towards more NoGo errors was made by pre-symptomatic carriers. C) Inverse efficiency, a global measure of task performance (RT/NoGo proportion correct) was impaired in the PLS group ($p = 0.025$). Median values within participants, mean values within group, error bars = SEM. Uncorrected for multiple comparisons.

Throughout the groups there was a significant effect of ISI duration on RT, such that participants were on average 35 ms faster following the longer ISI ($F(1,42) = 19.0$, $p < 0.001$). There was no group by ISI duration interaction.

The AGC group mean for erroneous responses on ‘NoGo’ trials was the highest at 26.5 %, although not significantly more so than healthy controls (10.6 %, $p = 0.08$, uncorrected, **Figure 3.3B**). A global measure of task performance, inverse efficiency, was calculated as $RT / \text{‘NoGo’ proportion correct}$. PLS patients performed worse relative to older controls (Wilcoxin RankSum $Z = 2.25$, $p = 0.025$, uncorrected, **Figure 3.3C**).

An increase in RT in the ‘Go’ trials following a ‘NoGo’ trial by 20 ms on average was consistently seen across all groups (**Figure 3.4**). This was an expected behavioural effect, equivalent to motor slowing induced by novel stimuli [Wessel and Aron, 2013], errors or greater cognitive demands [Gratton et al., 1992].

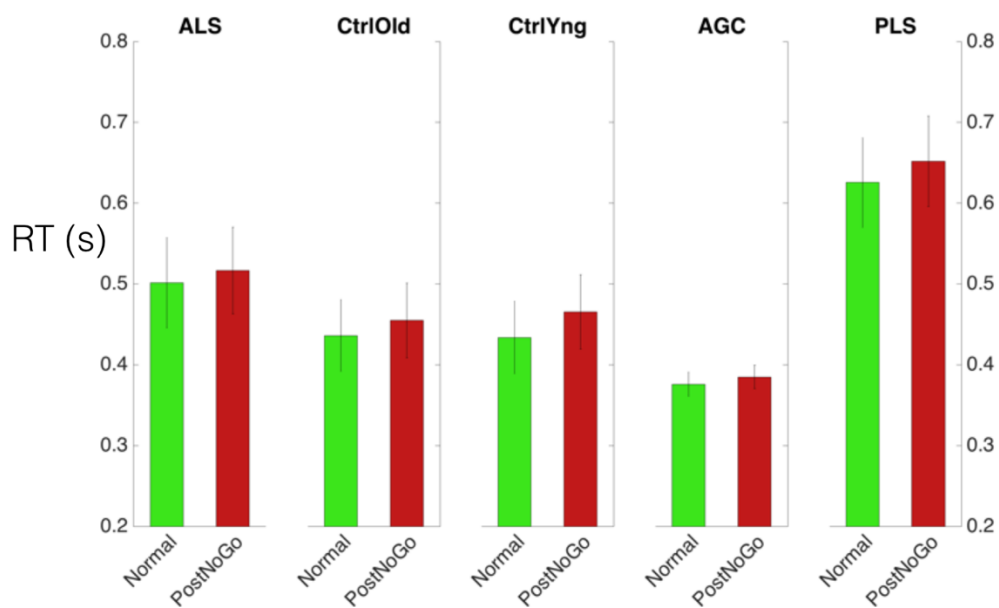


Figure 3.4: Post noGo slowing.

Go trials following a noGo trial typically feature slowed response latency, all groups displayed this behavioural effect.

3.3.2 Motor Preparation

Lateralised cortical changes in preparation for movement occurred shortly after cue processing in the form of regional beta-band desynchronisation. All groups demonstrated this preparatory beta-desynchronisation, which was maximal at around 600 ms following cue onset (healthy control data from motor ROIs shown in Figure 3.5A), and was more

prominent in the motor cortex contralateral to the prepared limb. No significant group differences were immediately apparent in the intensity of the preparatory beta desynchronisation from subject-specific functionally defined ROIs (Figure 3.5B,C). However, analysis of whole-brain MEG data, time-averaged around the maximal beta desynchronisation (t_0+500 ms : t_0+700 ms. t_0 = cue onset), revealed ALS patients to exhibit regions with significantly increased beta desynchronisation relative to controls, within (but not restricted to) both the contralateral and ipsilateral precentral gyrus ($p = 0.031$, Figure 3.5D). Directionally similar trends were noted in both PLS and AGC groups.

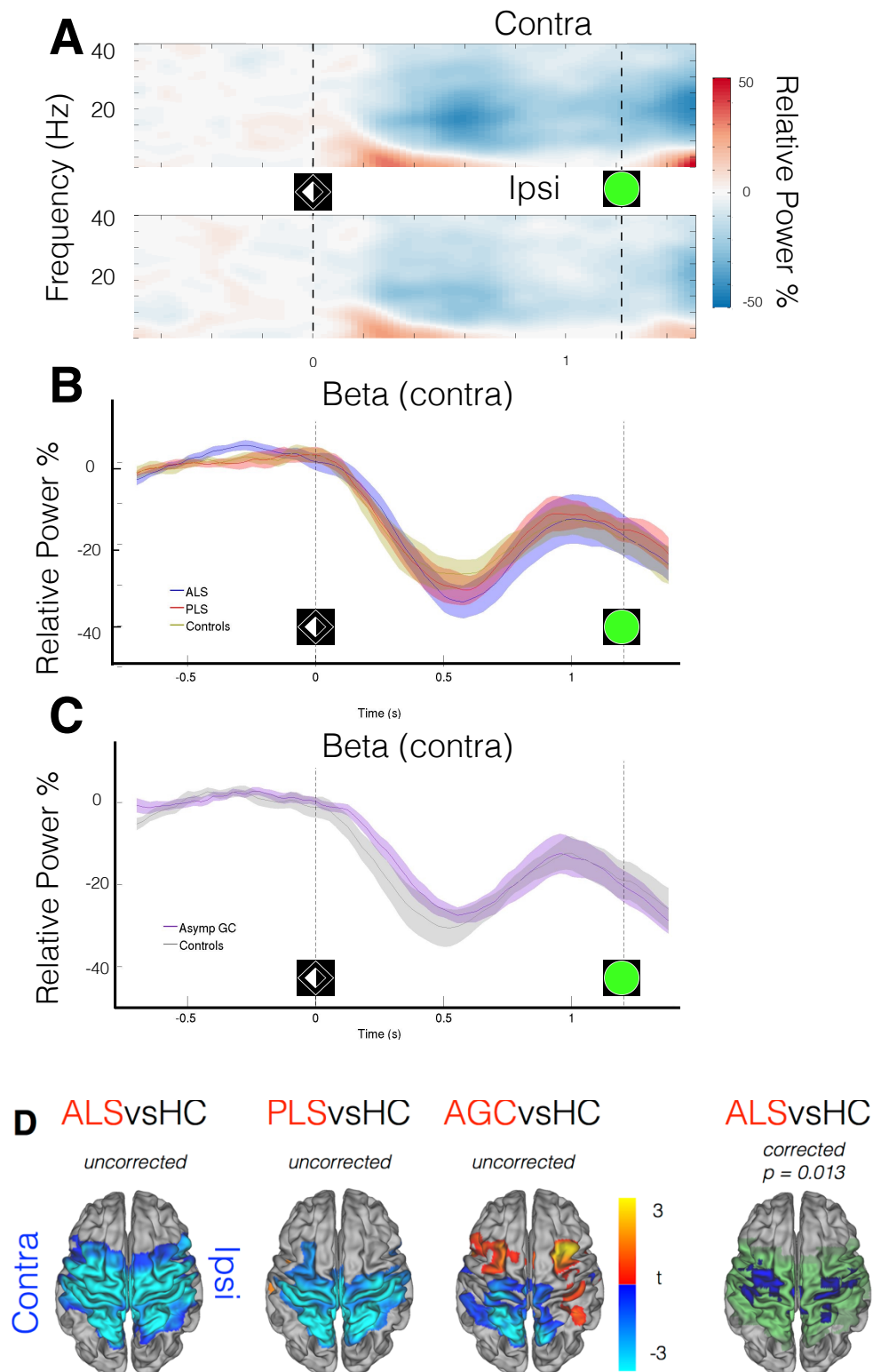


Figure 3.5: MEG data epoched around cue

t_0 = laterality cue appearance. A) Neural correlate of task performance across frequency range demonstrated in time-frequency representation (healthy controls only) from motor cortex ROIs, contra/ipsilateral relative to effector limb. Beta-band (15:30Hz) power decrease (desynchronisation) from baseline (more intense desynchronisation = deeper blue) occurs during motor preparation, particularly in the contralateral hemisphere, maximally 600ms post-cue. B&C) Beta-band power (relative to baseline) within contralateral motor cortex ROI, group comparisons. D) ALS patients show deeper beta desynchronisation. $t_0+500ms$: $t_0+700ms$. t stats in red/blue, motor cortex mask in green. Cluster correction within motor cortex mask, not across groups. Vertical lines denote appearance of visual laterality cue and go/noGo target.

3.3.3 Motor Execution

As a unilateral limb movement was executed, beta desynchronisation became more focal within the motor cortices, yet also more bilateral (control time-frequency representation (TFR) **Figure 3.6A**). The timecourse of the peri-response beta desynchronisation from the contralateral motor cortex ROI revealed it to be preserved in both ALS and PLS patient groups (**Figure 3.6B**). The peri-response beta desynchronisation extracted from the ROI appeared deeper within the AGC group although not significantly so ($p = 0.590$) (**Figure 3.6C**). Group contrasts were then statistically appraised in whole-brain data (t_0 : $t_0 + 200$ ms. t_0 = response). Although ALS patients exhibited only a trend towards deeper beta-desynchronisation, AGCs demonstrated regions with significantly deeper beta desynchronisation than controls over a large cortical area encompassing both motor cortices ($p = 0.013$, **Figure 3.6D**). This result was qualitatively similar after exclusion of the two *C9orf72* AGCs. No significant differences were found between PLS patients and controls.

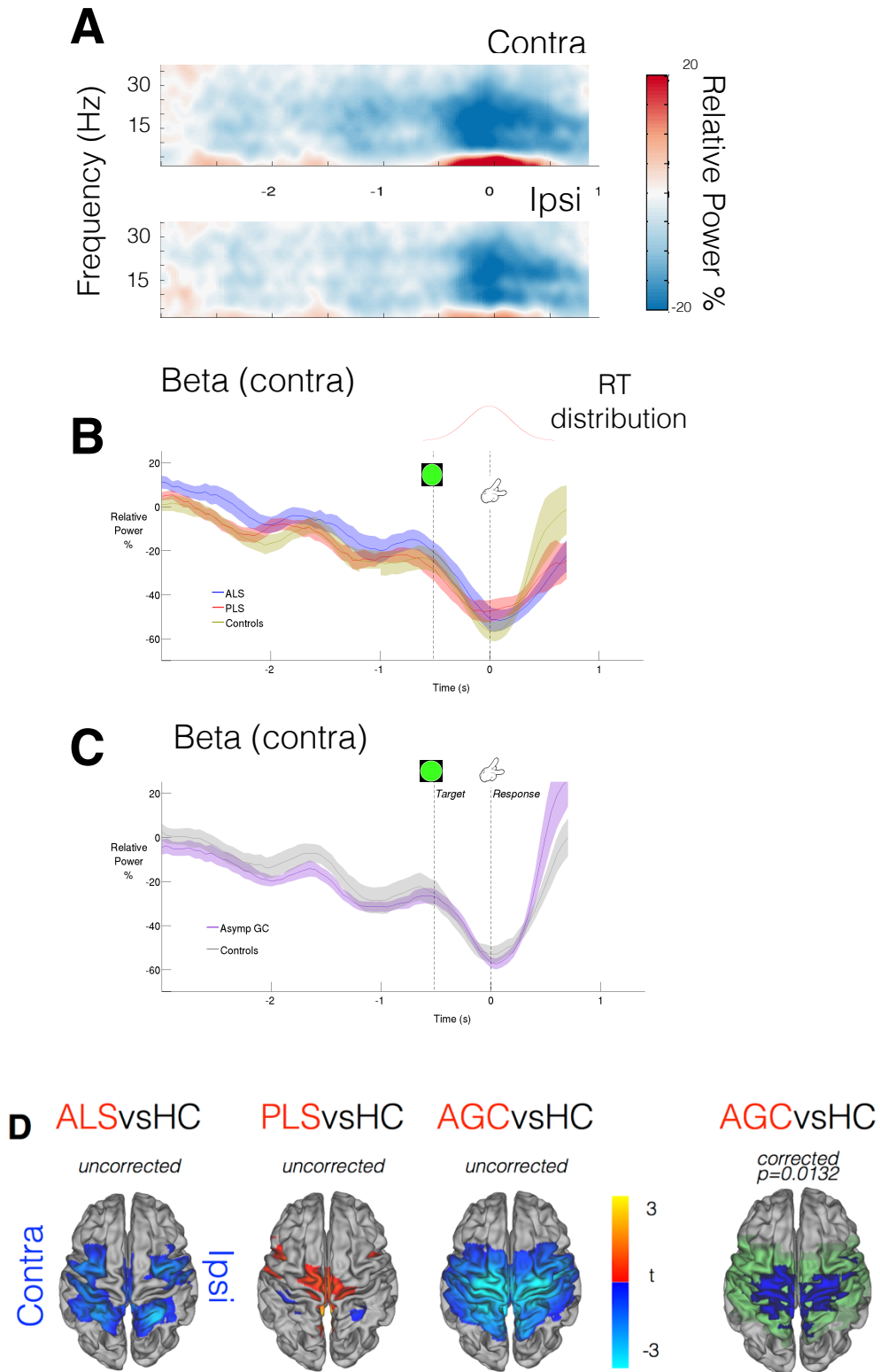


Figure 3.6: MEG data epoched around movement initiation

t_0 = response execution. *A*) Time-frequency representation from healthy controls demonstrates movement-related desynchronisation (ERD, in blue) as a bilateral motor cortical event. *B* & *C*) Beta-band power (relative to baseline) within contralateral motor cortex ROI; group comparison. Vertical lines indicate cue onset prior to median response time (distribution overlaid) *D*) AGCs show deeper beta desynchronisation [$t_0 : t_0 + 200\text{ms}$] relative to controls, with a directionally similar trend in ALS patients. t stats in red/blue, motor cortex mask in green. Vertical lines denote appearance of Go target and timing of response.

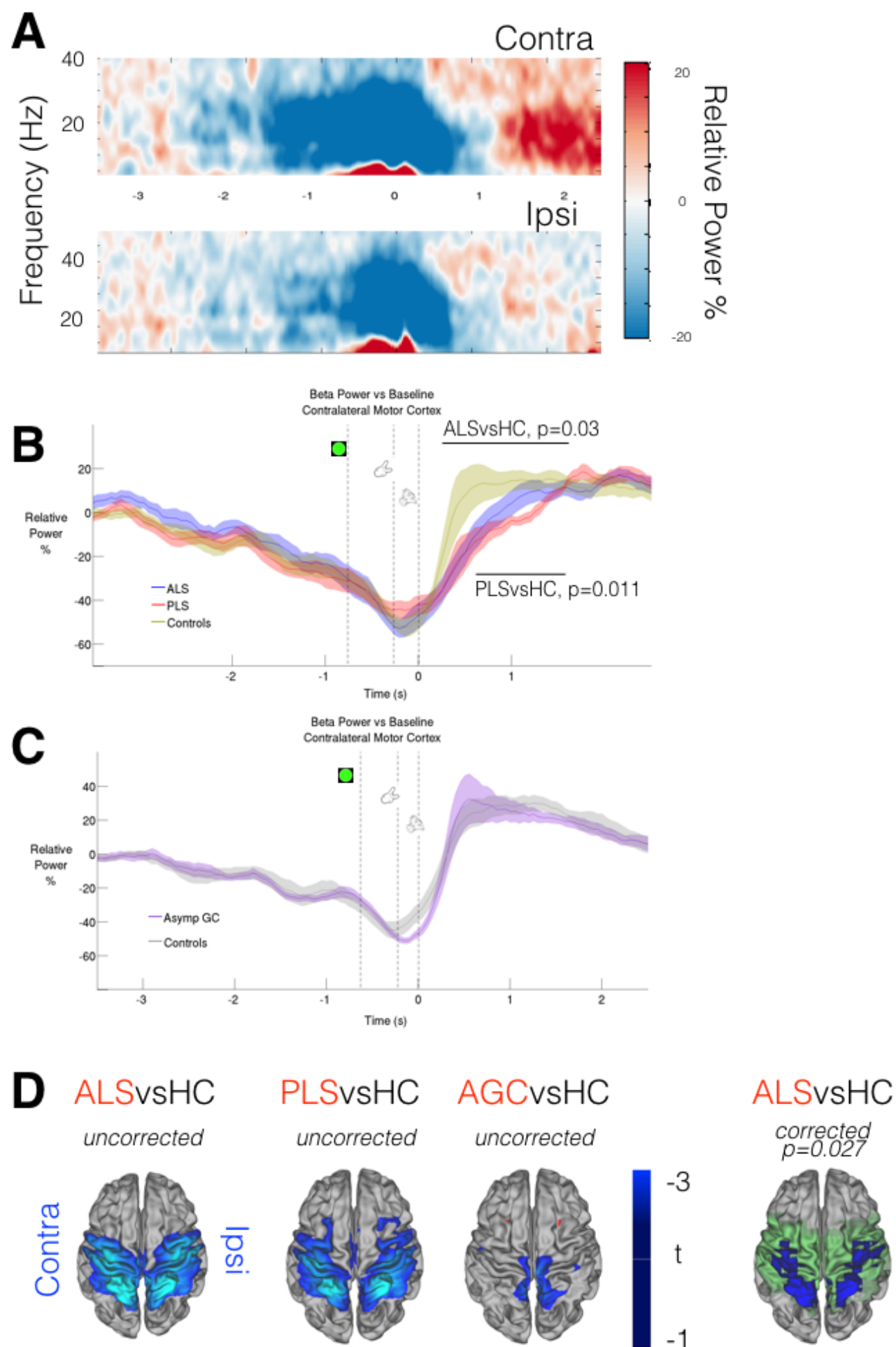
3.3.4 Post Movement

Post-movement beta rebound was expected to be observed from 500 ms after termination of EMG activity, and typically lateralised to the contralateral precentral gyrus [Cheyne, 2013] (control group TFR **Figure 3.7A**). Group differences in movement duration ($F(3,46) = 2.3$, $p = 0.07$) were accommodated by again realigning data epochs (t_0 = movement completion, as indicated by the fibre-optic trigger). An expected correlation was found between RT and both EMG peak amplitudes (Kendall $\tau_b(47) = 0.29$, $p < 0.001$), and speed of transition in the contralateral motor cortex from ‘beta desynchronisation’ (ERD) to post-movement ‘beta rebound’ (PMBR) ($\tau_b(47) = 0.25$, $p = 0.0045$) [Erbil and Ungan, 2007; Stancák and Pfurtscheller, 1996]. Inspection of beta power timecourses from the contralateral motor cortex confirmed significantly delayed beta rebound in both ALS (cluster permutation of groups, $n = 11/10$, $p = 0.03$) and PLS ($n = 10/10$, $p = 0.011$) patients (**Figure 3.7B**).

AGCs showed a more rapid and increased amplitude beta rebound, though the effect only tended toward statistical significance ($p = 0.062$, **Figure 3.7C**). Given this unexpected result in the AGC group, averaged rectified surface EMG timecourses were inspected, and confirmed faster EMG onset/offset relative to controls (**Figure 3.8**). Given that the transition from beta desynchronisation to beta rebound is a dynamic process, whole-brain analysis was focused on the initial time period of beta rebound ($t_0 + 500$ ms : $t_0 + 700$ ms). During this period, ALS patients were confirmed to exhibit regions with significantly reduced beta power ($p = 0.028$) relative to controls (**Figure 3.7D**), with a directionally similar trend in PLS patients.

Beta rebound in both patient groups was additionally noted to be less lateralised, most marked in the PLS patients. This was confirmed in both beta power timecourses from the subject-specific functionally defined motor ROIs (cluster permutation of groups, $n =$

10/10, $p = 0.017$, **Figure 3.7E**) and in the voxel-wise spatial maps of DoL (**Figure 3.7F**). Finally, the inter-hemispheric correlation between beta power timecourses (extracted from the anatomically defined motor cortex parcels, $t_0 + 1 \text{ s} : t_0 + 2.5 \text{ s}$) revealed significantly higher correlation in both PLS patients (permutation of groups, $n = 10/10$, $p = 0.0054$) and ALS patients ($n = 10/10$, $p = 0.0086$) relative to healthy controls. The implication of this finding is that beta power changes following movement are abnormally coherent between hemispheres in these patient groups. However, functional lateralisation was still evident in the PLS participants' PMBR after a further delay (**Figure 3.9**, shows TFRs for each group) and re-aligning epochs by group to the time-point of maximal PMBR negated the group differences in laterality. Beta rebound lateralisation was unaffected in AGCs.



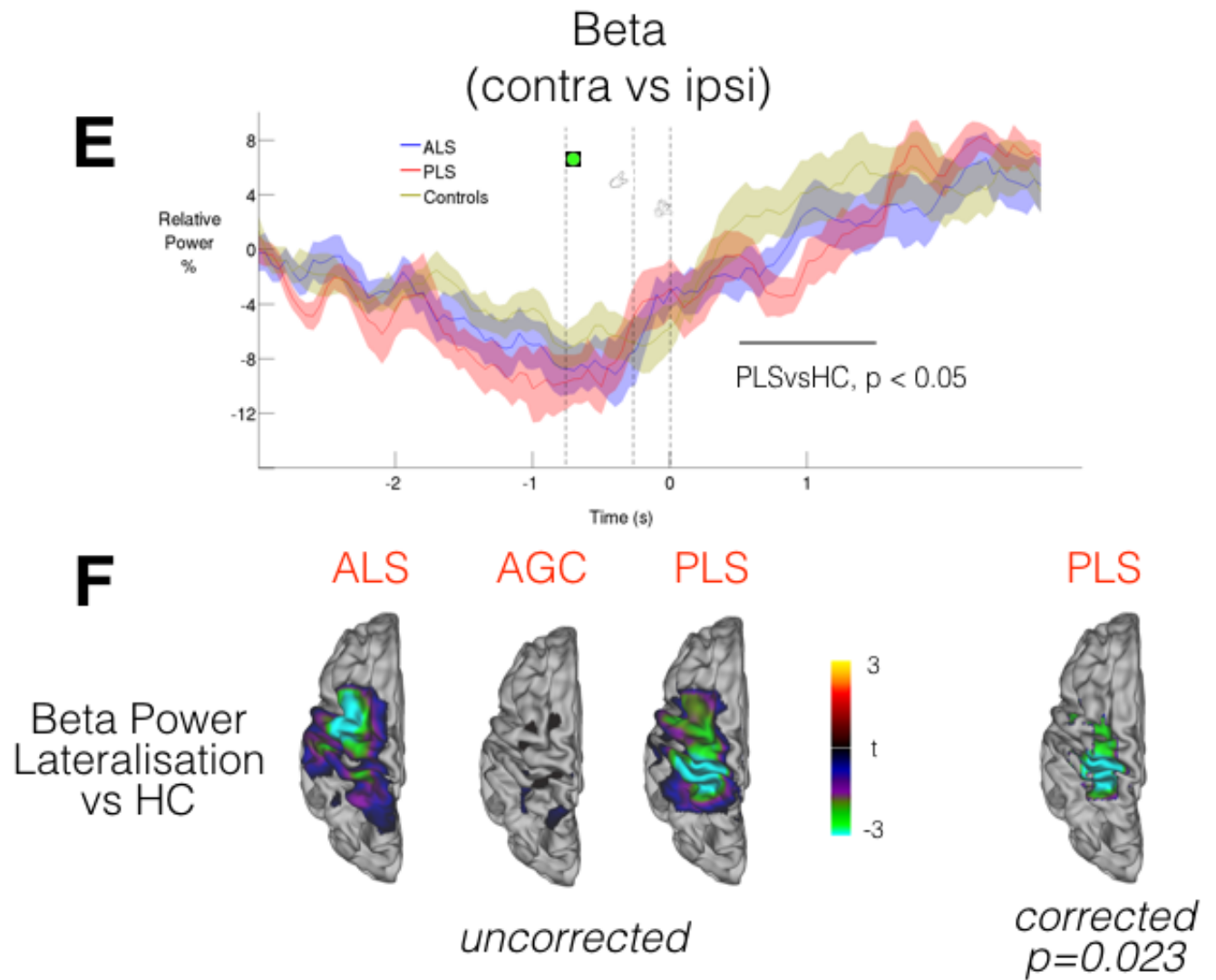


Figure 3.7: MEG data epoched around movement completion

$t0$ = finger replaced. A) Time-frequency representation (healthy controls only) from motor cortex ROIs relative to effector limb. Post Movement Beta Rebound (PMBR, in red) is predominantly contralateral in healthy controls. B&C) Beta-band power (relative to baseline) within contralateral motor cortex ROI; group comparison. Black bar = timespan of significant group difference via cluster permutation testing, $p < .05$. Vertical lines denote appearance of Go target, timing of response initiation and completion. D) ALS patients demonstrate lower beta power in early transition to PMBR [$t0+500\text{ms}$: $t0+700\text{ms}$]. t -stats in blue, motor cortex mask in green. E) Beta-band power lateralisation evolves over time around a response, PLS patients show a diminished degree of lateralisation (DoL) during PMBR (black bar, $p < .05$). F) PMBR DoL appraised in whole-brain data [$t0+1\text{s}$: $t0+2.5\text{s}$]. PLS patients again show significantly reduced DoL. t -stats in ROY-BIG-BL.

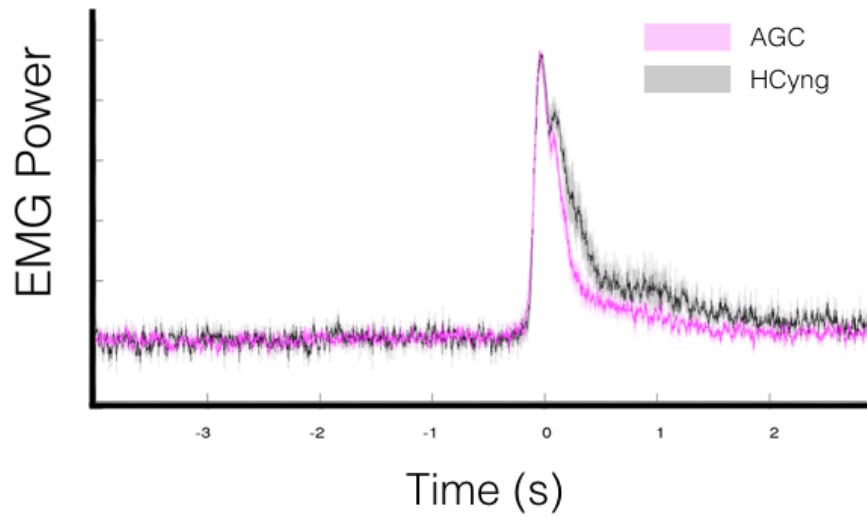


Figure 3.8: Surface EMG power AGCs & HCs.

Data locked to response initiation, rectified, averaged across trials and normalized to individual peak power. The AGC group demonstrate a more rapid return to baseline EMG activity, in line with a faster response execution. This behavioural difference is in keeping with a more pronounced PMBR in the contralateral motor cortex

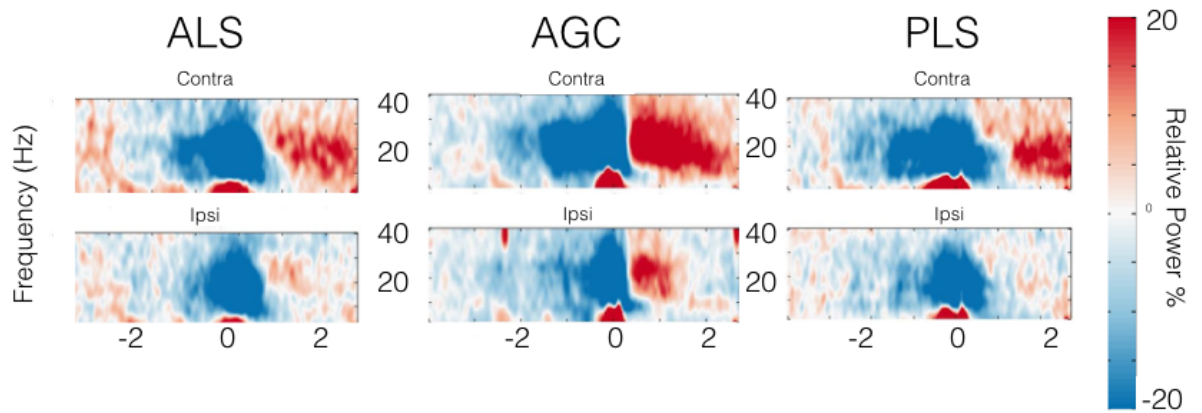


Figure 3.9 MEG TFRs centred on movement completion.

Time frequency representations of MEG data epoched around movement completion. Group averages in ALS and PLS patients, and AGCs. Baseline corrected (relative to pre-cue period).

3.3.5 Movement Inhibition

Available trials in which participants successfully withheld a preeminent motor response after appearance of the ‘NoGo’ target were examined to probe integrity of the inhibitory cortical network. Faster responders made more false alarms on ‘NoGo’ trials, as did those with deeper preparatory beta desynchronisation ($\tau_b = 0.25$, $p = 0.015$). Contrasting

correct ‘NoGo’ trials with ‘Go’ trials within the healthy control group, a relative increase in beta power was revealed in the frontal lobe and pre-motor regions. Data were re-epoched around t_0 = target presentation. The time period (t_0+100 ms : t_0+300 ms) was appraised in whole-brain data, revealing a beta power difference (‘NoGo’ versus ‘Go’ trials, healthy controls only) in clusters overlying the right frontal lobe and left motor cortex ($p = 0.0028$, **Figure 3.10A**).

Group contrasts were restricted to successful ‘NoGo’ trials during which the prepared response was inhibited. Within the same time period, no significant differences between ALS or PLS patients against controls were apparent in the degree to which beta power increased after ‘NoGo’ targets. AGCs however demonstrated a relative increase in beta power in the right lateral occipital cortex, extending to the precuneus ($p = 0.0466$, **Figure 3.10B**). Correlation analysis of beta power dynamics between selected cortical parcels (t_0 : t_0+1 second) also suggested reduced functional connectivity between rIFC and SMA in PLS patients only (permutation of groups, $n = 10/10$, FWE correction for 4x4 edges, $p = 0.042$). No group differences were noted in the correlation between motor cortex parcels, nor between ALS or AGC groups against controls.

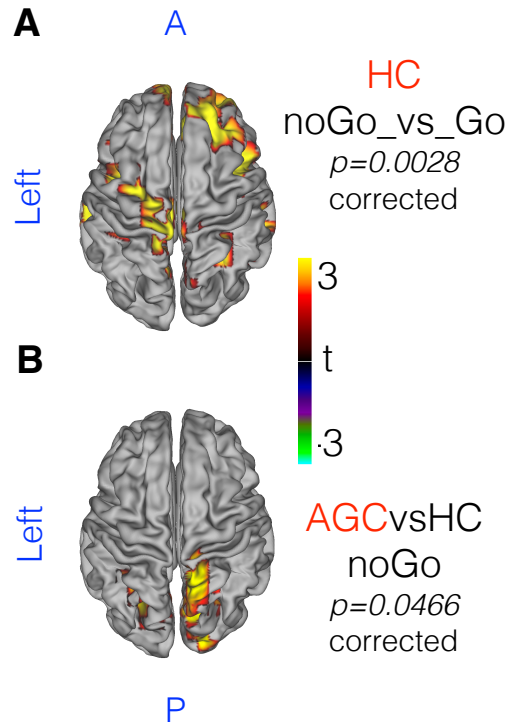


Figure 3.10: MEG data epoched around NoGo target presentation

t_0 = target appearance. Beta-band power increases over a diffuse cortical network in successfully inhibited NoGo trials, demonstrated in A) healthy controls, beta power NoGo > Go. [$t_0+100ms$: $t_0+300ms$]. B) AGCs contrasted against HC, NoGo trials only, reveals increased beta power in posterior cortical regions. No significant differences are noted in ALS or PLS patients. t -stats in ROY-BIG-BL. Whole brain cluster-permutation correction.

3.3.6 Clinical Correlations

Correlations between relevant behavioural measures, summary MEG statistics and clinical metrics are presented in **Table 3.2**. These were exploratory given the small numbers of participants per group, and not corrected for multiple comparisons. Across all patients, slower responses were correlated with increasing ALSFRS_r disability (global $p = 0.005$, upper limb $p = 0.02$) and longer disease duration ($p = 0.038$). Within the ALS group, impaired cognition (% correct ECAS or ACER) tended to correlate with noGo mistakes ($p = 0.073$) as did UMN score ($p = 0.057$). Baseline ERD and PMBR correlated negatively with disease duration ($p = 0.024$) and positively with rate of progression ($p = 0.036$) respectively.

	ALSFRSr Sum	ALSFRSr UL	UMN Score	Disease Duration	Progression Rate	Cognition	Median RT	noGo Mistakes	Preparatory ERD	Execution ERD	ERD Lateralisation	PMBR
ALSFRSr Sum	x											
ALSFRSr UL	.577**	x										
UMN Score	-.333	-.216	x									
Disease Duration	.187	-.112	.000	x								
Progression Rate	-.561*	-.187	.191	-.552**	x							
Cognition	.374	.299	-.191	-.139	.127	x						
Median RT	-.524*	-.785**	.343	.406*	.164	-.345	x					
noGo Mistakes	-.449	-.299	.458	-.011	.164	-.418	.418	x				
Preparatory ERD	.075	.262	.114	-.177	-.127	-.345	-.091	-.018	x			
Execution ERD	-.224	.000	.381	-.368*	-.018	-.309	.164	.236	.673**	x		
Beta Lateralisation	-.337	-.299	.191	-.243	.200	-.018	.236	.236	-.091	-.091	x	
PMBR	-.449	-.150	.000	.014	.491*	-.091	.091	.091	-.345	-.236	.345	x

Table 3.2: MEG

clinical correlations.

Correlations within the ALS patients (Kendall's Tau, uncorrected) between clinical measures, behavioural data and summary MEG statistics extracted from per-subject ROI timecourses. * $p < 0.05$, ** $p < 0.01$.

3.4 Discussion

3.4.1 Summary

The present study used MEG to investigate the neural basis of prepared voluntary movement generation, typified by modulation in beta-band power, revealing abnormalities across the MND phenotypic spectrum.

3.4.2 Disrupted Sensorimotor Rhythms

As reviewed in Chapter 1, direct evidence of cortical hyperexcitability in ALS has been provided by TMS studies [Vucic et al., 2013b], most successfully with conditioning-pulse protocols that reliably demonstrate reduced intracortical inhibition as a characteristic feature of ALS [Menon et al., 2015; Yokota et al., 1996; Ziemann et al., 1997]. Post-movement beta rebound corresponds well to a period of reduced cortico-spinal tract excitability, and the present data suggest that ALS patients differ in the speed of transition to this state after movement. The abnormalities in this characteristic motor system rhythm displayed by ALS patients (amplified beta desynchronisation and attenuated beta rebound) may therefore reflect or even contribute to an excitotoxic degeneration of neural microcircuitry, particularly given the apparent correlation with rate of disease progression. A more simplistic explanation of the beta desynchronisation difference in ALS patients might be the relative cognitive demands and task difficulty in comparison to healthy controls [Schoenfeld et al., 2005]. However, this fails to account for the corresponding abnormalities seen in high-performing AGCs and the lack of excess beta desynchronisation within equally disabled PLS patients. Future studies should reconsider a multimodal approach to the investigation of reduced intracortical inhibition; the aforementioned EEG study [Riva et al., 2012] also performed TMS on the ALS participants and indeed noted post-movement beta rebound to correlate positively with MEP to compound muscle action potential ratio and negatively with central motor

conduction times (CMCTs) but no measurement of short interval intracortical inhibition (SICI) was performed.

3.4.3 The Endophenotype of PLS

The nosology of PLS continues to be debated [Le Forestier et al., 2001; Singer et al., 2007], although some clinical [Gordon et al., 2009; Pringle et al., 1992], neuroimaging [Agosta et al., 2014b; Kolind et al., 2013; Kwan et al., 2013; Müller et al., 2012; Turner et al., 2007] and saccadic [Proudfoot et al., 2015] features support an apparent distinction from ALS. Involvement of the corpus callosum is a consistent feature of ALS [Filippini et al., 2010], thought to contribute to a functional impairment of interhemispheric inhibition, as evidenced by both TMS [Karandreas et al., 2007; Wittstock et al., 2007] and clinically evident mirror movements [Wittstock et al., 2011]. The corpus appears to be a particularly vulnerable structure in PLS [Agosta et al., 2014b; Ciccarelli et al., 2009; Iwata et al., 2011; Kolind et al., 2013] and the finding of delayed lateralisation of beta rebound is entirely in keeping with this observation. ‘Partial’ mirror movements during response epochs were also noted in some patients’ EMG. Previous EEG-based investigation of MRCPs also noted ipsilateral premotor recruitment among ALS patients with high UMN burden [Inuggi et al., 2011]. PLS patients by contrast demonstrated diminished preparatory MRCPs during a self-paced EEG motor task [Bai et al., 2006]. These findings were not in this instance accompanied by any obvious alteration to MRCP topography and beta desynchronisation appeared preserved, highlighting that distinct neural generators underpin each phenomenon [Toro et al., 1994]. The present study did not detect any significant excess in beta desynchronisation intensity between PLS patients and age-matched controls in whole brain data. In contrast to the hyperexcitability typically detected in ALS, the motor cortex of PLS patients is often strikingly resistant to TMS stimulation [Brown et al., 1992; Kuipers-Upmeyer et al., 2001; Zhai et al., 2003], in

keeping with the present PLS data failing to demonstrate additional beta-desynchronisation.

3.4.4 Presymptomatic Cortical Dysfunction?

Characterisation of any pre-symptomatic phase is a priority for all neurodegenerative conditions if preventative strategies are envisaged. Assessment of asymptomatic familial Alzheimer's disease gene carriers has highlighted the added sensitivity of functional neuroimaging [Chhatwal et al., 2013] in keeping with the age-dependent impact of APOE $\epsilon 4$ status on both fMRI [Filippini et al., 2011] and MEG [Cuesta et al., 2015] in the task-free state.

Both patients with ALS and AGCs differ from controls in beta rebound latency, but the group effect directions are divergent. Review of the averaged EMG timecourses revealed that AGC participants completed their responses faster than controls, functionally corresponding to a more rapid transition from beta desynchronisation to beta rebound. However, across all groups EMG metrics and behavioural measures correlated poorly with beta rebound latency and intensity. Conflicting abnormalities between pre-symptomatic carriers and manifest patients have previously been noted on fMRI studies of both Huntington's [Kloppel et al., 2009] and monogenetic Alzheimer's disease [Quiroz et al., 2010], therefore compensatory or pathological neural abnormalities may still underpin these MEG group differences. Slight differences in task performance pose a challenge in the interpretation of functional data from particularly motivated asymptomatic ALS gene mutation carriers. Blinded genetic testing of at-risk individuals is a solution that raises novel ethical considerations as well as practical complexities, especially with regards to future therapeutic trials [Kim et al., 2015].

3.4.5 Does Motoric Inhibition Reflect Executive Dysfunction?

Although cognitively impaired ALS patients are predictably under-represented in demanding functional neuroimaging tasks, comparatively reduced activation in the dorsolateral prefrontal cortex has been demonstrated [Witiuk et al., 2014], while other frontal regions reveal increased activation during inhibition of prepared manual movements [Mohammadi et al., 2015]. The present finding of abnormal beta power in AGCs during successful inhibition was limited to posterior cortical regions in the context of task-induced inferior and pre-frontal activity. Despite previous findings of reduced stop-signal ERPs [Thorns et al., 2010], no abnormalities in beta-band dynamics were noted in ALS patients, so that the changes in AGCs might represent very early compensatory neural changes. In contrast to an ERP study utilising the Stroop task [Amato et al., 2013], but in keeping with eye-tracking findings [Proudfoot et al., 2015], the present data suggest that executive control dysfunction may not spare PLS patients, given that task relevant functional connectivity was diminished between rIFC and SMA. Multiple non-exclusive biological and methodological restrictions may underlie the lack of correlation between the MEG data and cognitive profiles of the ALS participants [Verstraete et al., 2015], not least the brevity of the ECAS test as opposed to more comprehensive and granular neuropsychological assessment.

3.4.6 Study Limitations

These results complement existing EEG based investigations of sensorimotor oscillations in ALS which also found abnormally attenuated beta rebound but did not report increased beta desynchronisation [Bizovičar et al., 2014; Riva et al., 2012]. These previous studies differed from the present investigation not only in acquisition technologies, but also in protocol design by requiring self-paced movements of the right hand only, whereas the present study was a laterally-cued task. It thus facilitated analysis of the specific preparatory period and of hemispheric lateralisation and correlation. Additional analysis

variables pertinent to neural signal interpretation include the selection of baseline period and frequency band of interest. Furthermore, patient groups may differ in the degree to which they actively participate in a task. This severely limits the conclusions that can be drawn even from tasks of motor imagery (Lulé *et al.*, 2007; Stanton *et al.*, 2007; Kasahara *et al.*, 2012). Riluzole administration could possibly dilute the reported ALS group effects, although analysis of the five untreated patients revealed a directionally similar trend. Unique challenges arise in the investigation of a genetically and phenotypically heterogeneous condition such as ALS. Comparative studies against other neurological conditions with significant upper motor neuron burden of disease remain valuable. Furthermore, longitudinal study, particularly of a precisely defined group of AGCs before and after conversion to symptomatic ALS could pinpoint important aetiological pathways but might have restricted relevance to the wider sporadic ALS population.

MEG benefits from improved spatial resolution over EEG, as neuromagnetic signals pass through skull structures without spatial smearing. Reconstruction of the MEG signal into source-space components overcomes the ambiguity inherent in selection of specific EEG sensors, but co-registration errors are still likely to limit precise anatomical conclusions regarding the current group differences. The present methodology included selection of an ROI-based purely on subject-specific functional data, in addition to anatomically defined sources perhaps more vulnerable to co-registration error. Comparison of the present study with an EEG-based replication (same experimental design but no attempt at source localisation) would be a worthwhile given the more widespread availability of EEG, perhaps a more pragmatic option in biomarker-informed future clinical trials.

Chapter 4 Functional Connectivity Changes in ALS Confirmed by MEG

This chapter considers the effects of ALS on long-range cortical communication as measured by MEG during resting-state recordings.

4.1 Functional Architecture of the Human Brain

4.1.1 From Lesions to Connectomes

Everyday clinical practice in neurology remains dependent upon an appreciation of the precise functional specialisation that characterises the mammalian central and peripheral nervous system (CNS and PNS). Localisation of an abnormality within either the CNS or PNS, the ‘lesion’, is a key stepping stone towards diagnostic certainty and subsequent therapeutic optimism. Discoveries in localisation span the early history of neurology from Ancient Egypt through to Paul Broca’s (1828-1880) description of hemispheric dominance for language and then to the unforgettable consequences to personality caused by prefrontal cortex damage [Bigelow, 1850; Damasio et al., 1994; Harlow, 1868].

[Previously] The most efficient and capable *[man]* ... Gage was no longer Gage ...

As the advent of functional neuroimaging heralded a new era of localisation, to the extent that covert cognitive processes might successfully be decoded from signal analysis [Haynes and Rees, 2006], there was simultaneously a growing appreciation of biological systems above a reductionist focus on component parts. Notwithstanding the evident modularity in cerebral anatomy and accompanying functional segregation, complex human experiences and actions also clearly require integration of distributed neuronal sub-populations [Tononi et al., 1994]. It therefore remains a priority to better characterise the extent and manner in which topologically disparate cortical and sub-cortical regions are able to communicate. A long-held assumption that the functional properties of neuronal networks are limited by their anatomical, chiefly synaptic, connections [Kanai

and Rees, 2011] may yet prove to be inadequate in light of more nuanced separation of structural and functional connectivity. Functional connectivity may be powerfully mediated by both indirect structural pathways [Honey et al., 2009] and pervasive neuro-modulation for the task at hand. Nevertheless the complex and plastic matrix of white matter tracts comprising the human *connectome* continues to inform key aspects of human development, learning, susceptibility and response to disease [Sporns, 2013].

4.1.2 The Brain at Rest

A rewarding line of investigation in recent years has led neuroscientists to consider ongoing activity in the brain during an ostensibly task-free *resting* condition. Most early functional neuroimaging studies considered this activity to comprise background biological noise and effectively subtracted this data (obtained during a rest block) from the (typically Blood Oxygen Level Dependent (BOLD) MRI) signal acquired during task performance, thus surmising the neural activity subserving the cognitive process under investigation. More considered analysis of combined data from a range of visual-processing PET studies revealed certain areas, notably the precuneus and posterior cingulate, to consistently demonstrate *decreased* blood flow during active task performance [Shulman et al., 1997]. The large-scale topography of these regions, quickly gaining the designation *default mode network (DMN)*, was further delineated using the oxygen extraction fraction obtained during resting PET studies, strengthening the hypothesis that tonic activity in these regions at baseline is reliably suspended during attention demanding task performance [Raichle et al., 2001]. Study of the interdependence of these regions was facilitated by the discovery that low frequency fluctuations in the BOLD timecourse at rest were temporally correlated across anatomical sites [Biswal et al., 1995], in keeping with existing definitions of functional connectivity (FC). The application of seed-based approaches rapidly defined a number of cortical and sub-cortical networks that orchestrate their activity coherently in the resting-state; the biological relevance of these

networks appears even to expand upon the known functions of their components, for instance the *salience* network's dissociable correlation with subject anxiety [Seeley et al., 2007] and the degree to which impulsivity in young offenders is related to the connectivity of motor planning areas with either the DMN or executive controls networks [Shannon et al., 2011].

4.1.3 Clinical Relevance of Intrinsic Connectivity Networks

The inherent value in detailing the functional organisation of the brain is further demonstrated by translational studies assessing the impact of neurodegenerative disease on resting-state networks (RSNs), including Alzheimer's disease [Greicius et al., 2004; Wang et al., 2007], Parkinson's disease [Szewczyk-Krolikowski et al., 2014; Tessitore et al., 2012] and Huntington's disease [Werner et al., 2014]. Early work noted an impressive spatial correspondence between the DMN (as characterised by task-free acquisitions in healthy young adults) and regions vulnerable to amyloid deposition in older patients with Alzheimer's disease, hinting at a causal relationship given the consistent involvement of DMN components in active memory tasks [Buckner et al., 2005]. Connectivity within (but not restricted to) the DMN has reliably been shown to be modified by Alzheimer's disease, correlating with the degree of Pittsburgh compound B uptake [Koch et al., 2015]. As a further example, group activation differences between Alzheimer's patients and healthy elders during a memory task spatially correspond to functional connectivity *increases* within the right fronto-parietal RSN [Zamoni et al., 2013]. The latter study underlines the relevance of RSN connectivity measures to the cognitive sequelae of neurodegeneration, perhaps unsurprising given the close approximation between RSNs and the distribution of cortical *activations* resulting from diverse task protocols [Smith et al., 2009]. Further insight into pathological *mechanisms* resulted from Seeley and colleagues description of grey matter atrophy patterns in clinically distinct neurodegenerative diseases that correspond spatially to unique RSNs identifiable in health [Seeley et al.,

2009]; this subsequently informed the prediction via graph theoretical measures, that regional spread from disease *epicentres* occurs through vulnerable neural networks [Zhou et al., 2012]. The applications of RSNs to the neurodegeneration field are therefore manifest: 1) RSNs may add diagnostic discriminatory power, for example distinguishing Alzheimer's disease and FTD with seemingly high accuracy [Zhou et al., 2010], 2) marking longitudinal progression within individuals, as seen in the increasingly aberrant network *hub* connectivity as individuals with pre-manifest Huntington's disease approach expected symptom onset [Harrington et al., 2015], 3) generating explanatory hypothesis for the expression of key symptomatology, such as the apparently heterogeneous distribution of lesions underlying hemiballismus [Laganiere et al., 2016] or the link between depression in multiple sclerosis and functional disconnection of the hippocampus [Rocca et al., 2015] or 4) perhaps in future detecting a biological response to therapy, largely limited thus far to psychopharmacological examples such as the effects of anxiolytic benzodiazepines on increasing medial visual FC [Pflanz et al., 2015]. Without exhausting the potential applications for RSNs, a pertinent final consideration is that the interpretation of resting-state group differences is relatively immune from criticism that abnormal neural *activations* largely reflect differential cognitive engagement during neuroimaging task execution [Fox and Greicius, 2010].

4.1.4 Resting-state Studies in ALS using fMRI

Early evidence from the investigation in ALS of cortical function at rest suggested a mismatch between the deficits in structural connectivity clearly outlined by reduced fractional anisotropy and apparently preserved functional organisation [Verstraete et al., 2010]. This was accentuated by restricting calculation of functional connectivity to an ALS-impacted tractography-derived spatial map, revealing overlying significant increases in FC among ALS patients that furthermore varied with both disease duration and rate of progression [Douaud et al., 2011]. Subsequent resting-state MRI (rs-fMRI) studies

provided evidence of mixed alterations to FC: within the DMN for example, connectivity was decreased to the right orbitofrontal cortex but increased to the left precuneus [Agosta et al., 2013a]. Uncertainty remains regarding the consistency of these conclusions however, given a positive correlation between FC and anatomical connectivity (derived by diffusion tensor imaging) in a larger group of 64 patients [Schmidt et al., 2014]. Methodological differences in analysis, as well as clinical heterogeneity in patient populations, may contribute to these discrepancies. Even less well replicated are studies of other MND phenotypes. A study of PLS patients used a seed-based approach to detect increased FC, notably cerebro-cerebellar [Meoded et al., 2015], while an ICA approach detected increased FC in the sensorimotor network (with a positive relationship to structural pathology) and increased FC to the right superior frontal gyrus (correlating positively with cognitive abilities) [Agosta et al., 2014a]. Our group have also recently described (within an overlapping subset of participants to the present chapter) abnormally increased FC between the cerebellum and a RSN comprising the precuneus, cingulate, and middle-frontal gyrus **Figure 4.1**. The connectivity patterns were found to be shared by both ALS patients and AGCs [Menke et al., 2016], suggesting that increased FC may be detectable early in, and hence presumably a core feature of, ALS pathophysiology.

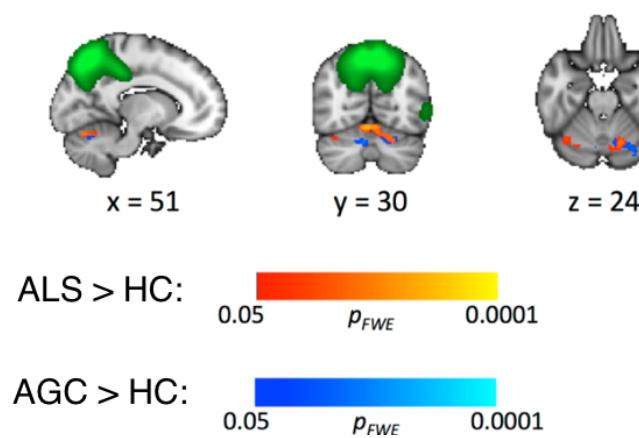


Figure 4.1 rs-fMRI study of ALS patients and AGCs

Increased FC is revealed relative to healthy controls [Menke et al., 2016]. Regions within the cerebellum (in red and blue) show increased functional coupling to a precuneus-cingulate-middle frontal network (shown in green).

4.1.5 Cortical Neurophysiology of the Resting Brain in Neurodegeneration

While quantitative EEG recordings can contribute to the diagnostic differentiation of some neurodegenerative diseases to an extent [Bonanni et al., 2008], typical findings in early Alzheimer's disease of reduced alpha band power accompanied by lowering of peak frequency rhythms [Moretti et al., 2004] remain insufficiently explained. In part this is due to the ambiguity inherent in source localisation of surface EEG signal. Measuring coherence between the signals obtained at two distant EEG sites is an appealingly simple estimate of functional coupling between the underlying cortical sources, albeit one tempered by the confounding factor of volume conduction [Gross et al., 2001]. Nevertheless such studies have proved powerful enough to predict conversion to Alzheimer's disease from mild cognitive impairment [Rossini et al., 2006], to show MS lesion load correlating with anteroposterior coherence [Leocani et al., 2000b], and to demonstrate increased connectivity to the anterior cingulate cortex (ACC) and fronto-insular regions in ALS [Iyer et al., 2015]. By comparison, MEG typically extends the localisation capabilities of non-invasive neurophysiological recording (even to deep sources such as the hippocampus [Engels et al., 2016]) by negating the dispersive and attenuating effects of the skull and scalp. MEG should therefore offer some advantage, albeit at a financial cost relative to EEG, in the assessment of degenerating cortical networks [Stam, 2010]. Complicating the conclusions that can be drawn from the expanding number of studies in this domain however are investigator choices to restrict analysis to particular frequency bands and the plethora of techniques for measuring connectivity (ranging from simple coherence, to methods negating zero-lag coherence and accounting for non-linear relationships among sources, reviewed in [van Diessen et al., 2015]). Furthermore, the direction of FC alteration by the disease may not be uniform across the brain. Alzheimer's patients were noted to have decreased (particularly left-

hemispheric) long-range FC in alpha and beta bands while FC was simultaneously increased locally in parieto-occipital regions [Stam et al., 2006]. Increased FC was also described in posterior regions amongst 117 Alzheimer's patients in whom only one minute of resting-state MEG (rs-MEG) data across multiple sites was recorded [Verdoorn et al., 2011]. Similarly, patients with early, untreated Parkinson's disease demonstrated increased FC within the alpha band, extending to a wider frequency range with disease progression [Stoffers et al., 2008a]. The application of MEG derived FC measures as a biomarker of neurodegeneration still requires caution; for Parkinson's patients, rs-MEG scans pre- and post-levodopa administration revealed divergent effects on FC depending on the degree of motor improvement as an individual moved from an 'off' to 'on' state [Stoffers et al., 2008b], and longitudinal alterations in FC across 4 years were interpreted via graph theoretical measures to represent a reduction in global efficiency [Olde Dubbelink et al., 2014].

The present experimental aim was therefore to investigate whether neurophysiological indices, generated from source-space MEG data, would corroborate the existing rs-fMRI findings of increased FC in ALS.

4.2 Methods

4.2.1 Participants

ALS and PLS patients were recruited from the Oxford MND Care and Research Centre. AGCs were recruited either from the Pre-FALS study or contacted the research team proactively after learning of our work from local or national services. Participants underwent a resting-state acquisition as a component of the same MEG session as the experiments described in either Chapter 3 or Chapter 5. The resulting samples sizes were thus larger, aiding analysis of group comparisons of FC between ALS, AGC and healthy control (HC) participants (Chapter 3 additionally includes PLS patients, Chapter 5 included disease

mimics). Clinical and brief cognitive assessments were performed as described in Chapter 3 alongside standard baseline demographic calculations. Demographics for all participant groups are detailed in **Table 4.1**.

Mean $\pm$ SD (<i>range</i>)	ALS (n = 24)	PLS (n = 9)	AGC (n = 15)	Controls Old (n = 18)	Controls Yng (n = 14)	Mimics (n = 7)
Age (years)	63.3 $\pm$ 9.1 (46:78)	59.6 $\pm$ 8.0 (44:70)	46.2 $\pm$ 12.0 (20:66)	61.7 $\pm$ 9.3 (45:75)	51.0 $\pm$ 9.5 (37:64)	60.8 $\pm$ 12.8 (45:76)
Gender	17 M : 7 F	2 M : 7 F	1 M : 14 F	9 M : 9 F	5 M : 9 F	5 M : 2 F
Site of Onset Genetics Diagnosis	7 bulbar 2 RUL, 6 LUL 5 RLL, 4 LLL	1 bulbar 2 both legs 1 RLL, 5 LLL	12 <i>SOD1</i> 3 <i>C9orf72</i>	N/A	N/A	2 SBMA 5 MMN
ALSFRS-r	37.1 $\pm$ 7.2 (21:48)	35.1 $\pm$ 6.3 (24:43)				
Disease Duration from Symptom Onset (months)	30.2 $\pm$ 24.5 (5:100)	121.0 $\pm$ 57.2 (47:283)				
Progression Rate (48 – ALSFRS-R / duration in months)	0.58 $\pm$ 0.45 (0:1.6)	0.12 $\pm$ 0.06 (0.05:0.46)				
Cognition Score (% correct) <i>Intact/Borderline/Impaired</i>	82.9% $\pm$ 8.7 (69:95) (19 ECAS, 2 ACE-r) 15 / 1 / 5	84.6% $\pm$ 9.4 (73:95) (8 ECAS, 1 ACE-r) 5 / 1 / 3				

Table 4.1: Clinical and demographic details.

Demographics of participants contributing resting-state MEG data. SBMA = Spinal and Bulbar Muscular Atrophy (Kennedy Disease).

4.2.2 Acquisition

Approximately ten minutes of MEG resting-state data were acquired per participant in one continuous block. The participant was seated comfortably in the scanner and instructed to remain still and awake, but without performing any specific task. The recording was made in the ‘eyes open’ state with loose visual fixation on a black cross printed on paper and placed 90 cm away. Eye-blinks and saccades were monitored continuously using a combination of surface EOG and infra-red eyetracker. ECG was monitored at the wrists.

4.2.3 Preprocessing

Raw data (.fif) were converted to SPM8 format and inspected to identify bad channels prior to passing the data (.fif) through Maxfilter v2.2 (-ST extension, including both signal space separation and continuous head movement compensation). Post-Maxfilter, the filtered data (.fif) were converted to SPM8, downsampled to 250 Hz, and again visually inspected. Bad segments were manually marked in the continuous data stream. Data were then cleaned using the semi-automated OSL tool ‘OPT’, initially applying a high-pass filter at 0.3 Hz. The ICA components corresponding to physiological artefact generated by blink and cardiac cycle were identified semi-automatically using the OSL tool *AFRICA* and removed from the data. Coregistration was then performed using either SPM8 or (if nose points had been collected) the OSL tool *RHINO*. Coregistration fit was checked for each individual, and errant headshape points were manually removed if necessary prior to repeating the coregistration step. Data were then beamformed using a single-shell forward model into MNI space at a 3D gridstep of 6 mm. Source-space covariance maps were created in .nii format and inspected for each individual using the FSL tool *FSLview*. At this stage, a limited number of participants were identified as having sub-optimal source-space MEG data that, either due to remaining contamination by artefact or failure of the beamformer algorithm to perform adequately. Raw data were re-inspected for these

individuals but no correctable source of noise was typically identified; it was noted that several individuals without structural MRI available for co-registration fell into this category. All participants unable to complete MRI examinations (due to claustrophobia, respiratory insufficiency or other contra-indication) were therefore excluded from the present experiment. In addition to this exclusion, a number of source-space data sets were qualitatively judged sub-optimal for inclusion (examples of ‘good’ and ‘bad’ source variance maps in **Figure 4.2**). The participants excluded at this stage were not systematically drawn from any one group (1 ALS, 1 PLS, 2 AGC, 1 HC). Their data are not included in the demographic **Table 4.1**.

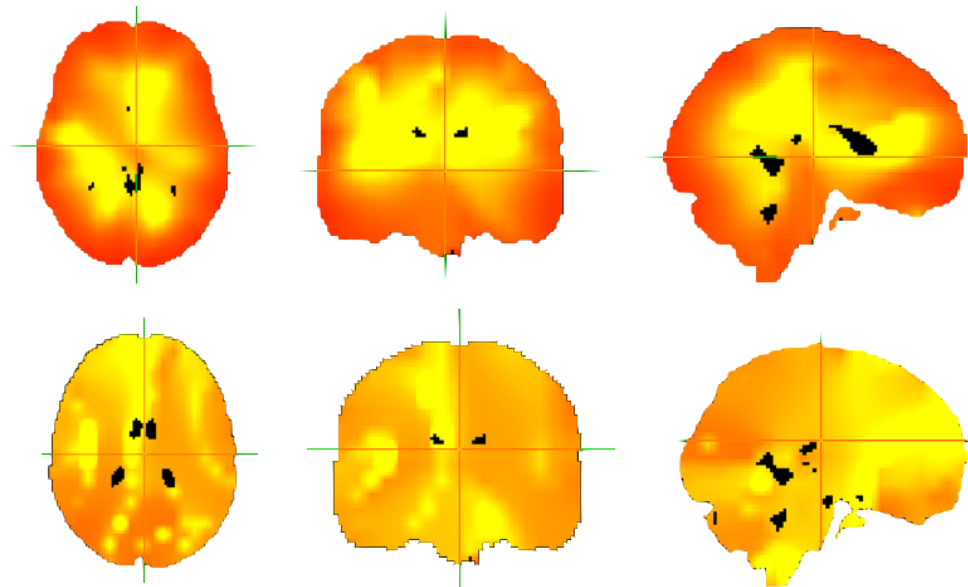


Figure 4.2: Beamformed resting MEG data.

Two individual examples of source variance maps after beamforming, top row = good example, bottom row = bad example (data set rejected), given anatomically improbable distribution of variance peaks.

4.2.4 Network Analysis: Parcellation

A recently developed orthogonalisation algorithm [Colclough et al., 2015] was used to generate a connectivity matrix between a pre-defined set of ROIs. The ROIs were assigned from 38 cortical ‘parcels’ extracted via high-dimensionality spatial ICA from resting-state fMRI data within the Human Connectome Project [Van Essen et al., 2013]. These parcels therefore represent functionally quite specific local modules, which were

additionally split by hemispheric laterality. In brief, a single time-series was decomposed from each parcel by taking the first PCA component, and the data were orthogonalised with respect to all other parcels using a symmetric multivariate approach that eliminates spurious zero-lag connectivity [Hipp et al., 2012] between neighbouring parcels while maintaining a close approximation to the original time-series. The time-series was then converted into a band-limited power time-course by taking the Hilbert envelope of the ‘broad-band’ signal (3-40 Hz) across 2-second sliding windows. This power envelope time-course was then correlated between parcels for each individual, resulting in a Fisher Z-normalised score for each connection edge. Group contrasts (using age-matched controls) were appraised against 5000 permutations of the subject group-membership labels and corrected for multiple comparisons on a per-contrast basis (thus accounting for the number of edges contributing to each group contrast). P-values ($p < 0.05$) corrected using family-wise error were deemed significant.

4.2.5 Network Analysis: Dual Regression

Resting-state MEG data were also subjected to a second methodology applied that expands on coherence analysis of the power envelope time-courses (in contrast to phase relationships) as a voxel-wise measure of cortical communication [Bruns et al., 2000]. Long-range coherence within frequency band power envelopes has been shown to be modulated by cognitive requirements independently of changes in the source power [Siegel et al., 2008]. This particular measure of FC is therefore an appealing option to investigate RSN integrity, the clinical and behavioural importance of which was outlined above, negating some of the potential limitations of BOLD response interpretation [Logothetis, 2008]. The approach, initially seed-based, has previously yielded MEG RSNs that spatially correspond to the most frequently observed fMRI RSNs [de Pasquale et al., 2010]. Even without anatomical priors, a frequency-band-dependent set of stationary RSNs was extracted from beamformed resting MEG data using ICA decomposition in

the temporal dimension [Brookes et al., 2011]. As above, the data were enveloped between 4 and 30 Hz, then temporally downsampled to 0.5 Hz. Data from the entire experimental set were concatenated in the temporal dimension, and an ICA decomposition was performed to create 20 temporally orthogonal spatial networks. Inspection of these spatial maps confirmed the relatively poor spatial resolution of MEG in comparison to high-field fMRI (**Figure 4.3**). Therefore, to ensure meaningful comparison between the present study and the existing ALS literature, a set of independently acquired rs-fMRI RSNs (the 8 most biologically plausible ICA networks derived from data acquired in an unrelated study of healthy older adults) was used as a spatial template for *dual regression* [Filippini et al., 2009], adapted for MEG and implemented in OSL. In brief, participant-specific versions of the spatial maps were generated by regressing the fMRI set into the participant's 4D MEG dataset. The new set of individual timeseries, one per group-level spatial map was then regressed into the original individual 4D dataset, resulting in a set of participant-specific MEG spatial maps, one per fMRI spatial map. Group inference was performed using FSL's *randomise* permutation-testing tool, applying 10,000 permutations and threshold-free cluster enhancement (TFCE) to correct for multiple comparisons across all brain voxels.

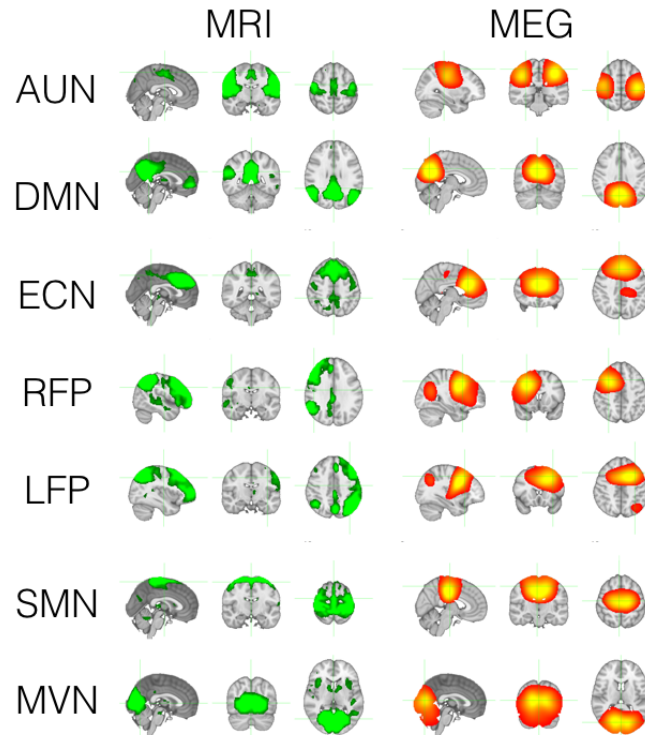


Figure 4.3: MEG and fMRI resting-state networks compared.

RSNs generated from MEG data using ICA reveal relatively poor spatial precision in contrast to fMRI RSNs. The 7 MEG RSNs corresponding most closely to the independently acquired fMRI RSNs were selected for visual comparison. AUN auditory network, DMN default mode, ECN executive control, RFP right fronto-parietal, LFP left fronto-parietal, SMN sensorimotor, MVN medial visual. Lateral visual MRI not shown - no definite spatial correlate of the lateral visual network was noted in the MEG data.

4.3 Results

Data from 79 individual participants were available for analysis.

4.3.1 Increased Functional Connectivity between Cortical Parcels

Connectivity matrices representing the group differences in FC (as indexed by group contrasts in parameter estimates) are presented in **Figure 4.4**. Each point along the x and y axis represents a cortical parcel or *node* and each square, an *edge*, in the matrix is the output of a parametric statistical comparison using a GLM framework contrasting groups in terms of their correlation in band-limited power time-course. Most strikingly, FC appeared globally increased relative to age-matched controls throughout the cortical networks. The FC group differences were more marked in both ALS and PLS patient groups than those observed in the AGC group. A degree of spatial selectivity to the group

FC differences was noted; edges from the PCC (including to the right motor cortex) and edges within the right visual and occipital regions demonstrated notably increased FC. The PLS patients showed more diffuse increases in FC particularly between posterior and parietal nodes bilaterally. Increased FC, albeit not reaching statistical significance, was also noted in the AGCs, affecting an overlapping spatial distribution. Remarkably, no edges in any groups appear to show decreased FC relative to age-matched HCs.

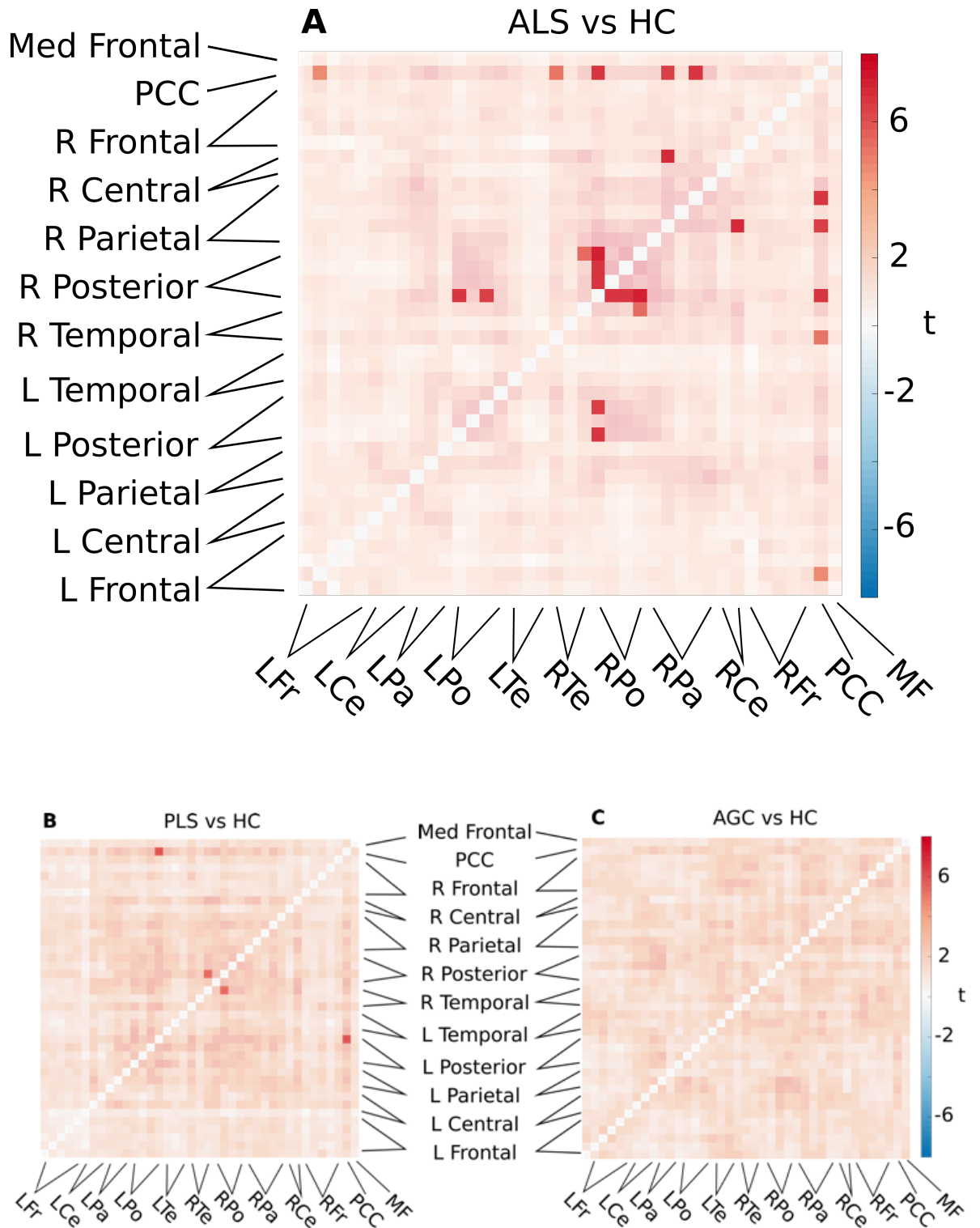


Figure 4.4: Functional connectivity between cortical parcels.

Connectivity matrix between cortical parcels. Group comparison against HCs revealed global increases in FC in all 3 study participant groups. After multiple comparison correction edges between the PCC and principally posterior nodes remained significantly stronger than in HCs in both ALS (4.4a) and PLS (4.4b) patients, but not AGCs (non-significant edges masked, significant edges FEW $p < 0.05$ unmasked, colour denotes t value, red = stronger FC in patient groups, blue = stronger in HC).

Clinical measures did not correlate significantly with the present FC values as described by a global mean of the inter-parcel edges.

4.4 Diverse Impact of MND on RSNs Revealed by MEG

On comparison to age-matched HCs, ALS patients demonstrated significantly abnormal MEG data FC within two distinct RSNs only, out of the 8 MRI spatial sets appraised. Raw t-values contrasting groups (for each spatial set denoted in green) are presented as maps in **Figure 4.5**, with statistically significant group difference spatial clusters (TFCE) overlain in yellow). Widespread increases in FC were noted within the medial visual network and in its coupling to frontal opercular regions, particularly on the left ($p < 0.01$, **Figure 4.5a**). In addition, significantly decreased FC was noted between the SMN and the left inferior frontal gyrus (left IFG, $p < 0.025$, **Figure 4.5b**). Although not statistically significant after correction for all voxels, a trend towards higher FC within the motor cortices ($L > R$) was observed for the SMN component. On comparison between ALS patients and disease mimic patients, again significantly increased FC was noted within the medial visual network of ALS patients ($p < 0.025$, **Figure 4.5c**).

PLS patients also demonstrated alterations in FC on comparison with HCs. A decrease in FC was noted on regression of the lateral visual MRI RSN within the inferior frontal regions ($p < 0.05$, **Figure 4.5d**). In addition, both PLS patients ($p < 0.02$, within right IFG, **Figure 4.5e**) and AGCs ($p < 0.02$, bilateral parietal and right temporal lobe, **Figure 4.5f**) demonstrated decreased FC in contrast to their age-matched HC groups with respect to the executive-control network.

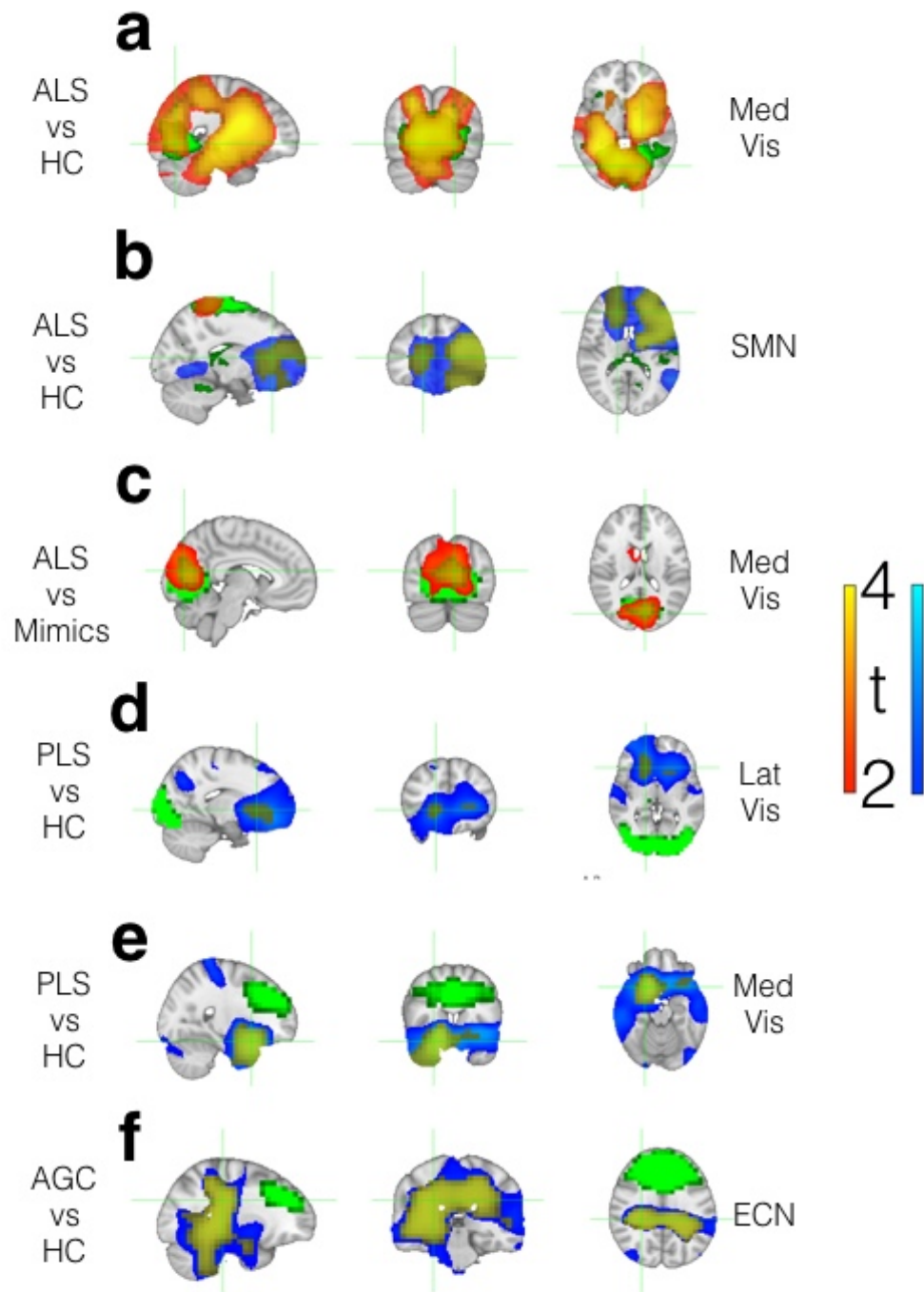


Figure 4.5 Impact of MND on RSNs revealed by MEG

fMRI spatial component in green. Raw t-stats for group comparison in red/ blue (red = increased FC vs HC, blue = decreased FC). Regions of significant differences ($p < 0.05$, TFCE corrected) overlain in yellow.

4.5 Discussion

4.5.1 Summary

The investigations presented in this chapter revealed marked effects of both ALS and PLS phenotypes on resting-state FC, as measured by the degree of correlation between band-limited power envelopes, across both parcellated cortex and wholebrain RSNs. Limited evidence was obtained in support of alterations to FC prior to the development of overt symptoms in AGCs. These abnormalities may have considerable mechanistic importance given the key role of neural oscillations for the long-range synchronisation of information across the brain [Fries, 2009; Kopell et al., 2014]. If confirmed, they might contribute significantly to the development of accessible biomarkers and be used to help define and assess neuroprotective therapy.

4.5.2 Reconsidering FC in ALS

That the present results do not precisely conform to the existing rs-fMRI literature in ALS (increases in FC particularly affecting postero-occipital regions) is predictable given the manifest types of neural activity, including modulation of oscillatory power, that may contribute to the BOLD response [Brookes et al., 2005]. The present study focused purely on dynamic changes to oscillatory power, therefore the abnormal FC previously reported in ALS cannot be fully explained by pathological alterations to neural-BOLD coupling, nor indeed is there any obvious mechanistic reason to suspect this, in contrast to disorders such as cerebrovascular disease [Rossini et al., 2004] and HIV-associated neurocognitive disorder [Ances et al., 2011]. Increased FC in ALS has been hypothesised to result from the well documented loss of intra-cortical inhibitory influence (reviewed in [Turner and Kiernan, 2012] and [Bae et al., 2013]) consequent to (pathologically confirmed) vulnerability of parvalbumin-binding interneurons [Maekawa et al., 2004; Nihei et al., 1993]. To an extent, this inference is supported by multimodal studies in healthy volunteers combining MRS with rs-fMRI that have found evidence of FC's dependence

on the balance of glutamatergic and GABAergic neurotransmitter concentrations (although anatomical specificity complicates translation to clinical populations – glutamate levels in the posteromedial cortex correlate positively with DMN FC [Kapogiannis et al., 2013] but in the anterior hippocampus correlate negatively with FC to medial prefrontal cortex and ACC [Wagner et al., 2016]). These findings may however also reflect direct modulation by GABA of the haemodynamic response function rather than solely alterations to the underlying neural activity [Muthukumaraswamy et al., 2012].

FC changes extending beyond the corticospinal tracts encourage consideration of ALS as a multi-system disorder with considerable cognitive burden beyond the core motor phenotype [Phukan et al., 2007]. Decreased FC to the left inferior frontal cortex was previously reported [Agosta et al., 2013a] and the occipital poles are reported to acquire a stronger network prominence in ALS as measured by the voxelwise graph theory FC metric, *degree centrality* [Zhou et al., 2016]. FC increases related to the sensorimotor cortex may be prominent only early in the ALS disease process, being notably present in patients without corticospinal tract DTI changes [Agosta et al., 2011] (relative to the Agosta study, the present ALS group had similar ALSFRS scores but longer disease duration, 30 months versus 20). FC increase might therefore reflect a physiological attempt to functionally compensate for early pathology, which subsequently becomes overwhelmed with further disease progression. This is perhaps in keeping with the more marked FC increases between cortical regions less vulnerable to structural damage in MND more broadly, ie posterior and parietal nodes, that both ALS and PLS patients demonstrated in the current experiment. However, no corresponding particular increase in sensorimotor FC is noted within the AGC group; the sensitivity to detect such changes may yet be outweighed by their heterogeneous composition in terms of genotype and age (they remain perhaps many years away from symptom onset).

4.5.3 Limitations and Future Considerations

Before addressing the factors that temper the conclusions drawn from the current investigation, it is worth taking stock of the tangible advantages to rs-MEG studies in ALS. First and foremost, patient participants were able to contribute to the study despite moderate disability and in a more comfortable scanning environment than MRI (some ALS patients do not tolerate a supine posture due to orthopnoea or salivary secretions). This advantage is diluted by the consideration that only participants with structural MRI available remained in the final analysis, but it remains conceivable that sensor-level or source-reconstructed analysis, blind to the individual structural anatomy, might still have value. Furthermore, in common with all current biomarker development projects, considerable gains are to be made by longitudinal study; repeated rs-MEG studies are more feasible than rs-fMRI as encroaching respiratory compromise precludes participants from lying supine (while their original structural scan could still contribute to co-registration). The analysis opportunities also continue to evolve. Of particular interest is the possibility to detect transient *states* that have a spatial confirmation homologous to the above described RSNs [Baker et al., 2014]. These techniques may have particular relevance to neurodegenerative disorders given previous rs-fMRI findings of differential ‘dwell times’ in certain DMN sub-configurations for patients with Alzheimer’s disease [Jones et al., 2012]. Preliminary attempts to apply OSL’s Hidden Markov Model pipeline to the current dataset however yielded atypical spatial configurations to these states – further development in the context of healthy older adults is warranted before this method can be applied to translational work.

A broad (4:30 Hz) frequency band was selected for the power envelope since most resting-state structure and connectivity is present within theta, alpha and beta bands

[Brookes et al., 2011]. More specific frequency bands are likely to yield similar results [Ranasinghe et al., 2014], but potentially with decreased signal to noise ratio (particularly if higher gamma ranges were explored), furthermore appraisal of multiple frequency bands would necessitate further multiple comparisons correction [van Diessen et al., 2015]. Statistical correction for the number of RSNs appraised is not typically performed in the clinical literature, so that most studies are therefore vulnerable to type I error, including the current report [Agosta et al., 2013a; Menke et al., 2016]. The selection of nodes for the parcellation analysis could alternatively be guided by anatomical landmarks, but this could have negative consequences since multiple oscillatory sources might be combined within one anatomical parcel, or split across a functionally irrelevant anatomical divide. Selecting neural sources on the basis of decomposed functional data is therefore closer to a physiological parcellation, but uncertainty remains over the total number of components to be raised – this remains a balance between interpretability, uniqueness and potentially arbitrary sub-division of sources (of note, Maxfilter software significantly reduces the dimensionality of MEG data). Similarly, the decision to use a rs-fMRI regression basis set was motivated by a wish to preserve spatial accuracy until first-level regression; a counter-argument would support the more data-driven approach of regression to the study concatenated group ICA maps. Provisional analysis without rs-fMRI spatial constraints again demonstrated widespread increased in FC among ALS patients, in keeping with the parcellation analysis, but lacked much selectivity to particular RSNs. More profoundly, the selection of an RSN ‘of interest’ is non-trivial and the interpretation of the functional significance of alterations in FC within and beyond RSNs remains speculative. Future work might look to better define functional networks by applying ICA to task structured data, thus maximising the signal in regions less well localised by MEG such as the hippocampus [Luckhoo et al., 2012] or perhaps by integrating some anatomical priors such as DTI connectivity [Pineda-Pardo et al., 2014].

Further considerations reflect more on the study design than analysis particulars and could guide future replications. The acquisition took place as participants rested with eyes open, fixation is desirable to minimise saccade artefacts in the MEG signal, but many rs-fMRI data sets, including our group's most recent analysis, have been conducted with eyes closed. Since Berger's (1873 – 1941) description, posterior alpha-power is famously increased on closing the eyes [Adrian and Matthews, 1934], the impact of this change on band-limited envelope coherence is not certain but likely to be positive for occipital regions at least. Whether this would differentially influence clinical groups remains to be seen. ALS, in common with most neurodegenerative diseases causes a subtle slowing of dominant alpha, contributing to increased low-frequency power. These differences were appraised in the current rs-MEG data set, but not found to be significant after the same FWE correction for number of parcels included. Unfortunately, not all the described participants underwent contemporaneous rs-fMRI, and those who did contributed to two different study protocols, thereby precluding well powered comparative analysis of these complementary techniques. Finally, CNS active medications may accentuate the group difference in FC [Scheidegger et al., 2012]. Patients continued any regular medications for the study since withdrawal of agents providing symptomatic relief was considered unethical. Most importantly around half of the ALS patients choose to receive the anti-glutamatergic disease-modifying agent riluzole. Splitting the ALS data according to riluzole use did not reveal any marked differences in FC in keeping with the only short-term effect on cortical hyper-excitability [Geevasinga et al., 2016b].

Chapter 5 **Cortico-Muscular Coherence Reflects Cortico-Spinal Tract Dysfunction in ALS**

Chapter 3 focused on the dynamic physiological processes within the cortical sensorimotor system that accompany and seemingly enable simple motor function in both health and ALS. Similarly framed within neural oscillations, Chapter 4 considered resting communication between diverse cortical regions, and the impact ALS has on measures of functional connectivity. Chapter 5 will extend these concepts to a functional axis of communication from motor cortex to muscle, probed by MEG during a structured motor task.

5.1 Background

5.1.1 Physiological Communication from Brain to Muscle

The characteristic physiological phenomenon of simultaneously coherent oscillations within both primary motor cortex and the musculature of the contralateral effector limb was first captured using only a single MEG sensor and surface EMG [Conway et al., 1995]. Since then, multiple studies have incrementally defined key characteristics of cortico-muscular coherence (CMC). The precise functional remit of CMC has still not been completely ascertained [van Wijk et al., 2012]. EEG studies rapidly recognised voluntary prolonged (often isometric) contraction to be accompanied by (indeed seemingly a prerequisite for) significant CMC restricted to the beta band (15:30 Hz) range [Halliday et al., 1998; Salenius et al., 1997]. Invasive studies confirmed CMC (operating via phase-locked pyramidal tract neurons) to be readily modifiable according to evolving task demands [Baker et al., 1997; Baker et al., 1999]. Not simply the extent of muscular contraction [Brown et al., 1998], but more the precision and predictability of force parameters (for example a compliant versus static response device), affect beta CMC amplitude [Kilner et al., 2000; Omlor et al., 2011]. To an extent, therefore, CMC indexes the quality of motor performance on both a trialwise basis [Kristeva et al., 2007] and after

a sustained period of motor skill learning (independent of EMG and EEG power) [Perez et al., 2006].

Early investigations claimed CMC to reflect unidirectional efferent driving of EMG activity by pre-central cortical oscillations. This was suggested on the basis of a calculated phase lag roughly consistent with central motor conduction times [Gross et al., 2000; Mima and Hallett, 1999; Ohara et al., 2000]. This simplistic account was challenged by evidence of detrimental effects on CMC when incoming somatosensory input is diminished, for example by arm cooling [Riddle and Baker, 2005], digital nerve anaesthesia [Fisher et al., 2002] or pathological deafferentation [Kilner et al., 2004]. By contrast however, further evidence in support of a predominantly cortical generator was provided by the striking (and perhaps relatively unique) circumstance of perinatally acquired hemiplegic lesions [Gerloff et al., 2006]. In such cases there is functional reorganisation of primary motor cortex to the ipsilateral hemisphere (relative to the hemiplegia). CMC and MEPs followed the plastic reorganisation while somatosensory function remained contralateral. Nevertheless, it seems likely that effectively closing a sensorimotor ‘loop’ to allow accurate movement calibration requires input from the peripheries [Baker, 2007], as demonstrated by directional causality analyses of CMC [Lim et al., 2014; Witham et al., 2011] and the direct impact of external joint position perturbation on CMC amplitude [Campfens et al., 2013].

Finally, CMC can vary with the cognitive demands of a motor task, in keeping with broader neural mechanisms to enhance the salience of relevant information [Coull and Nobre, 1998; Egner and Hirsch, 2005; Rohenkohl and Nobre, 2011] that include modulation of beta oscillations in sensory regions [Todorovic et al., 2015], in the motor cortex [Koelewijn et al., 2008; van Wijk et al., 2009] and (still independent of action performance) in peripheral muscles [van Ede and Maris, 2013]. Quite intuitively therefore,

beta CMC appears to reduce in both amplitude and frequency when attention is split between a motor task and a distracting cognitive performance such as mental arithmetic [Kristeva-Feige et al., 2002], even without any obvious accompanying drop in motor control [Johnson et al., 2011]. As demonstrated by Fries and colleagues, attentional focus may be translated into more effective corticospinal communication by frequency-specific modulation of oscillatory synchrony. During a visuo-motor task in which the hazard-rate of a go-cue (and correspondingly also reaction times) was systematically varied, CMC within the gamma-band (40 to 70 Hz) was up-regulated with increasing motor preparation [Schoffelen et al., 2005]. CMC extending beyond the beta range has been experimentally described in other paradigms: requiring periodic modulations to the outputted force induces gamma CMC [Omlor et al., 2007] while rapid alterations to force output are accompanied by transient replacement of beta CMC with both alpha and gamma coherence peaks which furthermore may have dissociable functional roles [Mehrkanoon et al., 2014] and anatomical generators [Feige et al., 2000].

5.1.2 Assessing CMC in Disease States

Prior to the first descriptions of CMC, it was already well recognised that motor unit firing within different muscles could be synchronised during certain routine patterns of activity, particularly respiration [Kirkwood et al., 1982] and locomotion [Nielsen, 2002]. Shared corticospinal input to these muscle groups was held accountable and in keeping with this assumption, disrupted *intermuscular* coherence (IMC) was noted in the paretic hand muscles of recovering stroke patients [Farmer et al., 1993]. Conceptually similar findings of reduced *beta* IMC were found on recording from two sites above tibialis anterior while patients with incomplete spinal cord lesions walked on a treadmill [Hansen et al., 2005]. Such abnormalities resolved with successful rehabilitation [Norton and Gorassini, 2006]. Interestingly, both IMC [Jaiser et al., 2016] and CMC [Johnson and Shinohara, 2012;

Kamp et al., 2013] appear preserved (if not increased) by the normal aging process, which should encourage their consideration as robust markers of neurodegeneration.

Diverse cerebral pathologies are reported to affect CMC. Stroke survivors manifest a more distributed range of cortical locations for peak CMC than healthy controls, in keeping with plastic reorganisation of sensorimotor functionality [Rossiter et al., 2012]. Not unexpectedly though, acute stroke also reduces CMC unilaterally, concordant with side of the resultant deficit [Nielsen et al., 2008], although this may still normalise with good functional recovery [von Carlowitz-Ghori et al., 2014].

Studies of CMC in the context of tremor and other hyperkinetic movement disorders have proven useful in distinguishing, for example, a cortical origin for non-progressive multifocal myoclonus [Grosse et al., 2003a], which was not found to be present when myoclonus accompanies the neurodegenerative condition of cortico-basal degeneration [Grosse et al., 2003b]. Subtle ‘physiological’ tremor around 10 Hz may also reflect coherent oscillations within the CNS [McAuley et al., 1997]; a cerebello-thalamo-cortical loop may receive these afferent communications to enable fine adjustment of ongoing motor commands [Gross et al., 2002]. Essential tremor however, despite its high prevalence, remains difficult to characterise fully. Coherence between EEG signal and tremor frequency [Hellwig et al., 2001] is inconsistently replicated, perhaps reflecting sporadic and variable degrees of tremor oscillation entrainment in multiple loops [Raethjen et al., 2007].

Given the oscillatory nature of resting tremor, the well-established finding of pathological beta oscillations in the basal ganglia (reviewed in [Little and Brown, 2014]) and the therapeutic capability to alter neural signals with DBS, CMC in Parkinson’s disease is relatively well studied. L-Dopa [Mckeown et al., 2006; Salenius et al., 2002] and DBS [Airaksinen et al., 2015] appear at least to modulate if not restore to normal CMC,

although the ‘off’ state deviation from normality appears variable and CMC is preserved in early drug-naïve patients [Pollok et al., 2012]. Such studies are made more technically challenging by the inevitable presence of movement artefacts during tremor and DBS artefacts requiring advanced de-noising [Oswal et al., 2016].

5.1.3 Cortico-Spinal Tract Dysfunction in ALS

The current formal diagnostic criteria for ALS [Brooks et al., 2000] require identification on clinical examination of UMN signs but for diverse and not mutually exclusive reasons, UMN pathology is not always easy to detect [Swash, 2012]. ALS biomarker development has therefore aimed to include functional markers of corticospinal tract (CST) integrity, most successfully revealing abnormalities using a variety of TMS measures (the plausible pathophysiological contributions were discussed in Chapter 1 and are reviewed in depth in [Vucic et al., 2013b]). Key findings over more than 20 years of research include inconsistent reductions to corticomotor threshold [Eisen et al., 1990; Mills and Nithi, 1997] that may depend on the individual patient’s balance of UMN/LMN pathology [de Carvalho et al., 2003]. Other measures such as the cortical silent period may reduce over the course of the disease [Mills, 2003] or vary with the underlying pathogenesis of ALS (intracortical inhibition was preserved in more slowly-progressive D90A SOD1 patients [Turner et al., 2005b]). Paired and triple-stimulation techniques evolved and improved the reliability of these investigations [Magistris et al., 1999]. Reduced SICI emphasises cortical hyperexcitability as a key feature of ALS [Vucic and Kiernan, 2006b; Zanette et al., 2002a]. Investigation with TMS is therefore relatively powerful in demonstrating the subclinical involvement of the CST [Komissarow et al., 2004], to the extent that it may formally contribute to diagnostic criteria in the future [Menon et al., 2015]. However, most neurostimulation remains heavily dependent on operator skill, is not tolerated by all patients, and may be unsuccessful (albeit not uninformative) in certain subgroups of

MND (in particular PLS patients frequently have ‘inexcitable’ motor cortices [Geevasinga et al., 2015a]).

A single published study has investigated the impact of two contrasting MND phenotypes, PLS and PMA, on oscillatory drive between motor cortex and peripheral muscles [Fisher et al., 2012]. Beta-band IMC was recorded from both upper and lower limbs during an active contraction; CMC measurement was attempted via EEG but not reliably ascertained in this setup. In marked contrast to healthy controls, PLS patients as a group expressed **no** significant evidence of beta IMC, while IMC was relatively preserved within the PMA group. Combining IMC values from multiple muscle pairs improved the discriminatory power versus healthy controls and an examination of a single *suspected* case of ALS (subsequently identified to carry a *SOD1* mutation) confirmed absent beta IMC without clinically evident UMN signs.

In the following experiment, my principal aim was therefore to leverage the more practical acquisition of neural signals using MEG to characterise CMC in patients with classical ALS.

5.2 Methods

5.2.1 Participants

Patients with ALS were recruited from the Oxford MND Centre alongside ‘disease mimics’ – patients with a non-ALS diagnosis in whom there was at initial presentation some clinical suspicions of ALS (typically multi-focal motor neuropathy (MMN) with conduction block). The ALS and HC participants are a non-overlapping group to those described in Chapter 3, but all participated in the pilot experiment described in the appendix, in addition to providing rs-MEG data for Chapter 4. A limited number of new AGCs were furthermore recruited from previously described sources. Demographics for all participant groups are detailed in **Table 5.1**.

Mean $\pm$ SD (<i>range</i>)	ALS (n = 17)	AGC (n = 5)	Controls (n = 11)	Mimics (n = 6)
Age (years)	62.6 $\pm$ 9.4 (46 : 78)	43.9 $\pm$ 11.4 (30 : 61)	60.2 $\pm$ 12.5 (41 : 84)	60.6 $\pm$ 12.9 (47 : 76)
Gender	12 M : 5 F	5F	8 M : 3 F	4 M : 2 F
Site of Onset Genetics Diagnosis	5 bulbar 1 RUL, 3 LUL 5 RLL, 3 LLL	3 <i>SOD1</i> 2 <i>C9orf72</i>	N/A	1 neuropathy 5 MMN
ALSFRS-r	36.6 $\pm$ 6.4 (24 : 46)			
Disease Duration from Symptom Onset (months)	32.6 $\pm$ 26.0 (5:100)			
Progression Rate (48 – ALSFRS-R / duration in months)	0.59 $\pm$ 0.47 (0.03 : 1.56)			
Cognition Score (% correct)	83.2% $\pm$ 10.46 (54:94)			

Table 5.1: Demographic and clinical details.
Demographics for participants in the CMC experiment.

5.2.2 Experimental Design and Acquisition

In order to optimise the conditions for recording CMC, the Go-NoGo task presented in Chapter 3 was modified in order to allow for a more consistent and prolonged forearm muscular contraction during the preparatory period of each trial prior to making a unilateral response. The same visual stimuli were again used to orient the participant's response within a temporally structured and lateralised framework. Prior to the start of each of (ideally) three experimental blocks of 100 trials, maximum voluntary contraction (MVC) was recorded by measuring the grip strength of each hand using a fibre-optic auxotonic-force response device (resistance increasing linearly with displacement) optimised for use in a scanning environment (Current Designs, PA, USA). Using live visual feedback before the trial commenced, in the form of force 'thermometers' **Figure 5.1**, participants were required to maintain a light grip on the response devices with both hands equating to approximately 20% MVC during a 1s period.

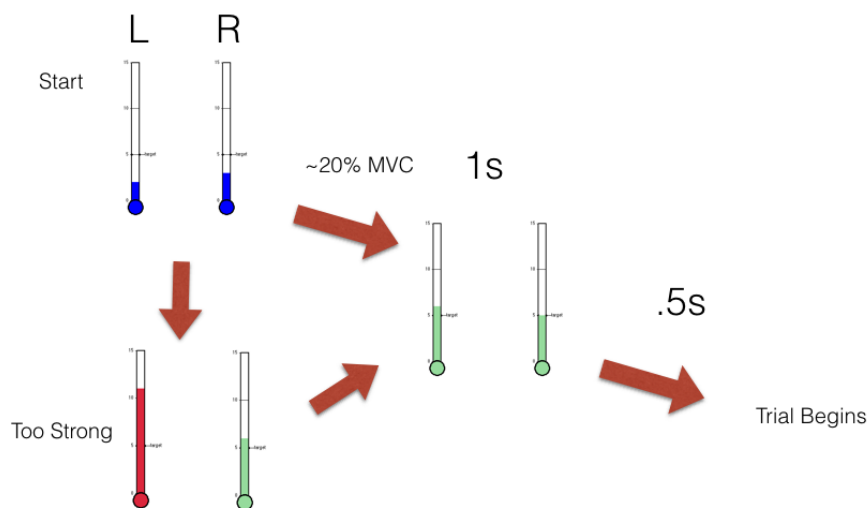


Figure 5.1: Grip force guidance.

Participants were required to maintain a light grip in both hand (guided by on-screen live feedback) for 1 s before a trial began.

The trial then began with a white fixation cross centrally displayed for 0.5s. The remainder of the trial structure then followed the parameters laid out in Chapter 3, with the

additional inclusion of on-screen visual warnings to the participant if grip fell below 10% MVC in either hand during a trial or if a premature response (defined for the purposes of live feedback as 60% MVC) was detected prior to the onset of the Go target. In this instance the trial was repeated. Short breaks were encouraged on screen every 10 trials. These were self-terminated by squeezing the right response device, thus both trial start times and breaks were self-paced. The stimulus presentation and response device interface was coded in Psychtoolbox on Matlab [Brainard, 1997]. A practice session of 10 trials was performed outside of the MSR and repeated if further training was required (< 9/10 correct responses).

Acquisition parameters were identical to those described in Chapter 3, other than the positioning of surface EMG over *flexor digitorum superficialis* using a bipolar configuration with electrodes 2 cm either side of the mid-point of the lead line (depicted in **Figure 5.2**) and a reference electrode on each elbow's lateral epicondyle.

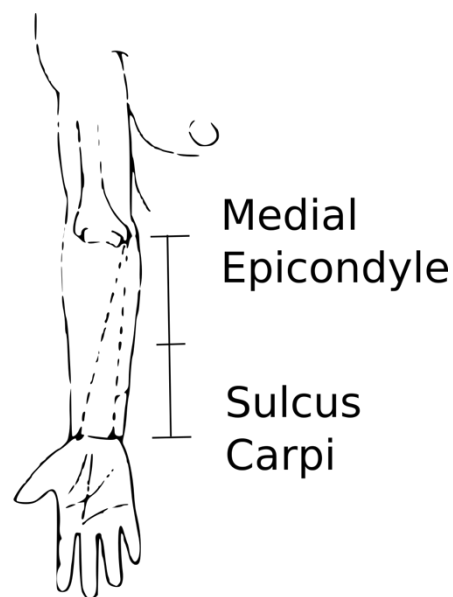


Figure 5.2: Surface EMG placement.

Bipolar surface EMG was positioned mid-way down the ulnar anterior aspect of the forearm.

Two ALS participants had severe enough hand weakness of one hand to necessitate *ad hoc* alteration of the presentation script in order to facilitate unilateral performance of the task. For much of the subsequent MEG analysis, explicitly stated below, this necessitates their exclusion from the study.

5.2.3 Behavioural Data Analysis

Offline analysis of behavioural performance was coded in Matlab. The linear output from each force response device was written to the .fif file as a separate channel. Responses could therefore be ascertained making use of the same stimulus trigger codes used to epoch the MEG data and were also verified by inspection of surface EMG traces contained within the same data structure. A baseline grip period was defined as time of cue appearance ± 0.3 s. Gripper outputs were summed within a sliding window of 60 ms and responses defined as values more than 3 SD above the mean gripper output in the baseline period. A similar analysis was performed on rectified EMG signal after first passing it through a Butterworth low-pass filter; visual examples of this methodology are presented in **Figure 5.3**.

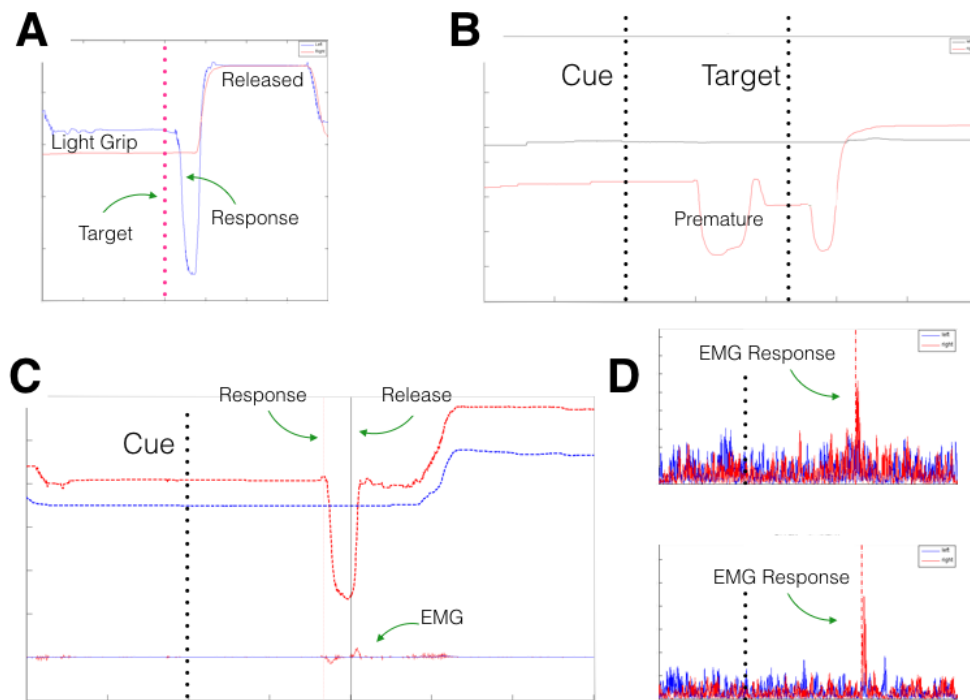


Figure 5.3: Behavioural analysis methods.

Off-line analysis used a combination of gripper and EMG signals. Responses were typically easily detectable unilaterally in the grippers (A) but the algorithm was adapted to detect premature responses (B) and also to detect the time of gripper release (C). Incorrect trials were checked using a similar algorithm for EMG, infrequently detecting responses in EMG only (D).

Each trial result was as a minimum visually checked in a 4x4 array on screen and algorithm failures adjusted accordingly. In summary, a custom-written semi-automated approach enabled reliable and complete appraisal of behavioural performance in a patient cohort with very variable grip strength. Incorrect trials were discarded from the MEG analysis.

5.2.4 MEG Data Analysis

Preprocessing of the current MEG data set followed a very similar pipeline to that presented in earlier chapters, with the addition of off-line creation of new trigger events in the file corresponding to the response grip onset and offset times as determined in the behavioural analysis. Three of 43 participants (one HC, one Mimic and one AGC) could not tolerate MRI due to claustrophobia. Their data remain in the MEG analysis at present, substituting canonical MNI brain templates for coregistration. No ALS participants had significant respiratory compromise to preclude MRI. Within each individual, trials were

excluded on the basis of incorrect behaviour or after falling beyond ‘outlier’ detection thresholds due to noisy MEG data. The outlier detection algorithm *OPT* was implemented in OSL, parameters identical to those applied in Chapter 3.

Analysis of this MEG data set, in parallel with Chapter 3, uses a combination of dimensionality reduction to functionally defined cortical parcels and voxelwise whole-brain multivariate approaches. The detection of task relevant modulations to neural oscillation power is however made more complex by the imprecise temporal definition of a baseline period owing to the self-paced nature of the experimental design.

5.2.4.1 ROI Time Frequency Power

Exploration of time and frequency varying modulation of power was firstly achieved (as in Chapter 3) in epoched data by designating a single timecourse as representative of primary motor cortex. The parcellation structure derived from the Human Connectome Project (also used in Chapter 4) was used to define the region of interest spatially. A single timecourse was extracted by taking the first PCA component (without orthogonalisation to neighbouring parcels). Modulation of neural oscillation power was contrasted either against a pragmatic choice of baseline period (with the proviso that some trial baselines may potentially be contaminated by neural correlates of the participant’s preparation to achieve the light grip) or by comparing oscillatory power in contra versus ipsilateral fashion without imposing a baseline period. Time-frequency transformations were performed using discrete prolate spheroidal sequence (DPSS) tapers with fixed window length (300 ms, 5 Hz of frequency smoothing) as implemented in the Fieldtrip toolbox.

5.2.4.2 Whole-Brain Time Frequency Power

Whole-brain analysis herein circumvented the baseline definition ambiguities by performing multivariate GLM statistics on a continuous data set pertaining to the entire block’s recording. This analysis took advantage of the continuous nature of both the

gripper response output and surface EMG readings, which after some custom preprocessing in Matlab, were entered as dynamic explanatory regressors (one for each laterality) to the first-level GLM. In brief, a baseline value for each gripper output was estimated from a heavily smoothed version of the output. The times of trial engagement and of response execution were then ascertained by identifying gripper output values respectively greater than 1 SD above baseline and values of the differential of the output (within a sliding window) above 10 SD (preprocessing steps represented in **Figure 5.4**).

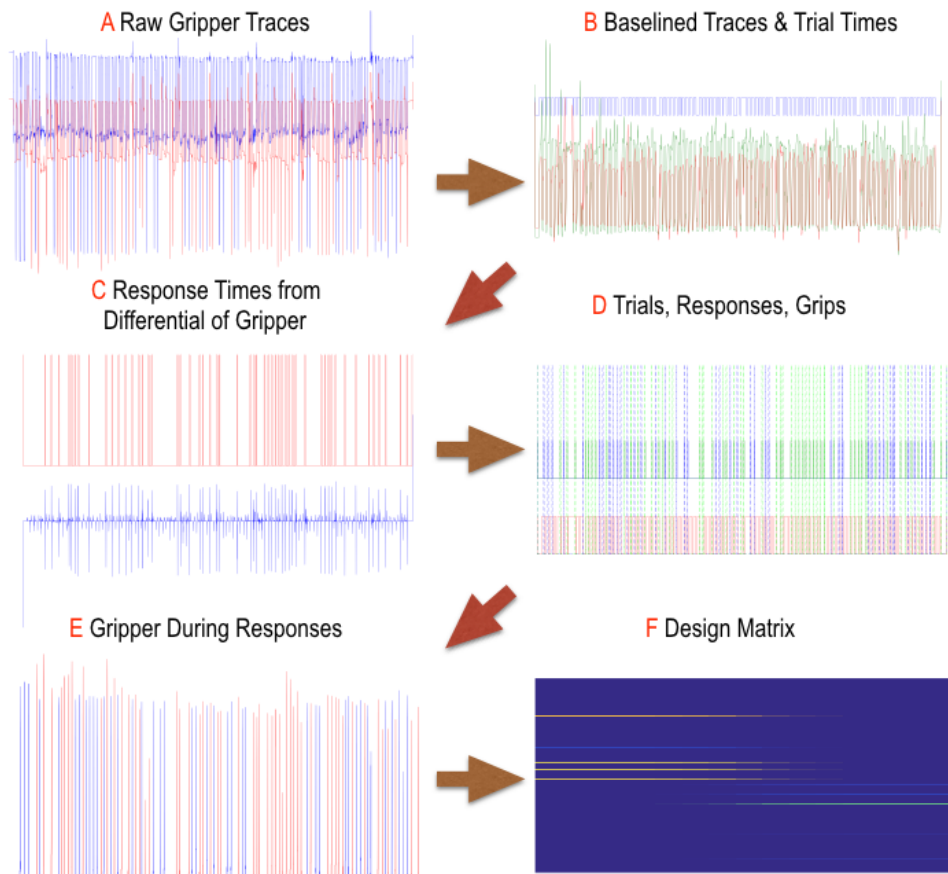


Figure 5.4: Behavioural regressor creation.

Preprocessing steps in the formation of a regressor (F) from the response gripper outputs. Only the gripper output during responses (E) was required, but this first necessitated measurement of baseline during trials (B), identification of response times from the differential of the gripper signal (C) and then restriction of the baselined gripper output to those response times (D).

The continuous EMG regressor from each forearm was more simply formed by taking the Hilbert transform of band-passed EMG data within 55:95 Hz. Both EMG and gripper outputs therefore contain information not only about the timing of a response, but also

the force with which a response is made. The analysis output takes the form of a 3D set of beta band power COPEs (with a 7-mm grid resolution) formatted as .nii which can then be passed to FSL's *randomise* for group inference. 10,000 permutations were performed for group inference using 12 mm of spatial smoothing and threshold-free cluster enhancement to correct for number of voxels included.

5.2.4.3 Cortico-muscular Coherence

A further principle aim of this chapter was the description of CMC in ALS. To this end, the task structure was leveraged to maximise signal to noise ratio in CMC calculation; only the period of auxotonic forearm contraction during response preparation (1.1 s in short trials, 2.1 s in long trials) was selected, since maintenance of a tonic force reliably induces high levels of cortical beta. EMG data were superficially preprocessed using a highpass filter of 1 Hz and then rectified (CMC was readily estimated regardless of rectification [Dakin et al., 2014; McClelland et al., 2012]). Cortico-muscular *communication* was calculated using two complementary methods. Firstly, conventional coherence (a phase based measure, weighted per trial by amplitude, as implemented in FieldTrip) was calculated between Fourier transformed EMG and MEG (all voxels within the 'M1' HCP parcel, non-orthogonalised) using DPSS tapers with a frequency smoothing kernel of 5 Hz across 0.25 Hz steps from 1 to 40 Hz. This transformation was performed twice, initially keeping time resolution and subsequently collapsing across time to reduce within subject variability (CMC was quite consistent across that preparatory time period). Secondly cortico-muscular *communication* was also estimated from 5 Hz Hilbert envelope time-courses that were generated from the parcellated data and EMG in 1-Hz steps from 3 to 40 Hz. Coherence was then calculated as a Pearson correlation between the time courses. The output from both methods was averaged across the number of voxels (~130 at 6-mm gridstep) that made up the cortical parcel.

5.2.4.4 Cortico-cortical Coherence

The final analysis approach to this data set concerned the estimation cortico-cortical communication during an active task setting. Of *a priori* interest was the strength (in terms of functional connectivity) with which the two motor cortices (designated as seed regions) communicated with the remaining brain [Nicolo et al., 2015]. This method corresponds very closely to the Hilbert enveloped correlation calculation of CMC and selectively took account of the same specific preparatory time period in the task structure. Importantly however, neural time-series from each of 39 cortical parcels were orthogonalised (as per Chapter 4) prior to the first PCA component being extracted. Data were concatenated across sessions, and then Hilbert transformed in 7-Hz envelopes from 4 to 45 Hz in 0.5 Hz steps. For group inference, sensori-motor parcels ($n = 5$) contralateral to motor-cortex seeds were simply averaged (permutation across parcels is not readily interpretable due to varying dimensions and complex 3D arrangement). A single vector of cross-hemispheric power-enveloped coherence resolved by frequency was thereby generated per participant. Group comparisons were performed using cluster-permutation statistics as implemented in FieldTrip with 5000 permutations in group labels and cluster-forming alpha of 0.025.

5.3 Results

Data from 39 individual participants were available for the analysis.

5.3.1 Behavioural

In general, the participants adhered well to the task. Limiting factors restricting the total number of trials acquired included fatigue, time restraints and (in the case of one AGC) claustrophobia. The average total number of trials successfully recorded by each participant is shown by group in **Figure 5.5a**, the number recorded by ALS participants was not significantly different from HC ($p = 0.094$). Across all participants combined, there was no significant effect of cue validity on reaction times to short ISI trials **Figure 5.5b** ($p = 0.77$) nor was there any effect of ISI length (foreperiod) in reducing RT ($p =$

0.85). Repeated measures ANOVA did not reveal any significant interaction between group and either ISI ($p = 0.72$), validity ($p = 0.23$) or ISI*validity interaction ($p = 0.33$). Non-significant group differences in median RT (collapsing across trial type, correct trials only) are displayed in **Figure 5.5c** (one-way ANOVA, $p = 0.63$, confirmed in post-hoc unpaired t-tests). There were no group differences in the rate of mistakes made during noGo trials (**Figure 5.5d**, $p = 0.97$), nor were there in the calculated inverse efficiency (**Figure 5.5e**, $p = 0.73$). Across groups there was an effect of post-noGo slowing by a mean of 12.1 ms ($t(39) = -2.66$, $p = 0.01$) and with this measure was a group interaction approaching significance (**Figure 5.5f**, $F(3,38) = 2.82$, $p = 0.052$, driven by the mimic group).

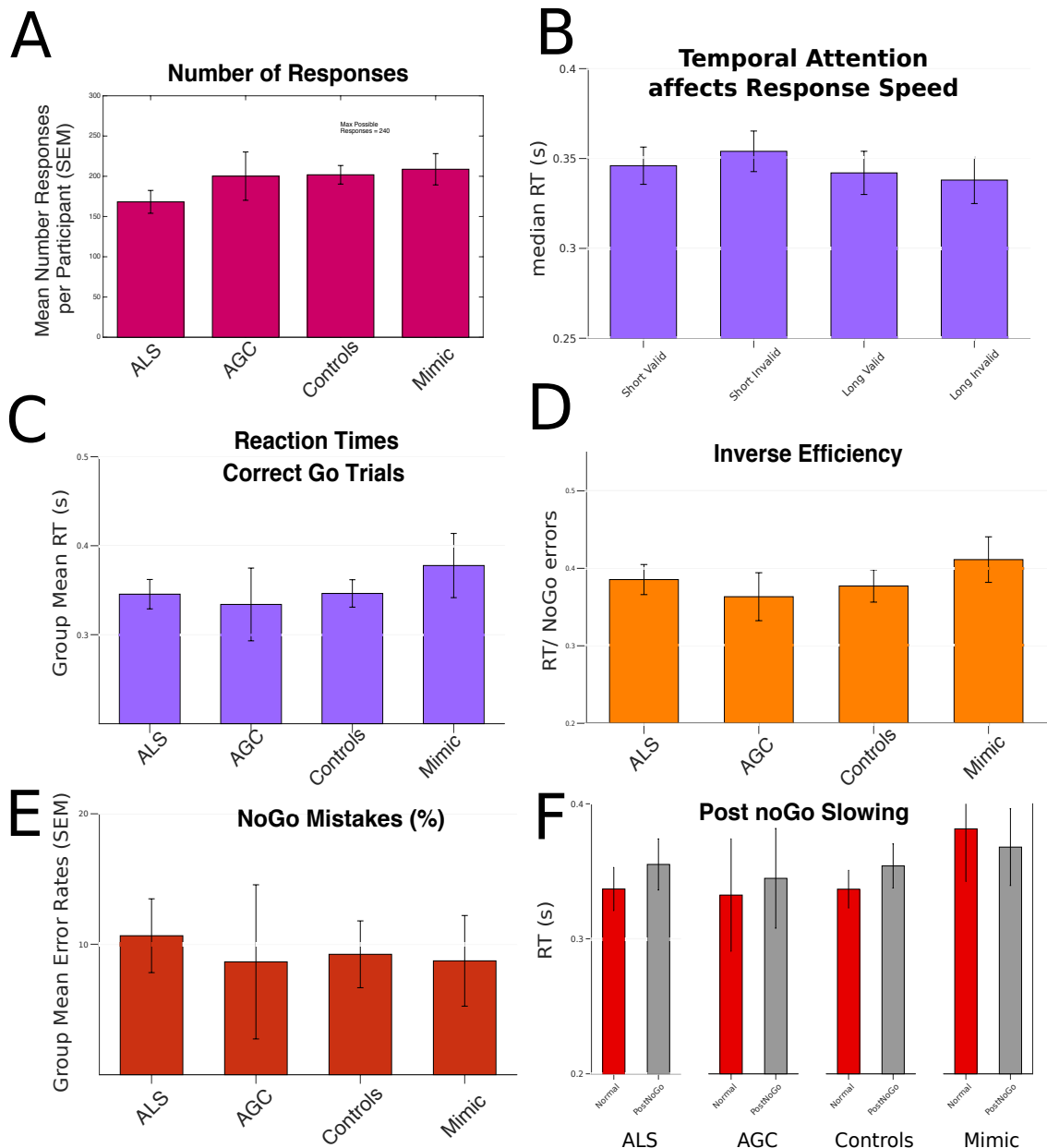


Figure 5.5: Behavioural results.

Behavioural data demonstrating overall comparable task performance between participant groups. On average, slightly less data were acquired from ALS patients (A, $p = 0.094$) and disease mimics did not show the expected pattern of slower response in the trial after a noGo event (F, $p = 0.045$) but there were no other significant group differences in RT (C), inverse efficiency (RT/noGo % error, D) or noGo % error (E).

5.3.2 Motor Cortex ROI Oscillations

Figure 5.6 shows the overall impact of task performance on neural oscillations within the motor cortices. During the period of auxotonic grip (approximately 1 s either side of cue at $t=0$), power in the beta-band range was elevated in all 4 participant groups. Beta power

appeared relatively reduced in both ALS and AGC groups, but this failed to survive correction for multiple comparisons. After baseline subtraction the increase in beta power was more prominent, but statistically reduced in the ALS group in comparison to HCs (permutation of groups with cluster-based inference across time and frequency, $n = 17/11$, $p < 0.01$). A decrease in beta power lateralisation (contralateral relative to ipsilateral hemisphere) was also noted and appeared less prominent in the ALS group (relative to HC, $p = 0.37$, not significant). No clear attentional modulation by temporal cues of time-frequency power was demonstrated (contrasting short-cue trials against long-cue) in any group.

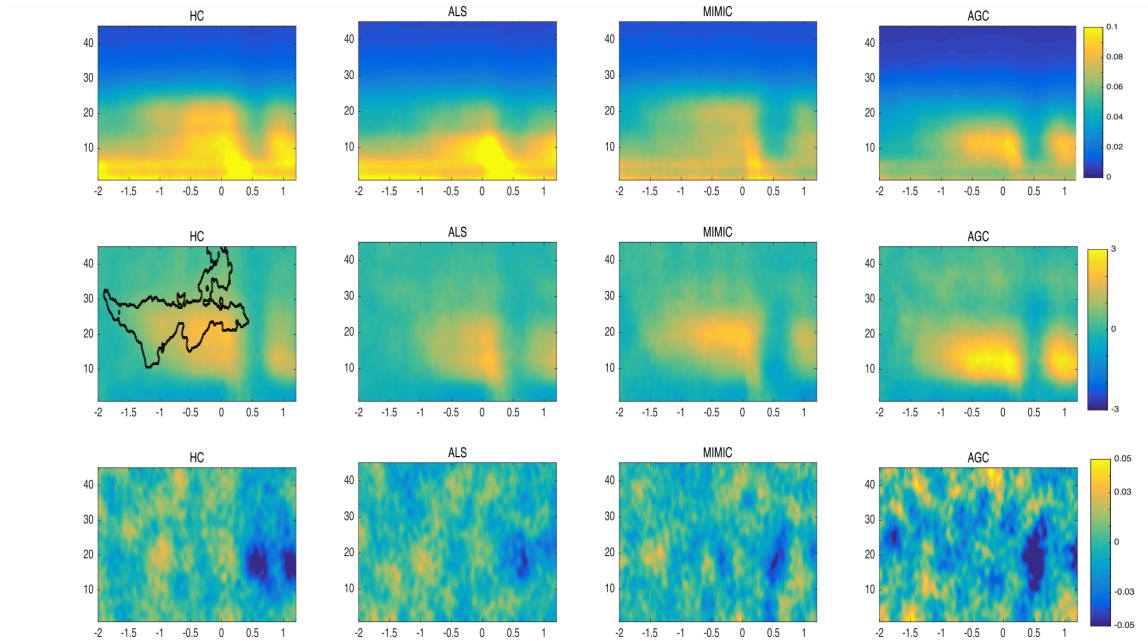


Figure 5.6: TFRs from the motor cortex ROIs

$t_0 = \text{cue}$. Non-baselined data (top row) shows increase in beta power during auxotonic grip, most prominent in HC. Baselined data (middle row, decibel scale, baseline period -2.5: -1.5 s) shows ALS patients increased beta power less far from baseline than HC (significant cluster outlined in black, $p < 0.01$). After the cue was visually presented (t_0), beta power was decreased in the contralateral ROI (relative to cue laterality) versus the ipsilateral (bottom row). This effect appears less prominent in the ALS group than HC (but not significantly so, $p = 0.37$).

5.3.3 Whole-Brain Beta Oscillations

Source reconstructed MEG data were generated to track the beta power envelope continuously over the course of a ten-minute task block. This confirmed event-related

desynchronisation that temporally correlated with the continuous regressors generated from both gripper responses (**Figure 5.7**) and filtered EMG power (**Figure 5.8**).

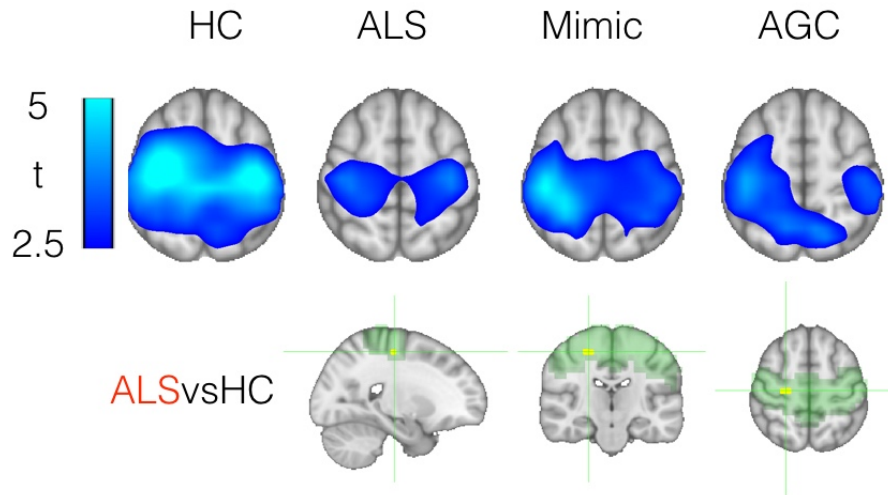


Figure 5.7: Voxelwise MEG data – gripper output regressor.

Top row shows beta desynchronisation within participant groups regressed out by the gripper output traces from each hand. Bottom row shows contrast between ALS and HC, statistics restricted to a bilateral motor cortex mask (green), small significant cluster (yellow, $p = 0.049$) within the contralateral motor cortex.

All groups demonstrated this neural response, bilaterally over the motor cortices, but ALS patients in particular showed a reduced tendency to desynchronise beta coincident with responses. Statistical comparisons found two group contrasts to remain significantly different. In the gripper regression data ALS versus HC revealed a small cluster in the contralateral hemisphere (**Figure 5.7**, bottom row), while in the EMG regression data ALS versus Mimics revealed large areas of significantly reduced beta desynchronisation including motor cortices bilaterally (**Figure 5.8**, bottom row).

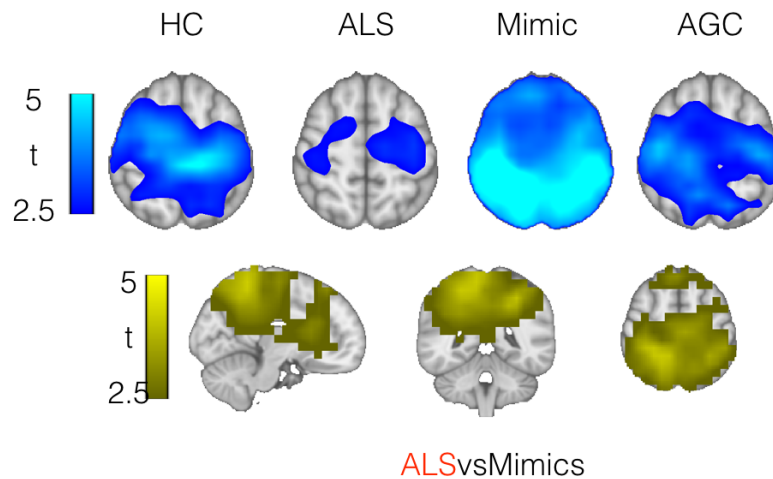


Figure 5.8: Voxelwise MEG data – surface EMG regressors

Top row shows beta desynchronisation within participant groups regressed out by the filtered EMG power traces from each forearm. Bottom row shows contrast between ALS and Mimics, large significant clusters (yellow, $\min p = 0.015$) including bilateral motor cortices.

5.3.4 Cortico-Muscular Coherence Reduced by ALS

CMC was first investigated in all subjects across the timespan of the trial structure (Figure 5.9, t_0 = cue). This did not reveal any definite modulation of CMC in preparation for impending movement; the CMC is therefore assumed to be primarily generated in the course of auxotonic grip maintenance.

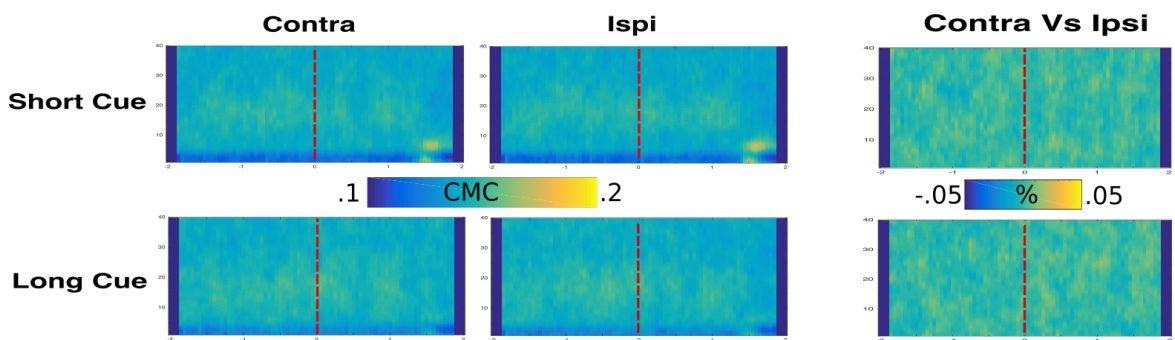


Figure 5.9: Lack of task structure effect on CMC

CMC data from all participants combined, measured between motor cortices and contralateral forearm (t_0 = cue, red dashed line). CMC is evident throughout the course of preparation for movement, regardless of either the anticipated movement's laterality or the temporal proximity of the upcoming target appearance. Contra- and ipsi- labels refer to the direction of the cue with respect to the hemisphere generating CMC. No clear frequency dependent CMC band in the contra versus ipsi contrast was evident.

An event-related field effect common to both muscle and cortex was demonstrated at the time of response (typically 1.5 s), but there was no evidence of a gamma-band modulation to CMC centred around the response time (**Figure 5.10**, $t_0 = \text{response}$).

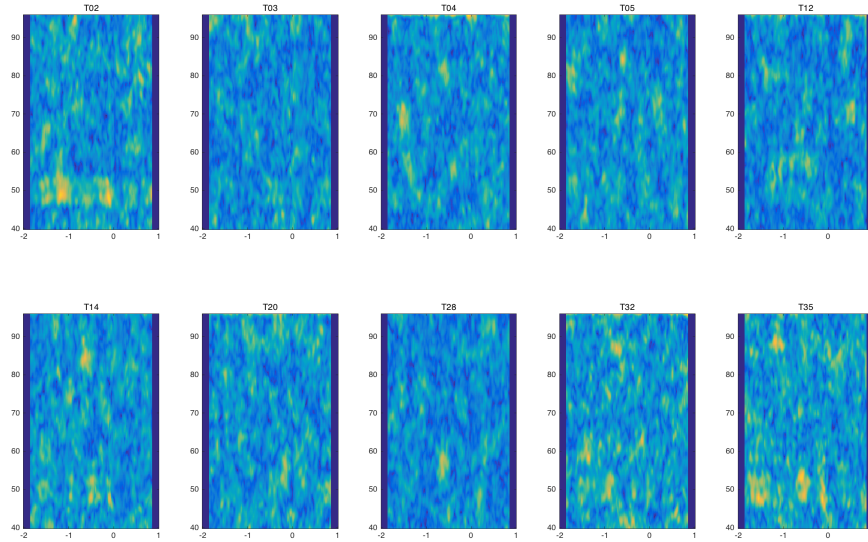


Figure 5.10 Absence of gamma-band CMC

CMC from motor cortex contralateral to responding arm ($t_0 = \text{response}$). Data from 10 individual HCs did not reveal any response related increase in CMC in the gamma band (some line noise coherence at 50 Hz was noted in two participants).

CMC (between motor cortex and the contralateral forearm) did not appear to differ significantly with respect to the subsequent response laterality nor with respect to the expected timing of target appearance (as denoted by temporal information content within cue). Comparisons across groups (**Figure 5.11**) did however clearly suggest an effect of ALS group membership on beta CMC strength (without any interaction with cue laterality or temporal nature). Group contrasts were therefore appraised after collapsing time within the auxotonic grip preparatory period only.

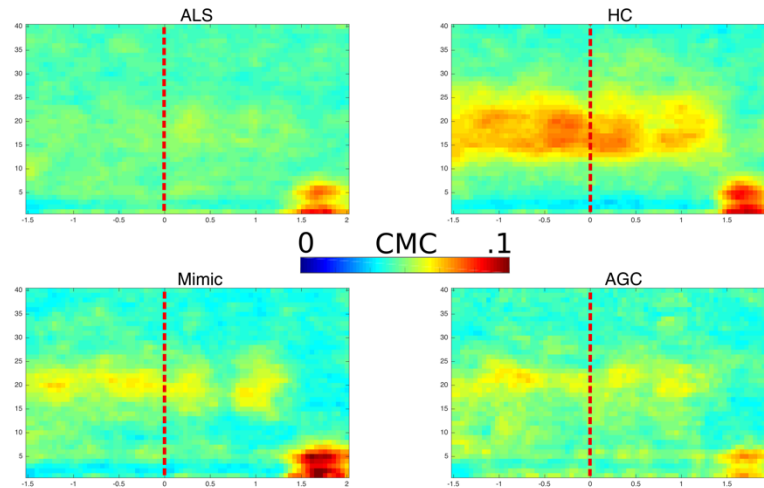


Figure 5.11: Beta-band CMC across time.

Time resolved CMC split by groups (t_0 = cue, red dashed line). Loss of CMC particularly within the beta range was noted particularly in ALS participants (top left) versus HCs (top right). Statistical comparison was performed on time collapsed CMC (below) to reduce noise within individuals.

Contrasting ALS participants against HCs revealed a striking loss of frequency-specific CMC expression. CMC was significantly reduced within the range 20:28 Hz (cluster permutation across frequency, $n = 17/11$, $p = 0.021$, **Figure 5.12**).

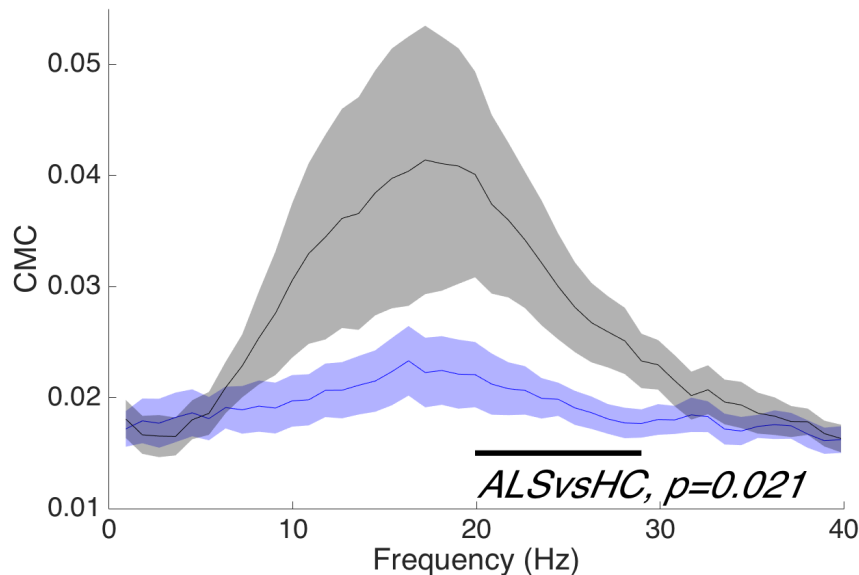


Figure 5.12: Beta-band CMC – time collapsed.

Time collapsed CMC in HC (grey) and ALS (blue). Shaded area = SEM. Horizontal bar = frequency range of significantly different CMC after cluster permutation correction.

As demonstrated in **Figure 5.13**, CMC was preserved within the group of AGCs but (non-significantly) disrupted with the disease mimic group.

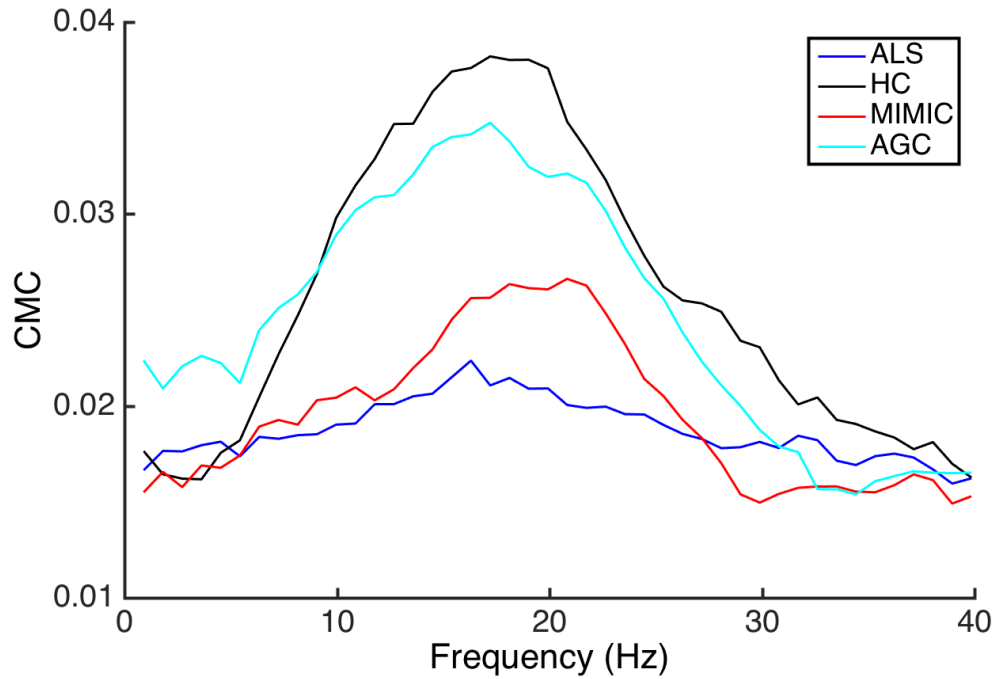


Figure 5.13: Beta-band CMC – all groups.

Mean CMC within each participant group.

Inspection of Hilbert envelope cortico-muscular correlation also confirmed a very similar loss of frequency specific CMC in ALS, significant between 17:24 Hz ($n = 17/11$, $p = 0.011$, **Figure 5.14**).

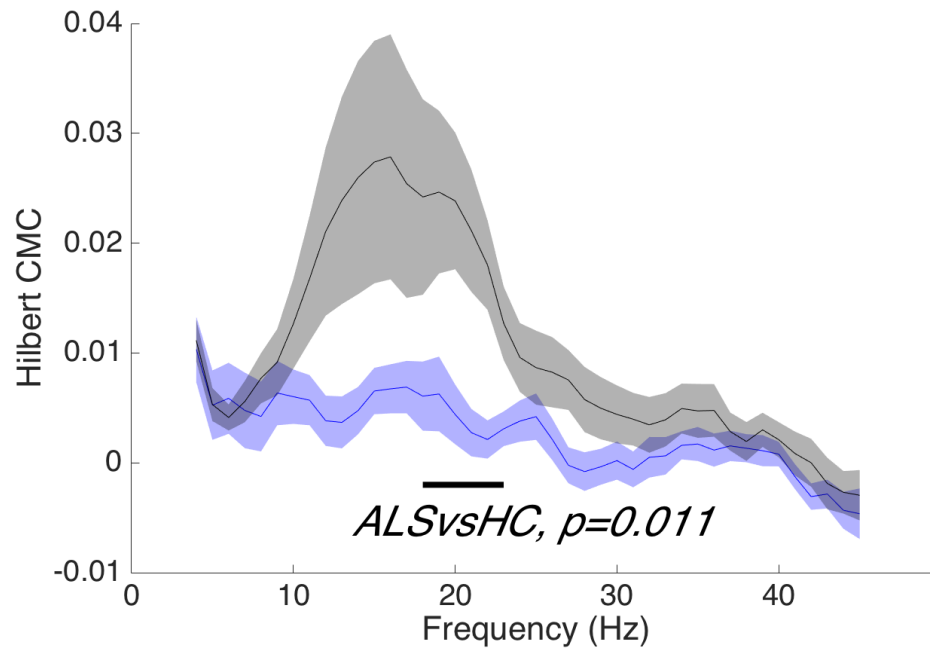


Figure 5.14: Time collapsed Hilbert CMC – ALS and HC.

HC (grey) and ALS (blue). Shaded area = SEM. Horizontal bar = frequency range of significantly different Hilbert CMC after cluster permutation correction.

The group differences were directionally similar to the conventional coherence metric of CMC. CMC between motor cortex and ipsilateral forearm was consistently lower than between motor cortex and contralateral forearm. A non-significant augmentation of contralateral Hilbert CMC was evident in the AGC group.

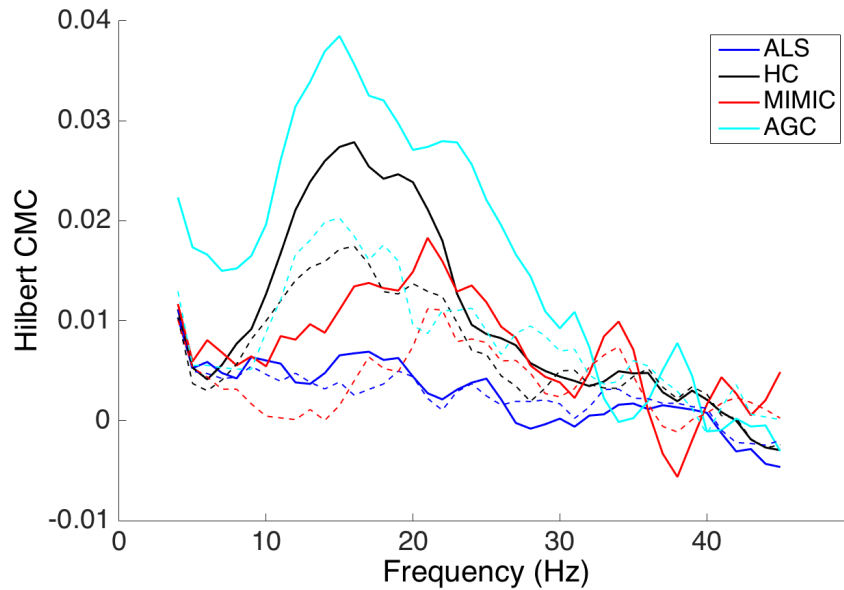


Figure 5.15: Hilbert CMC – all groups, contra and ipsi.

Mean Hilbert envelope CMC within each group. Solid line = correlations between Hilbert envelopes of motor cortex and contralateral forearm, dashed line = ipsilateral forearm.

Both measures of contralateral CMC (individual measures averaged within the frequency range of the above described significant group differences) were found to be non-parametrically distributed according to both Kolmogorov-Smirnov and Shapiro-Wilk tests. Kendall's Tau was therefore chosen as a more robust indicator of clinical correlations. Across all participants there was no significant correlation between CMC (whether calculated conventionally or via Hilbert envelope) and measures of peripheral grip strength (according to the individual's target grip value), mean or SD of the surface EMG and mean or SD of the gripper output. CMC was not therefore simply related to total muscle activity.

Task performance, as indexed by the inverse efficiency, was worse with increasing age ($\tau = 0.37$, $p = 0.001$). Partial correlations were therefore performed within the 15 remaining ALS participants after correcting for age. No significant linear correlations were found between standard clinical metrics and either CMC or Hilbert CMC (Kendall's Tau values presented in **Table 5.2**).

	<i>Median RT</i>	<i>noGo Mistakes</i>	<i>Inv Efficiency</i>	<i>CMC</i>	<i>Hilbert CMC</i>	<i>ALSFRS ALSFRS</i>	<i>ALSFRS ul</i>	<i>Rate</i>	<i>Duration</i>	<i>UMN</i>	<i>Cognition</i>
<i>Median RT</i>											
<i>noGo Mistakes</i>	-.384										
<i>Inv Efficiency</i>	.654	.445									
<i>CMC</i>	.291	-.332	-.008								
<i>Hilbert CMC</i>	.044	-.556	-.409	.527							
<i>ALSFRS</i>	-.269	-.090	-.341	.140	.163						
<i>ALSFRS ul</i>	-.237	-.011	-.252	.305	.141	-.196					
<i>Rate</i>	.142	-.250	-.085	-.008	-.229	-.654	.378				
<i>Duration</i>	-.104	.008	-.048	-.274	.190	.282	-.520	.653			
<i>UMN</i>	.529	-.234	.329	-.256	-.115	-.496	.152	.496	-.254		
<i>Cognition</i>	.367	-.205	.184	.132	.082	.276	-.166	-.128	.415	.140	

Table 5.2: Non-significant CMC clinical correlations

Correlation values (Kendall's Tau) between clinical metrics and CMC. No significant correlations were found.

5.3.5 Cortico-cortical Communication Disruption

Communication between cortical parcels was appraised after source-leakage correction (a spatial structure emphasising the functional relevance of this connectivity metric) was revealed. Motor cortex Hilbert enveloped (ie band-limited power, BLP) timecourses correlated strongest with anatomically neighbouring regions and also with corresponding sensorimotor regions in the opposite hemisphere. A frequency structure was also noted, with coherence highest in the beta range, in keeping with the elevated beta power induced by the light grip (during which this measure of FC was appraised). Group differences were suggested on inspection of coherence between motor seeds and all remaining parcels. FC appeared to be decreased in ALS patients (**Figure 5.16**) and increased in AGCs (**Figure 5.17**).

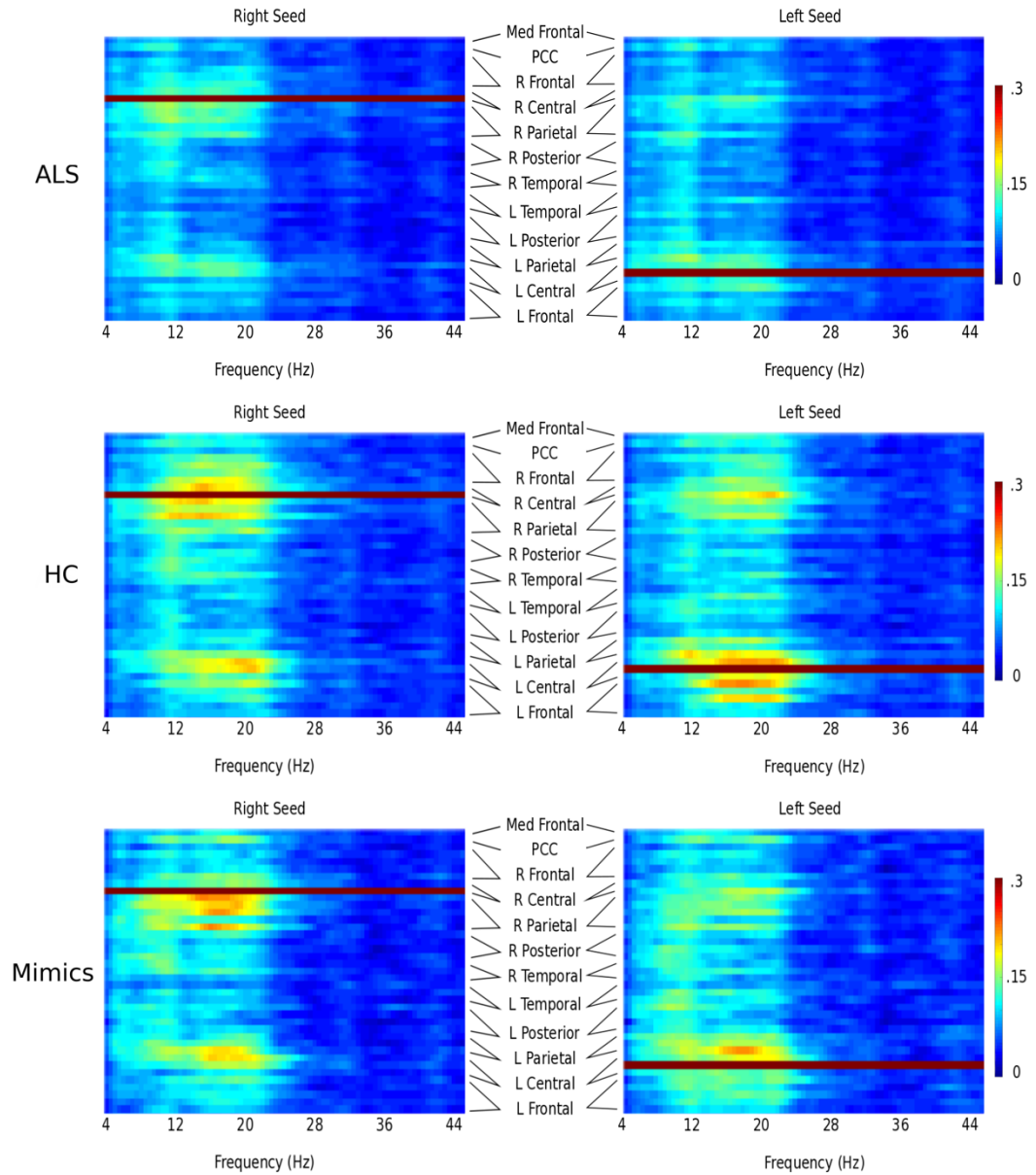


Figure 5.16: Cortical functional connectivity – ALS, HCs & Mimics.

Hilbert envelope power correlation between cortical parcels during light grip. In all groups, the highest correlation was within the beta range and with parcels anatomically proximal to the motor cortex seed but also to the contralateral sensorimotor regions. Correlation values appeared lower in ALS.

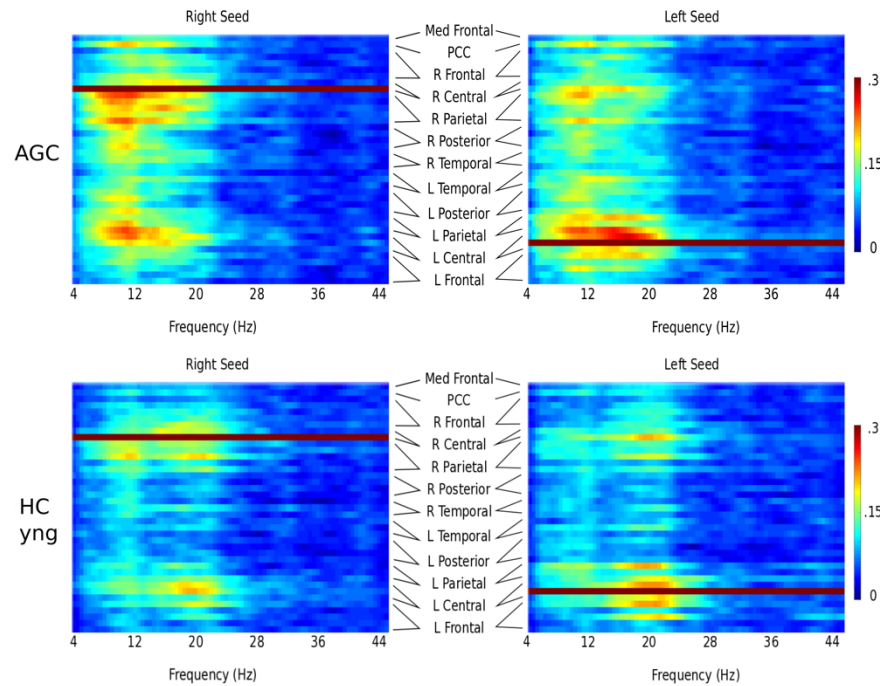


Figure 5.17: Cortical functional connectivity – AGCs & HCs.

Cortical Hilbert envelope power correlations in AGCs appeared higher than in age-matched HCs, with similar spatial structure but slightly lower in frequency.

Statistical group comparisons were limited to the cross-hemispheric communication between sensorimotor regions. The frequency-dependent structure to FC, maximal in beta, was again confirmed. Permutation and clustering across frequencies detected lower FC in ALS patients than HC ($n = 17/11$, $p = 0.021$, **Figure 5.18**) but not significantly lower than disease mimics (**Figure 5.19**).

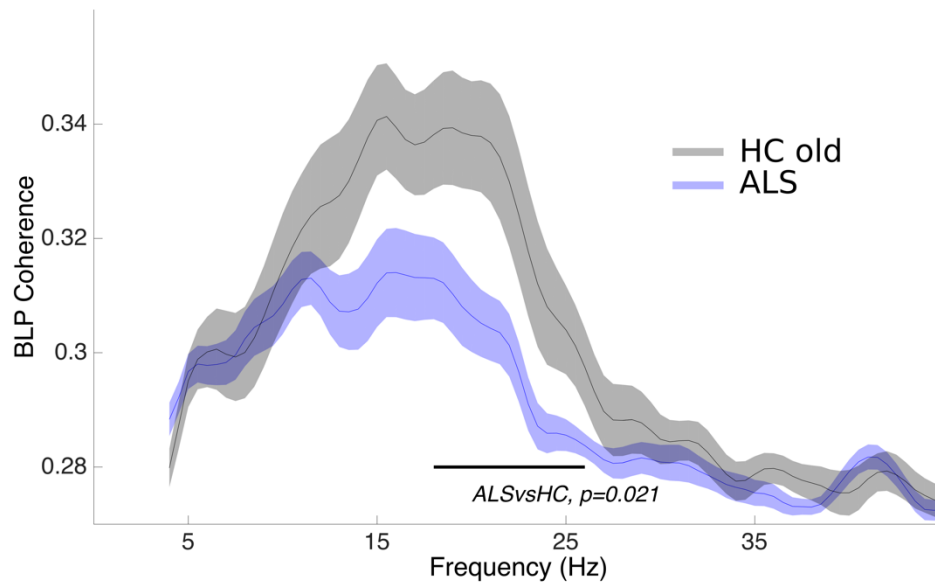


Figure 5.18: Motor functional connectivity across hemispheres – ALS versus HC.

Hilbert envelope power correlations between motor ROIs and contralateral sensorimotor parcels. Shaded area = SEM. Horizontal line = significant frequency cluster.

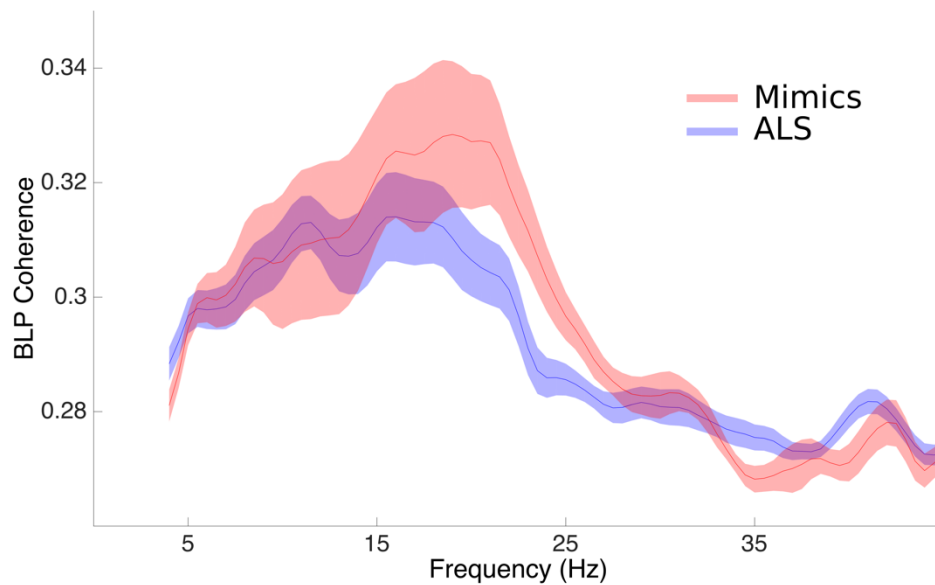


Figure 5.19: Motor functional connectivity across hemispheres – ALS vs mimics.

Motor cortex Hilbert envelope power correlation contrasted between disease mimics and ALS. No significant differences were found after cluster permutation correction.

AGCs appeared to have a slightly lower peak frequency of FC between sensorimotor regions, with a similar absolute level of BLP coherence, and no significant group differences by permutation testing.

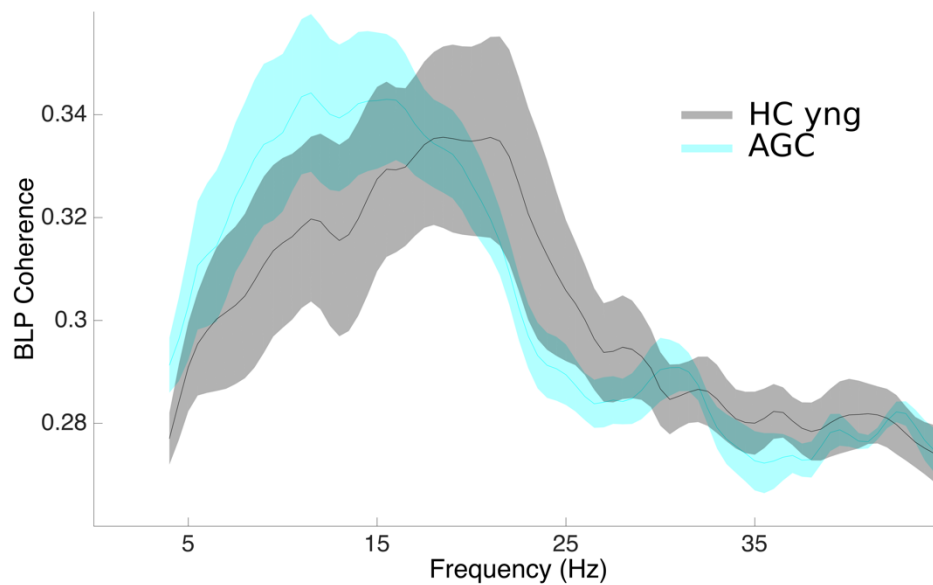


Figure 5.20: Motor functional connectivity across hemispheres – AGC vs HC.

Motor cortex: Hilbert envelope power correlation contrasting AGCs and younger HCs. No significant group differences were detected.

5.4 Discussion

5.4.1 Summary

This chapter presents novel evidence of functional alteration to cortical motor output in ALS. Beyond CMC, communication between the motor cortices and other cortical regions also appears to be altered by ALS. In particular, during an auxotonic light grip, interhemispheric beta oscillation coherence was significantly diminished relative to healthy controls (with a directionally similar tendency relative to disease mimics). AGCs did not appear to share abnormal CMC values, and, to an extent, also showed directionally divergent effects on cortico-cortical coherence.

5.4.2 Activity Dependent Functional Connectivity in ALS

The results confirm expectations set by the reliably abnormal IMC values demonstrated within a group of PLS patients [Fisher et al., 2012], emphasising therefore that CMC, IMC or even bilateral EMG coherence (to the extent that it shares some common input [Boonstra et al., 2009]) could serve as a marker of UMN dysfunction in ALS. Moreover,

the Newcastle group have, in unpublished work [Jaiser, 2014], subsequently demonstrated that ALS patients also show reduced IMC, albeit not to the extent needed for a diagnostic test. IMC had comparable discriminatory power to CMCTs in the same patient cohort (ROC area under curve 0.83 in the upper limb). Of particular relevance to the present chapter's failure to distinguish between ALS and Mimics on the basis of their CMC, the Newcastle group also demonstrated abnormally low beta IMC in a group of 7 patients with MMN. Both sets of results might therefore be explained by either abnormal (but necessarily subclinical) sensory dysfunction in MMN [Corse et al., 1996; Delmont et al., 2009] or a direct influence of MMN on the CST itself, in keeping with occasional 'soft' UMN clinical signs [Cats et al., 2010] and prolonged CMCTs in patients with anti-ganglioside antibodies [Oshima et al., 2002].

Considering the absence of correlation with admittedly crude clinical rating scales, what is the functional consequence of alterations to both the physiological neural oscillations associated with a grip task and their synchronisation through the CST? Rather than simply reflecting CST dysfunction, might reduced beta CMC perhaps be a manifestation of attempted compensation for motor system degeneration? Periods of elevated beta synchrony have been associated with prolonged reaction time latencies [Gilbertson et al., 2005; Matsuya et al., 2013] and beta CMC reliably dissipates with movement. Reduced CMC could therefore result from ALS patients' need to disproportionately mentally prepare for the upcoming movement, ostensibly in keeping with subjectively greater task difficulty since task practice has been shown to result in higher levels of beta CMC [Larsen et al., 2016]. The lack of evolving gamma CMC in the course of preparation renders this line of reasoning difficult to defend, but relative CMC lateralisation in the ALS group might simultaneously have been compromised by dysfunction of interhemispheric communication [Karandreas et al., 2007].

Minor sensory deficits in ALS [Iglesias et al., 2015] might also affect the ascending component of CMC. Nerve conduction studies were not always required in the diagnostic workup for the ALS participants and this cannot therefore be excluded. However, sensory abnormalities would fail to account for the finding of impaired interhemispheric FC in ALS in the present chapter, which in itself warrants further consideration given the prevailing resting-state findings of increased FC in ALS. A key factor is the substantial difference in physiological state between the motor cortices at rest and during a task, in this instance requiring active maintenance of a prolonged constant grip force. Coupling within the sensorimotor system may depend upon the pyramidal neuron activity levels (spike counts increase with movement [Lemon et al., 1986], so that beta oscillations are not simply an ‘idling’ rhythm). Higher beta power is likely (but not inevitably) to translate to higher beta envelope correlations and group differences in other frequency envelope correlations were negligible. The directionally-divergent findings in the small group of AGCs might be a chance finding, but other examples of so-called ‘inverted U-shaped’ evolution of abnormalities as neurodegeneration progresses are reported and often concluded to be examples of short-lived (but perhaps transiently successful) compensation [Scheller et al., 2014]. Somewhat tangentially, increased CMC overnight is described in the context of idiopathic REM sleep behaviour disorder, suggestive of inappropriately increased locomotor drive [Jung et al., 2012]. The severity of these symptoms is a well-known predictor of subsequent Parkinson’s disease development [Postuma et al., 2010], therefore abnormally increased CMC, albeit confirmed only in specific circumstances, might be an early marker of neurodegeneration.

5.4.3 Limitations and Future Considerations

Group differences in behaviour were reassuringly minimal in this task setting, but even slight alterations in, for example, movement speed could have substantial impact on the accompanying neural oscillations and their coupling [Toma et al., 2002]. In contrast to the

experimental design presented in Chapter 3, certain identification of an activity-free baseline period (inasmuch as that ever exists) was prohibited by the visual feedback used to guide consistent grip. The time-frequency plots from motor cortex ROIs, even without baselining, are still suggestive of reduced beta power during grip in patients with ALS (both absolute and baseline relative levels of beta are important age-dependent co-factors for successful movement [Heinrichs-Graham and Wilson, 2016]). Furthermore, the continuous whole-brain analysis and all measures of coherence are not baseline dependent. An additional potential confounder to consider is that ALS patients (as expected) typically had weaker MVC than HCs, and the light grip required was a proportion of MVC. The reduced cortical beta could directly reflect this, and in turn lead to reduced CMC. However, as previously discussed, neither measure is simply related to force exertion [Stančák et al., 1997] and, in this study, CMC correlated poorly with grip outputs and surface EMG. Additional reassurance is provided by findings that muscle fatigue, in this instance experimentally induced by prior sustained effort to exhaustion, enhances beta CMC [Ushiyama et al., 2011].

A further consideration is that the cortical sources implicated in the generation of CMC could, as a result of plastic reorganisation in the face of ALS pathology, be more dispersed across extra-motor regions thereby leading to an underestimation of beta CMC values. Evidence in favour of this hypothesis draws on the task-fMRI literature in ALS that include abnormal activations in the ipsilateral motor [Schoenfeld et al., 2005], parietal [Poujois et al., 2013] and superior temporal regions [Stanton et al., 2007a]. Although the whole-brain analysis in this chapter did not reveal a unique spatial distribution of beta desynchronisation during responses, a future analysis strategy could compare groups via the peak spatial location for CMC, the results of which would not detract from the present findings.

The diagnostic discriminatory capabilities of CMC are principally limited in the described results by the wide variation of beta CMC levels within the HC group, which hinders the definition of normative range of values. Experimental paradigms can be carefully designed to maximise the expression of CMC within all individuals, for instance inducing motor adaptations via a learning task before measuring CMC [Mendez-Balbuena et al., 2012b]; this would however complicate interpretation of group differences if learning was not evenly effective.

CMC might in future prove more useful as a longitudinal marker of disease progression within individuals, and might also respond favourably to symptomatic treatment (CMC varied with fatigue levels in MS patients [Tomasevic et al., 2013]) or a disease-modifying agent (although no IMC difference across patients was noted with respect to riluzole use [Fisher et al., 2012]). Modulation of CMC is possible with neuro-stimulation: rhythmic cortical TMS stimulation at beta frequencies was shown to have variable CMC entrainment capability, enhanced by adjusting stimulation to intrinsic beta rhythms [Romei et al., 2016], while transcranial direct current stimulation (tDCS) may also effect movement-related cortical oscillations [Hanley et al., 2015]. Neural oscillations and their propagation through extensive motor systems remain therefore a potentially attractive, non-invasive, pharmacodynamic marker of target engagement, particularly relevant to therapies aimed at successful long-term reduction of cortical hyper-excitability.

Chapter 6 Conclusions

In this final chapter, I will first consider the contributions made by these investigations to the neurodegeneration biomarker field, both in terms of furthering evidence for disease mechanisms and in expanding the range of methods to measure the ALS process *in vivo*. Secondly I will discuss potential improvements to the current MEG experimental paradigms and analyses, addressing their limitations and considering some expanded applications. Finally, I will consider novel directions into which MEG technology could be applied for ALS clinical research with particular respect to neuro-pharmacology, neuro-stimulation and multimodal studies.

6.1 Cortical Neurophysiology in Context

6.1.1 Mechanistic Insights into ALS

In broad terms, the findings presented in Chapter 3 provide further evidence in support of excitotoxicity as a key mechanism behind ALS development. A more pronounced beta ERD and delayed PMBR are in keeping with hyper-excitable physiology [Steriade and Llinás, 1988; Whittington et al., 1995; Yamawaki et al., 2008]. As indexed by increasing MEP amplitude, motor cortex excitability is elevated in advance of EMG activity (albeit without modulation by task difficulty) [Leocani et al., 2000a] while PMBR closely corresponds to TMS excitability decreases [Chen et al., 1998]. A positive correlation has been described between resting primary motor cortex GABA levels measured by MRS and PMBR intensity [Gaetz et al., 2011]. By contrast, a multimodal task-based MRS and EEG study demonstrated a relationship between lateral occipital cortex glutamate concentration and only visually evoked gamma, not beta or alpha [Lally et al., 2014]. Pharmacological manipulations in healthy volunteers have also explored these physiological relationships. Beta ERD was augmented (and PMBR unaffected) during increased GABA-A tone 30 minutes after diazepam administration [Hall et al., 2011b]. Unlike the simultaneous increase in baseline beta power and contrary to expectations, this

facilitation of beta ERD was not associated with performance benefit. It was consequently explained in terms of a secondary effect mediated by remote neural circuitry. In a complementary MEG study, blocking GABA re-uptake with tiagabine confirmed the enhancement of beta ERD but also noted augmentation of PMBR (without affecting gamma reactivity), potentially indicating diverse effects of GABA subtypes [Muthukumaraswamy et al., 2013]. These dynamic relationships between neurotransmitter levels (only portions of which are visible to MRS [Cousijn et al., 2014]) and neural oscillations may therefore vary depending on the cognitive context and cortical region of interest. For example, visual but not motor gamma power increased with lorazepam administration [Lozano-Soldevilla et al., 2014].

Excitotoxic disease mechanisms should not be considered unique to ALS pathophysiology. An imbalance between neural excitation and inhibition has been implicated by TMS studies in a diverse range of neurological and psychiatric conditions, including (but not limited to) autism [Dickinson et al., 2016], schizophrenia [Daskalakis et al., 2002], progressive epilepsies [Manganotti et al., 2001], Alzheimer's disease [de Carvalho et al., 1997; Ferreri et al., 2011; Di Lazzaro et al., 2004; Pierantozzi et al., 2004] (but not in [Pepin et al., 1999]) and, yet more inconsistently, Parkinson's disease (reviewed in [Lefaucheur, 2005] and explored longitudinally in [Kojovic et al., 2015]). The impact of such diseases on cortical oscillations has accordingly been quite widely appraised in both motor and cognitive paradigms. Similar inferences regarding hyper-excitable cortical neurons are frequently drawn though compensation for dopamine depletion [Rowland et al., 2015] or pathological synchronisation with sub-cortical circuitry are additional major considerations [Brown, 2007]. By way of example, marked increase and topographic expansion of beta ERD and frequent absence of PMBR were noted in Unverricht–Lundborg type progressive myoclonic epilepsy [Silén et al., 2000; Visani et al., 2006],

although beta ERD appeared reduced pre-movement in patients with juvenile myoclonic epilepsy [Hamandi et al., 2011]. As in our own investigations, the confounding influence of concomitant medication was considered but not readily confirmable, in contrast to studies specifically investigating the acute effects of L-Dopa administration to Parkinson's patients [Devos et al., 2003; Magnani et al., 2002]. The late onset of mu ERD during preparation for self-generated movement is considered a neural correlate of akinesia [Defebvre et al., 1996; Magnani et al., 1998]. Reduced beta ERD before and during movement has also been confirmed in source-space MEG data [Heinrichs-Graham et al., 2014]. Modulations of cortical oscillations by L-Dopa (typically correcting delayed ERD latencies) generally parallel the therapeutic improvements in behavioural performance, thus conflating cause and effect. In a recent carefully designed paradigm however, Parkinson's patients prepared movements under both temporally predictable and random conditions. While reaction times were helpfully equivalent to those in healthy controls, beta oscillations in Parkinson's patients were more reactive than predictive, suggesting neural timing mechanisms to be at fault rather than simple hyper-excitability [Te Woerd et al., 2014]. Self-paced motor paradigms might therefore fail to appraise key cognitive components normally contributing to more nuanced movement plans, but have still revealed ERD/S abnormalities in diverse motor-related conditions such as essential tremor [Tamás et al., 2006] (delayed PMBR), paroxysmal kinesigenic dyskinesia [Hsu et al., 2013] (reduced and less lateralised PMBR), multiple sclerosis [Leocani et al., 2005] (late latency mu ERD) and obsessive-compulsive disorder [Leocani et al., 2001] (late latency mu ERD and reduced PMBR).

Increases in resting-state functional connectivity (FC) demonstrated in ALS are, as discussed in Chapter 4, generally considered to reflect relative dysfunction of cortical inhibition; given a correlation with disease progression rate this is further assumed to be

of mechanistic importance [Douaud et al., 2011; Verstraete et al., 2010]. Confirming correlations, across a group of ALS patients, between increased resting FC (whether measured using MEG or fMRI), cortical hyper-excitability measured by TMS (reviewed in Chapter 1) and neurotransmitter concentrations measured with either MRS [Foerster et al., 2012] or indirectly with flumazenil PET [Turner et al., 2005a], would greatly support these conclusions. Perhaps reflecting a lack of support from pre-clinical models, increases in resting FC discovered in other neurodegenerative conditions have generally not been attributed to lack of cortical inhibitory influence [Hsiao et al., 2014]. In studies of Parkinson's patients, EEG [Silberstein et al., 2005], MEG [Stoffers et al., 2008a] and fMRI [Wu et al., 2009] ascertained increases in FC have more frequently been explained in terms of either dopaminergic deficiency or cortical compensation for basal ganglia dysfunction. In general terms however, and regardless of proposed aetiological mechanisms, FC studies can inform regarding downstream and perhaps widespread dynamic consequences of seemingly focal lesions [Corbetta, 2012; Honey and Sporns, 2008], as is evident from the cognitive consequences of FC increases with the DMN in patients with MS [Hawellek et al., 2011] and increased co-activation of visual and motor regions when early Alzheimer's patients complete a movement task [Vidoni et al., 2012].

The findings described in Chapter 5 are difficult to directly ascribe either to cortical hyper-excitability or to interneuronal dysfunction. This notwithstanding, impaired long-distance communication from the precentral gyrus during active task performance is not *prima facie* evidence against excitotoxicity. ALS is a progressive disorder; models to stage the disease emphasise limited functional consequences early in the disease course [Balendra et al., 2014; Tramacere et al., 2015], corresponding to assumed anatomical restriction of pathology [Braak et al., 2013]. One of the very earliest consequences of ALS pathology, assuming this originates in recently evolved motor networks enabling definitively 'human'

behaviours [Eisen et al., 2013], is therefore highly likely to be impaired transmission of motoric information from the primary motor cortex. Even shortly after diagnosis then, accumulated pathology perhaps already overwhelms any modulation of FC that might be evident elsewhere in the cortex or only in resting sensorimotor systems.

6.1.2 New Tools to Detect ALS

While biomarker investigations have undoubtedly contributed to ALS research by way of inspiring novel or reaffirming existing disease mechanism theories, another equally important goal is a measurable correlate of overall disease activity with individually precise prognostic weight [Turner and Benatar, 2015]. Neurofilament light chain (NfL) is a promising candidate in this regard. It is elevated in both serum [Gaiottino et al., 2013] and CSF [Tortelli et al., 2012] of patients with ALS, highly predictive of survival duration [Lu et al., 2015] and potentially responsive to therapies [Bacioglu et al., 2016]. As a key protein component of neuronal cytoskeleton however, NfL release is detectable in many neurodegenerative conditions, particularly those with sub-cortical pathology [Skillbäck et al., 2014]. The diagnostic utility of this marker is therefore inevitably limited. Formal assessment of the diagnostic capabilities for any novel test for ALS should always consider differentiation between ALS and (admittedly rare [Turner and Talbot, 2013]) disease mimics, given that distinction from good health is clinically unchallenging [Turner et al., 2013]. Only a limited number of studies have contrasted ALS patients against disease mimics, typically focussing on the identification of covert cerebral pathology. Diffusion tensor measures of the intracranial corticospinal tract were shown to distinguish ALS from cervical spondylotic myelopathy [Koike et al., 2015]), task-based fMRI has revealed expanded BOLD signal during hand movement relative to peripheral nerve lesion patients [Stanton et al., 2007a] and perhaps most convincingly, SICI estimations of cortical hyperexcitability were (in contrast to ALS and PLS participants) normal in both LMN mimics [Vucic et al., 2011] and patients with hereditary spastic paraplegia [Geevasinga et al.,

2015a]. The study of corticomuscular coherence (CMC) presented in Chapter 5 was in some respects less successful in distinguishing a group of LMN mimics from ALS and potential explanations were discussed in terms of multifocal motor neuropathy pathology (or even compensation) reaching beyond the peripheral motor nerves. The results in Chapter 5 also highlight that cortical neural signals may be more discriminatory; both beta ERD and beta cortico-cortico coherence were seemingly preserved in disease mimics, but statistical distinction was under-powered given the small number of mimic patients recruited to the study ($n = 6$, c.f. $n = 52$ in [Vucic et al., 2011]).

Another important and related theme of this thesis concerns use of biomarkers to detect the process of ALS *in vivo* and in advance of manifest symptoms [Benatar and Wu, 2012; Turner and Benatar, 2015]. As can be surmised from the limited number and variable nature of the investigations presented in the relevant introductory section, this aspect of ALS research is still a nascent field of study. The summary findings of this thesis with respect to AGCs include deeper movement related beta ERD, increased beta power in posterior regions during ‘noGo’ preparation, and non-significant increases in FC during both rest and light grip. The limited numbers of AGCs available for study reflects both the rarity of familial ALS in comparison to sporadic ALS, and the complex ethical and practical considerations regarding presymptomatic testing (even without disclosure) in the research setting [Benatar et al., 2016; Kim et al., 2015]. Any evidence contributing to the advancement of this field is therefore welcome, but given the increasing breadth of therapeutic strategies proposed [Zhu et al., 2015] and indeed considered as preventative options by this group of at-risk individuals, urgent work remains to be done before AGC clinical trials can realistically prove informative. ALS researchers should continue to take stock of presymptomatic research progress in related neurodegenerative conditions [Jiskoot et al., 2016]; the recognition of prodromal symptoms of Parkinson’s disease for

example [Noyce et al., 2016] opens new avenues. Extra-motor symptoms are an expanding focus of attention in Parkinson’s disease [Chaudhuri et al., 2006; Zis et al., 2015]; ERS and PMBR were both altered in patients with primary restless legs syndrome [Tyvaert et al., 2009]. Prediagnostic Huntington’s studies have notably highlighted the sensitivity added by functional neuroimaging (reviewed in [Klöppel et al., 2009]). Abnormal activations have typically still been interpreted as compensatory [Feigin et al., 2006], adaptations that may be increasingly required to maintain normal motor performance as Huntington’s symptom onset approaches [Scheller et al., 2013]. In keeping with this framework, our group has therefore initiated the first task-based fMRI study of AGCs in ALS, making use of the high-field capabilities of Oxford’s 7T scanner (a structural 7T study of ALS is described in [Cosottini et al., 2015]).

6.2 Immediate Considerations

6.2.1 Protocol Refinement

Certain future considerations directly arise from the experience of the present research projects, some of which aim to address noteworthy limitations of the described experimental setup and analysis strategy choices.

Recent advances in the coregistration process (including acquisition of nose-shape points) were already mentioned in Chapter 2, but further incremental improvement has been demonstrated by more effective immobilisation of the participant’s head within the MEG helmet. A subject-specific 3D printed head-cast has been used to minimise head movement both within and between sessions with resulting gains in source localisation down to 1-2 mm accuracy [Troebinger et al., 2014]. Simpler measures such as improved seat cushioning might also enable physically disabled participants to better engage in MEG recordings for longer periods of time and longer periods of behavioural training prior to the acquisition might further maximise the volume of useable data. Selecting only

participants able to undergo structural MRI acquisition would obviously result in coregistration gains, but this decision would necessarily exclude a good fraction of ALS participants thus potentially compromising the generalisability of the conclusions. Some caution is still advised however given the likely effects of hypercapnia on neural oscillation power [Hall et al., 2011a]).

Resting-state study design choices are essentially limited to a quality/quantity trade-off in the specification of session duration and also the decision to instruct an ‘eyes-open’ or ‘eyes-closed’ state; RSNs were reportedly more ‘organised’ in the ‘eyes-open’ state, given measured increases in ‘nodal efficiency’ metrics [Jin et al., 2014]. By contrast, design of any active task is fraught with a multiplicity of prioritised considerations, the consequences of which may unintentionally compromise certain subsequent analytic pathways, attenuate or exaggerate group differences [Monchi et al., 2007]. One pertinent consideration to M/EEG motor paradigms is the duration of the inter-trial interval. Shorter intervals enable more trials to be performed within a given acquisition time-span and thus improve reliability, but this is counter-balanced by the enduring effects of PMBR on neuronal oscillations that (at up to 7 s) can readily extend into the subsequent trial’s baseline period [Fry et al., 2016]. An insistence on a behaviourally (and hence *neurally*) ‘clean’ baseline period is another key consideration, particularly given recent findings in healthy older adults that larger movement beta ERD relative to younger adults is related to higher baseline spontaneous beta power [Heinrichs-Graham and Wilson, 2016]. The experimental design described in Chapter 5 was deliberately better aligned to CMC measurement, hence the required (and quite novel) use of a continuous movement regressor. Convolution models akin to those relied upon in fMRI analysis have been developed for use in continuous M/EEG data [Litvak et al., 2013] and successfully applied to discriminate processing of overlapping multisensory stimuli [Spitzer et al.,

2016]. The considerable differences in analytic strategies between Chapter 3 and 5 may go some way to explaining divergent findings in beta ERD. However, additionally, behavioural performance was quite different – auxotonic grip prior to movement differentiated groups in terms of the beta power generated, and neural sources were identified from pre-defined anatomical parcels rather than functionally defined ROIs. Further mapping the plastic reorganisation of motor function in ALS may yet prove worthwhile [Mohammadi et al., 2011], as evidenced by a navigated TMS study in which alterations were dependent on disease duration [Chervyakov et al., 2015], though MEG is perhaps imperfect for a study in which spatial precision would be paramount.

An over-arching observation drawn from personal experience of this work is that in the investigation of a neurodegenerative condition principally affecting older individuals, less complex task designs are rewarded with more engaged participation. Nevertheless, certain protocol modifications might result in noticeable gains in consistency of neural data, and might therefore accentuate ALS group differences from the healthy controls comparators [Alegre et al., 2003; Boiten et al., 1992; Kaiser et al., 2001]. Use of rhythmicity would be an interesting consideration given the important contributions of the motor system to the active sensing to temporally predictable sensory stimuli [Morillon et al., 2014]. One important source of variance between individual HCs is in the magnitude of CMC expression during light grip, as mentioned in Chapter 5, a motor learning protocol might maximise CMC expression in all individuals and could be adapted to require HCs to match the force output of ALS participants [Mendez-Balbuena et al., 2012b; Perez et al., 2006]. Active training may not be the only consideration: introduction of tactile noise has been described to improve motor performance [Mendez-Balbuena et al., 2012a], operating via enhanced CMC [Trenado et al., 2014] and the imposition of unexpected movement-

execution error further induces modulation of beta power both before and after movement [Torrecillos et al., 2015].

6.2.2 Study Expansion

The most rewarding expansion to all three of the experimental chapters described in this thesis would surely be the longitudinal study of at least the ALS participants; longitudinal biomarker evaluation has thus far been more successful for LMN measures [Neuwirth et al., 2015]. Despite the potentially rich insights into disease natural history, a relative paucity of longitudinal neuroimaging studies have been performed in ALS (18 were identified in a recent review [Schuster et al., 2015]), in part reflecting the inherent limiting factors unique to ALS such as sialorrhoea and orthopnoea. In common with the selective drop-out from clinical trials of faster progressing individuals (as considered in Chapter 1), longitudinal biomarker cohorts are also almost inevitably enriched with relatively benign ALS cases and sensitivity to detect change may accordingly be compromised [Turner and Benatar, 2015]. These concerns notwithstanding, recent novel findings include the unexpected discovery that sub-cortical grey matter atrophy accumulates over time far more than white matter pathology, which is perhaps already well established at the point of diagnosis [Menke et al., 2014]. These results emphasise that floor and ceiling effects, regardless of clinical progression, may limit the utility of diagnostically helpful biomarkers to measure progression [de Carvalho and Swash, 2010]. Longitudinal functional neuroimaging studies are also particularly vulnerable to confounding effects of either performance improvement with task practice or deterioration as motor disability accrues. Passive movements [Houdayer et al., 2012], movement observation [Hobson and Bishop, 2016; Honaga et al., 2010] or peripheral stimulation [Hamada et al., 2007] might still have value (for instance in the measurement of PMBR [Keinrath et al., 2006]). Repeated study of a healthy control group, or disease comparators such as PLS [Kwan et al., 2013], may also be desirable. Longitudinal follow-up of a discovery cohort, regardless of the feasibility

to repeat investigations, will also permit appraisal of the prognostic value of the biomarker [Shibuya et al., 2016]. Suspected cases of ALS could be assessed prior to firm diagnosis and confirmed cases might subsequently enrol for brain donation to permit correlation between pathological findings at autopsy and biomarker results in life. Given the typically focal onset of ALS, subsequent progression of weakness to other limbs serves as a means to consider regional ‘near-symptomatic’ disease activity within a given individual [Benatar et al., 2013]. For example, CMC might be expected to decrease significantly in the *next* limb to be affected. Bulbar and lower limb studies would inevitably require development to maximise such an application [Kollewe et al., 2011]; reduced cortical activity during swallowing was noted in ALS patients in a small MEG study [Teismann et al., 2011]. Other future considerations to empower such longitudinal study might include the use of portable EEG caps and transmitting EMG sensors; also worthy of consideration is the possible inclusion of rare patients choosing to undergo sub-dural electrode grid implantation with a view to brain-computer interface control [Grosse-Wentrup and Schölkopf, 2014; Pandarinath et al., 2015] or in future perhaps for restoration of limb function [Bouton et al., 2016].

Relatively unexplored in ALS, high-density electrode grids have been particularly successful in the detection of abnormal phase-amplitude coupling (PAC) in the motor cortices of (albeit not exclusively) patients with Parkinson’s disease [de Hemptinne et al., 2013; Kondylis et al., 2016], although PAC may itself have diverse physiological origins [Cole et al., 2016]. Other future analytic strategies do not depend on invasive recording of neural signals. Effective connectivity measures [Friston, 2011] describing the influence of selected cortical regions among each other, typically using the framework of Dynamic Causal Modelling (DCM), may distinguish patients with ALS. A DCM analysis of a motor fMRI task reported the ipsilateral motor areas to be increasingly influential with advancing

age in [Boudrias et al., 2012]. Connectivity values have also been successfully applied in graph theoretical analyses of both MEG [Stam et al., 2009], EEG [Iyer et al., 2015] and MRI [Agosta et al., 2013b; Dennis and Thompson, 2014; Zhou et al., 2016] resting-state data from neurodegenerative diseases, although the direct physiological relevance of the outputted metrics is necessarily interpreted in quite speculative terms [Aerts et al., 2016; Tijms et al., 2013].

6.3 Future Research Directions

6.3.1 PharmacoMEG

The role of MEG as a marker of therapeutic efficacy in ALS, or indeed any other disease, is yet to be defined. Conceptually however, two potential designs are envisaged: a) longitudinal MEG studies within a phase-two clinical trial contrasting intervention and placebo in terms of progressive abnormalities on MEG indices and b) within-subject comparisons pre and then during novel drug administration as a pharmacodynamic marker. While the former application focuses on long-term disease modification (and is therefore also suitable for new cell-based therapies [Chen et al., 2016; Lepore et al., 2008; Li et al., 2015]), the latter would be equally appropriate for symptomatic therapies.

Several examples of pharmacological manipulations to healthy volunteers in basic neurophysiology MEG experiments have already been detailed in preceding chapters, demonstrating the immediate feasibility of pharmacoMEG studies; CMC is similarly responsive to neuro-pharmacology [Baker and Baker, 2012]. In contrast to L-Dopa studies in Parkinson's disease, insufficient human studies have thus far considered the (particularly longer-term) effects of riluzole in ALS – a drug with a diverse array of neurotransmitter targets [Bellingham, 2011; Doble, 1996]. While transient reductions in cortical hyper-excitability have been described [Geevasinga et al., 2016b; Vucic et al., 2013a], similar findings were noted with diazepam and gabapentin [Caramia et al., 2000]

yet these drugs proved ineffective in disease modification. While TMS is eminently suitable to detect *some* neurophysiological consequences of CNS therapeutics [Paulus et al., 2008], to the extent that sub-receptor sensitivity to different benzodiazepines can be discerned [Mohammadi et al., 2006], alterations to neural oscillations may be equally important in predicting therapeutic response [Hall et al., 2014; Yamawaki et al., 2008]. For both mechanistic and ethical reasons, future experimental designs are likely to consider the addition of new agents to baseline riluzole therapy (for example combined treatment with riluzole and a modifier of transcriptional dysregulation was synergistic in a mouse model [Del Signore et al., 2009]). Animal and cell models continue to inspire new therapeutic avenues including correction of hyperexcitability with the K⁺ channel activator, retigabine (a licensed anti-epileptic drug) [Wainger et al., 2014] and blockage of voltage-gated calcium channels (thus preventing downstream excitotoxicity) with lomerizine [Tran et al., 2014].

6.3.2 NeuroStimulation

Extending beyond the scope of this thesis, a wealth of recent studies have made use of non-invasive neurostimulation techniques in experiments not limited to therapeutic induction of plasticity post-stroke [Meinzer et al., 2016], interference with motor learning via synaptic GABA_A increases [Amadi et al., 2015] or facilitation of learning with alternating current stimulation at 20Hz [Pollok et al., 2015].

It remains an open question whether disease (or even symptom) improvement is possible in ALS using existing neurostimulation techniques. Looking to other neurodegenerative diseases (beyond the clear-cut benefits of DBS in selected Parkinson's patients) sparse reports of successful interventions exist in treating cognitive symptoms in Alzheimer's disease [Ahmed et al., 2012] (reviewed in [Hsu et al., 2015]). ALS, however, may be distinguished by a relative resistance to TDCS, to the extent that the lack of effect on

corticospinal excitability was considered as a diagnostic marker [Munneke et al., 2011]. Nevertheless repeated sessions of theta burst stimulation (cTBS) did transiently attenuate MEPs in ALS patients without affecting SICI or intracortical facilitation [Munneke et al., 2013]. An interesting and quite feasible investigation could attempt to improve dysphagia with neurostimulation; in healthy volunteers, anodal TDCS increased cortical activity related to swallowing alongside performance gains [Suntrup et al., 2013] while stroke patients also improved relative to sham stimulation [Kumar et al., 2011].

MEG recordings of cortical oscillations would be a suitable tool to discern the intermediary effects of neurostimulation [Hanley et al., 2015]. For example, increased beta power is demonstrated in the motor cortices of healthy volunteers, only if cTBS successfully reduced their corticospinal excitability (as also measured by TMS) [McAllister et al., 2013]. Recent demonstrations of the capability to entrain intrinsic sensorimotor neural oscillations with rhythmic TMS [Romei et al., 2016] and animal studies demonstrating effects on non-neural cells [Monai et al., 2016] highlight the diverse means by which cortical plasticity might in future be encouraged to relieve the effects of neurodegeneration [Poujois et al., 2013], perhaps even in the adverse neural context of older age [Rossiter et al., 2014].

6.3.3 Multimodal Investigation

The optimisation of both the sensitivity and specificity of biomarker investigations in ALS may well require a combination of techniques within a multimodal study – this is particularly relevant to progressive neurodegenerative conditions wherein one biomarker abnormality may precede another [Jack and Holtzman, 2013]. Very few multimodal investigations of ALS have been performed: an MRI study combining DTI and MRS measures improved disease detection accuracy [Foerster et al., 2014] and CSF NfL concentrations were inversely correlated with DTI fractional anisotropy [Menke et al.,

2015]. Multivariate analysis of a panel of 35 different plasma and CSF constituents was able predict disease duration with reasonable accuracy without resorting to higher-order models [Su et al., 2013], but a more parsimonious design might incorporate biomarkers from completely separate domains by recognising an abnormal threshold for a test result as a temporally defined *event* [Fonteiijn et al., 2012]. Building on this technique, sequentially evolving abnormalities in biomarkers (CSF, MRI and cognitive) were helpful in defining disease stages in patients with Alzheimer’s disease that were then predictive for the conversion from mild cognitive impairment to Alzheimer’s disease [Young et al., 2014]. Future work might also look to incorporate genetic tests shown to be reliably expressed in cortical resting-state network organisation [Hawrylycz et al., 2015], and rich anatomical detail to functional cortical organisation was recently demonstrated using large-scale multimodal MRI investigation [Glasser et al., 2016] – such precise parcellation could soon be leveraged into neurodegeneration studies.

6.4 Closing Remarks

While new therapeutic horizons have appeared following great progress in our understanding of the genetic contributions to ALS, the disease as a whole remains stubbornly resistant to modern medical interventions thus far. A redoubling of efforts to better characterise patho-mechanisms in ALS, simultaneously accompanied by biomarker informed therapeutic trials, remains a high priority for research in neurodegeneration. MEG is already well placed to contribute to this process, and as a relatively nascent technology, will continue to improve with expanded analytic pathways and broader accessibility.

Chapter 7 Appendix

7.1 MEG Antisaccades: A Pilot Study

One crucial domain insufficiently appraised by the MEG investigations thus far is the cognitive impact of ALS. I will therefore describe a completed pilot study in which a *limited* amount of MEG data was acquired for each of the recent participants while a *delayed antisaccade* task was performed

7.1.1 Functional Neuroimaging of Cognitive Performance

Given the above concerns regarding the potential confound of ALS limb disability in the performance of motor tasks, functional neuroimaging studies incorporating cognitively challenging tasks (preferably with minimal motor requirements) are an attractive alternative (reviewed in [Shen et al., 2015]). Furthermore, such investigations have proven informative in related neurodegenerative conditions, demonstrating for example in patients with FTD, reduced MEG source activity in both early temporo-parietal and later fronto-parietal responses to presentation of visual images for semantic categorisation [Hughes et al., 2011]. Within ALS patients, a marked dissociation between cognitive and motor performance, both in terms of longitudinal progression and response to future therapies, is not inconceivable [Terada et al., 2011; Zalonis et al., 2012]. Cognition-focused functional neuroimaging biomarkers could serve to illuminate this [Stoppel et al., 2014]; citalopram partially restored evoked potential abnormalities measured in patients with FTD during a *behavioural inhibition* paradigm [Hughes et al., 2015]. Although such indices of ‘cognitive control’ [Alegre et al., 2004] are appealingly quantifiable neuropsychological attributes with relevance to ALS [Pettit et al., 2013], ‘inhibition’ remains a multi-faceted concept with diverse proposed cognitive and neural mechanisms [Aron, 2007]. Regardless of such concerns, different task designs have successfully identified inhibition activity differences in patients with ALS. Increased fMRI activity was described in frontal gyri, putamen and pallidum [Mohammadi et al., 2015], and during an ‘Erikson flanker’ conflict

choice task, executive dysfunction in ALS patients was associated with enhanced lateralised readiness potentials [Seer et al., 2015]. As described in Chapter 1, translation of these paradigms into tasks purely dependent on saccadic responses will overcome most limitations imposed by physical disability and thus extend their longitudinal capabilities.

7.1.2 Neural Substrate of Saccade Performance in Health and Disease

The cognitive mechanisms to control eye movements (reviewed in [Hutton, 2008]) are closely integrated with shifts in spatial attention [Clark, 1999; Nobre, 2001]; the antisaccade paradigm is a classic methodology by which these abilities can be appraised [Hallett, 1978; Munoz and Everling, 2004]. Gaze control is served by a distributed cortical network that connects the dorsolaterally positioned frontal eye fields (FEF) to the more medial supplementary eye fields (SEF) and the inferior parietal lobe (IPL); a right hemisphere dominance characterizes this system [Anderson et al., 2012]. The functional criticality of these regions for complex voluntary saccades was highlighted by lesion studies [Gaymard et al., 1994; Guitton et al., 1985]; considerable anatomical overlap is noted with the typical distribution of ALS pathology [Geser et al., 2008; Maekawa et al., 2004; Turner et al., 2012b]. Antisaccade performance is also notably impaired by the (intimately linked to ALS) neurodegenerative condition FTD [Burrell et al., 2012]. FTD patient error rates inversely correlated with right FEF volume [Boxer et al., 2006], in keeping with a pathological extrapolation of the normal covariance between that region's volume and antisaccade performance in healthy individuals [Ettinger et al., 2005].

Diverse fMRI experiments encompassing the antisaccade task have further confirmed the cortical mechanisms behind deliberate gaze control to include increased (relative to prosaccades) activations within the FEF [Connolly et al., 2002], IPS [Ettinger et al., 2008], DLPFC and ACC specifically during a preparatory period [Brown et al., 2007] and the SEF particularly if a saccade is suddenly and deliberately cancelled [Curtis et al., 2005].

The constituent cognitive components of successful antisaccade performance go beyond inhibition of a prepotent response and (depending on the exact experimental design) typically include visual detection, selective attention and stimulus-response remapping in space. This complexity accounts for the broad array of described cortical activations [Brown et al., 2006; Curtis and Connolly, 2008]. Expanding these investigations to healthy older adults revealed increased right FEF activation to be correlated with *worse* antisaccade performance while connectivity to the right DLPFC and ACC correlated with *improved* performance [Pa et al., 2014]. Of particular relevance to the present pilot study, 12 ALS patients were noted to activate the DLPFC significantly less than HCs during an antisaccade task, while SEF and FEF over-activity appeared to partially compensate given an inverse correlation with errors of automatic commission [Witiuk et al., 2014].

The neural activity underlying successful saccadic control has also been directly investigated using both invasive and non-invasive techniques. Studies in non-human primates identified neurons in the FEF that project to the superior colliculus but have *lower* activity during antisaccades than prosaccades [Everling and Munoz, 2000] (despite confirmation of increased BOLD signal in FEF in monkeys as in humans [Ford et al., 2009]). Other anatomical locations have also been considered: intracortical microstimulation of macaque SEF improved the ability to stop prepotent saccades [Stuphorn and Schall, 2006] by increasing saccade latency specifically in a ‘stop’ context, while ACC neurons fired in response to erroneous performance [Schall and Boucher, 2007]. Early attempts to measure this neural activity with MEG suggested activity in FEF, followed by posterior visual regions, in response to saccade errors [Herdman and Ryan, 2007]. Of greater mechanistic importance perhaps, was the finding of sustained lateralised gamma-band power enhancement in the posterior parietal cortex contralateral to planned saccade direction, while posterior alpha was more responsive to stimulus presentation

[Van Der Werf et al., 2008]. These effects were similar in a delayed two-step saccade task [Medendorp et al., 2007]. Gamma power increases during saccade planning and execution were recently confirmed and shown to be particularly responsive to internal target selection above external visual cues, while alpha/beta power showed the reverse [Carl et al., 2016]. Antisaccade preparation may enhance beta power in both DLPFC and FEF; this effect appeared to correlate with behavioural performance and varied by age across adolescent development [Hwang et al., 2016].

In the following pilot experiment, we aimed therefore to identify a neural explanation, framed within ongoing cortical oscillations, for executive dysfunction in ALS as indexed by performance of a visually cued, delayed antisaccade task.

7.1.3 Methods

7.1.3.1 Participants

Participants were drawn from the same sources as previously described chapters. The task was well tolerated and performed therefore no participants were excluded from the data set. The MEG data was acquired in two blocks interleaved with the upper limb motor tasks described in Chapters 3 and 5. Participant demographics are summarised in **Table 7.1**.

Mean $\pm$ SD (<i>range</i>)	P/ALS (ALS = 18) (PLS = 4)	AGC (n = 5)	Controls (n = 14)	Mimics (n = 6)
Age (years)	61.3 $\pm$ 9.5 (44 : 78)	43.9 $\pm$ 11.4 (30 : 61)	60.2 $\pm$ 12.5 (41 : 84)	60.6 $\pm$ 12.9 (47 : 76)
Gender	13 M : 9 F	5F	11 M : 3 F	4 M : 2 F
Site of Onset (<i>ALS</i>) Genetics Diagnosis	5 bulbar 2 RUL, 3 LUL 5 RLL, 3 LLL	3 <i>SOD1</i> 2 <i>C9orf72</i>	N/A	1 neuropathy 5 MMN
ALSFRS-r	36.6 $\pm$ 6.4 (24 : 46)			
Disease Duration from Symptom Onset (months)	51.2 $\pm$ 40.0 (5:219)			
Progression Rate (48 – ALSFRS-R / duration in months)	0.48 $\pm$ 0.46 (0.03 : 1.56)			
Cognition Score (% correct)	83.0% $\pm$ 11.46 (61:94)			

Table 7.1: Demographic and clinical details.

Demographics for participants in the delayed antisaccade pilot study.

7.1.3.2 Acquisition

Prior to acquiring MEG data, the antisaccade task was explained with mime and participants were trained inside the MSR on a minimum of two practice blocks of ten pseudo-randomised trials, until 9/10 trials were correctly performed. Two experimental blocks were performed, each comprised of 40 trials, split evenly and distributed randomly between prosaccades and antisaccades. A schematic for the experimental design is shown in **Figure 7.1**.

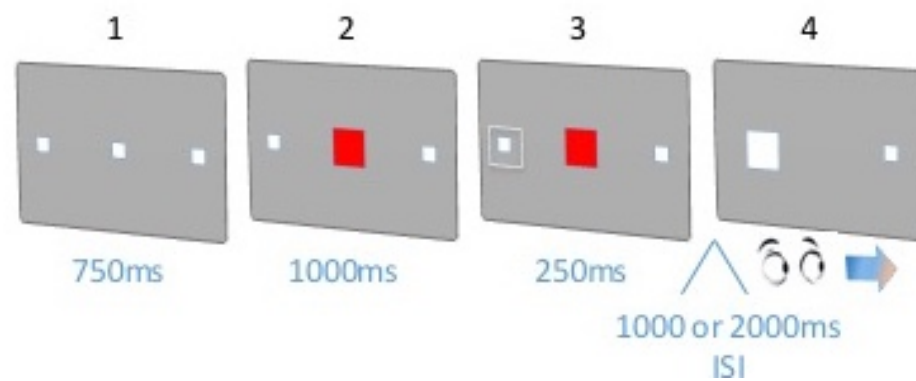


Figure 7.1: Schematic of Delayed Antisaccade Paradigm

This trial demonstrates a correctly performed antisaccade. 1) Visual placeholders at trial start. 2) Central anti/pro (A/P) cue (green would denote prosaccade). 3) Lateral covert left/right (L/R) cue, 100% predictive of target laterality. 4) After a variable ISI, (pro-direction) saccade target appears 100ms after central A/P cue disappears. Arrow denotes correct (anti-) saccade direction.

Three horizontally distributed (at 9° visual angle) placeholder squares appeared at the start of each trial and remained on screen throughout, followed by a larger coloured central fixation square denoting the trial type (red = antisaccade, green = prosaccade, blue/yellow version used for one colour blind participant). A brief (250ms) peripheral cue (empty white square) then surrounded one lateral placeholder, to which the participant is instructed not to saccade but attend covertly. Following a variable ISI (1 or 2 seconds), the target (solid white square) covered one lateral placeholder as the coloured fixation square disappeared. At this point the participant is required to saccade. Visual feedback (a ring around the correct saccade destination) appeared after 750ms. Laterality of targets

was split evenly and randomly distributed between trials. The first block was randomly assigned as either ‘short’ or ‘long’ ISI duration, the subsequent block was designated to the alternative. Within each block, 20% of trials had unexpected invalid temporal durations for the ISI (long trial in a short block or vice-versa).

Behavioural performance was monitored live by the experimenter and recorded (binocularly) by an infra-red eyetracking camera (Eyelink 1000, [SR Research](#)), digitised at 1000Hz. The eyetracker was mounted in ‘desktop’ position below the subject’s line of vision. 3-point calibration was performed before the start of each block.

7.1.3.3 Eyetracking Data Analysis

Offline analysis of behavioural performance was completed using custom Matlab scripts, making combined use of both eyetracking and EOG data aligned to trial event markers in the MEG *.fff* file. Saccadic responses were identified for each individual trial. The latencies and direction were recorded to ascertain non-suppressed reflexive prosaccades or premature saccades during the covert attention period. These trials were marked and subsequently discarded prior to analysis of the MEG data. The 250-Hz downsampled EOG and eyetracker outputs were further smoothed using a sliding window of 30 or 10 time-points respectively. The differential of each smoothed output was taken and a baseline period (A/P cue $\pm$ 0.3 s) selected over which mean and SD values were taken. Saccades were marked as deviations in smoothed differential beyond 5 SD in the EOG and 10 SD in the eyetracker. Examples are shown in **Figure 7.2**.

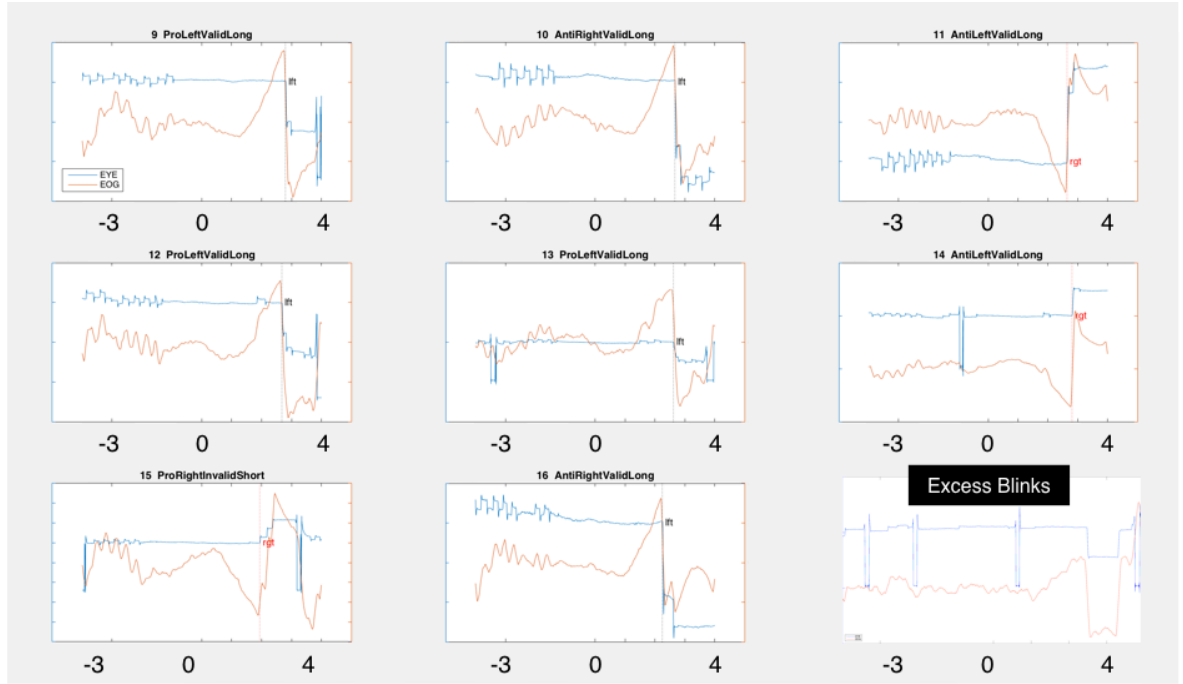


Figure 7.2: Offline behavioural analysis of saccade performance.

t_0 = instructional cue. Sequential trials from an individual participant are shown (labelled 9:16 with trial code). Sharp deflections in both eyetracker (blue) and EOG (red) mark the time of saccade onset. A different participant is displayed bottom right in whom excess blinks compromised automated saccade identification.

Occasional participants blinked frequently around the instructional cue and necessitated *ad hoc* alteration of the SD limits or calculation from only EOG or eyetracker outputs. All trials were visually inspected to ensure complete behavioural capture. Behavioural performance was compared across groups using one-way ANOVA and post-hoc t-tests between P/ALS patients (4 and 18 respectively) and the 14 HCs.

7.1.3.4 MEG Data Analysis

MEG data were pre-processed as per the pipeline described in Chapter 2, but without transformation to source-space. Epochs were defined around the time-point of L/R cue appearance. Trials that were behaviourally incorrect (including premature saccades) or that were identified as statistical outliers using the FieldTrip variance summary tool, were excluded from the analysis. The key contrast of interest was between prosaccades and antisaccades (therefore not requiring baseline correction and collapsed across laterality), but both trial types were additionally inspected relative to a pre-cue baseline (-3 s to -2 s

relative to L/R cue, decibel scale presented). All sensors were initially inspected in the pro and antisaccade conditions, identifying a cluster of posterior sensors as contributing to the task effect in lower (alpha/beta) frequencies. MEG signal in the combined gradiometers was then averaged across sensors within this cluster. Time-frequency transformation was performed using multi-tapers within fixed window sizes of 0.3 s, allowing 5 Hz of smoothing. A frequency range from 1 to 95 Hz was explored in 1 Hz steps every 0.01 s. Groups differences were appraised, contrasting all ALS and PLS patients against HC, in the 2 s window around L/R cue presentation, using cluster permutation testing across time and frequency.

7.1.4 Results

Data from 47 individual participants were available for analysis.

7.1.4.1 Behavioural Performance

Overall saccade latency, collapsed across pro and antisaccades, is presented in **Figure 7.3**. Further behavioural analyses are presented in the **Supplementary Figures**. No significant group differences were found on any of the anti or prosaccade measures, with the exception that both patients and AGCs made a higher proportion of premature saccades.

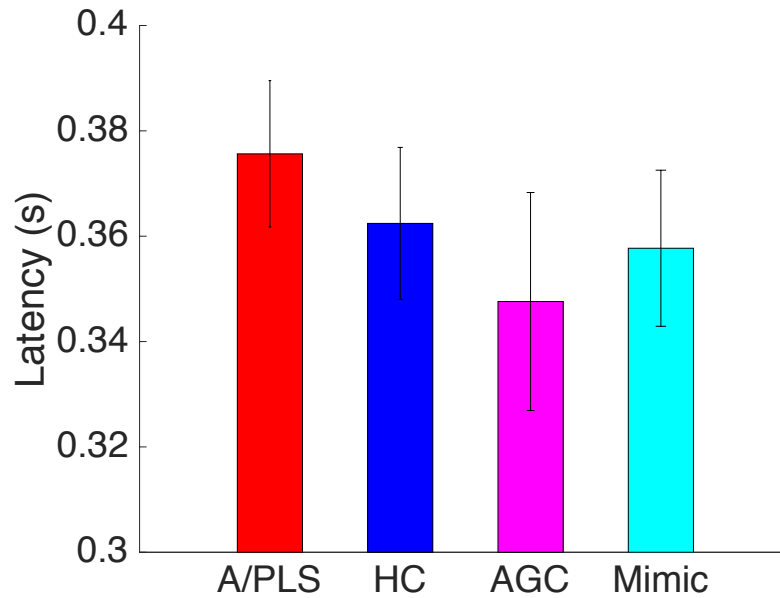


Figure 7.3: Saccade latencies.

Measured from target appearance. Collapsed across laterality and condition. Median within each participant, mean within groups, vertical bar = SEM.

7.1.4.2 Sensor Level MEG Data

MEG data were first explored in HC only across a broad time-frequency space in all sensors (**Figure 7.4**). This demonstrated oscillations from posterior-central (probably parietal) areas to be most obviously modulated during task performance.

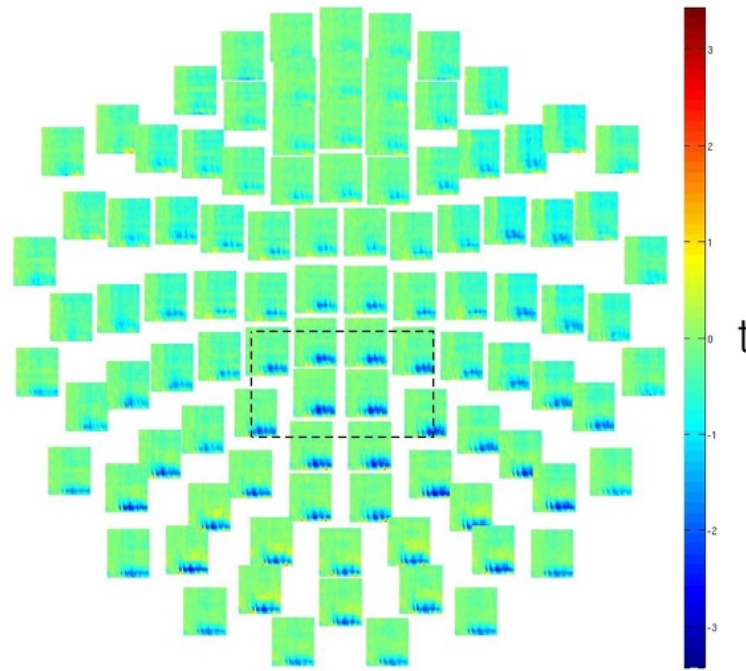


Figure 7.4: Prosaccade HC MEG data all sensors.

The prosaccades condition generates widespread alpha/beta desynchronisation in posterior-central sensors. Dashed box = sensors explored in Figure 7.5.

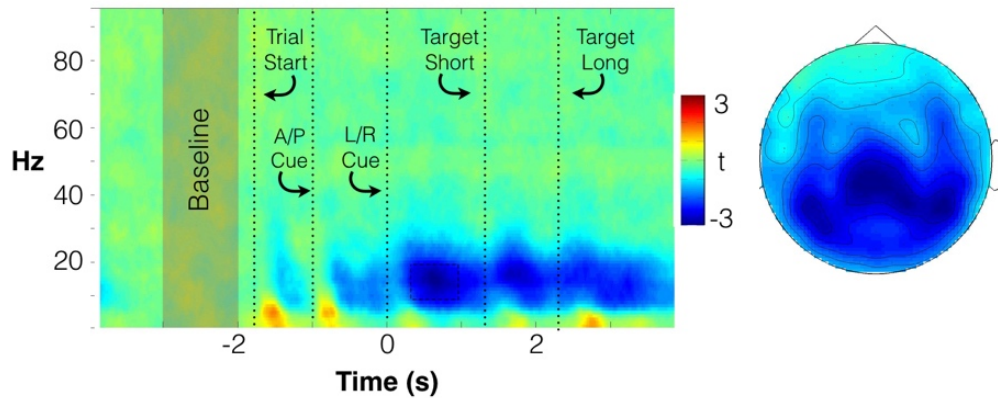


Figure 7.5: Time-frequency representation, prosaccades HC only.

MEG data from a small manual selection of postero-central sensors demonstrates task induced desynchronisation centred at 14 Hz, extending through both alpha and beta frequencies. The topography of the effect, 10 – 20 Hz, 0.3 – 0.9 s post L/R cue, is displayed on the right.

Baselined trials, separated into pro and antisaccade conditions, were contrasted between the patient and HC groups. The condition difference was generated per participant without baseline compensation according to the formula $(anti - pro) / (anti + pro)$ and the

results are displayed after averaging across a more generous manually selected postero-central cluster of 22 (combined-gradiometer) sensors (shown in **Figure 7.6**).

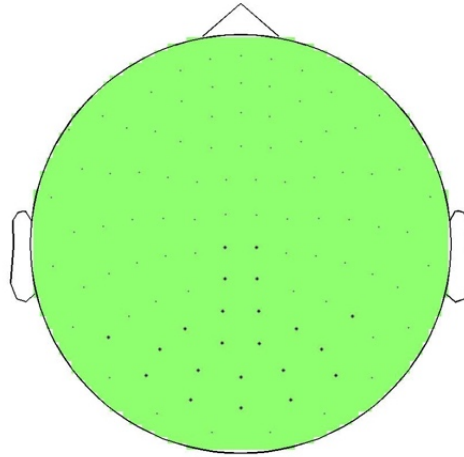


Figure 7.6: Selected sensors for MEG antisaccades.

Data was averaged from the marked channels for group comparison.

Differences between groups did not survive corrections for multiple comparisons (over time and frequency), therefore uncorrected t values are displayed in **Figure 7.7**. The results demonstrate that anti and prosaccades share much of the same impact on neural oscillations (at least within this selection of sensor level data). More significant alpha/beta desynchronisation was noticeable in baselined antisaccade trials than prosaccades. Directly comparing the conditions without baseline confirmed this impression and also suggested some increase in power in the 60-80 Hz range during the time period between A/P cue and L/R cue (-1 to 0 s). This was, to an extent, sustained into the preparatory period between L/R cue and target (0 to 1s). Both patients and HC showed these neural features but desynchronisation during antisaccade preparation appeared more profound in the patient groups around t_0 but less so in a high-beta (~ 40 Hz) range prior to saccade generation ($\sim +1$ s).

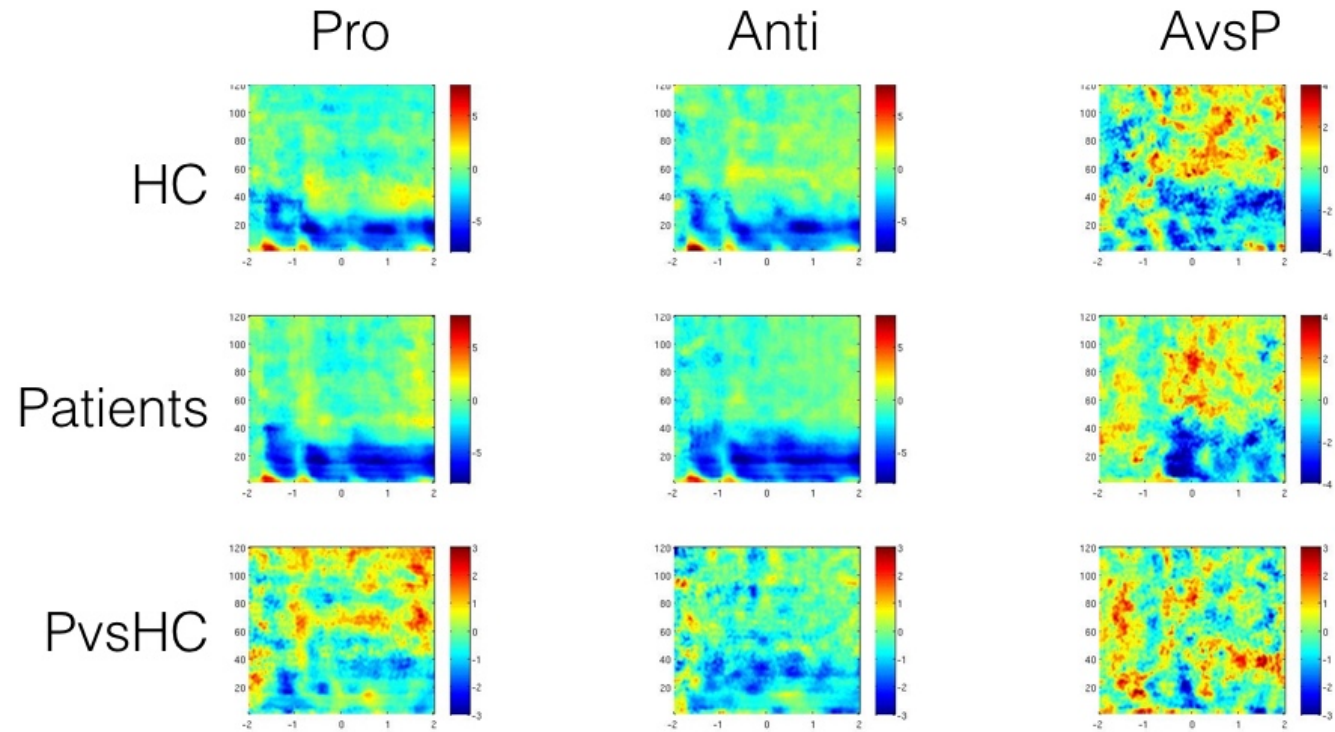


Figure 7.7: TFRs - contrasts between conditions and groups

Time frequency representations during antisaccades, prosaccades and the contrast between conditions for healthy controls (HC), patients and the contrast between groups. Uncorrected t value presented according to colour scales. t_0 = L/R cue appearance. AvsP = anti vs prosaccade. PvsHC = patients vs HCs

7.1.5 Summary

Despite encouraging patterns of behavioural data that indicated overall satisfactory task engagement by all groups, this pilot study was in all likelihood under-powered to detect group differences at either the behavioural or the neural level. The most immediate modification to the paradigm would be a large increase in the number of trials performed by each participant in line with the recent MEG saccade studies referenced in the introductory section. An increase in the amount of MEG data available for analysis would then also enable a more confident analysis within source space, although this is still somewhat problematic given the array of different cortical regions described to be involved in antisaccade performance.

Patients with significant cognitive impairment were under-represented in the study, again decreasing the likelihood of group differences. Further modification of the experimental design in order to present solely antisaccades during some experimental blocks might facilitate performance and thus allow more correct trials to remain in the analysis. Such an experimental design should also allow the inclusion of patients with FTD as a useful comparator group.

Other eyetracking devices are now designed to be extremely portable without any major loss in accuracy and could be used in the clinic or even home setting for patients with more severe disability. Performance on portable devices should be correlated with the present experimental setup. Similar to resting-state studies, the above design would lend itself to repeated examination over time; the learning curve noted during practice blocks would support repeat examination also of HCs over time to compensate for long-term retained practice effects.

In summary this pilot study shows promise as a non-invasive method for the *in vivo* detection of the neural consequences of (or compensation for) ALS pathology beyond the primary motor cortex [Prudlo et al., 2016].

7.2 Supplementary Figures

7.2.1 Delayed Antisaccade Behaviour

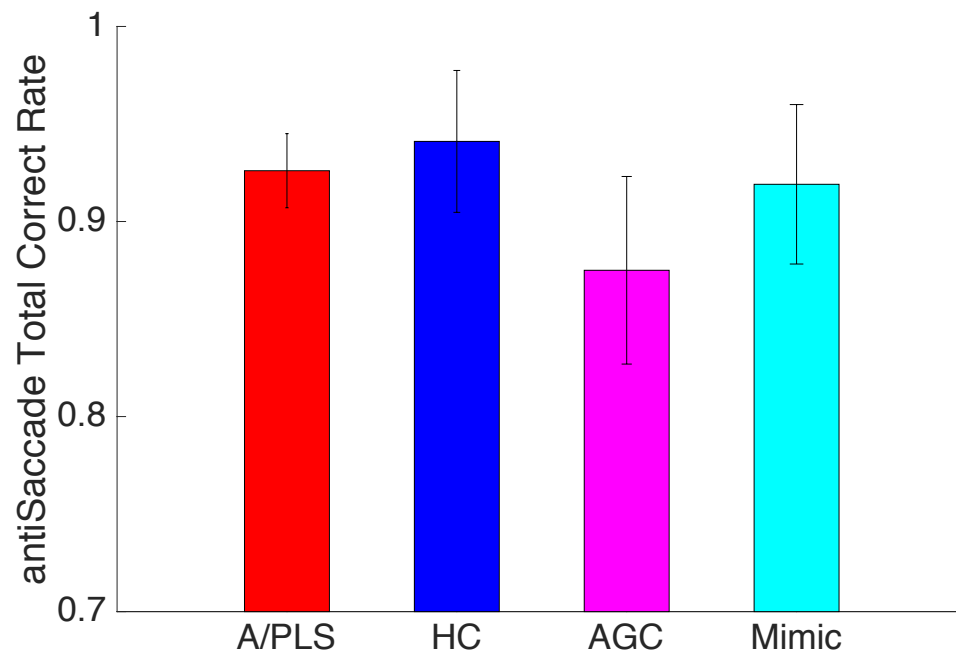


Figure 8.1: Antisaccade Accuracy

No significant group differences are noted; patients still get 90% of antisaccade trials correct.

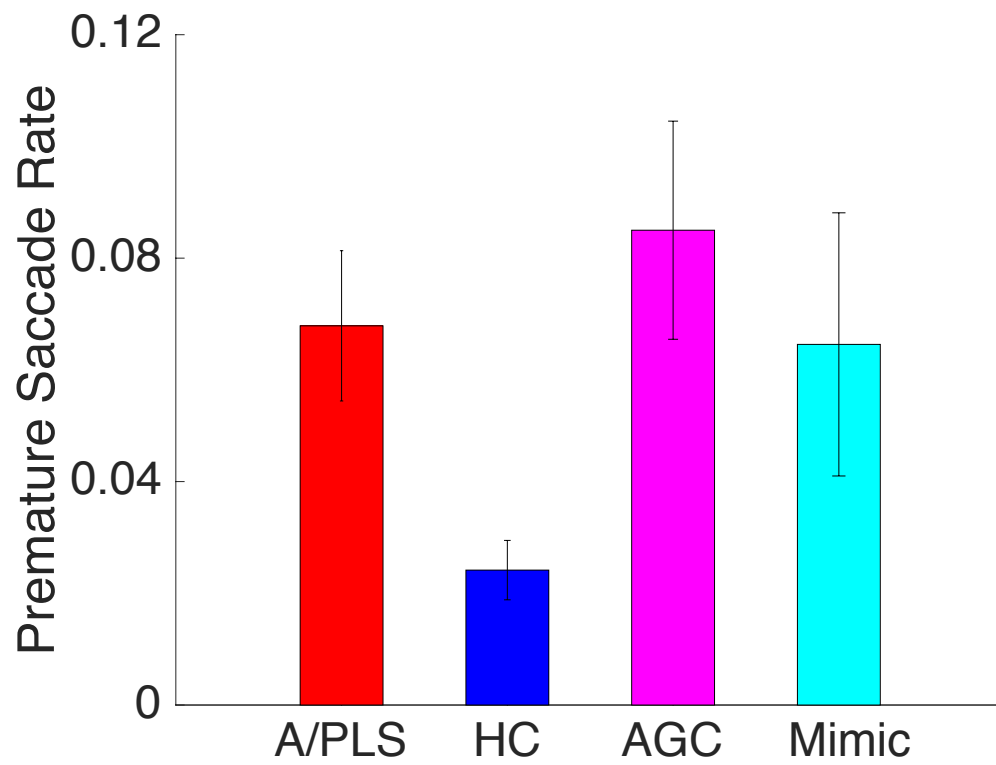


Figure 8.2: Premature Saccade Rates

Both patients ($t(34) = 2.50, p = 0.017$) and AGCs ($t(17) = 4.26, p < 0.01$) make significantly more premature saccades than HCs.

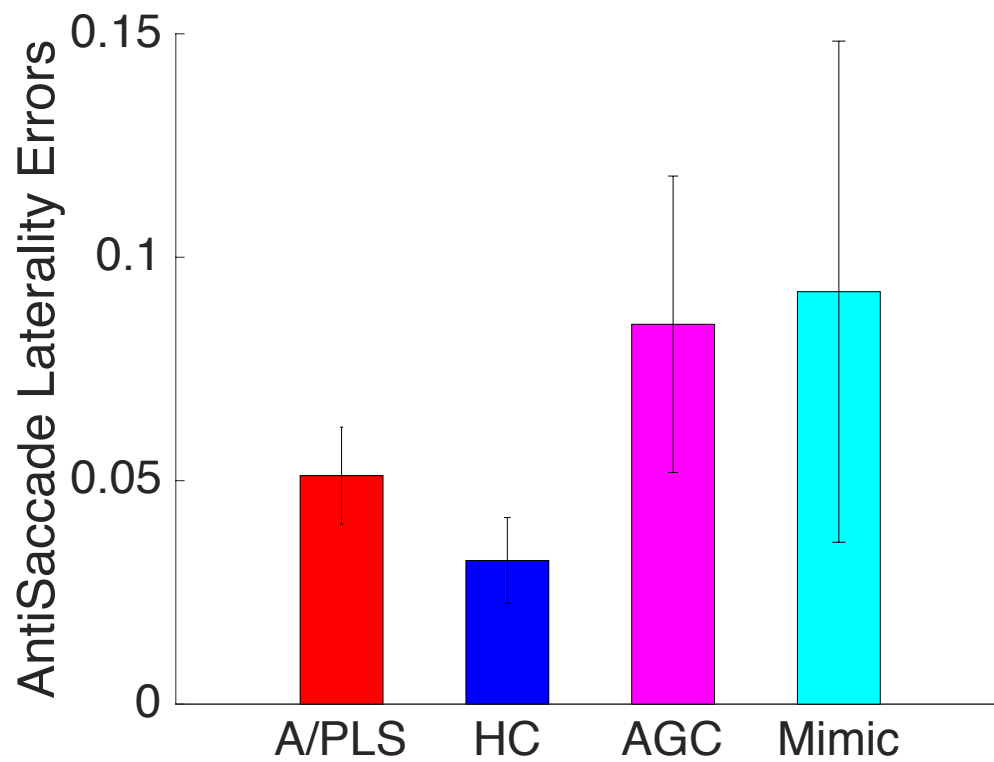


Figure 8.3: Antisaccade Laterality Errors

In a small proportion of antisaccade trials, a reflexive prosaccades is erroneously made to the target. No significant group differences noted in ANOVA but post-hoc t -test without correction, HC vs AGC is borderline ($t(17) = 2.12$, $p = 0.047$).

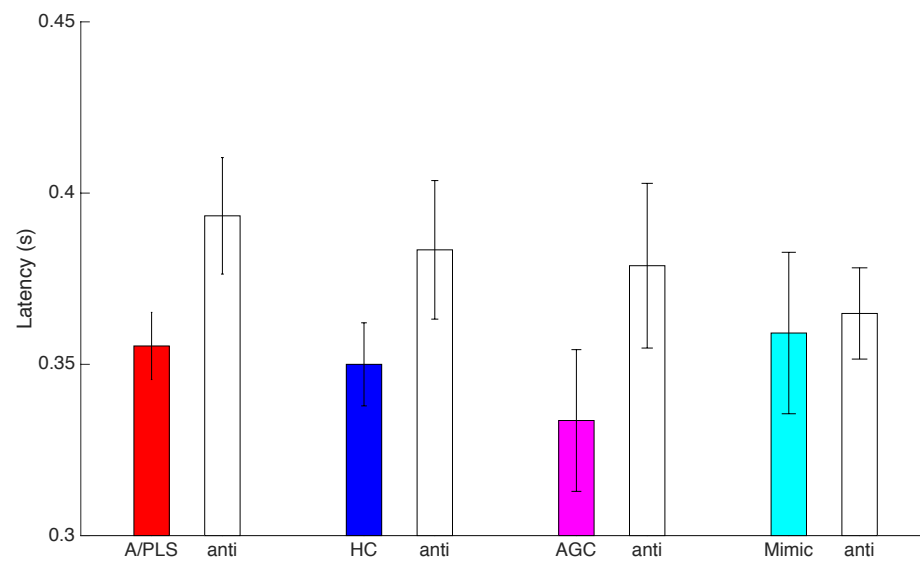


Figure 8.4: Saccade Latencies by Pro & Anti Conditions

All groups show a latency cost in the antisaccade condition, with no significant group interaction. Coloured bars = prosaccades. White bars = antisaccades.

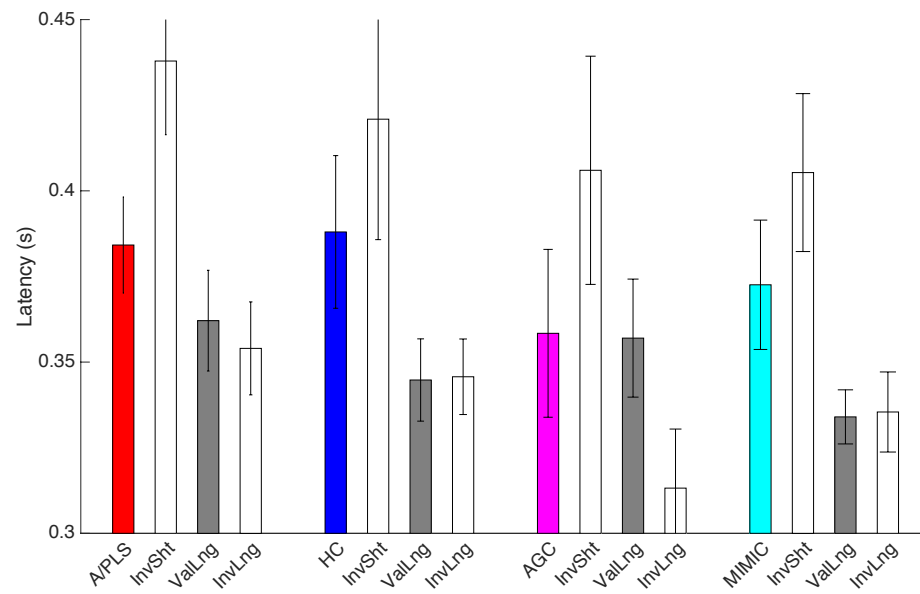


Figure 8.5: Saccade Latencies Reflect Temporal Expectation

Without any group interaction, this effect demonstrates faster saccade onset after long ISIs and a behavioural cost during short trials with an invalid expectation of a long ISI. Coloured bar = Valid Short, Inv = Invalid Cue, Val = valid, Sht = short ISI, Lng = long.

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