Therapeutic options for the fatal neurodegenerative disorder ALS are urgently needed. Trials rely on blunt outcome measures such as survival because of a lack of objective markers of disease activity and progression. The C9orf72 hexanucleotide repeat expansion (HRE) is associated with 10% of all cases of ALS, bringing the near-future prospect of oligonucleotide therapeutic trials. The development of biomarkers will reduce trial duration and cost by providing more sensitive measures of disease-slowing and/or evidence of target engagement. ALS is consistently associated with cortical hyperexcitability (CE), based on transcranial magnetic paired stimulation (TMS) to induce short-interval cortical inhibition (SICI). This project builds on the potential shown by non-invasive neuroimaging to provide biomarkers in ALS. We develop functional neuroimaging biomarkers that reflect the phenomenon of CE, including markers of pre-symptomatic pathology. Affected ALS patients carrying the C9orf72 HRE and a group of asymptomatic carriers are studied using a combined functional MRI (FMRI and MRS) and neurophysiological (MEG) readout. This study offers novel non-invasive biomarkers based on a consistent neurophysiological mechanism in ALS to advance therapeutic development.