

Structural and functional connectivity in amyotrophic lateral sclerosis

Molly Claire Chapman¹, Laura Marie Jelsone-Swain², and Robert Cary Welsh²

¹School of Medicine, University of Michigan, Ann Arbor, MI, United States, ²Radiology, University of Michigan, Ann Arbor, MI, United States

Introduction

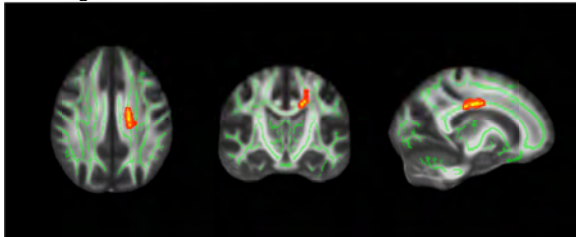
Amyotrophic lateral sclerosis (ALS) is a devastatingly progressive and fatal neurodegenerative disease that affects more adults than any other motor neuron disease [1]. Unfortunately, the etiology of ALS is not well described [2]. Additionally, diagnosis is complicated by the fact that clinical confirmation of both upper and lower motor neuron (UMN, LMN) involvement is required for final diagnosis. While LMN involvement is easily detectable using electromyography, UMN lesions are only detected on clinical exam, signs of which only appear after as many as 50% of motor neurons are lost. There is evidence for a phenomenon called "mirror movements" in some patients that can be observed before standard UMN signs, and their presence indicates damage to the trans-hemispheric inhibitory connections passing through the corpus callosum (CC), ostensibly affecting the fibers that pass between primary motor cortices [3]. For this reason we sought to elucidate the role of transcallosal connectivity between motor cortices. Both diffusion tensor imaging (DTI) and resting state functional connectivity magnetic resonance imaging (rs-fcMRI) data were collected. We integrated these modalities with the goal of developing an imaging biomarker for diagnosis and disease progression.

Methods

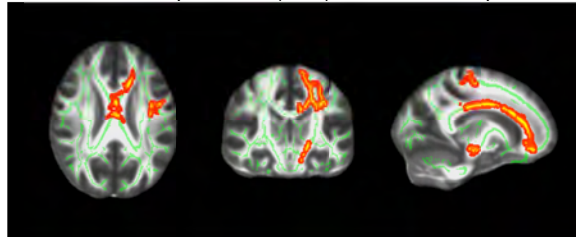
Twenty-five high-functioning ALS patients (17M, mean age = 58.4 ± 7.3 years, ALSFRS-r = $38.16 \pm 5/48$) and twenty-two age-matched controls (11M, mean age = 57 ± 5.3 years) underwent MR imaging on GE 3T Excite 2 magnet at the University of Michigan (General Electric, Milwaukee, WI). High-resolution axially-oriented 3D anatomical volumes were acquired (SPGR, TE = 1.85 ms, TR = 9.06 ms, flip-angle = 15° , 256^2 matrix, 256 mm FOV, 1.2 mm slice thickness, 124 slices). Resting state fcMRI was collected over a six-minute period while subjects kept their eyes open and fixated on a cross-hair. fcMRI data were de-trended and slice-time corrected, and cardiac/respiratory cycles and movement data were regressed out using FSL. White matter and cerebrospinal fluid principal components were removed and a bandpass filter of 0.01 – 0.10 Hz was used. A series of ROIs (9mm diameter) were left-right symmetrically placed in grey matter on a 12mm grid in all three directions across the whole brain using a dilated (5x) AAL mask to define grey-matter, resulting in 932 ROIs. Pairwise ROI correlation coefficients were calculated between each ROI pair for each individual and converted to z scores. Significant (Bonferroni $p < 0.05$) connections were counted and averaged for each group and compared. Diffusion tensor imaging (DTI) was acquired in a ten-minute period with fifteen diffusion directions [4]. This data was processed using tract-based spatial statistics (TBSS) [5] and voxelwise t-tests comparing fractional anisotropy (FA) and radial diffusivity (RD) maps between groups and were performed using permutation-based nonparametric inference. Additionally the corpus callosum was segmented into five regions from anterior to posterior. Connectivity ROI pairs were re-coded according to which functional area (numbered 1-5) of the CC could potentially mediate a structural connection. We extracted mean values from the FA and RD maps of individual patients in the different CC regions that were anatomically defined. Of the subjects from whom we acquired complete DTI data, 22 healthy controls and 22 patients were also included in the fcMRI analysis.

Results/Discussion

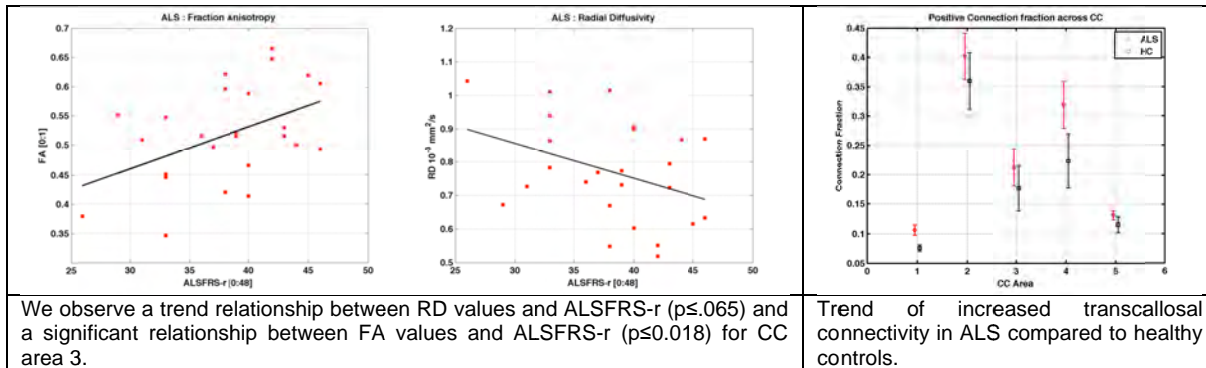
Globally, ALS patients exhibited a trend toward increased ROI functional connectivity, which was consistent in the number of connections across the CC, including area 3. The DTI data showed decreased FA and increased RD in the corticospinal tract (CST) and CC in ALS patients.



FA : HC > ALS, $P \leq 0.05$ (Corrected)



RD : ALS > HC, $P \leq 0.05$ (Corrected)



We observe a trend relationship between RD values and ALSFRS-r ($p \leq 0.065$) and a significant relationship between FA values and ALSFRS-r ($p \leq 0.018$) for CC area 3.

Trend of increased transcallosal connectivity in ALS compared to healthy controls.

Conclusion

The trend of increased fcMRI data corresponding to areas of degraded structural connectivity may support the theory of loss of transcallosal inhibition, which may also be related to mirror movements seen in ALS. These data bring the field closer to an understanding of the pathogenesis of ALS.

Supported by NIH R01-NS052514.

References:

- [1] Gelb, D. *Introduction to Clinical Neurology*. 4th ed. Oxford: Oxford University Press, 2010.
- [2] Bruijn L, Miller T, and Cleveland D (2004)., *Annu Rev Neurosci* 27: 723-49.
- [3] Wittstock M et al. *Clin Neurophys*, 118 (2007), 301-307.
- [4] Basser, P. J., & Pierpaoli, C. (1998). *Magn Reson Med*, 39(6), 928-34.
- [5] S.M. Smith, et al... *NeuroImage*, 31:1487-1505, 2006.
- [6] Cedarbaum, J. M., and N. Stambler. 1997. *J Neurol Sci* 152 Suppl 1:S1-9