Functional Ultrasound in the Brain of TrJ mice, a model of the neurodegenerative disease of Charcot Marie Tooth

Background, Motivation and Objective

Charcot-Marie-Tooth's (CMT) disease is the most commonly human inherited neurological disorder, and is described as a peripheral nervous alteration. Trembler-J (TrJ) mice model this condition with the same spontaneous mutation as in human variant CMT1E . Recent studies in TrJ evidenced alterations in the central nervous system (Damián et al 2021, Biomolecules). To further verify this hypothesis, in this work we used functional ultrasound (fUS) to examine the vascular brain's response to an external stimulus. To our understanding, this is the first neurological functional analysis that studies this disease.

Statement of Contribution/Methods

Three months old TrJ (n=8) and healthy WildType (WT, n=10) mice were used. Each mouse was anesthetized and placed in a stereotaxic system to image the coronal plane of the brain (Fig. 1A). For fUS, a 15MHz, 128 elements linear array driven by a Verasonics Vantage System was used. The stimulus consisted in brushing the whiskers with a periodic ON-OFF pattern of 40 seconds (Fig. 1B). We compute the activation maps (Fig. 1A), which is the correlation between the stimulus and the Doppler signal. As expected, the response is in the primary somatosensory cortex S1BF (white dashed line in Fig. 1A) and perfusion increases (Doppler signal in Fig. 1B) when stimulus is ON (green patch, Fig. 1B). For both models we compared the correlation values, the activated area and the response speed by computing the slope of the Doppler low pass (LP) filtered S1BF signal (red line in Fig. 1B).

Results/Discussion

No significant differences were found in the size of the S1BF region, however, the size of the activated area was larger for WT (Fig. 1C) with a significantly higher correlation (Fig. 1D). The response speed was also larger for WT mice (Fig. 1E shows the median for each stimulus considering all mice). We also observe differences in the slope between 1st and 2nd stimulus only in TrJ mice (Fig.1E), suggesting a learning process. Based on the results, and compared to WT, we observe an overall diminished functional response in TrJ mice. Therefore, this study contributes to the hypothesis that this disease also affects the central nervous system. The fUS proves to be a powerful tool for studying the underlying mechanisms of brain dynamics and opens the possibility for better understanding the neurological consequences of CMT.

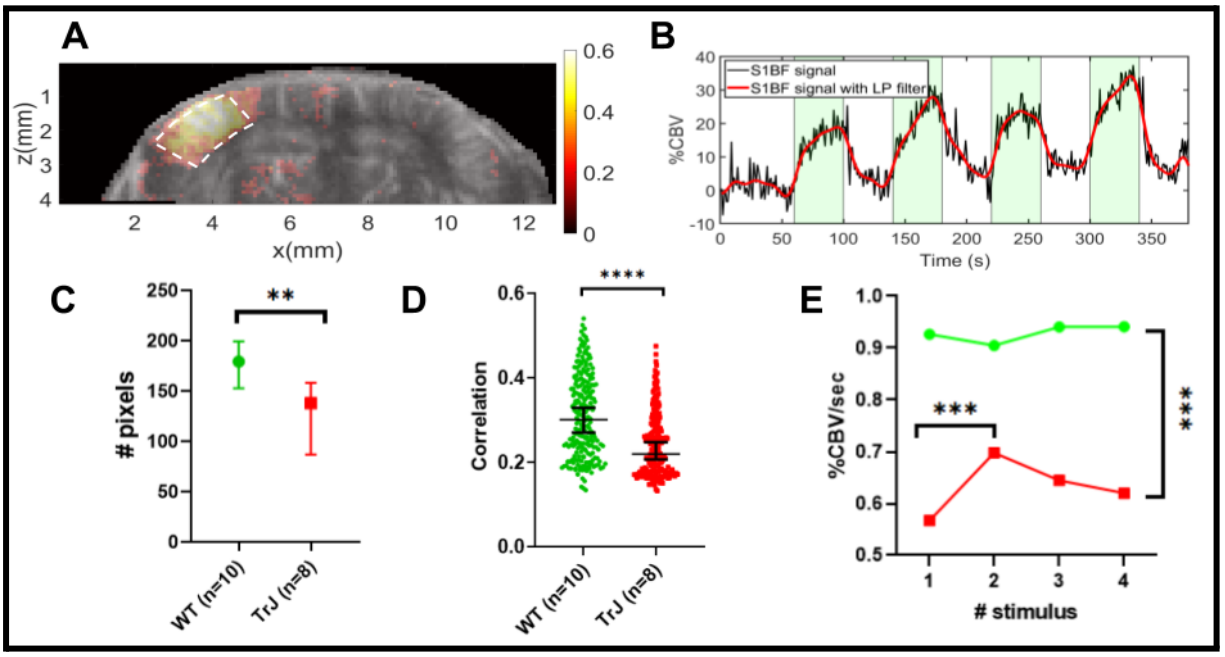

Figure 1