Decreased Delta Synchrony, Reduced Frontal Lobe Delta Power, and Increased Network Homogeneity in a Mouse Model of Frontotemporal Dementia

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Introduction

Decrease in functional connectivity between brain regions in sufferers of dementia possibly contributes to cognitive decline. For this reason, functional networks of brain regions are of interest as biomarkers for dementia, but the complex nature of such large networks renders them difficult to describe qualitatively. The mathematical field of graph theory allows us to quantify network structure.

Electrophysiological data taken from a mouse model of frontotemporal data (FTD) is explored mathematically in order to search for significant differences in the network structures of wild type (WT) and transgenic mice to increase understanding of how functional brain networks are affected in dementia.

CHMP2B Mouse Model of Frontotemporal Dementia

- Transgenic mouse model based on Danish and Belgian families of FTD sufferes.
- Expresses mutant form of CHMP2B gene, causing ubiquitin-positive inclusion bodies (figure 1), gliosis, and axonal degeneration similar to that seen in FTD.

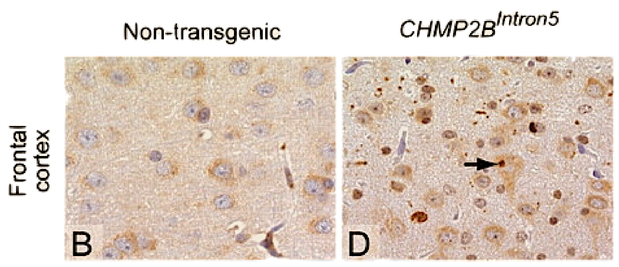

Fig. 1: Inclusion bodies in the transgenic CHMP2B$^{\text{intron5}}$ mice (right) not seen in the wild type mice (left). Ghazi-Noori et al (2012)

All procedures were carried out according to the Animal (Scientific Procedures) Act 1986.

Methods

- Microscrews were implanted in the skulls of 4 WT and 6 CHMP2B male mice aged 11-12 months and 3×20s artifact free epochs of EEG per animal were selected while the animals were inactive.

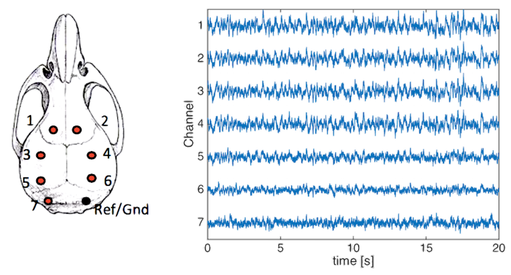

Fig. 2: Skull screw recording locations and example EEG trace

- Filtered into Delta (1-3Hz), Theta (4-12Hz), Beta (15-30Hz) and Low Gamma (30-48Hz) bands.
- Functional networks constructed through calculation of cross correlation between waveforms of each pair of signals. A number of graph theory metrics were used to quantify properties of the network and to search for significant differences.

Results - Decreased Frontal Lobe Delta Power

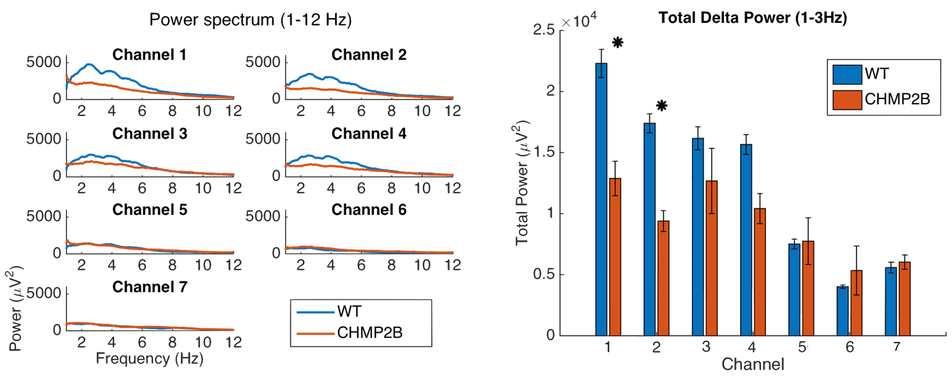

Fig. 3: (Left) Decreased power was observed in the frontal electrodes, whilst the posterior electrodes remained unchanged. (Right) Pairwise comparison of total power of electrodes in the delta band. (* denotes $p < 0.05$, error bars = ±standard error)

Results - Network Measures

Figure 4 shows the average functional networks in the delta band for each cohort of mice.

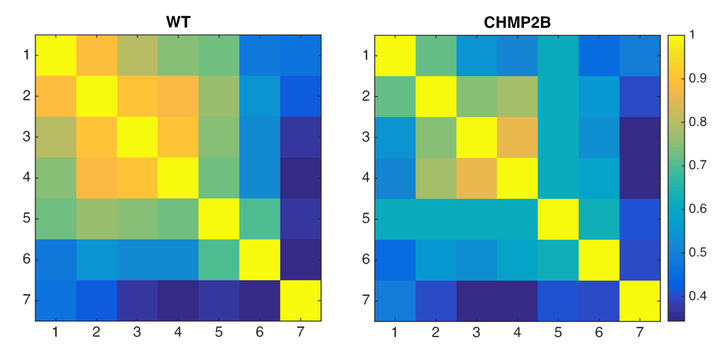

Fig. 4: Average delta band networks over all subjects and epochs in WT (left) and CHMP2B (right) mice.

The WT mice show a heirarchical network structure tending towards high functional connectivity betewen frontal regions and low functional connectivity towards posterior regions. The CHMP2B mice show a less locally dependent network structure; the frontal regions have a structure more similar to the posterior regions in CHMP2B.

Statistical analysis of a number of graph theory metrics demonstrated significant differences in network structure. These include mean degree, local efficiency, degree variance and local efficiency variance.

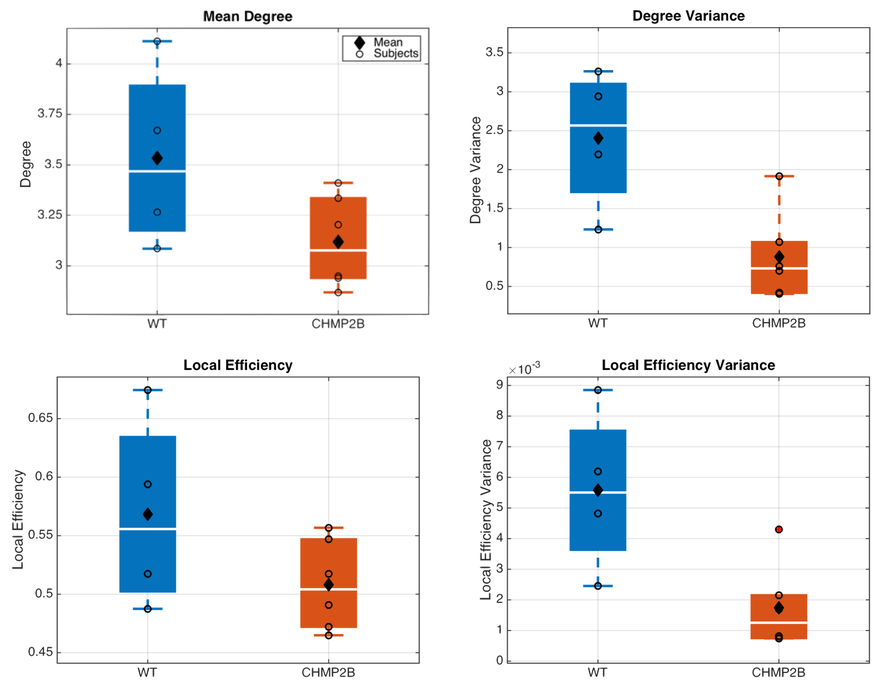

Fig. 5: Mean degree (top left), degree variance (top right), local efficiency (bottom left) and local efficiency variance (bottom right) were significantly decreased in the delta band (1-3 Hz).

Conclusion

In a graph theoretical analysis of large scale functional neural networks from EEG, a number of metrics indicated significant change in the network structure in a mouse model of dementia. Mean degree was significantly reduced, demonstrating a loss of synchrony between regions in the CHMP2B mice. Local efficiency was also significantly decreased, suggesting information transfer between neighbouring regions is less efficient in the CHMP2B mice. A number of graph metrics quantifying the variance of local network properties over the brain, including degree variance and local efficiency variance, were significantly reduced. This suggests a more homogeneous network structure in the CHMP2B mice.

Visual inspection of the networks, alongside a power spectrum analysis showing significantly decreased delta rythm power in the mouse model, suggets these results are due to a loss of functional connectivity in the frontal lobe. Future work will involve the use of mathematical models to explore the mechanisms behind the differences found in this work. We will also explore the structure of small scale networks in these mice using calcium imaging of neural networks, and attempt to understand the relationship between network structures on different scales.

Acknowledgements

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