Title: Phenotype of frontal lobe glioma determines the frequency band specific functional connectivity alteration.

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Abstract: Background: Highly prevalent frontal lobe glioma is associated with pathologically high brain activity, which relates to rapid progression. Regional and whole brain functional connectivity is altered in these patients impacting the treatment and the survival of these patients. Molecular characteristics, such as isocitrate dehydrogenase (IDH) mutations and 1p/19q codeletion, are proved to be survival deterministic biomarkers. We investigated the whole brain functional connectivity of frontal glioma in IDH-wild and IDH-mutant type tumors and their relationship with the disease progression. **Methods:** We evaluated 150 patients with frontal lobe glioma from the UCSF medical center who completed presurgical magnetoencephalography during 2011 to 2022. All these patients underwent surgery and their histopathological and molecular findings were noted. Each participant underwent a 10 minute resting-state MEG at the UCSF Biomagnetic Imaging Laboratory. For each patient, the voxel-level brain source time series was computed using adaptive spatial filters at a resolution of 10mm. Subsequently, functional connectivity was computed using imaginary coherence after parcellating the voxels into 246 brain regions using brainnetome atlas. Such interactions were evaluated at 5 different frequency bands including delta (1-4Hz), theta(4-8Hz), alpha(8-12Hz), beta(12-30Hz), and gamma(30-70Hz). Within and between group non-parametric statistical tests were computed at the ROI level ($p<0.05$) after correcting for multiple comparisons with permutations testing. **Results:** This study included 150 patients (male=60.7%; age=50.7±14.8) diagnosed with frontal lobe glioma (hemisphere left -77 and right-73). The most common integrated diagnosis was glioblastoma with IDH-wildtype in 72 patients (48%) and IDH-mutant in 78 patients (52%). Regardless of the type of tumor, all these patients consistently show pathologically increased whole brain connectivity particularly in the lower frequency bands (delta, theta and alpha). IDH-wildtype tumors have substantially increased connectivity specifically during delta and beta frequency bands when compared with mutant type tumors; on the contrary, IDH-mutant tumors have increased connectivity in the theta and alpha frequency bands when compared with wild type. We observed statistically significant differences in the distribution of connectivity patterns between the IDH-mutant and IDH-wildtype groups in all the frequency bands except the gamma band. Frontal and insular regions showed relatively decreased clustering coefficient compared to the other regions of the brain. **Conclusion:** Patients with frontal gliomas exhibit a frequency band specific alterations in the connectivity and low network clustering. This study might provide insight into our understanding of the aggressive nature of the tumor and its progression with prognostication.

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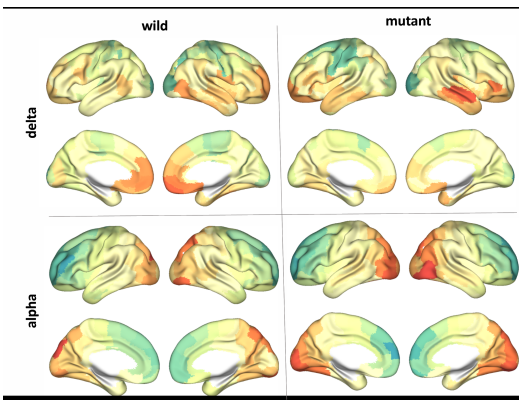

Figure-1: This figure illustrates the regional level connectivity differences in the delta and alpha frequency band of the wild and mutant phenotype of frontal gliomas.