 DOI: 10.3217/978-3-85125-467-9-209

Frontal-Temporal Connectivity Dysfunction in a Mouse Model of Schizophrenia

Y. Shahriari[1*], D. J. Krusienski[2], J. H. Choi[3]

[1]University of California, San Francisco , San Francisco, CA, USA; [2]Old Dominion University, Norfolk, VA, USA; [3]Korea Institute of Science and Technology, Seoul, South Korea

*E-mail: yalda.shahriari@ucsf.edu

Introduction: Development of an appropriate neuro-psychopharmacology model of schizophrenia remains a challenge. Hallucination in schizophrenia patients is representative of perceptual and sensory processing malfunction and the auditory steady state response (ASSR) is a common approach for evaluating the auditory and sensory deficits in the brains of these patients. In this study we investigate the frontal-temporal connectivity pattern in mice models with lack of the PLC-β1 enzyme as schizophrenia-like endophenotypes through their brain functional analysis using quantifying dynamic neural interactions of cortico-subcortical connections. The results show altered brain connectivity to the left auditory cortex in these mutant types. The multidisciplinary goal of this study can aid to differential diagnosis of schizophrenia, validating of novel medications via histology on this animal model, and eventually facilitating the development of a closed-loop BCI system as a neurofeedback therapy for the disease.

Material, Methods and Results: Chronic surgery was performed on 6 histologically confirmed PLC-β1 heterozygous mice and 7 controls for electrode implantation on frontal and auditory cortex (2 frontal EEG and 2 auditory LFP recording). The animals were passively stimulated using frequency-modulated (FM) auditory steady state stimulation (ASSS) with four different frequencies of 20, 30, 40 and 50 Hz while EEG was recorded. An adaptive directed transfer function (ADTF) was built to quantify the neural dynamic interactions between each pair of electrodes. Significant ADTF values were determined based on 200 surrogate data constructed from random phase shuffling. Using a significance level of 0.05, significant and non-significant ADTF values were set to 1 and 0, respectively, to show the percentage of animals with significant connectivity values for each connection, frequency, and time point. Figure 1 shows the percentage of animals with significant connectivity between each pair of connections at stimulus frequency of 40 Hz. The results show an obvious decrease of connectivity from both hemispheric frontal channels to the left auditory cortex for the mutants.

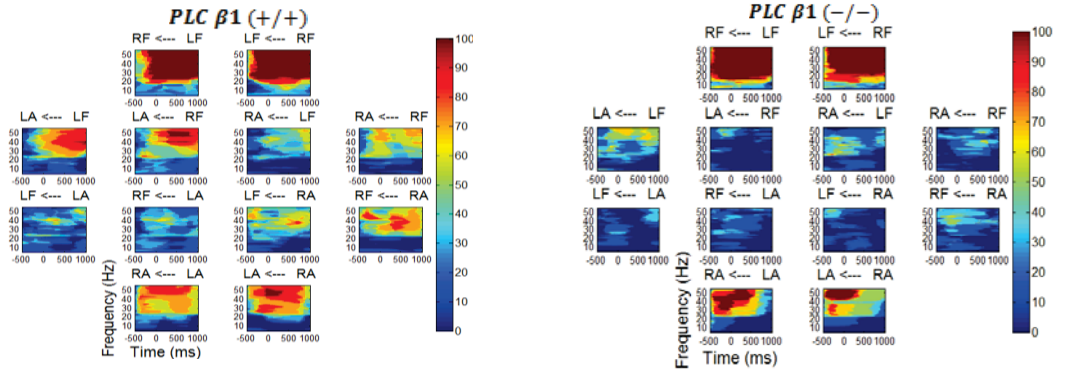

Figure 1. *The percentage of significant ADTF values for the control (left panel) and PLC- β1 (-/-) (right panel) groups at the 40 Hz stimulus frequency.* The *direction of information flow is indicated above each subplot..*

Discussion: The connectivity analysis showed considerable deficits in the long range connections to the left auditory cortex in the mutants compared to the control group. This can be representative of frontal-temporal connectivity dysfunction that affects the long range connections and supports the the existing schizophrenic dysconnection hypothesis in the mice models with lack of the PLC-β1 gene [1]. Moreover, these results corroborate prior studies that showed disruption of left hemisphere neurophysiology and neuroanatomy in humans with schizophrenia [2-3].

Significance: Characterization of the connectivity deficits in animal models of schizophrenia represents the first step toward the design of therapeutic BCI systems for humans with schizophrenia. These systems will provide neurofeedback of connectivity measures in EEG to stimulate normal or alternate connectivity patterns with the objective of improving undesirable symptoms or associated behaviors of schizophrenia.

References

[1] Stephan, K. E., Baldeweg, T., & Friston, K. J. Synaptic plasticity and dysconnection in schizophrenia. *Biological psychiatry*, *59*(10), 929-939, 2006.

[2] Spencer, K. M., Niznikiewicz, M. A., Nestor, P. G., Shenton, M. E., & McCarley, R. W. Left auditory cortex gamma synchronization and auditory hallucination symptoms in schizophrenia. *BMC neuroscience*, *10*(1), 85, 2009.

[3] Onitsuka, T., Shenton, M. E., Salisbury, D. F., Dickey, C. C., Kasai, K., Toner, S. K., ... & McCarley, R. W. Middle and inferior temporal gyrus gray matter volume abnormalities in chronic schizophrenia: an MRI study. *American Journal of Psychiatry*, 2014.