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Editorial

The Future Role of *In vivo* Electrophysiology in Preclinical Drug Discovery

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Although a mainstay of preclinical drug discovery, the translational value of animal behavioral models of neurodegenerative diseases and psychiatric disorders remains controversial [1]. Thus, there is an unmet need for better animal models.

In vivo electrophysiology permits the measurement of drug-induced changes in neural network activity while providing the investigator with objective biomarkers of neurological function which can be used to increase the translational value of behavioral observations made with preclinical animal models [2]. This powerful method, which can be used in freely behaving animals, typically employs microelectrode arrays, which in turn allow investigators to simultaneously record single unit activity and local field potentials (LFPs) from multiple cells in multiple brain regions. Recordings can also be made from specific brain regions implicated in disease. For example, drug-induced changes in both single unit activity and LFPs in the CA3 and CA1 subregions of the hippocampus are potential biomarkers of drug effects on spatial learning and memory function implicated in animal models of prodromal Alzheimer's disease. This translational preclinical method is also well suited for target-based as well as repurposing studies. We have previously shown that age-related changes in the firing dynamics of hippocampal place cells in rats are improved by acute systemic co-administration of low doses of the FDA approved anti-epileptic drugs levetiracetam and valproic acid [3]. Although relatively few studies have used this technology to investigate the effects of systemically administered drugs, because it provides investigators with real-time information about neural activity in freely behaving animals, there is nevertheless a growing body of literature to suggest it holds tremendous promise as a preclinical drug discovery tool [2-9].

The value of monitoring neural network activity in real-time is further exemplified by the fact that pharmaco-electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) studies have been used extensively to assess for the *in vivo* effects of drugs in humans with neurological disorders. Although regional cerebral blood flow and surface EEG studies are sensitive noninvasive measures of localized neuronal activity in humans, these biomarkers are not specific for evaluating drug-induced effects on different cell types (e.g., pyramidal cells vs interneurons). The advantages of *in vivo* electrophysiology over functional imaging studies of regional cerebral blood flow are also not limited to the specific type of cells from which data can be recorded. For example, an action potential carries additional information about the specific events that evoked it which in turn can be evaluated and quantified with respect to how this neurological response is modified by a specific class of drugs. Our laboratory has shown that baseline and drug-induced changes in neural network activity measured with this technique in a rodent model of age-related amnestic mild cognitive impairment (aMCI) are consistent with the changes in regional cerebral blood flow observed in humans with aMCI [3]. In addition, the use of *in vivo* electrophysiology allowed us to measure changes in the spatial information content contained within the action potential of CA3 and CA1 pyramidal cells that could not be obtained with fMRI or surface EEG [3].

By coupling preclinical animal behavioral models with *in vivo* electrophysiology and systemically administered drugs shown to provide clinical relief in humans, investigators will be able to extract relevant information about the changes in neural network activity associated with different classes of drugs. This reverse engineering approach will augment our understanding of the specific changes in neural network dynamics associated with clinical improvement following systemic administration of various drugs while providing a path forward to aid in the discovery of novel therapeutics. Since this approach uses behavioral and neural network changes induced by systemic drug administration it is likely to lead to better therapeutics for neurological disorders than target based models.

In conclusion, *in vivo* electrophysiology is rapidly emerging as a powerful tool capable of providing pharmacologists with important preclinical data about how drugs modulate neural activity in freely behaving animal models of disease that cannot be obtained with other behavioral or functional measures.

Bibliography

1. McGonigle P and Ruggeri B. "Animal models of human disease: challenges in enabling translation". *Biochemical Pharmacology* 87.1 (2014): 162-171.

2. Watson BO and Buzsáki G. "Neural syntax in mental disorders". *Biological Psychiatry* 77.12 (2015): 998-1000.

3. Robitsek J., *et al.* "Combined administration of levetiracetam and valproic acid attenuates age-related hyperactivity of CA3 place cells, reduces place field area, and increases spatial information content in aged rat hippocampus". *Hippocampus* 25.12 (2015): 1541-1555.

4. Robbe D., *et al.* "Cannabinoids reveal importance of spike timing coordination in hippocampal function". *Nature Neuroscience* 9.12 (2006): 1526-1533.

5. Manns JR., *et al.* "Hippocampal CA1 spiking during encoding and retrieval: relation to theta phase". *Neurobiology of Learning and Memory* 87.1 (2007): 9-20.

6. Wells CE., *et al.* "Novelty and anxiolytic drugs dissociate two components of hippocampal theta in behaving rats". *Journal of Neuroscience* 33.20 (2013): 8650-8667.

7. Newman EL., *et al.* "Cholinergic blockade reduces theta-gamma phase amplitude coupling and speed modulation of theta frequency consistent with behavioral effects on encoding". *Journal Neuroscience* 33.50 (2013): 19635-19646.

8. Newman EL., *et al.* "Grid cell spatial tuning reduced following systemic muscarinic receptor blockade". *Hippocampus* 24.6 (2014): 643-655.

9. Balakrishnan S and Pearce RA. "Midazolam and atropine alter theta oscillations in the hippocampal CA1 region by modulating both the somatic and distal dendritic dipoles". *Hippocampus* 24.10 (2014): 1212-1231.

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