In recent years, neuroimaging has become an integral part of drug development for neurodegenerative, neurodevelopmental and rare diseases, offering highly valuable insight into structure & function of the brain and downstream pathological changes. In preclinical research, several imaging methods, such as MRI and PET imaging are essential, because of the previous translational component - ability to utilize the same tools and methods in basic/clinical settings and in patients. Despite the plethora of available imaging modalities, they all possess certain limitations, such as methodological complexity, costs, invasiveness, poor sensitivity etc. That is why neuroimaging is a constantly evolving field, with new tools and methods appearing steadily, driven by current demands and technological advancements and development in computational methods.

In this work we present the applications and our implementation of a novel neuroimaging platform for preclinical research - Functional Ultrasound Imaging (fUS), a state-of-the-art method, utilizing cutting edge technology for high-speed Doppler-based imaging of cerebral vascularization and structural changes in cerebral volume (CBV).

Here we present several application examples of fUS in preclinical drug development framework:

• Somatosensory stimulation in Oxaliplatin-induced neuropathic pain model in mice
• Pharmacological stimulation in mice and comparison with phMRI
• Vascular imaging in thrombosis (TBE) stroke model in rats

Functional ultrasound experiments were performed using a prototype fUS system (Inconieus, Paris, France), consisting of ultrasound imaging system, miniature probe with 128 ultrasound transducers and acoustic lens, motorized positioning system allowing precise positioning of the probe in 3 orthogonal planes. Plane-wave imaging at 24 h with fUS.

In-vivo functional ultrasound is a cutting-edge research tool for research in CNS area, particularly useful for such studies, fUS makes it possible to run a panel of readouts, such as vascular imaging, connectivity, signal change upon contralateral to unilateral TBE stroke, etc. Here we have tested all of this options, with representative examples of fUS images shown in Figure 3, 4-E.

3.1 OIPN – Oxaliplatin-Induced Peripheral Neuropathy model

Using classical functional MRI simulation paradigm, we tested the tactile sensory processing in trigeminal system with fUS. During its in vivo measurements, we gained time-activity curves (TACs) for the experiment in 4-OXP animals, with 1 min of stimulus duration.

Quantification of the stimulation epochs as integral area under the curve (AUC), Mean ± SEM.

4 CONCLUSION

In-vivo functional ultrasound is a cutting-edge research tool for research in CNS areas, particularly useful for preclinical drug discovery, due to its non-invasiveness, high sensitivity and high spatial resolution. These features make it highly applicable for longitudinal functional studies in neurodegenerative and rare diseases models.

Here we presented only a glimpse of data and applications that are enabled by this novel platform, which already possesses certain limitations, such as methodological complexity, costs, invasiveness, poor sensitivity etc. That is why we are planning to develop this methodology for further utilization.

Another fUS reaction that is not possible to cover in the current paper due to space limitation is the resting-state functional connectivity (FC) analysis, where correlation of slow activity between different brain regions is analyzed (Fig. 5). Because of higher temporal resolution and sensitivity to small structural signal, fUS is a perfect tool to examine structural connectivity changes, i.e., areas that show connectivity changes after pharmacological and somatosensory stimulation trials, in the same subjects in multiple timepoints.

We have successfully applied this analysis to zQ175 mouse model of TBE (Fig. 6). The fUS FC in zQ175 mice showed the same functional connectivity changes as observed with conventional fcMRI.

In both cases we observed the same functional connectivity changes as observed with conventional fcMRI.

This demonstrates the potential of fUS as a powerful tool for drug discovery research.


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