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A bright future for the tree shrew in neuroscience research: Summary from the inaugural Tree Shrew Users Meeting

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ABSTRACT

Tree shrews (*Tupaia* spp.) have been used in neuroscience research since the 1960s due to their evolutionary proximity to primates. The use of and interest in this animal model have recently increased, in part due to the adaptation of modern neuroscience tools in this species. These tools include quantitative behavioral assays, calcium imaging, optogenetics and transgenics. To facilitate the exchange and development of these new technologies and associated research findings, we organized the inaugural "Tree Shrew Users Meeting" which was held online due to the COVID-19 pandemic. Here, we review this meeting and discuss the history of tree shrews as an animal model in neuroscience research and summarize the current themes being investigated using this animal, as well as future directions.

Keywords: Tree Shrew Users Meeting; Animal models; *Tupaia*; Neuroscience

INTRODUCTION

On March 29th, 2021, we organized the Tree Shrew Users Meeting, the inaugural international gathering of neuroscientists who use the tree shrew (*Tupaia* spp.) as a model organism in their research or are interested in doing so in the future. The goal of this meeting was to facilitate communication between these groups to foster a community and further establish this animal as a major model in neuroscience. Here, we briefly introduce the tree shrew animal model and its history in neuroscience research and follow with a review of the content of the inaugural meeting.

TREE SHREWS AS AN ANIMAL MODEL IN NEUROSCIENCE

Tree shrews are diurnal animals originating from South-East Asia. The earliest archived description of a tree shrew comes from William Ellis, a surgeon in Captain Cook's third expedition in 1780 (Lyon, 1913). Given their similar appearance, tree shrews were initially thought to be squirrels and were later classified as insectivores and primates (Simpson, 1945). Today, they are classified within their own order, Scandentia (Van Valen, 1965) (Figure 1).

Tree shrews present numerous advantages as a model organism in neuroscience; they are the closest phylogenetic relative of primates (Janečka et al., 2007; Ni & Qiu, 2012) that can be kept in a laboratory setting (Fuchs, 2015; Hubrecht & Kirkwood, 2010). Their breeding cycle is short and year-round and, as such, they can thrive in captivity. In addition, tree shrews are born in a relatively undeveloped state, allowing measurement and manipulation of neurodevelopmental
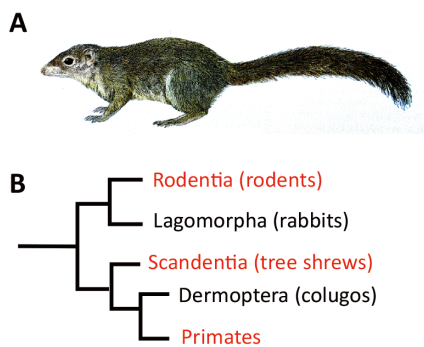
Figure 1 Tree shrew phylogeny

A: Illustration of a Northern Tree Shrew (*Tupaia belangeri*) adapted from Wilson & Mittermeier, (2009); B: Schematic representation of the phylogenetic position of tree shrews and relationship to primates.

processes (Drenhaus et al., 2006).

Tree shrews can be trained on different forms of detection and discrimination tasks, making them a suitable model to study the neuronal underpinning of sensory-motor and cognitive behaviors (Casagrande & Diamond, 1974; Khani & Rainer, 2012; Mustafar et al., 2018; Petry et al., 1984). Unlike rodents, they are diurnal (Emmons & Greene, 2000), possess a cone dominated retina (Müller & Peichl, 1989), and exhibit interesting visually guided behaviors (Mustafar et al., 2018). These properties have made tree shrews a suitable model particularly in the field of visual neuroscience.

Recent surge in the use of tree shrews in neuroscience research

Tree shrews have been a model organism for Neuroscience research in Europe and the United States since the 1960s. There has been a surge of interest in this animal model following recent publication of the tree shrew genome (Fan et al., 2013, 2019; Xu et al., 2012) and several novel findings using state-of-the-art methods (Dimidschstein et al., 2016; Lee et al., 2016; Smith & Fitzpatrick, 2016). However, since the use of tree shrews is not as widespread as mice, zebrafish or drosophila, there is a lack of standardized resources, methodology and genetic tools. To accelerate the development of such resources and further establish the tree shrew as a major model organism in neuroscience, we decided to gather the community of tree shrew researchers for an inaugural international meeting. The meeting was held virtually due to the COVID-19 pandemic and was attended by 91 participants. It contained four sessions: a "Community Introduction" session showcasing the work of 18 groups with brief presentations, two sessions dedicated to important questions for the community: creating transgenic animal models and tree shrew colonies and breeding in the US, as well as a keynote session on the history of tree shrews in visual neuroscience. To allow the continuation of information exchange beyond the meeting, an online channel was created for all interested participants.

Current and past status of research

The Community Introductions sessions provided brief updates from most of the research groups participating in the meeting.

Broadly, the groups could be categorized in three research directions: retina (Sajdak et al., 2019), including retinal models of disease and injury (El Hamdaoui et al., 2021; Gawne et al., 2017; Norton et al., 2021) as well as retinal information processing (Johnson et al., 2019); development and function of cortical and subcortical sensory systems (Maher et al., 2021) including visual cortex and superior colliculus (Lee et al., 2016; Petry & Bickford, 2019; Sedigh-Sarvestani et al., 2021); and higher order cognitive functions including pattern and object discrimination and decision making (Mustafar et al., 2018).

The panel on transgenic tree shrews featured Dr. Yong-Gang Yao of the Kunming Institute of Zoology and Dr. Hirofumi Nishizono, of Kanazawa Medical University who are leading the effort in the creation of transgenic tree shrews. These groups are independently developing novel genetic engineering approaches to produce transgenic tree shrews (Darwish et al., 2019; Li et al., 2017). Dr. Yao is also working on the development of inbred lines of tree shrews to reduce genetic variability and facilitate the development of disease models.

In the panel about tree shrew colonies and breeding in the United States, Susan Freling from the Max Planck Florida Institute for Neuroscience, Dr. Alev Erisir from the University of Virginia, and Dr. Raphael Grytz from the University of Alabama at Birmingham summarized the current state of their colonies and highlighted challenges for the community.

The keynote was delivered by Dr. Jon Kaas of Vanderbilt University, who gave an extensive description of the contribution of tree shrews to our understanding of the visual system. LeGros Clark's early studies of the visual pathway of tree shrews reported similarity to primates (Le Gros Clark, 1924), leading to adoption of the tree shrew as a model organism by visual neuroscientists including Irving Diamond (Snyder & Diamond, 1968). Indeed, recent studies suggest that ancestral primates had similar brain morphology compared to tree shrews (Mantilla et al., 2021). Dr. Kaas gave an overview of the early contributors of tree shrew research and the connections between the different laboratories in the United States that started using this animal model in the 1960s. He particularly highlighted the contributions of the late Dr. Viviana Casagrande, notably her work on the X and Y cells (Sherman et al., 1975) of the LGN as well as the contribution of the superior colliculus to vision (Casagrande & Diamond, 1974). He concluded with comparative work demonstrating the evolution of the tecto-pulvinar pathway, and the emergence of higher visual areas involved in the processing of motion in primates.

Future directions

The Tree Shrew Users Meeting gave an overview of the current efforts in the transfer of state-of-the-art neuroscience approaches from rodents to tree shrews. Viral targeting has become available through promoter-based approaches (Dimidschstein et al., 2016), allowing cell-type specific recordings and optogenetic manipulations. Additional tools, such as a 3D anatomical atlas are under development and will facilitate further establishment of the tree shrew as a major model organism in neuroscience. The upcoming transgenic

lines will also open the door to the study of neuro-degenerative and neuro-developmental disorders. The recent surge of interest in tree shrews is related to a growing need for alternative animal models in neuroscience to complement investigations currently performed predominately in rodents (Yartsev, 2017). Given their phylogenetic proximity to primates, small size and short gestation cycle, tree shrews serve as an ideal animal model for neuroscience research.

Next meeting

We look forward to hosting an extended meeting in 2022 and further growing the community. This meeting will be hosted at the Max Planck Florida Institute of Neuroscience in the United States and will have a virtual component to allow participation of non-local attendees. We welcome all interested participants including prospective tree shrew users from broad subfields within neuroscience. Interested participants should contact treeshrewmeeting@gmail.com

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

E.S, M.S-S., R.W. and D.F. conceived the review and prepared the draft. All authors contributed to the discussions, read, and approved the final version of the manuscript.

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