Keynote Lecture

Professor David P. Wolfer

Institute of Anatomy, University of Zurich and Institute of Human Movement Sciences and Sport, ETH Zurich, Switzerland
dpwolfer@anatom.uzh.ch

About the speaker

David P. Wolfer (born 1960) has been associate professor of anatomy at the Institute of Anatomy at the University of Zurich and at the Institute for Human Movement Sciences at ETH Zurich since 2005. He studied medicine in Zurich and got his doctorate in 1988. His research group investigates the biological basis of cognitive functions, in particular the role of the hippocampus in memory and control of behavior. The group works with genetically modified mice as well as with classical genetics and lesion studies. In the context of this research new methods of behavioral analysis are developed, allowing to measure cognitive functions more efficiently and reliably.

The teaching activities of David P. Wolfer cover the whole microscopic and macroscopic human anatomy with special emphasis on the nervous and musculoskeletal system. At the advanced level, his teaching covers the topics of neuroanatomy and genetics of behavior.

Automated testing of mouse behavior in the home cage:can it meet its promises?

The sequencing of the human and mouse genomes as well as powerful methods to manipulate genes in the mouse have created new challenges for behavioral neuroscientists. The rat as the traditional rodent model of experimental psychology is now often replaced by mutant mouse lines. Many of them have been created to model disorders such as dementia, depression, schizophrenia or autism, hoping that mouse behavior can model the symptoms of human patients. Chemical mutagenesis screens, large scale transgenesis and gene targeting projects, as well as drug screening programs ask for high throughput behavioral analysis of mice. The attempt to respond to these challenges by adapting existing behavioral paradigms has only been partially successful, leading some to consider behavioral analysis as a bottle-neck hindering the progress of neuroscience [1]. Behavioral tests fail to provide the expected sensitivity and specificity. For example, most mouse models of severe human mental retardation lack deficits in cognitive tests or show only very minor changes which can also be found in mouse lines created for other purposes. Behavioral analysis of mice has gained the reputation of being unreliable with results failing to reproduce from test to test and from lab to lab. Finally, because behavioral testing is slow, the generation of mouse models often takes less time than their functional analysis.

Several factors need to be considered. Many of the current tests have originally been developed for rats and were transferred to mice without sufficiently considering the behavioral differences between the two species. Also, many tests are used in a careless way outside the context for which they have originally been validated. In most experiments the mice are socially isolated, handled by humans, transferred into novel and aversive apparatus, and their diurnal activity cycle is disturbed. This introduces stress, increases variability and complicates interpretation. Behavioral testing of mice is slow and labor intensive, because they adapt slowly to experimental procedures and are slow learners in many tasks. In addition, most applications require that animals be tested in a battery of multiple tests. To make things even worse, the behavior of mice tends to be variable and their performance unreliable, creating a need to analyze relatively large samples. In an attempt to reduce costs and to standardize conditions, housing environments are often inappropriate, leading to stimulus deprivation and development of behavioral stereotypies. Finally, to eliminate genetic variability most experiments use inbred strains which have been bred for morphological and/or behavioral extremes.

During the past few years, behavioral testing of mice within their home cage has emerged as a new approach promising to solve many of the problems of conventional behavioral tests [2]. The wish list of features of an ideal system is long. It should minimize the need to handle the animals and allow them to express their behavioral repertoire in an enriched an social environment. The cage should have sensors collecting rich data, permitting not only monitoring of activity but also identification and quantification of defined behaviors including social interactions. Recording of ambient variables (temperature, light, etc.), of body weight, and if needed of physiological parameters should also be possible. As cues, reward or punishment, the cage should permit to present stimuli of various modalities at defined locations and precisely controlled time points. Further, the system should have operant elements permitting animals to interact with the system and to influence its operation. The software should permit flexible and intuitive design and debugging of complex protocols and support fully automated use once protocols are established. The software should not only provide fully automated control of experiments, but also permit real time monitoring of critical variables and produce alarms if an animal fails to perform or is in a critical state. After the experiment the user expects intuitive and flexible software functions for visualization and exploration of the data, data mining tools and the opportunity to fully automate established analyses, including statistics.

Several systems have been developed that implement part of the features in the above wish list. PhenoTyper by Noldus, HomeCageScan by CleverSys, SmartCube by PsychoGenics bring video-tracking technology into the home cage of a single animal and combine this with sophisticated image analysis software to quantify and characterize movements. These systems can be used to monitor spontaneous behavior, but most of them also offer the possibility to present stimuli and to add operant elements. The PhenoMaster project of TSE Systems plans to add interactive elements to extend the possibilities of the existing metabolic cage LabMaster. This system already permits to record physiological parameters and to monitor activity using IR beams or heat sensors. Laboras by Metris places the cage on piezo sensors to record the vibrations generated by the animal and uses specialized software to identify and quantify defined behavioral elements. IntelliCage by NewBehavior uses transponder technology and is the only system to allow monitoring and testing of mice housed in social groups. The IntelliMaze project develops automated gates than can guide mice from the group cage to specialized arenas for additional tests.

The availability of systems permitting automated testing of mouse behavior in the home cage represents an enormous progress. In addition, large efforts are being made to further improve, refine and extend these systems and to increase their usefulness by developing and validating test protocols for various applications. However, many of the actual problems in mouse phenotyping are of conceptual nature and cannot be resolved by technical developments alone. Mere automation of already existing tests will not automatically improve their ethological relevance, nor will it resolve the question whether standardization or controlled variation yield more valid data. Fully automated high throughput screening of mouse behavior may soon be a reality, but is unlikely to be more than a fist step if the goal is to understand behavior [3]. Systems permitting automated testing of mouse behavior in the home cage are a very welcome and powerful new tool that may help us to solve many burning problems of mouse phenotyping, but we first need to learn how to use them in creative ways.

References

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