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Improving biomedical research by automated behavior monitoring in the animal home cage – action needed for networking

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Under Review

The key goal in biomedical research is a better understanding of disease etiologies, which ideally results in strategies and recommendations for the prevention of diseases before they arise, and in the development of effective therapies. However, many concerns have been expressed about the reproducibility and the translational validity of preclinical research in animal models to inform clinical trials in humans [1,2]. It has been proposed that improving internal, external and construct validity of animal studies will lead to improved translatability [3,4].

There is much public interest toward the use of animals in research, with heightened calls for an outright ban having been addressed at the European Commission (for example, https://www.europarl.europa.eu/doceo/document/PETI-CM-653736_EN.pdf). Therefore, the research community has the responsibility not only to follow the 3Rs (Replacement, Reduction, Refinement) and to uphold high animal welfare standards, but also to explain to the public and colleagues with opposing views how such standards are upheld, and how the use of animals in research is in many cases essential and still irreplaceable [5,6].

Legally and ethically, animals can only be used when there are no valid alternative methods with which to address a specific scientific or clinical question. One example is that of unmet medical need in the unraveling of complex brain diseases such as dementia, for which *in-vivo* assessment of behavior and physiology ~~are vital~~remain instrumental for the understanding of disease mechanisms and the development of therapies [6]. Neuropsychiatric and neurological diseases pose a significant burden for patients, their relatives, and society at large. Globally, in 2016, neurological disorders were the leading cause of disability-adjusted life-years and the second leading cause of deaths [7]. In 2010, the total cost of brain disorders in Europe amounted to €798 billion [8]. To alleviate this burden and ~~to fully~~ better understand these complex disorders, animal models are still widely used. However challenging, ~~S~~such models ~~are especially valid and~~ can hold the promis~~ing~~e ~~in terms of~~for ~~the potential for~~ translational potential only ~~when~~ if the relevant mechanisms and effects of the disease are conserved between the species studied and humans. To realize this potential, it is important to improve not only the construct validity of the models themselves, but also the methodological quality of preclinical studies by making them closer to—and more predictive of—clinical trials.

One aspect that frequently differs between preclinical animal and clinical human studies is that of drug treatment regimens. Typically, acute, single drug administrations are applied in animal models and short-term effects are measured. However, for effective treatment of neurological and neuropsychiatric diseases in humans it is often important to embark on long-term treatment and to follow the evolution of symptoms over time [3]. Similarly, the examination of ~~developing phenotypes~~disease symptoms and humane endpoints in animal models is often done in small 'snap-shots' of time, by infrequent monitoring, which can potentially miss subtle early signs of disease. Th~~erefore~~us, the functional ~~characteris~~characterization ~~tics~~ of disease-related phenotypes in animal models is often ~~may be~~ limited and ~~affected by poor~~of unclear translational relevance. Automated ~~behavior~~ monitoring of behavioural and physiological parameters in the animal's home cage, which allows for longitudinal assessment of individual trajectories over sufficiently long intervals for (chronic) drug treatment or phenotype progression, is a promising solution to these problems.

Over the last 15–20 years, manufacturers and research groups have developed various systems for this type of monitoring, using a number of technologies (like video-tracking, infrared sensors, radiofrequency identification, capacitance changes etc) either separately or in combination. ~~Using cutting-edge technologies (such as machine learning, video monitoring and radio frequency identification),~~ These home-cage-monitoring (HCM) systems allow automated 24/7 collection of longitudinal data, while requiring minimal handling or any other interference by the experimenter. This delivers data that is less biased and reduces the impact ~~on animals~~ of unspecific stressors associated ~~of stress from~~ with experimental ~~procedures~~interventions in animals, thereby increasing the reproducibility of the studies and refining the animal experience. We believe that ~~Therefore,~~ automated ~~behavior~~ monitoring in the animal home cage is becoming an important tool for the improvement of animal welfare, reproducibility and external validity of animal models [9]. In addition, the recording of more high-quality data per individual has the potential to lead to significant reductions in the number of animals required. However, storage, processing and analysis of these large datasets requires novel approaches, expertise in data science and application of cutting-edge tools (machine learning, artificial intelligence).

In the future, researchers will strive for automated detection of as many behavioral and physiological parameters in the animal home cage as possible, including those related to social behaviors. The more that phenotypes with translational value can be validated and robustly measured in the home cage, the better will be the alignment between preclinical research and animal welfare. However, assessing the full behavioral repertoire and physiology of a rodent is a complex task. Reliable tracking of individuals in a group and the recognition of subtle and sporadic behaviors are especially demanding. Each of the current technologies has strengths and limitations, and no single system currently exists that meets all the needs of biomedical research. ~~Moreover~~Importantly, the integration and interpretation of the large amounts of complex data gathered poses another demanding task. F~~Thus, f~~urther technological developments and additional data analysis tools are ~~needed~~ crucial for HCM to become a reliable standard in preclinical research. In addition, critical comparisons of HCM with already established, standard methods that assess complex, disease-relevant behaviors outside of the home cage will be required to evaluate whether automated behavior monitoring in the home cage is a suitable replacement for any such methods.

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Substantial progress toward solving the aforementioned technical and data analysis problems could result in the development of translational digital biomarkers; i.e., objective, quantifiable measures collected by means of digital technologies, that can serve as indicators of normal or pathophysiological biological processes, or of responses to an exposure or intervention. These new measures would aim to be more clinically relevant and to better translate from preclinical studies to clinical trials [10; see also Translational Digital Biomarkers – NA3RsC].

In the summer of 2020, a network of biomedical researchers, veterinarians, neuroscientists and data analysis professionals from 23 European countries came together to start a discussion forum on current topics in animal models. These discussions paved the way for the COST Action 20135 (COST_TEATIME), launched in October 2021, for improving and broadening the use and development of automated HCM.

The COST_TEATIME action pursues several goals (outlined in the Action's Memorandum of Understanding, available at www.cost-teatime.org). Firstly, the Action aims to identify currently unmet community needs for further technological development in HCM. To this end, ~~;~~ COST_TEATIME will conduct a survey among researchers in mouse behavior, laboratory animal science and data science from both academia and industry. The purpose of this survey is to assess the unique opportunities for HCM by gathering the views to inform future developments and challenges in the field. A ~~second aim of the survey~~broader aim of the Action is to expand our network by connecting researchers across ~~these various~~various disciplines who are using and developing HCM systems, as well as those in industry, and manufacturers, and to bring together a critical mass of European experts in this emerging technology. This endeavor will also result in the establishment of communication channels to expand the possibilities for knowledge transfer, which will also be valuable for other activities within the Action.

Complementary to the survey, a systematic review of literature on existing HCM systems will allow comparison of their features, potential and limitations. In addition, Action participants will exchange knowledge about the various HCM systems available to them, compare experimental designs and parameters measured in the members' laboratories, and share baseline data collected. This will also help to determine how datasets from different HCM systems can be integrated. Both the systematic review and direct comparisons will contribute to identifying future requirements for these systems. Eventually, our activities aim to develop new lasting forums to bridge behavioral and data science to achieve breakthroughs in the integration and analysis of complex datasets, which will be useful for other projects in biomedical research beyond HCM in the future.

The scientific community can benefit from the activities of the Action in multiple ways. Apart from the systematic review, a catalog of available HCM systems with standard operating procedures established by Action members will be developed and made available on the Action's website. The goal of this activity is to reduce fragmentation of HCM development and to share best practice on HCM system use with the wider research community. However, the most important activity will likely be the COST_TEATIME training program — workshops, webinars (recordings available at https://bit.ly/3nIJWUG) and short-term scientific missions (STSM, funding of short research visits to another lab/country), fundable through the Action. These measures will build capacity, not only with regard to the emerging HCM technologies, but also by establishing a sustainable, interconnected and well-trained European network of mouse behavior analysts spanning all ages and career levels. The Action encourages representation and active participation of Early Career Investigators and researchers from inclusiveness target countries with fewer resources in the field of HCM and other related research areas. Of note, to date more than 100 researchers from 32 European countries have joined the Action.

New members can join the Action throughout the funding period (2021—2025) and further information is available through our website www.cost-teatime.org. News about the outcomes, upcoming events, workshops, webinars, laboratory rotations, grants and more are instantly shared on our social media accounts (Twitter @COST_TEATIME and LinkedIn COST_TEATIME).

Authors / disclosures: VV is a chair, SW is vice-chair and grant-holder scientific representative, SH is science communication coordinator of COST Action 20135.

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Data availability statement. No experimental data has been collected for this perspective paper.

Ethics statement. Our study did not require an ethical board approval because it did not contain human or animal trials.

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