Combining Classical and Automated Neurophenotyping in Mice and Rats

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Introduction

Translational research requires the establishment of comprehensive neurobehavioral screening systems, dedicated to fill the gap between post genomic generation of state-of-the-art animal models (i.e. transgenic rodents) on the one hand and their added value for really predictive experimental preclinical therapy on the other hand. Due to these developments in the field, neuroscientists are frequently challenged by the task of detecting discrete behavioral differences in rodents. Systematic, comprehensive phenotyping covers these needs and represents a central part of the process. Here we provide an overview on theoretical issues related to classical comprehensive neurobehavioral phenotyping and propose specific procedures as well as concepts for integrating automated, intra-home-cage technologies. The latter allows continuous screening of various behavioral and physiological dimensions on an ethological basis, which represents important added value to the comprehensiveness of the screening approach.

Approach and Methods

Comprehensive phenotyping of rodents is a process of defining characteristics during their ontogeny. During the past 20-30 years rather standardized approaches evolved using combinations of classical behavioral assays spanning all different behavioral domains. Specific guidelines for the appropriate conduction of such classical phenotyping work have been proposed. However, more recently, due to the consideration of certain short-comings in classical approaches (non-ethological based, stress-confounded, non-repeatable under the same test-construct), intra-home-cage automated phenotyping technology was developed, partly validated, and is now up to be integrated/associated with comprehensive classical phenotyping approaches.

Here we will connect the present status of guide-lines for classical neurobehavioral phenotyping and focus on open questions and issues brought up by integrating automated phenotyping into large comprehensive screens. Among other reasons, most of those problems are derived from the novel quality of multidimensional parallel acquisition of behavioral outputs within the automated systems. These issues span areas such as data mining, analysis of multiple parallel measures in longitudinal intraindividual experimental designs, provide new chances for the identification and interpretation of novel complex multidimensional combined output variables and – last but not least – require feasibility and validation of cognitive testing within home-cage-environment on an ethological based non-touch testing scenario.

To deal with these presumptions, transgenic Huntington's disease (tgHD) rats were repeatedly screened within modular, intra-home-cage phenotyping systems measuring spontaneous activity, feeding, temperature, metabolic performance, cognition by operant procedures, social, and emotional parameters. This investigator-independent (ethological) approach was further validated and compared with classical behavioral assays (social interaction test, prepulse-inhibition, accelerod, two-way active avoidance) in the same animals. Apart from outlier detection, multivariate analysis was used to explore correlation patterns of variables in each genotype as well as for finding similarities and dissimilarities between genotypes and the key variables that discriminate between genotypes. Along with circadian changes in energy metabolism, automated phenotyping revealed higher specific motor activities in tgHD rats, with spontaneous free rearing correlating with individual performance in the accelerod test. Principle component analysis revealed a separation by genotype in juvenile tgHD rats that differed from adult animals, being further resolved by Partial Least Squares Discriminant Analysis detecting "temperature" (juvenile) and "rearing" (adult) as phenotypic key variables in the tgHD model. These studies illustrate that automated-intra-home-cage-phenotyping in combination with multivariate analysis is capable of characterizing a

complex phenotype by detecting novel physiobehavioral markers at similar sensitivity and presumably better standardization using fewer resources.

Conclusion

We propose a broadening of the guidelines for comprehensive phenotyping in order to cope with issues derived from automated phenotyping and provide proof-of-concept for operant learning paradigms with the home-cage using intra-home-cage automated technology. Multivariate statistics were successfully applied to identify components with the parallel multivariate data sets that correlate with classical behavioral responses.