



## Review

## Behavioural methods used in rodent models of autism spectrum disorders: Current standards and new developments

Markus Wöhr<sup>a,\*</sup>, Maria Luisa Scattoni<sup>b</sup><sup>a</sup> Behavioral Neuroscience, Experimental and Physiological Psychology, Philipps-University of Marburg, Gutenbergstr. 18, D-35032, Germany<sup>b</sup> Neurotoxicology and Neuroendocrinology, Cell Biology and Neuroscience, Istituto Superiore di Sanità, Viale Regina Elena 299, I-00161 Rome, Italy

## HIGHLIGHTS

- Autism severity scores: important starting point for treatment studies in rodents.
- Scent marking behaviour: an ethologically valid measure for rodent communication.
- Social facilitation, observational learning, and empathy: new behavioural endpoints.
- Generation of rat knockout models: several advantages for behavioural phenotyping.

## ARTICLE INFO

*Article history:*

Received 4 January 2013

Received in revised form 24 May 2013

Accepted 25 May 2013

Available online 13 June 2013

*Keywords:*

Social approach

Social facilitation

Observational learning

Ultrasonic vocalization

Scent marking

Communication

## ABSTRACT

Autism is a behaviourally defined disorder including attenuated or abnormal social interaction and communication, as well as aberrant repetitive behaviour, with symptoms emerging early in childhood. Although the cause of autism has not been discovered, several data strongly support the role of genetic factors in autism aetiology. For this reason, preclinical research is now focusing on generating transgenic and knockout mice, and more recently also rats, with mutations in genes identified in autistic children, with the main aim of understanding the role of those genes in autism aetiology, discovering the biological mechanisms underlying autistic behaviours detected in these mutant lines and evaluating potential treatments. Over the last years, a huge number of behavioural phenotyping assays for rodent models of autism and related disorders have been designed. In the first part of our review, we focus on current standards, i.e. state-of-the-art behavioural phenotyping tasks to assess autism core symptoms in rodent models. The second part is devoted to some few, in our view, very promising examples of new developments, namely an autism severity score, scent marking behaviour as an additional, ethologically valid measure for communication, plus a number of new developments in the behavioural domains of social facilitation, observational learning, and empathy. Finally, we will highlight the huge potential impact of newly generated rat knockout models of autism.

© 2013 Elsevier B.V. All rights reserved.

## Contents

1. Introduction .....	6
2. Current standards .....	6
2.1. Qualitative impairments in social interaction .....	6
2.2. Qualitative impairments in communication .....	6
2.3. Restricted, repetitive and stereotyped patterns of behaviour, interests and activities .....	8
3. New developments .....	8
3.1. Autism severity score .....	8
3.2. Scent marking behaviour as an additional ethologically valid measure for communication .....	9
3.3. Social facilitation, observational learning, and empathy .....	9
3.4. Rat knockout models of autism .....	11

\* Corresponding author at: Behavioral Neuroscience, Experimental and Physiological Psychology, Philipps-University of Marburg, Gutenbergstr. 18, D-35032 Marburg, Germany. Tel.: +49 6421 28 23612; fax: +49 6421 28 23610.

E-mail address: [markus.woehr@staff.uni-marburg.de](mailto:markus.woehr@staff.uni-marburg.de) (M. Wöhr).

4. Summary .....	12
Acknowledgements .....	12
References .....	12

## 1. Introduction

Autism is a behaviourally defined disorder including attenuated or abnormal social interaction and communication, as well as aberrant repetitive behaviour, with symptoms emerging early in childhood [1]. Although the cause of autism has not been discovered, several data strongly support the role of genetic factors in autism aetiology [2–12]. For this reason, preclinical research is now focusing on generating transgenic and knockout mice, and more recently also rats, with mutations in genes identified in autistic children, with the main aim of understanding the role of those genes in autism aetiology, discovering the biological mechanisms underlying autistic behaviours detected in these mutant lines and evaluating potential treatments. Validation of rodent autism models is based on the identification of one or more of the distinctive clinical features of autism through a set of behavioural tests to assess social deficits, impairments in communication, and repetitive behaviours in rodents. Mice and rats are particularly helpful to model neurodevelopmental disorders in which unusual social behaviours are major components. In fact, mice and rats are social species with a wide repertoire of social behaviours that range from parenting and communal nesting their pups, juvenile play to sexual and aggressive behaviours as adults.

## 2. Current standards

Over the last years, a huge number of behavioural phenotyping assays for rodent models of autism and related disorders have been designed and there are a number of excellent reviews describing them [13–18]. In the first part of our review, we focus therefore only on current standards, i.e. state-of-the-art behavioural phenotyping tasks to assess autism core symptoms in rodent models (Table 1). The second part is devoted to some few, in our view, very promising examples of new developments, e.g. an autism severity score, scent marking behaviour as an additional, ethologically valid measure for communication, plus a number of new developments in the behavioural domains of social facilitation, observational learning, and empathy (Table 1).

### 2.1. Qualitative impairments in social interaction

The first DSM-IV diagnostic criterion, qualitative impairment in social interaction is the most investigated in autism animal models [19–53]. Several behavioural tests are available for assaying social approach, reciprocal social interactions, nesting, sexual interactions, parental behaviours, and aggressive encounters [32,54–63]. However, scientists working in the autism field have developed and selected specific social behaviour assays to model the social interaction abnormalities seen in autism (unusual and inappropriate social approach behaviours, lack of social reciprocity and of spontaneous seeking of interactions with others [64]). Specifically, Jacqueline Crawley's lab designed and developed an automated three-chambered social approach task to detect unusually low levels of normal mouse sociability that may be analogous to the deficits in appropriate social interactions seen in many cases of autism [32,57]. The subject mouse can freely explore the apparatus and make a choice between spending time with another, unfamiliar mouse (called stimulus mouse or stranger 1) present in one compartment under a wire cup or spending time with a non-social object (the wire cup) contained in the other compartment [65].

Mice that prefer to spend time with the stimulus mouse rather than in contact with an object show normal sociability. Mice that spend equal time with the stimulus mouse and the novel object show absence of sociability, analogous to the tendency of individuals with autism to engage in non-social activities such as playing with one toy train, repeatedly assembling a jigsaw puzzle, excellence at a videogame, rock collecting, or comprehensive knowledge of baseball statistics [66–68]. The social approach task can also be used as acquisition phase for studying social recognition by exposing the subject mouse to the stimulus mouse used during the social approach task and a novel mouse (called stranger 2) not presented before. Typically, mice display a preference for stranger 2.

Unfortunately, in the three-chambered social approach apparatus it is possible to measure only the social approach initiated by the subject mouse given that the stimulus mouse is contained under a wire cup. For this reason, it is often useful to associate this task to a more fine-grained evaluation of social behaviours that the subject mouse exhibits when placed together with a freely moving stimulus mouse in a neutral arena [23,27,38,41,43–46,52]. When two unfamiliar mice are placed together, they investigate each other mainly by sniffing their head, the body, and the anogenital region or pushing past each other with physical contact, crawling over and under each other with physical contact, and following. This test can be applicable to animals of both sexes and can be performed at all post-weaning ages, making it suitable for studying developmental trajectory of social behaviours relevant to autism. When testing sexually mature mice, sessions should last no longer than 3–5 min to avoid aggressive or mounting behaviours that are not relevant to modelling symptoms of autism [44]. Recently, a computerized video analysis tool, MiceProfiler, was developed that uses geometrical primitives, i.e. “information concerning the position, orientation, distance and speed of each mouse's body part”, to model and automatically track mice during social interaction paradigms without requiring tagging [69].

### 2.2. Qualitative impairments in communication

The second DSM-IV diagnostic criterion, qualitative impairments in communication [66–68,70–72], is the most difficult to model in rodents since mice and rats do not use language. However, a wide range of rodents, such as mice, rats, hamsters, and gerbils belonging to the family Muridae, emit ultrasonic vocalizations (USVs) in a variety of situations. Such USVs have been detected from infants at the time of birth, from pups removed from the nest, during social play in juveniles, from adults during courtship and mating, during social interactions between unfamiliar females, and from adults during aggression and/or exploration (for review see: [73–85]). Among all, neonatal USVs have been most extensively studied as an early communicative behaviour of the pup–mother dyad. In 1956, Zippelius and Schleidt [86] discovered that infant mice emit USVs during separation from mother and littermates with frequencies up to 80 kHz. Following Konrad Lorenz, they have suggested that isolation-induced USVs reflect a negative affective state and named them accordingly as “Pfeifen des Verlassenseins” (“whistles of loneliness”). Importantly, they also hypothesized that such USVs serve communicative purposes. In fact, Zippelius and Schleidt found that mothers leave the nest to retrieve pups which were scattered outside the nest. They further showed that mothers are selectively retrieving vocalizing pups, but not anesthetized or sacrificed pups, indicating that pup USVs

Download English Version:

<https://daneshyari.com/en/article/6259058>

Download Persian Version:

<https://daneshyari.com/article/6259058>

[Daneshyari.com](https://daneshyari.com)