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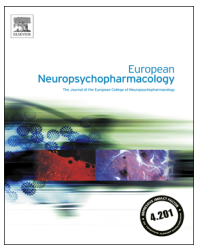

Enhancing the value of psychiatric mouse models; differential expression of developmental behavioral and cognitive profiles in four inbred strains of mice

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Abstract
The behavioral characterization of animal models of psychiatric disorders is often based upon independent traits measured at adult age. To model the neurodevelopmental aspects of psychiatric pathogenesis, we introduce a novel approach for a developmental behavioral analysis in mice. C57BL/6J (C57) mice were used as a reference strain and compared with 129S1/SvImJ (129Sv), BTBR T+tf/J (BTBR) and A/J (AJ) strains as marker strains for aberrant development. Mice were assessed at pre-adolescence (4 weeks), adolescence (6 weeks), early adulthood (8 weeks) and in adulthood (10–12 weeks) on a series of behavioral tasks measuring general health, neurological reflexes, locomotor activity, anxiety, short- and long-term memory and cognitive flexibility. Developmental delays in short-term object memory were associated with either a hypo-reactive profile in 129Sv mice or a hyper-reactive profile in BTBR mice. Furthermore, BTBR mice showed persistent high levels of repetitive grooming behavior during all developmental stages that was associated with the adult expression of cognitive rigidity. In addition, strain differences in development were observed in puberty onset, touch escape, and body position. These data showed that this longitudinal testing battery provides sufficient behavioral and cognitive resolution during different development stages and offers the opportunity to address the behavioral developmental trajectory in genetic mouse models for neurodevelopmental disorders. Furthermore, the data revealed that the assessment of multiple

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behavioral and cognitive domains at different developmental stages is critical to determine confounding factors (e.g., impaired motor behavior) that may interfere with the behavioral testing performance in mouse models for brain disorders.
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1. Introduction

The causes of most psychiatric disorders are still unknown. One of the major obstacle in finding etiologies is the clinical and genetic heterogeneity of these disorders (Bruining et al., 2010; Geschwind and Levitt, 2007; Kas et al., 2007; LaPorte et al., 2008). It is assumed that the onset of most psychiatric disorders is already in early development (Paus et al., 2008), but is has proven difficult to track the onset and early stages of these disorders (Wittchen et al., 2011). In this context, studies using animal models can contribute considerably to the understanding of the development of psychiatric disorders as they allow systematic studies of phenotype expression in a controlled genetic background and environment (Kalueff et al., 2008; Kas et al., 2011; Tecott and Nestler, 2004). Most studies using these models predominantly focus on adult ages and surpass earlier windows of development that may already be affected. One study considered the importance of social development and focused on aspects directly related to social deficits (Ricceri et al., 2007). Taking into account the diversity of social and non-social impairments, as well as the cognitive performance deficits in neurodevelopmental disorders, extension of a longitudinal phenotype battery approach for these heterogeneous disorders is needed. Recently, several new strategies have been proposed to improve and refine phenotype assessments in psychiatric research, such as the endophenotype-approach (Gould and Gottesman, 2006) and cross-species trait genetics (Kas et al., 2007). Another suggested approach is the domain-interplay concept (Kalueff et al., 2008) that advocates a more integrated continuum with common genetic and environmental determinants. This concept is based on assessing the interplay between distinct behavioral domains in relation to genetic susceptibility but has thus far not been thoroughly tested. To extend the use of mouse models into a wider developmental window, we measured both basal motor and neurological development as well as the emergence of cognitive abilities starting from 4 weeks of age in relation to later behavioral outcome. We systematically investigated these in four genetically defined inbred strains of mice from early adolescence into adulthood in order to detect distinct behavioral profiles and the way they change over time in relation to genetic background. Mouse strains C57BL/6J, 129S1/SvImJ, BTBR T+tf/J and A/J inbred mouse strains were chosen based on known behavioral contrast in the absence of gross abnormalities in general health. C57BL/6J mice were selected as they are commonly used as a reference or control strain, as they show sufficient exploratory motivation and do not show extremes in the affective domain and perform well on cognitive tasks (Brigman et al., 2012; Crawley, 1999; Rogers et al., 1999; Ryan et al., 2010). By contrast, 129S1/SvImJ and A/J are known for their low exploratory drive and mild cognitive impairments. For example, all 129 derived strains carry a natural mutation in the Disc1 gene (Clapcote and Roder, 2006) that is associated with impaired working memory performance in this strain (Kvajo et al., 2008). Furthermore, BTBR T+tf/J mice are currently in favor as a model for neurodevelopmental disorders as they show several features related to autism and fragile-X syndrome, such as impaired social interaction, cognitive deficits and high levels of repetitive behaviors (Amodeo et al., 2012; McFarlane et al., 2008; Pearson et al., 2011).

2. Experimental procedures

2.1. Animals

Breeding pairs of C57BL/J (C57), 129S1/SvImJ (129Sv),BTBR T+tf/J (BTBR) and A/J (AJ) strains were originally purchased from the Jackson Laboratory (Bar Harbor, Maine, USA) and further bred at the University Medical Center Utrecht, The Netherlands. Male mice were weaned at postnatal day 28 (P28, 4 weeks of age), ear punched for identification purposes and housed with litter mates in groups of 2–4 mice per cage.

2.2. General measures

Litter size and the onset of puberty were measured during weaning on P28 (4 weeks of age), body weight was measured at three different time points during adolescence (4, 6 and 8 weeks of age) and adulthood (between 10 and 12 weeks of age). Onset of puberty was determined by assessing the progression of balano-preputial separation (BPS) (Deboer and Li, 2011; Zhou et al., 2007) and scored as either 0 (no separation), 1 (separation but not full) or 2 (full separation).

2.3. Extended SHIRPA screen (eSH)

The extended SHIRPA screen used in the present study was a modified version of the standard SHIRPA primary screen that is widely used to assess basic sensorimotoric functions and various reflexes in mice (Lalonde et al., 2005; Rogers et al., 1999). Behavior during the test was recorded with an overhead camera. Mice are placed in a viewing jar to assess body position, tremor, palpebral closure, coat appearance, whiskers, lacrimation, defecation. Consequently the mice are transferred to a novel arena to observe: transfer arousal, locomotor activity, gait, tail elevation, startle response, touch escape. Further measures include: positional passivity, skin color, trunk curl, limb grasping, pinna reflex, corneal reflex, contact righting reflex, evidence of biting and vocalization. A table of SHIRPA measures and scoring system can be found in the Supplementary material (Table S1).

During the arena-phase of the SHIRPA screen, additional measures were taken, to extend the number of behavioral domains that could be measured. Integrating multiple measures in a single test was done to avoid extensive and repeated testing in adolescent mice that may have interfered with the normal development of the mice due to stress-related factors. Additional measures to the

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