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Early Behavioural Alterations in Mouse Models of Autism Spectrum Disorders: A Step Forward Towards the Discovery of New Therapeutic Approaches

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1. Introduction

Historically, research in non-human beings, primarily rodents, has played a fundamental role in understanding neural dysfunctions underlying pathological conditions and how they can be treated. To date, several animal models have been proposed to recapitulate autism spectrum disorders (ASD).

We can never fully recapitulate human neuropsychiatric symptomatology in non-human beings; some symptoms, such as low self-esteem and suicidal ideation, are impossible to model in mice. Moreover, brain anatomy between humans and mice is considerably different (i.e. the cerebral cortex is highly elaborated in humans). However, the brains of vertebrates have a common structural organization in which the cerebral cortex is intimately interconnected with subcortical structures that are well conserved across mammals (Tecott, 2003). Furthermore, many fundamental physiological and behavioural responses have been evolutionarily conserved between species. The study of these responses in lower species can therefore provide a better understanding of the neural circuits and the genetic factors subserving them and, through inference, of human behaviour and disease.

One of the criteria that are commonly used to validate an animal model (McKinney, 1984) is based on a conceptual analogy of the proposed model to the causes of the human disease (*construct validity)*. Mutant mice with a targeted mutation in a gene implicated in a given neuropsychiatric disorder, neuroanatomical lesions, prenatal drug exposures, and environmental toxins offer examples of putative causes of human diseases that can be replicated in animal models.

The etiopathogenesis of autism however has not been clearly elucidated so far and diagnosis of ASD is mainly based on presentation of three core symptoms: profound alterations in social interaction, communication deficits and stereotyped behaviours (i.e. repetitive behaviours and restricted interests). Different approaches have therefore been adopted to model these pathologies in rodents. Table 1 provides a schematic view of currently available mouse models of ASD-like symptomatology.

1.1 Lesions models

One approach is to generate defects in brain regions that are analogous to neurochemical or anatomical abnormalities seen in autism. This includes models obtained after neonatal lesions of brain areas abnormal in autistic patients, such as the cerebellum, the amygdala (Wolterink et al., 2001) or the medial prefrontal cortex (Bobee et al., 2000). Indeed, those models suggest that lesions in specific brain regions leads to the development of specific or general behavioural abnormalities that are comparable to those observed in autism. Importantly, the age at which the lesion is made has a significant impact on the phenotypic outcome (Auvray et al., 1989; Daenen et al., 2002; Wolterink et al., 2001), thus highlighting the need for a better understanding of the role played by abnormal development in ASD pathophysiology.

Although such models actually reproduce altered behaviours related to ASD-like traits, the lesions employed destroy entire brain regions and do not reproduce the underlying genetic or developmental pathways of autistic spectrum disorders. These models are thus quite useful, but bear little *construct validity*.

1.2 Enviromental models

The search for environmental causes of autism arose from the observation that autism prevalence has considerably increased over the last 20 years and monozygotic (MZ) twins do not show complete concordance for autism. In fact, environmental challenges during prenatal and early postnatal periods are known to modify brain development and result in behavioural abnormalities and cognitive deficits that appear later in life (Landrigan, 2010).

Among the environmental factors that may have an etiological role in autism, in utero exposures to teratogens, including valproic acid, a commonly used antiepileptic drug, thalidomide, a sedative drug, and misoprostol, an abortifactant, have been proposed to increase incidence of autism (Dufour-Rainfray et al., 2010). Mouse models have therefore been produced by means of prenatal or neonatal environmental challenges, including early exposure to valproic acid, inflammatory agents and anticonvulsant exposure of the fetus. Immunological abnormalities have also been suspected to be involved in autism [reviewed in (Krause et al., 2002) and (Torres, 2003)] and several groups have described behavioural deficits in rodents as a consequence of immunological challenges or anomalies (Patterson, 2002; Shi et al., 2003; Vojdani et al., 2003). Those include, among others, exposure during gestation to Trichinella spiralis (Rau, 1983), neonatal exposure to Borna virus (Hornig et al., 1999; Pletnikov et al., 1999); reviewed in (Pletnikov et al., 2003) and prenatal exposure to maternal antibodies (Singer et al., 2009).

In all of these cases, the environmental nature of the perturbations potentially reproduces the conditions experienced by developing human subjects. Additionally, compared to lesions of selected brain areas, the action of these chemical and infectious agents is usually reported to provoke global effects on the brain, thus more closely resembling ASD pathophysiology.

1.3 Genetic mouse models

In the last decades, gene targeting procedures have been developed for the introduction into pre-determinated sites in the genome of planned mutations (null mutations as well as more subtle changes which alter, but do not eliminate gene function). Although genetic modifications can be engineered in the rat and even in higher mammals, the mouse is uniquely amenable to these techniques (Chaible et al., 2010). The development and application of novel molecular technologies has therefore led to an explosion in the use of mice in neuropsychiatric research as in other biomedical disciplines, with the creation of mouse models with genetic aberrations characteristic of human clinical disorders (Tecott, 2003).

Mouse models	*Behavioural alterations (compared to wt mice)*	*References*
Mice bearing genetic mutations		
BTBR T+tf/J	Social approach ↓ Reciprocal social interactions ↓ Juvenile play ↓ Repetitive behaviours ↑ Unusual repertoire of UVS	(McFarlane et al., 2008; Scattoni et al., 2008; Silverman et al., 2010)
NL-3 KO	Motor activity ↑ Social novelty preference ↓ PPI ↔ UVS ↓ Seizure susceptibility ↔ Sucrose preference ↔	(Radyushkin et al., 2009; Tabuchi et al., 2007)
En2 KO	Juvenile play ↓ Learning and memory ↓ Social behaviour ↓ Motor coordination ↓	(Cheh et al., 2006; Kuemerle et al., 2007)
Gabrb3 KO	Social behaviour ↓ Explorative behaviour ↓ Attention ↓ Seizure susceptibility ↑	(Chandra et al., 2008)
CAPS2 KO	Social interaction ↓ Hyperactivity Abnormal sleep–wake rhythm Anxiety in unfamiliar environments ↑	(Sadakata & Furuichi, 2010)
glut3 +/-	UVS ↓ SHIRPA ↔ Social behaviour ↓ Learning and memory ↓ Cognitive flexibility ↓ Abnormal motor stereotypies	(Zhao et al., 2010)
GAP43 +/−	Anxiety-like behaviour ↓ Social approach ↓ Sociability ↓	(Zaccaria et al., 2010)
Mthfr +/−	Recognition memory ↓ Hyperactivity	(Levav-Rabkin et al., 2011)
V1aR KO	Anxiety-like behaviours ↓ Social recognition ↓	(Bielsky et al., 2004)
Dvl1-deficient	Abnormal social interaction Abnormal sensorimotor gating	(Lijam et al., 1997)
Gene-environment interaction		
Orpm −/−	UVS ↓ Maternal potentiation ↓ Attachment behaviour ↓	(Moles et al., 2004)

Mouse models	*Behavioural alterations (compared to wt mice)*	*References*
patDp/+	UVS ↓ Anxiety-like behaviours ↑ Generalized fear Spatial learning ↔ Sociability ↓	(Nakatani et al., 2009)
NL-4 KO	UVS ↓ Social Interaction ↓ Social Memory ↓	(Jamain et al., 2008)
MALTT	Hyperactivity Social behaviour ↓ Hyperactive circling stereotypy	(Hamilton et al., 2011)
Exposure (E11) in utero to VPA	Sociability ↓	(Roullet et al., 2010)
Exposure (E14-E17) to B(a)P in $Cpr^{lox/lox}$ mice	Response to novelty ↓	(Sheng et al., 2010)
Exposure (P14) to VPA in GSTM1-/- mice	Play behaviour ↓	(Yochum et al., 2010)
Neonatal exposure to GVG in Mthfr+/- mice	Body weight ↔ Recognition memory ↓ Anxiety-related behaviour ↔ Activity ↑	(Levav-Rabkin et al., 2011)
Reelin $^{rl/+}$	Reversal learning ↓ Social behaviour ↔ Coordination ↔ Anxiety-related behaviour ↓ Motor impulsivity ↑	(Laviola et al., 2009; Macri et al., 2010; Ognibene et al., 2007a)
Neonatal thimerosal in SJL Mice	Motor coordination ↔ Social interaction ↔ Social recognition ↔ Anxiety-like behaviour ↔ Sensory gating ↔	(Berman et al., 2008)
	Brain lesions	
5,7-DHT (P0)	Exploratory behaviours ↓ Sensory motor reflex↔	(Hohmann et al., 2007)

Table 1. Selection of mouse models of ASD.

Abbreviations: KO: knockout*; UVS:* ultrasonic vocalizations; *PPI:* prepulse inhibition*; SHIRPA*: protocol for comprehensive phenotype assessment; *BTBR:* inbred mouse strain; *NL-3*: neuroligin-3, *En2*:engrailed genes, *Gabrb3:* gene, which encodes the β3 subunit of the GABAA receptor; *CAPS2*: Ca2+-dependent activator protein for secretion 2*; glut3:* Neuronal glucose transporter isoform 3*; GAP43:* growth-associated protein-43*; Mthfr*: methylenetetrahydrofolate reductase gene*;V1aR:* Vasopressin V1a Receptor*; Dvl1:* Dishevelled, *Orpm:* μ-opioid receptors; *patD*: paternal duplication of mouse chromosome 7 corresponding to the region of human chromosome 15; *NL-4:* neuroligin-4; *MALTT:* multiple autistic-like transgenic traits; *nervous: nervous gene mutation; VPA:* valproic acid; *B(a)P:* benzo(a)pyrene*; Cpr:* Cytochrome p450 reductase; *GSTM1:* glutathione-S-transferaseM1; Thimerosal (sodium ethylmercury thiosalicylate) is an antimicrobial preservative used in numerous vaccines; *GVG: vigabatrin; Rl:* reelin gene; *5,7-DHT*: 5,7-dihydroxytryptamine. ↔: unaltered; ↓: reduced; ↑: increased.

Thanks to these advances in the field of genetics and the discovery of relevant loci for autism susceptibility identified by association or linkage studies in human populations (Lintas & Persico, 2009), several mouse models that reflect genetic alterations associated with autism have been developed in recent years. Those mouse models provide useful tools to address the genetic hypothesis of autism and investigate genetic factors which are thought to contribute to the expression of ASD.

Known genetic causes of nonsyndromic ASD include gene copy number variations (i.e., submicroscopic deletions and duplications) (Weiss et al., 2008) or single gain- or loss-of-function mutations in identified genes (Lintas & Persico, 2009; Serajee et al., 2006). A great deal of interest has been recently devoted to the potential involvement of mutations in synaptic genes encoding for Neuroligin-3 (NL-3), Neuroligin-4 (NL-4), and Neurexin-1 (NX-1), which are cell adhesion proteins at nerve cell synapses, and SHANK3, which is a synaptic scaffold protein in autism susceptibility. Based on the rare-occurring mutations identified in the ASD population, mouse models carrying mutations in these genes have recently been generated (Berkel et al., 2010; Jamain et al., 2003; Kim et al., 2008; Laumonnier et al., 2004; Moessner et al., 2007). In line with findings from neuroimaging and genetic studies that indicate abnormalities in both structural and functional brain connectivity in autism, those mouse models recapitulate autism symptomatology, thus indicating that aberrant signaling between nerve cells may cause the ASD phenotype in the affected patients. Interestingly, NLGN3 expression was found to be reduced in several brain regions of mice exposed in utero to valproic acid, such as the hippocampus (Kolozsi et al., 2009), thus increasing the relevance of this gene for ASD.

Mutant animals displaying targeted gene mutation for neurotransmitters and developmental genes that may regulate social behaviours constitute another example of transgenic models of ASD. These include oxytocin knockout mice, which display deficits in social recognition and social memory (Bielsky & Young, 2004; Young, 2001), and vasopressin receptor subtype 1b knockout mice, which display reduced social motivation and aggression (Lim et al., 2005; Young, 2002). Indeed, the *construct validity* of those models is quite low. However, given that deviant social development is one of the core symptoms of autism and related disorders, they incorporate a conceptual analogy to the symptoms of the human disease, thus bearing high *face validity* (McKinney, 1984). In fact, children with classic autism are unable to "read" other people, ignoring them and often strenuously avoiding eye contact.

Most of the current mouse models of ASD have used reverse genetics, going from an a priori target (i.e. a specific genetic alteration) to phenotype. A different classical method for identifying unknown and potentially unpredicted genetic contributions to phenotypes is the forward genetics approach, first identifying a relevant phenotype and then elucidating the genetic underpinnings.

Relevant phenotypes include behavioural symptoms, neuroanatomical pathology, neurophysiological responses, and neurochemical abnormalities. Given the prominent role of behavioural symptoms in the diagnosis of ASD, particular attention in ASD research has been so far devoted to one of the disease components or endophenotypes that can be modeled in animals: behavioural abnormalities. A number of studies have described deficits in social, communication, and/or stereotypic domains in mouse models of ASD (see Table 1). However, only a few of these models have reported deficits in all

ASD-related behavioural domains. Among them, the most extensively studied is the BTBR inbred strain.

Initially, BTBR mice attracted a great deal of attention as a potential model for social deficiencies in general, and more specifically for the social and stereotypical changes that are characteristic of ASD. As a matter of fact, low levels of social behaviour (Bolivar et al., 2007; McFarlane et al., 2008; Moy et al., 2007) and poor social learning in the transmission-of-food-preference assay (McFarlane et al., 2008) have been reported in this strain. Core symptoms of ASD also include repetitive behaviours, a broad class of behaviours linked by repetition, rigidity, and invariance. Moreover, some children with autism never develop meaningful speech and fail to develop reciprocal communication either by speech, gestures, or facial expressions. For those who do, speech differs from that in normal children as stereotypic speech that may involve echolalia, pronoun reversal, and unusual inflections and intonations may be displayed. Although stereotyped behaviours have been less investigated than social behaviours in BTBR mice, high levels of repetitive self-grooming have been consistently observed (McFarlane et al., 2008; Yang et al., 2009; Yang et al., 2007a; Yang et al., 2007b). An unusual pattern of ultrasonic vocalizations has also been evidenced in BTBR mice. This behavioural abnormality is thought to represent a behavioural homolog to communication deficits (Scattoni et al., 2008; Scattoni et al., 2011). As a matter of fact, although mice do not use language, they do display social communication mechanisms. In particular, rodents communicate predominantly in the ultrasonic range of sound frequencies (Nyby et al., 1978). Ultrasonic vocalizations are emitted by mice under different social conditions throughout their life span. Pups separated from the nest emit vocalizations, and parents use them to locate the pup and retrieve it to the nest (D'Amato et al., 2005; Scattoni et al., 2009; Scattoni et al., 2008) (see below). Calls have also been reported in juveniles during social play and in adults during reproductive encounters and/or social investigation (Holy & Guo, 2005; Nyby et al., 1983; Panksepp et al., 2007; Sales, 1972). Interestingly, abnormal ultrasonic vocalizations emission was found at all the ages tested in BTBR mice (Scattoni et al., 2008; Scattoni et al., 2011). Early in development, BTBR pups showed an unusual pattern of vocalizations and a more frequent, loud harmonics than controls, thus resembling the atypical vocalizations seen in some autistic infants. As adults, BTBR mice when tested in three different social contexts displayed lower levels of both vocalizations and social investigation, thus confirming previous findings in pups of social communication deficits. Recently, however, a complete absence of the corpus callusum has been reported in this strain, which has not been clearly associated with ASD neuroanatomical changes. (Wahlsten et al., 2003).

Spontaneous mouse mutants have furthered our understanding of biological systems for more than one hundred years. One of the molecules that are under examination as a risk factor, playing a role in autism and schizophrenia, is Reelin (RELN). Reelin is a glycoprotein of the extracellular matrix that plays a key role in migration and positioning of neurons, thus bearing a fundamental neurodevelopmental role in the laminar and columnar organization of the cortex (Andersen et al., 2002; Costa et al., 2001; Costa et al., 2002; Keller & Persico, 2003). As a consequence, normal cortical development and mature function depend on appropriate levels of reelin protein, its receptors, and its cytoplasmic adapter, disabled-1 (Dab1) (Deguchi et al., 2003). Support for reelin's involvement in autism include finding of decreased RELN mRNA, decreased reelin protein, decreased mRNA for Dab1 (Fatemi et al., 2002a; Fatemi et al., 2005). Reduced plasma levels of reelin have been also reported in patients with autism (Fatemi et al., 2002a).

The deletion of a wide portion of the gene coding for reelin, which is highly conserved between the mouse (symbol *Reln*) and the human (symbol *RELN*) (Fatemi et al., 2002b), arose spontaneously in mice, showing autosomic recessive transmission. The homozygous reeler mouse completely lacks the protein, presenting an impaired phenotype characterized by striking neurological signs (dystonia, ataxia, tremor) and severe alterations in the architecture of laminar structures like the cerebral cortex, the cerebellum and the hippocampus (Caviness & Rakic, 1978; Goffinet, 1990; Goffinet et al., 1984). When levels of Reelin are reduced by 50% as in heterozygous mice compared to wild-type, lamination defects in the SNC and the classical reeler phenotype are not evident. The HZ phenotype, however, shows subtle neuro-anatomical and behavioural abnormalities (Laviola et al., 2006; Liu et al., 2001; Ognibene et al., 2007a; Ognibene et al., 2007b; Salinger et al., 2003; Tueting et al., 1999), thus suggesting a higher validity of the heterozygous mutation to model ASD.
Interestingly, mice haploinsufficient for the reelin gene have reduced numbers of cerebellar Purkinje cells, which is the most frequent neuropathologic finding in autism, and progressive loss of Purkinje cells of the cerebellum in the first weeks of life has been highlighted in heterozygous reeler mice (Marrone et al., 2006). Given the role played by reelin in the development of the central nervous system, this model has been extensively studied during the early phases of development (see below).

1.4 Monogenic syndromes associated with autistic-like behaviour

Among the genetic mutant lines which are expected to model ASD, some are based on the introduction in mouse genome of monogenic aberrations underlying syndromes associated with autistic-like behaviours. These include, among others, loss of methyl-CpG-binding protein-2 (Mecp2), a gene responsible for Rett syndrome.
Rett syndrome (RTT), classified together with autism into the DSM-IV in the group of the pervasive developmental disorders, affects primarily girls with a prevalence of 1 on 10.000 births. ASD core symptoms are associated with severe cognitive and physical impairments in RTT patients. Mutations in the MeCP2 gene, a transcriptional regulator binding to methylated CpGs (Dragich et al., 2000; Jorgensen & Bird, 2002), have been recognized as clear etiological factors in about 90% of classical RTT cases. This advance in RTT research allowed the generation, by means of strategies employing gene targeting, of several lines of mice carrying endogenous MeCP2 mutations (De Filippis et al., 2010b; Ricceri et al., 2008).
Although the causes of this syndrome have been clarified, the mechanisms leading to the severe, progressive and specific neuronal dysfunctions when these genes are mutated are currently unknown. RTT mouse models are therefore expected to be enormously beneficial for determining the functional outcome and the effects on organic and cellular functions of gene mutations and can have translational value in offering preclinical surrogate markers to evaluate treatment efficacy (Crawley, 2007). Indeed, although the behavioural characterization of some of these mutant mice, is at the moment far from complete, indications are available suggesting that their high *construct validity* [i.e. the extent to which a model reproduces the etiology and pathophysiology of a disorder (McKinney, 1984)] is accompanied by a high *face validity* [i.e. the degree to which a model resembles the symptoms of a disorder (McKinney, 1984)], as MeCP2 mutant mice have been reported to recapitulate many RTT symptoms (De Filippis et al., 2010a; De Filippis et al., 2010b; Ricceri et al., 2008).

2. Behavioural phenotyping

Given that the eziopathogenesis of ASD is still unclear, the primary diagnostic indicators are abnormal behaviours, rather than biochemical, neuroanatomical or other physiological indices. In this line, behavioural phenotyping plays a crucial role in the validation of mouse models of autism spectrum disorders and, accordingly, a number of behavioural assays have been developed that capture and model aspects of ASD-like core symptoms (Crawley, 2007).

Determining whether a proposed mouse model for autism recapitulates one or more of the core clinical symptoms can in fact provide valuable insight as to the functional impact of altered genes or environment. Moreover, since behaviour is the ultimate output of brain, behavioural phenotyping of mouse models of autism provides functional information hardly detectable using molecular, cellular or histological evaluations. Such functional information is not only helpful to identify the role of specific genes in neuropathologies, but it also provides a framework for understanding the role of genes in behaviour, identifying key stages of human brain development, and, eventually, targets for potential therapeutic interventions. To unravel the effects of genetic manipulations, deviations from the normal range of strain-specific behaviours and the age-dependent onset of normal response patterns can be investigated.

Another behavioural phenotyping strategy can be based upon the study of selected brain regions and of those neurochemical systems specifically targeted by genetic alterations: to assess their functional integrity, behavioural tasks known to be controlled by those circuits could represent a powerful tool and a very sensitive assay. Furthermore, the analysis of deviations in response to challenge with psychoactive drugs (direct receptor agonists or antagonists, acting on specific neurotransmitter systems) can complement this strategy. The use of drug challenge may indeed unmask neurobehavioural alterations not detectable under baseline testing conditions and provide crucial information on neurobiological impairments that can be subsequently confirmed in vitro (Bignami, 1996).

Table 1 summarizes our current knowledge on the behavioural phenotypes of the available mouse models of autism. Several reviews have already addressed this issue. However, no one is available dealing with the study of the early phases of development in mouse models of ASD.

2.1 Behavioural phenotyping of the early phases of development: The earlier the better

Typical clinical presentation strongly suggests that brain development is aberrant during early postnatal life in individuals with autism. Although the primary developmental disruptions have not been identified, redundancy of neurodevelopmental processes has been demonstrated in patients' brains. Early interventions may however be valuable even if they do not address autism's etiology; in line with the observation that neurodevelopment is regulated by multiple environmental factors, some studies suggest the efficacy of early behavioural treatments in contrasting ASD symptomatology, likely as a consequence of increased brain plasticity (Dawson & Zanolli, 2003; Kasari et al., 2006; Kashinath et al., 2006). Targeting the regulation of early neurodevelopmental processes and increasing neural plasticity may thus represent suitable pharmacologic interventions for young children with autism. Given the strict interplay between genes and environment during the development of a healthy individual, the possibility of an early intervention can result particularly important for autistic patients to reduce most of the carry-over consequences of a deviant

developmental trajectory. However, in spite of the clear value placed on early behavioural interventions for autism and suggestions to develop developmentally focused pharmacologic treatments (Rubenstein & Merzenich, 2003; Whitaker-Azmitia, 2001), few studies have addressed this issue in ASD research.

In models of human neurodevelopmental disorders, developmental analyses are expected to provide a behavioural phenotype on which potential therapeutic strategies could be tested starting from the early phases of development, when recovery could be more likely. Time of onset of selected somatic changes and the time of first appearance of various reflexes and behavioural patterns show a remarkable regularity, providing an effective tool to assess possible neurobehavioural/developmental alterations (Bignami, 1996). Particularly in models of neurodevelopmental disorders, it seems therefore critical to conduct behavioural phenotyping during the developmental period (Branchi & Ricceri, 2002; De Filippis et al., 2010a). As well as defining an Alzheimer animal model via its behavioural characterization only in the pre-weaning phase could be at least considered hazardous, it is similarly limiting and inappropriate to describe adult, but not infant or adolescent behaviour in animal models of neurological disorders such as autism with an early onset and developmental pathology. Moreover, in transgenic and knockout mice, developmental analysis can shed light on gene effects not accessible when studying adulthood alone. Behavioural testing during ontogeny can help our understanding of how a genetic manipulation affects central nervous system function in ontogeny and it can represent an appropriate strategy to identify possible compensatory and/or unexpected effects (Branchi & Ricceri, 2002). Since the development of different neural systems is differentially timed, the ontogenetic analysis of associated behavioural phenotypes can, for instance, represents a powerful strategy to investigate the effects of genetic manipulations on different brain functions before the occurrence of possible compensatory events.

Within the field of developmental psychobiology, the neurobehavioural profile of developing rodents has been extensively characterized (Hofer & Shair, 1991; Spear, 1990). A number of tests and experimental protocols are now available that take into account the practical constraints imposed by the peculiar physiological and behavioural responses of an immature subject. Although many of the behavioural tests were originally developed for rats, they have been successfully adapted to mouse competencies and now allow the performance of robust measurements of several aspects of the neonatal mouse behavioural repertoire (Bignami, 1996; Cuomo et al., 1996). Keeping in mind Pat Bateson's cardinal view of neurobehavioural development in mammals, as a process akin to the metamorphosis of a caterpillar into a butterfly, we can investigate appropriate behavioural endpoints for each selected maturational step, and use standardized methodological procedures to assess sensory-motor, emotional and cognitive domains in developing mice. However, this knowledge is rarely exploited by neurobiologists working with transgenic and knock-out mice (Branchi & Ricceri, 2002). To date such studies are primarily focused on adult phenotyping and neglect the crucial information provided by the study of ontogeny. Table 2 provides an overview of the behavioural analyses so far carried out on neonatal pups in mouse models of ASD. To better address the importance of behavioural phenotyping the early phases of development in these models, a focus will be made on two mouse models carrying genetic mutations related to ASD: the heterozygous reeler mice and the Mecp2-308 model for Rett syndrome. Which kind of tests can be applied to rodent pups and how our knowledge can benefit from a refined behavioural analysis of the early phases of development will be illustrated.

Mouse models	*Behavioural domains*			*References*
	UVS	**Motor reflex and coordination**	**Cognition and emotion**	
patDp/+	P5-14 ↑ Peak delayed	Not tested	Not tested	(Nakatani et al., 2009)
En2 KO	Not tested	Surface-righting↔ Negative geotaxis ↔ Mid-air righting ↓ Grip strength ↓	Not tested	(Cheh et al., 2006; Kuemerle et al., 2007)
MALTT	P3-7 ↔ P8-14 ↑	Not tested	Not tested	(Hamilton et al., 2011)
BTBR T+tf/J	P1-12 ↑	P2-14 Somatic growth and somatosensory reflexes: Advanced maturation	P9 Homing ↑	(Scattoni et al., 2008)
Orpm-/-	P4-8-12 ↓	Not tested	Not tested	(Moles et al., 2004)
nervous $^{nr/nr}$	Not tested	P1-12 Coordination ↓ Exploration ↓	P1-12 T-maze↓ P13–17 Morris maze ↓	(Lalonde & Strazielle, 2003)
Reln $^{rl\text{-}orl}$	Not tested	P1-12 Coordination ↓ Exploration ↓	P1-11 T-maze↓ P13–17 Morris maze ↓	(Lalonde et al., 2004)
Heterozygous Reeler	P7-11 ↓	P7-11 Coordination↔	P9 Nest-seeking↓	(Laviola et al., 2009; Macri et al., 2010; Ognibene et al., 2007b)
Neonatal exposure to vigabatrin (GVG) in Mthfr+/- mice	Not tested	Coordination ↔ Strength ↔ Righting reflex ↔	Not tested	(Levav-Rabkin et al., 2011)
Neonatal thimerosal in SJL Mice	Not tested	P8-10 Negative geotaxis ↔ Righting reflex ↔ Proto-ambulatory locomotion ↔	Not tested	(Berman et al., 2008)
Prenatal (E11) VPA	Not tested	P12-16 Eye opening: delayed	P9 Nest-seeking ↓	(Kolozsi et al., 2009)
Exposure (E11) to VPA	Not tested	P12-16: Eye opening: delayed	P9-11 Latency nest-seeking↑	(Roullet et al., 2010)

Table 2. Early behavioural alterations in mouse models of autism.

Abbreviations: KO: knockout*; UVS:* ultrasonic vocalizations; *patDp:* paternal duplication of mouse chromosome 7 corresponding to the region of human chromosome 15; *En2:* Engrailed genes*; MALTT:* multiple autistic-like transgenic traits; *nervous:* nervous gene mutation; *BTBR:* inbred mouse strain, *Orpm:* μ-opioid receptors; *Reln* $^{rl\text{-}orl}$*:* mice with the Orleans mutation; *GVG: vigabatrin; Thimerosal* (sodium ethylmercury thiosalicylate): antimicrobial preservative used in vaccines; *Mthfr+/-,* methylenetetrahydrofolate reductase gene; *VPA:* valproic acid. ↔: unaltered; ↓: reduced; ↑: increased.

2.1.1 Early behavioural alterations in the heterozygous reeler mouse as a model of ASD

Reelin plays a prominent neurodevelopmental role. Brain levels of this glycoprotein are in fact very high during late fetal life and gradually decline during late childhood to achieve a plateau during adolescence (Forster et al., 2006).

As previously mentioned, in rodents, ultrasonic vocalizations are emitted by pups when separated from the mother. Provided that these pup vocalizations elicit maternal orientation/approach and retrieval (Cohen-Salmon et al., 1985; Noirot, 1972; Smotherman et al., 1974) and reduce attacks or rough manipulation by the dam (Noirot & Richards, 1966), they are now widely recognized as precocious and reliable indexes of pups communicative/social behaviour, and are thought to constitute a marker on emotional/affective condition early in development (Farrell & Alberts, 2002a; Farrell & Alberts, 2002b; Santucci et al., 1994). Moreover, ultrasound vocalizations can be quantitatively analysed, can be elicited by measurable stimuli, and can be recorded with limited handling of the pup. On postnatal day (pnd) 7, null mutant reeler mice emitted fewer calls than wt controls, and heterozygous subjects emitted ultrasound vocalizations at an intermediate level (Laviola et al., 2006). These results confirm the relevance of these mice as behaviourally interesting model of early communication deficits in ASD.

We also detected effects of reelin gene dosage on behavioural and neuro-physical maturation during the first week of postnatal life: compared to wild-type littermates, null mice showed developmental retardation of the righting reflex (pnd 3) and a decelerated maturation of grasping reflex (around pnd 11) (Laviola et al., 2006). Neonatal grasping reflex and levels of general locomotion in infancy failed to show any difference between heterozygotes and wild-type subjects, thus suggesting that 50% of reelin level availability is sufficient to avoid major alterations in motor development (Macri et al., 2010).

The homing test paradigm allows a measurement of neonatal social recognition and early motivation towards a relevant social stimulus, i.e. the nest odor, as early as pnd 9. At this developmental stage, pups are able to coordinate body movements and move toward the nest. However, as their eyes are still closed, they recognize the nest by olfactory stimuli. Heterozygozous mice were found to be impaired in this test and these effects were apparently independent of general locomotion (Alleva et al., 1985; Laviola et al., 2006), thus suggesting an association with the reciprocal interaction deficits observed in autistic patients early in infancy (Rutgers et al., 2004).

As a whole, these results are particularly intriguing as some subtle alterations in early phases of development have been described in children later diagnosed for autism (Teitelbaum et al., 2004). Autism spectrum disorders are complex and multifactorial psychiatric diseases (Agid et al., 1999) and recent studies have emphasized the importance of gene–environment interaction in the etiology of these disorders (Tsuang, 2000). Indeed, while genetic vulnerability can be predictive of later-onset disorders, it is unlike that monogenic alterations can fully reproduce the underlying causes of ASD. Environmental factors can clearly exacerbate, or sometimes, mitigate the biological consequences of genetic alterations (Jobe & Harrow, 2005). More studies are therefore needed which address the interaction between genetic vulnerability and secondary external agents for the development of a given disease (Gottesman & Hanson, 2005).

In this framework, we hypothesized that lower expression of reelin could represent a factor of vulnerability for development of ASD-like symptomatology and that environmental

factors could either improve or worsen the behavioural outcome. To address this issue, we evaluated in a series of different studies, the effects of gene-enviroment interaction on the early behavioural phenotype of the mouse model. Three experimental manipulations were used as environmental challenges during the ontogenetic window: prenatal exposure to an organophosphate pesticide, maternal separation and estradiol treatment during early postnatal life (Laviola et al., 2006; Macri et al., 2010; Ognibene et al., 2007b).
For the latter, in line with the 'extreme-male brain theory' (Knickmeyer & Baron-Cohen, 2006) which suggests that elevated fetal testosterone levels may favor the onset of ASD symptoms, estradiol treatment on pnd 5 significantly affected the performance of heterozygous reeler mice in the homing test (Macri et al., 2010). Unexpectedly, the other two environmental challenges normalized the early behavioural phenotype of null mice (Laviola et al., 2006; Laviola et al., 2009; Laviola et al., 1990; Ognibene et al., 2007a; Ognibene et al., 2007b): both prenatal exposure to an aceticholinesterase agent (Chlorpirifos) and repeated maternal separation seemed to restore wt-like levels of ultrasound vocalization emission in homozygous reeler mice. Moreover, in contrast with our predictions, reelin deficiency seemed to play a protective role against maternal separation in the homing-test, where a reduced motivation towards the nest was found in separated mice. However, no effects of the treatment were found in mutant mice.
These results suggest that gene-related early behavioural alterations can be modulated by environmental factors, thus supporting the need for further studies during ontogenesis in mouse models of ASD. As a matter of fact, this kind of studies clearly represents a first step toward a better understanding of the underlying causes of ASD-like symptoms and, hopefully, toward the discovery of therapeutic interventions targeted at the early phases of life.

2.1.2 Early alterations in mouse models of Rett syndrome

One essential feature of RTT is an apparently normal prenatal and perinatal development until about 6-18 months of age, followed by a regression period, characterized by both a profound loss of acquired developmental skills in the areas of social contact, communication and hand use and a deceleration of head growth, usually leading to microcephaly. At the end of this period, which is extremely variable in duration, lasting few years in some individuals, development reaches a plateau associated with a wide variety of RTT peculiar symptoms (for a detailed review of symptoms see: (Hagberg, 2002; Mount et al., 2001).
In line with clinical observations, a peculiar progression of symptoms has been evidenced in all the RTT mouse models described so far (Ricceri et al., 2008). As a matter of fact, all of them experience an early developmental phase where no obvious deficits (i.e. visible by gross examinations) can be detected and after the onset of symptoms, undergo an escalating worsening until their premature death.
Increasing evidences from clinical studies, however, support the presence of early defects (i.e. during that developmental phase previously regarded as asymptomatic) (Charman et al., 2002; Kerr et al., 1987). Studies of family home videos, recorded before the disorder was clearly manifested (Charman et al., 2002; Kerr et al., 1987), would confirm that girls with RTT, during the first months of life, are not completely asymptomatic as it was thought. Motor deficits during the first 6 months of life (e.g. abnormal general movements and finger movements) (Einspieler et al., 2005) as well as alterations in communicative behaviours during the first 2 years of life (e.g. limited gestural communication) (Tams-Little & Holdgrafer, 1996) have been reported. Moreover, developmental delays and pre-regression abnormalities correlate in RTT girls with the severity of symptoms shown later on during development (Kerr & Prescott, 2005).

The analysis of the behavioural phenotype in RTT mouse pups confirmed the presence of subtle alterations during the so called "pre-symptomatic phase" (De Filippis et al., 2010a; De Filippis et al., 2010b). In particular, by means of a scale adapted to very young rodents, a delay in the acquisition of single reflexes and motor skills in both sexes was evidence in Mecp2-null mice (Fox, 1965; Ricceri et al., 2008) from postnatal day (PND) 4 to 21 (Picker et al., 2006; Santos et al., 2007). Interestingly, on PND 5 mutant males were also characterised by an abnormal emission of ultrasonic vocalizations and a different pattern of calls throughout the first postnatal week compared to WT controls. Females also showed an increase in ultrasonic vocalizations during the whole first week with a peak on PND 7.

Shortly after the creation of Mecp2-null mice, a mouse which expresses a truncated form of Mecp2 gene (Mecp2-308) has been generated (Shahbazian et al., 2002). In line with clinical observations that report a milder phenotype in RTT patients carrying C-terminal deletions of Mecp2 (about 10 % of RTT cases) (Chahrour & Zoghbi, 2007), this RTT mouse model shows both a later onset of symptoms [6 weeks of age (Shahbazian et al., 2002)] as well as a longer life expectation than the null mutants (De Filippis et al., 2010a; De Filippis et al., 2010b; Ricceri et al., 2008). In Mecp2-308 mutant male mice, a picture of increased arousal and hyperactivity and reduced motor coordination was evidenced during the first postnatal days. In contrast with null mutant mice, impaired emotional communicative behaviour in this mouse model involved a significant decrease in ultrasound vocalizations emission.

This discrepancy suggests that the behavioural phenotype of models carrying different mutations in the Mecp2 gene do not necessarily overlaps, thus supporting previous reports (Belichenko et al., 2008; Ricceri et al., 2008). Indeed, BDNF levels, a gene-target of Mecp2 (Chang et al., 2006), are decreased in Mecp2-null mice (Schaevitz et al., 2010), while appear not altered in Mecp2-308 mice (Ricceri et al., 2011), suggesting that the truncated form of Mecp2 could retain some of its functions, thus contributing to the milder neurobehavioural phenotype of Mecp2-308 mice. As clinical studies support the presence of differences in the clinical manifestation of the syndrome in RTT patients carrying different mutations in the Mecp2 gene, our results strongly support the need for further studies aimed at elucidating the genotype-phenotype correlation in RTT. Indeed, thanks to the development of international databases, many step forwards have been made in the study of genotype-phenotype correlations in clinical research. The availability of RTT mouse models carrying different mutations in the Mecp2 gene now offers the unique opportunity to preclinical research to uncover the neurobiological correlates of such clinical observations.

In the brain of RTT mouse models, morphological and functional alterations have also been reported to be evident early in development, thus preceding the appearance of gross behavioural changes. These include, among others, overall reduction in brain size (Saywell et al., 2006; Stearns et al., 2007) and imbalance between inhibitory and excitatory synaptic transmission in the ventrolateral medulla (Medrihan et al., 2007). Moreover, a longitudinal study (from birth to postnatal day 42) investigating the concentrations of major neurotransmitters in the brain of MeCP2-null mice, reported smaller concentrations of biogenic amine in the brain of mutant mice when compared with WT. Interestingly, this difference became larger with increasing age. Modifications in BDNF expression, early neuronal morphology and cortical synaptic plasticity were also confirmed in pre-symptomatic mice (Belichenko et al., 2008; Chang et al., 2006; Dani et al., 2005).

Taken together, these results suggest that some subtle alterations are already evident in both RTT patients (quite before the pre-regression period) and mouse models. A better

investigation and characterization of the pre-symptomatic phase in RTT mouse models could therefore be extremely worthwhile for a better understanding of the neurobiological correlates of these behavioural alterations and for the development of new therapeutic approaches targeted at early intervention in RTT.

3. Conclusion

As demonstrated by the large number of models that have been generated so far, several efforts have been made in ASD research. Increasing the validity of mouse models, by identifying new potential models and investigating further the existing ones, is however mandatory in order to fully recapitulate ASD neuropathological signs and symptomatology. A prominent role is expected to be played by behavioural techniques in this process. As a matter of fact, behavioural phenotyping represents a valuable tool to be exploited for both the identification and the validation of models. Moreover, as already discussed, once behavioural alterations have been detected, they represent markers to evaluate the efficacy of potential therapeutic approaches.

As diagnosis of ASD is mainly based on detection of core symptoms, the fundamental role of behavioural phenotyping has been widely acknowledged in ASD research. It is however worth mentioning that refined analyses of the behavioural phenotype in mouse models should not neglect the early phases of development. Such analyses are in fact expected to advance our knowledge on the developmental disruptions that take place in the brains of patients, thus considerably increasing the probability to find a cure that can be administered early in development. Such an approach would be extremely beneficial for patients as it would allow passing over the consequences of aberrant developmental trajectories.

In conclusion, good mouse models and refined behavioural analyses should be definitely regarded as fundamental prerequisites for advancing our knowledge in ASD research, and many efforts are expected from this field in this direction.

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5. Summary

Research in animal models, primarily rodents, has played a fundamental role in elucidating behavioural and neurological dysfunctions as well as the contribution of specific gene alterations and gene-environment interactions to the phenotype of some forms of neurodevelopmental pathologies. As the etiopathogenesis of autism has not been clearly elucidated so far and diagnosis is mainly based on presentation of three core behavioural symptoms (profound alterations in social interaction, communication deficits and stereotyped behaviours**),** different approaches have been adopted to model these pathologies in rodents. This chapter provides an overview of currently available mouse models of autism spectrum disorders (ASD)-like symptomatology.

The need for refined analyses of the behavioural phenotype in mouse models of ASD, which should not neglect the early phases of development, is also emphasized. Since behaviour is the ultimate output of brain function, behavioural phenotyping of these models provides integrated and reliable information hardly detectable using molecular, cellular or histological evaluations. Such functional information is also helpful to identify the role of specific genes -- and potential innovative molecular targets for therapy -- in neuropathologies and their interaction with the environment. As diagnosis of ASD is mainly based on detection of core behavioural symptoms, the fundamental role of behavioural phenotyping has been widely acknowledged in ASD research. However, only few studies have investigated the early phases of development in mouse models of ASD.

A number of tests and experimental protocols are now available that take into account the practical constraints imposed by the peculiar physiological and behavioural responses of an immature subject. Developmental analyses in fact provide a framework for understanding key stages of human brain development and unraveling deviations from the normal range as well as the age-dependent onset of normal response patterns.

Several reviews have already addressed our current knowledge on the behavioural phenotypes of the available mouse models of autism. However, very little literature is available dealing with the study of the early phases of development in mouse models of ASD. The present paper therefore provides an overview of the behavioural analyses so far carried out on neonatal pups in mouse models of ASD, particularly focusing on the heterozygous reelin mouse (haploinsufficient for the gene Reelin) and mouse models of Rett syndrome.

Such analyses are expected to advance our knowledge on the developmental disruptions that take place in the brains of patients, thus considerably increasing the potential for prevention or the identification of therapeutic approaches that can be administered early in development. Given the strict interplay between genes and environment during the development of a healthy individual, the possibility of an early intervention can result particularly important for autistic patients to reduce most of the carry-over consequences of a deviant developmental trajectory.

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