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THE ROLE OF GENE-ENVIRONMENT INTERACTIONS IN SOCIAL DYSFUNCTION: FOCUS ON PRECLINICAL EVIDENCE FROM MOUSE STUDIES

Giulia Castellano¹, Johana Bonnet Da Silva¹, Susanna Pietropaolo^{1*}

¹Univ. Bordeaux, CNRS, EPHE, INCIA, UMR 5287, F-33000 Bordeaux, France

*Correspondance to:

Susanna Pietropaolo

Institut de Neurosciences Cognitives et Intégratives d'Aquitaine, CNRS UMR 5287

Bâtiment Bordeaux Biologie Santé ;

2 rue Docteur Hoffmann Martinot,

33000, Bordeaux

France

Email: susanna.pietropaolo@u-bordeaux.fr

1. Introduction

Identifying the relative impact of genetic and environmental factors on human behaviors has been the topic of crucial scientific and philosophical discussion for a long time (also called the “Nature vs. Nurture” debate). The effort of identifying which factor may contribute more to the development of personality between genes and environment seems nowadays as meaningless as trying to define “what contributes more to the area of a rectangle, the length or the width” [Donald Hebb, reported by (Meaney, 2001)]. It is indeed widely accepted that behavioral functions rather emerge from the interactions between genetic and environmental factors, which constantly develops during the lifespan of an individual.

Similarly, the etiology and/or progression of most behavioral alterations and related psychopathologies reflect a complex mixture of genetic and environmental influences. The clinical manifestation even of psychopathologies whose etiologies are largely either environmental or genetic still depends on gene-environment (G×E) interactions. Indeed, gene expression is modulated by experience, and environmental factors induce their effects via gene activation and modification of their products. Despite their well-acknowledged relevance for understanding the biological processes underlying human behavioral physiopathology, the role of G×E is often overlooked in clinical and epidemiological studies, mainly because of methodological difficulties and limitations. Animal studies may therefore provide a valuable additional tool to dissect the role of G×E in behavioral function and dysfunction.

The present review intends to discuss the behavioral impact of G×E by focusing on social behaviors, a domain that has been largely neglected in comparison to the large number of recent reviews focusing on G×E and cognitive abilities or brain plasticity [e.g., (Hasan and Afzal, 2019; Macartney et al., 2022; Malave et al., 2022; Milbocker et al., 2024; Turner and Burne, 2013)]. Furthermore, while the independent contribution of genetic and environmental factors on social behaviors has been assessed in a variety of human and animal studies, the impact of their interactive effects on social functions has been more poorly investigated. Here we will focus on two examples of the most relevant pathological alterations of social behavior, i.e., aggressive/anti-social personality and autism spectrum disorder. This choice is based on the availability of a large body of research investigating the genetic underpinnings of these disorders in both human and animal studies, as well as the dramatic societal impact of these psychopathologies.

First we will introduce the basic concepts and methodological limitations related to the investigation of the role of G×E in modulating human behavior in general. We will then describe the impact of G×E on social dysfunction by summarizing experimental evidence obtained from (i) human and (ii) animal studies. For the latter, we will focus on the mouse species, since genetic rat models of

aggressive and autism spectrum disorders are less commonly employed in preclinical research, especially in combination with environmental manipulations.

The presentation of the findings obtained from mouse studies on G×E and social dysfunction will be preceded by an introduction of the major methodological tools used in this preclinical research, including a brief explanation of the major experimental strategies used to test social dysfunction in laboratory mice and to model the major genetic and environmental factors involved in aggressive, anti-social and autistic pathologies. In this section, a brief description of the environmental manipulations used in mouse studies on G×E will be provided, focusing on selected examples among the most widely used in this specific research field. We will include examples of manipulations of the physical and social environment (i.e., environmental enrichment, physical exercise, social isolation) and of maternal levels (i.e., cross-fostering, maternal enrichment, maternal separation), as well as the exposure to stressors. All the selected environmental manipulations have a high translational validity in modelling the environmental stimulation and adversity taken into consideration in human studies on G×E and social pathologies. Interestingly, few reviews on G×E have included a variety of environmental manipulations, taking into consideration both positive and aversive experiences. A large body of recent literature has instead reviewed preclinical and clinical findings on G×E focusing on environmental enrichment (Consorti et al., 2019; da Silva et al., 2024; Farmer and Lewis, 2023; Gubert and Hannan, 2019; Macartney et al., 2022; Milbocker et al., 2024; Rojas-Carvajal et al., 2022; Smail et al., 2020), so that the effects of this environmental manipulation on behavioral expression and neural plasticity have been extensively discussed.

The summary of the literature assessing the impact of selected environmental manipulations in genetic mouse models of aggressive, anti-social and autistic disorders will be followed by the critical discussion of the major conclusions that may be drawn from across-studies comparisons. This conclusive section will take into consideration the generalizability and robustness of the behavioral effects, as well as the importance of including sex differences and developmental processes in G×E preclinical research.

1.1 Gene-environment interactions: general definitions and methodological constraints

The definition of gene–environment interactions (G×E), although in a certain way intuitive, may be difficult to be univocally formulated since it may be affected by marked variations according to the interpretation of the « interaction » term (Thomas, 2010).

According to a strictly statistical view, an interaction represents a joint effect of at least two factors greater than what can be explained by their separate marginal effects, i.e., the effects of each specific factor averaged over all others. The estimate of an interaction effect depends on the statistical model used, e.g., multiplicative, or additive models; under the most widely used model in

epidemiological studies, i.e., the multiplicative approach, the hypothesis of null interaction corresponds to the condition where the joint effect of two factors is the product of their separate effects, and therefore any joint effect different from this can be considered as an interaction (Thomas, 2010). When the nature of the joint effect is considered, “quantitative interactions” can be defined when each factor has a separate effect but all in the same direction, while “qualitative interactions” can be described when the effects of the two factors follow opposite directions or when one factor has an effect only when the other one is also present (Thomas, 2010).

From a biological point of view, an interaction is usually defined as the condition where the effect of a factor is modified by the presence of the other. This general definition is the one which will be adopted in the present review, since it will be the most suitable to the evaluation of studies investigating G×E effects on human and animal behavior. This « biological » meaning of interaction implies the interest in understanding the physio-pathological, cellular, or molecular mechanisms underlying the interactive effects of the two considered factors. In the case of G×E, research interests may be focused mainly on the environmental component of the interaction and therefore include: (i) investigating the pathogenetic mechanisms by which the environmental factor can cause its effects by interacting with a gene on a certain pathway or (ii) evaluating whether the effect of the environmental factor is limited to a subgroup of individuals with a specific genotype. Research on G×E may also rather focus on the genetic component, (i) analyzing the contribution of the environmental factor in explaining the observed heterogeneity in the genetic effects across subgroups of individuals, or (ii) detecting genetic effects that become evident only in the presence of an environmental exposure.

The biological definition of G×E has immediate clinical implications. The information achieved through the study of G×E may indeed improve prediction of disease risk or prognosis in an individual, but also help to choose treatments based on the individual's genotype, thus minimizing side effects and maximizing clinical benefits. Hence, G×E studies may have important implications for public health policy decision-making (Collins and McKusick, 2001). Identifying variability in the response to a hazardous environmental exposure across subgroups of individuals could in fact allow implementing more cost-effective preventive measures, e.g., screening and health educational programs, as well as promote environmental regulations setting more appropriate standards to protect the most vulnerable individuals.

Despite their invaluable relevance for basic and clinical sciences, as well as in terms of public health perspectives, G×E studies are overall scarce, especially when compared to those investigating genetic factors alone. This is probably linked to some major methodological challenges affecting G×E studies, which may discourage their extensive implementation. These methodological issues mainly include (i) false negative results, due to inadequate sample size and statistical power, and (ii) false

positive results, due to multiple testing in the absence of adequate correction. In general, it is well known that detecting any statistical significant interaction between two factors requires much larger sample sizes than their main separate effects, i.e., at least four times larger for an effect of the same magnitude, as a rule of thumb (Smith and Day, 1984). In the case of G×E, sample size requirements are further amplified by the loss of statistical power associated with the inaccuracy of the environmental exposure assessment due to measurement error (Burton et al., 2009). Hence the lack of G×E effects showed by several studies may be instead due to insufficient sample size.

Beside the problem of false negative results, G×E studies are often limited by the occurrence of false positive results, mainly due to the use of multiple statistical tests on the same dataset. The issue of multiple tests becomes particularly important in G×E research, in which a high number of gene polymorphisms are often assessed in interaction with a variety of environmental exposures on a multitude of related outcomes. The attempt of evaluating all possible gene–exposure–outcome combinations may indeed lead to perform a large number of statistical tests, thus increasing the probability of spurious findings if no appropriate correction is applied to the calculation of statistical significance.

The problematic issue of multiple tests is especially severe in the context of genome-wide association studies, where millions of genomic variants can be tested for interaction with several environmental factors. In these studies, unprecedented sample size requirements may be therefore necessary in order to adopt stringent significance thresholds to protect against false positive findings (Khoury and Wacholder, 2009). A large body of methodological work has been developed (Thomas, 2010) and is still ongoing (Zhu et al., 2024) to devise analytical approaches that can maximize statistical power; concomitantly, the scientific community joins its forces to fulfill the demanding sample size requirements of G×E studies, as demonstrated by the growing number of international collaborative initiatives (Davis and Khoury, 2007).

1.2 Behavioral effects of gene-environment interactions: basic concepts and examples

The psychopathological relevance of G×E interactions has been the subject of a variety of conceptualizing efforts across the last decades. The “canalization” model, originally provided by Waddington in 1957 and re-interpreted by Grossman (Grossman et al., 2003), has for instance proposed that normal development can be conceived as a groove in a model surface representing the normative developmental process over time. The normal developmental trajectory can be viewed as the progression of an individual like a ball rolling along a canal initially specified by the genome. Over time, genetic and environmental factors can influence the direction of this trajectory: adverse factors can push the individual up the slopes of the canal toward the thresholds of psychopathological expression, whereas “canalizing” experiences can push the trajectory back

toward the middle of the canal, i.e., the normalized state. As development progresses, the banks of the canal become steeper, i.e., more resilient to adverse experiences.

Another conceptualizing attempt of understanding the link between G×E and psychopathological processes can be provided by the model of “allostatic load” (AL) introduced first by McEwen and Stellar (1993). AL is the cumulative physiologic toll exacted over time on the body by the individual efforts to adapt to life experiences (McEwen and Stellar, 1993). AL can be scored through parameters related to several important regulatory systems, e.g., the hypothalamic-pituitary-adrenal axis, sympathetic nervous system, cardiovascular system and metabolic processes. These AL scores represent a valid index of the interactions between environmental factors and psycho-physical health: for instance, positive social interactions in early life were associated with low AL in adulthood (Singer and Ryff, 1999) and slower cognitive and physical decline during aging (Seeman et al., 2001; Seeman et al., 1997). The AL model is not alternative to the canalization concept, but it rather added a more specific physiological interpretation of the G×E evoking the involvement of neuroendocrine adaptive mechanisms.

A more biological view of G×E has been implemented in the theoretical framework of the “differential-susceptibility” perspective (Belsky et al., 2007; Belsky and Pluess, 2009). One of the best known examples that may be included in this theoretical approach is probably the “two-hit” hypothesis of schizophrenia, postulating that environmental insults during development (the second hit) may go unnoticed in individuals that have not been “primed” by earlier genetic factors (the first hit). More largely, the “differential-susceptibility” model proposes that individuals’ susceptibility to environmental effects (both negative and positive) differ depending upon genes that are involved in responsivity to environmental states, coined as “plasticity genes.” Plasticity genes can either aggravate the risk of psychopathology in negative environments, or alleviate the risk of psychopathology in positive environments, such that the most distressed individual in an undesirable environment is also the one who is most likely to be aided in a positive environment (Belsky and Pluess, 2009).

The concept of “load” has been somehow converted in a more general concept of “buffer” by the “cognitive reserve hypothesis” which more specifically faces the role of G×E interactions in the context of brain functionality and cognitive abilities (Stern, 2002). This hypothesis has been particularly developed in relation to Alzheimer disease (AD) (Stern, 2006), but could be interpreted in the larger context of behavioral pathophysiology. The cognitive reserve model posits the presence of passive and active components (Stern, 2002): the passive reserve encompasses the biological capacities that an individual brings into old age and that may provide a buffer against the clinical expression of the brain pathology. The passive component can be viewed as the degree of the

development of “normal” brain function, which results from pre- and post-natal development. This reserve can be protected during midlife by exercise, diet, intellectual and social activities, as well as physical health care. The active component of the cognitive reserve is viewed as the brain’s ability to adapt or compensate for the presence of the pathology. Several brain mechanisms may mediate this active reserve, and their identification is probably one of the most challenging aspects of modern neuroscience research. Imaging studies have, for instance, suggested that recruitment of atypical brain pathways may represent a possible compensatory mechanism against AD-related cognitive decline (Stern, 2002). A typical example was provided by neuroimaging studies demonstrating that AD patients showed bilateral recruitment patterns on language and memory tasks, which are usually strongly left lateralized in normal subjects (Becker et al., 1996; Grady et al., 2003). Hence, the concept of cognitive reserve implies the existence of a neural reserve, provided by preexisting brain networks that are more efficient and may be less susceptible to disruption (by pathological or aging processes) and a neural compensation, due to alternate networks able to compensate for pathology's disruption of preexisting networks (Stern, 2006).

All these conceptualization models, although through different views (e.g., either more genetic, endocrine- or cognitive-oriented), underline the critical relevance of G×E in brain functions (and therefore behavioral expression) and related pathologies. As already mentioned, a large part of research has been classically devoted to the study of the impact of G×E on cognitive abilities and their related decline. This may be due to the existence of a long-term tradition of research on the genetic and environmental origins of human intelligence, beside the widespread societal impact of studies on aging-related cognitive decline.

2. Gene-environment interactions and social behavior: human studies

After cognitive abilities, social behavior is another domain which has been largely investigated in human studies on G×E interactions. This research interest is not surprising, as, by definition, social behaviors consist of a direct interaction between the individual and its environment, represented by its conspecifics providing the social context. Furthermore, for humans as well as for other mammalian species, social behavior develops exclusively through social experiences throughout the lifespan of an individual, including first the parental care received, then the quality of social relationships occurring within the family unit, educational and professional contexts (Esposito et al., 2017; Opendak et al., 2017).

While the role of environmental factors on social behaviors is therefore almost intuitive, the impact of genetics has required extensive research efforts. The genetic control of human social behavior is indeed highly complex, reflecting the variety of expression modalities of this behavior and

the complexity of the underlying neurobiological mechanisms. An interesting research approach lies in investigating the genetic modulation of the pathological rather than physiological expression of social behaviors. Several genes have been indeed linked to pathologies mainly characterized by social alterations, e.g., aggressive/anti-social or autism spectrum disorders, as summarized in Fig. 1. Environmental stimulation (e.g., enhanced parental care, physical exercise, social bonds) or adversity (e.g., parental abuse/neglect, chronic stress, social isolation) may respectively attenuate or exacerbate the social alterations displayed by these classes of pathologies (Fig. 1). Genetic risk factors and environmental changes can indeed influence each other through complex mutual effects, e.g., inducing synergistic, antagonistic or interactive outcomes on the behavioral phenotype of these social disorders.

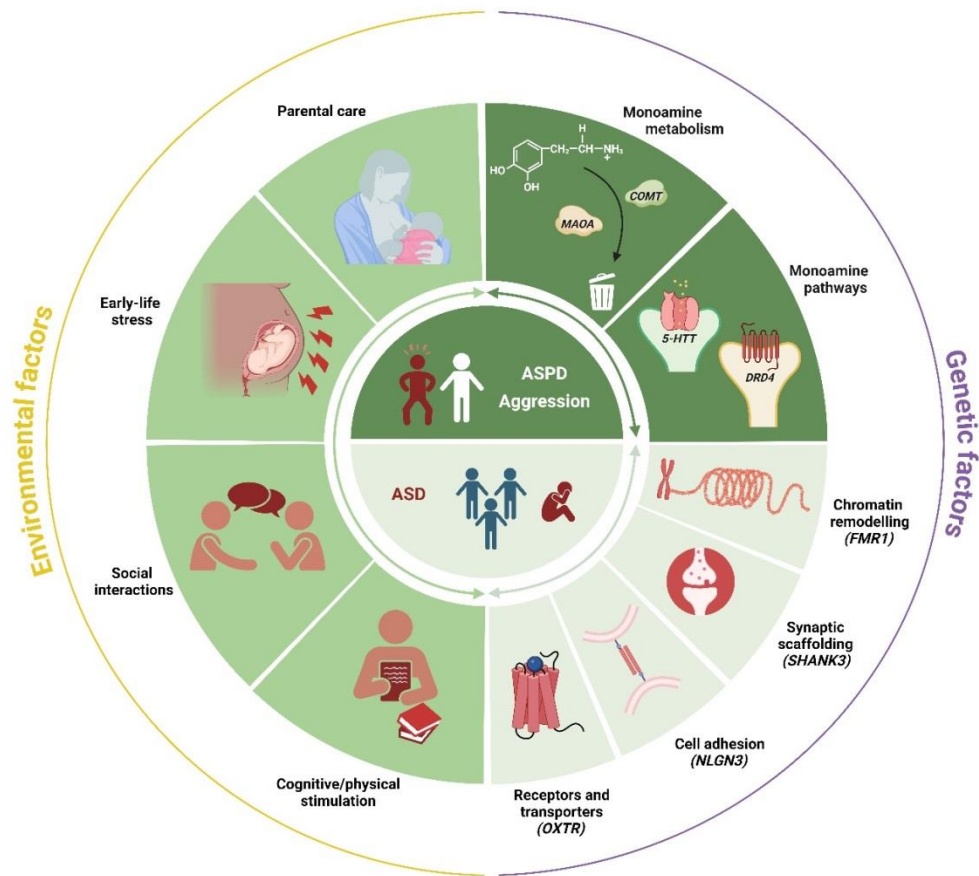


Fig.1: Examples of G×E affecting social dysfunction in humans. Human studies have highlighted the role of G×E interactions in the etiopathology of social pathologies, e.g., aggressive/anti-social personality (ASPD) and autism spectrum (ASD) disorders. Mutations and polymorphisms in genes involved in monoamine metabolism and their receptors/transporters have been for instance linked to ASPD (dark-green slices on the right side), while a variety of genes involved in chromatin remodeling, synaptic scaffolding and neuronal functionality has been involved in ASD (light-green slices on the right). All these genetic risk factors can interact with environmental factors (medium-

green slices on the left) which may induce aversive (e.g., parental neglect/abuse, stress exposure, social isolation, lack of engagement in cognitive/physical activities) or beneficial experiences (e.g., rich parental and social relationships, sustained cognitive and physical stimulation). Abbreviations of the genes are explained in the text. Created with BioRender.com.

2.1 The role of G×E in aggression and anti-social personality disorder (ASPD)

Aggression is a highly functional form of social behavior that ultimately contributes to increase the fitness and survival of individuals: animals and humans fight each other for territory, status, mates, food and other vital resources. While most individuals engage in these social conflicts with appropriate and well-controlled forms of aggressive behavior, others may become extremely violent, thus displaying presumably less adaptive forms of aggression, often defined as “anti-social personality disorder” (ASPD) in humans. This category refers to a chronic, pervasive pattern of disregard for (and violation of) the rights of others, as well as manifestations of aggression and violence and a high propensity to engage in criminal activities (American psychiatric association, 1980). While ASPD is framed as a disorder of adulthood, it is typically preceded by analogous manifestations in adolescence and childhood.

Several human studies have demonstrated that genetic variants leading to exaggerated dopaminergic, noradrenergic and serotonergic transmission, i.e., those monoamine neurotransmitters implicated in the regulation of aggressive behaviors, are often associated with anti-social profiles (Fig. 1). Individuals carrying a *COMT* allele leading to the lower activity of the catechol-O-methyl transferase, involved in dopamine and noradrenaline metabolism, are, for instance, generally more prone to develop ASPD than those carrying the variant conferring high *COMT* activity (Lachman et al., 1998; Rujescu et al., 2003; Vevera et al., 2009). Similarly, genetic polymorphisms leading to low levels of *MAOA* (Monoamine oxidase A), a key enzyme for the degradation of serotonin, norepinephrine and dopamine, known to be implicated in human and animal aggression (Kolla and Bortolato, 2020), have been found in individuals with ASPD (Alia-Klein et al., 2008; Beaver et al., 2010). Strikingly, in a recent cross-species analysis of eight aggression gene lists (encompassing more than 1700 genes) from adult and children genome-wide association studies, transcriptome-wide studies of rodent models, as well as sets from Online Mendelian Inheritance in Man and knock-out (KO) mice revealed that *MAOA* ranked highest by number of occurrences and weighted ranks for aggression (Zhang-James et al., 2019). Furthermore, brain-imaging studies validated that *MAOA* activity in most brain regions is negatively correlated with the multidimensional personality questionnaire score of trait aggression (Alia-Klein et al., 2008).

Moreover, variants of all these genes, together with others involved in the same neurotransmitter functions (e.g., dopamine D4 receptor or *DRD4*), have been especially found to be associated with an increased risk to develop antisocial and violent behaviors in response to aversive environmental conditions [reviewed in (Iofrida et al., 2014)]. Converging lines of evidence have, for instance, suggested that parental maltreatment increases the risk of violent and aggressive behaviors and that this risk is higher in carriers of pro-dopaminergic alleles (Palumbo et al., 2022). The best known example of G×E affecting human aggressive behavior has involved the role of the *MAOA* gene in moderating the association between early life trauma and increased risk for violent and antisocial behaviors (Gordon and Greene, 2018; Haberstick et al., 2014; Huizinga et al., 2006). Genetic polymorphisms leading to low MAOA activity were indeed a significant risk factor for these dysfunctional social behaviors in adults who report victimization as children, while those individuals who were abused as children, but have a genotype conferring high levels of MAOA expression, were less likely to develop antisocial symptoms (Caspi et al., 2002). The findings obtained through the seminal work by Caspi and colleagues (2000) were replicated through a variety of studies (Byrd and Manuck, 2014; Foley et al., 2004; Frazzetto et al., 2007; Kim-Cohen et al., 2006; Taylor and Kim-Cohen, 2007), with very limited exceptions (Haberstick et al., 2005).

2.2 G×E and Autism Spectrum disorder (ASD)

Beside aggression and ASPD, a second major line of research on G×E interactions and social behaviors has been generated by studies on autism-spectrum disorder (ASD), as this neurodevelopmental disorder (NDD) is mainly characterized by behavioral deficits in the social domain, e.g., reduced social interest, increased social avoidance/withdrawal and abnormal social communication. Compared to the work on anti-social behaviors, these studies have been complicated by difficulties in identifying the genetic origins of ASD.

Although ASD has been originally considered somehow an “environmental pathology” (Bettelheim, 1967), according to the initial erroneous theories pointing to a causal role of parental style in ASD etiopathology [as discussed in (Fombonne, 2003)], an increasing number of studies have supported during the last decades the genetic roots of this NDDs. The genetic alterations known to be associated to ASD are extremely heterogeneous (Fig. 1), since they include a large part of those genes involved in neuronal function and development (Abrahams and Geschwind, 2008). Only to give an incomplete overview, these genes code for molecules involved in: i) chromatin remodelling and regulation of transcription (e.g., *MeCP2*, *FMR1*), ii) actin cytoskeleton dynamics (*TSC1*, *TSC2*, *NF1*) iii) synaptic scaffolding proteins (e.g., *SHANK3*), iv) receptors and transporters (e.g., *GRIN2A*, *GRIK2*, *GABAR*, *SLC6A4*, *SLC25A13*, *OXTR*, *AVPR1*), v) second-messenger systems (*PRKCB1*, *CACNA1C*, *NBEA*), vi) cell adhesion (e.g., *NLGN3*, *NLGN4*), and vii) secreted proteins (e.g., *RELN*, *LAMB1*) (reviewed in

(Persico and Bourgeron, 2006)). Such list is only indicative, as the number of genes implicated in ASD is supposed to be many-fold greater (Buxbaum et al., 2012).

The role of these genes in brain development is at the basis of some hypotheses on ASD etiology, e.g., the so-called “many genes, common pathways” theory (Geschwind, 2008), emphasizing the role of defective synaptic functioning and abnormal brain connectivity, both leading to altered information processing. Despite the strong genetic contribution to ASD, environmental factors must also play a role in ASD etiopathology, since they account for 55% of the variance in autism risk among twins (Hallmayer et al., 2011). Multiple lines of evidence have indeed suggested that ASD risk may be reduced by improving the quality of the maternal lifestyle (Bragg et al., 2022; Curtis and Patel, 2008; Modabbernia et al., 2017), and of the prenatal environment, e.g., exposure to pesticides (Shelton et al., 2012) or air pollutants (Kern et al., 2016; Lyall et al., 2014). Conversely, ASD risk may be exacerbated by prenatal exposure to intense stressors (Kinney et al., 2008a; Kinney et al., 2008b) which may contribute, together with genetic risk factors, to profoundly alter fetal brain development (O'Donnell et al., 2009). Furthermore, environmental/behavioral stimulation, especially during early life phases, has been proposed as a key element for successful therapeutic approaches for the treatment of ASD (Aldred et al., 2004; Curtis and Patel, 2008).

Recently, the concept of “exposome” has been proposed to underline the multifactorial nature of ASD etiopathology, including the variety of environmental risk factors and their interactions with genetic vulnerability (De Felice et al., 2015). Indeed, it has been proposed that ASD may be not only the sole product of congenital genetic alterations, but may be elicited by environmental variables via epigenetic mechanisms, e.g., DNA methylation, histone modification, and noncoding RNAs (Bastaki et al., 2020; Bhandari et al., 2020; Saxena et al., 2020; Yoon et al., 2020). In vitro studies have demonstrated for instance that some environmental toxicants induce transcriptional modifications that are comparable to those found in brain samples from ASD patients (Kubota et al., 2012; Miyake et al., 2012). It is therefore also possible that environmental stimulation/adversity may modulate similar epigenetic mechanisms thus compensating/exacerbating the pathological neurobiological processes underlying ASD symptoms (Genovese and Butler, 2020).

Hence, understanding the role of G×E interactions is of critical relevance to disentangle the complex etiopathology of ASD, and subsequently to design preventive and therapeutic strategies targeting specific environmental factors. Interestingly, while diverse genetic pathways including complex combinations of rare and/or common variants may contribute to the presence of ASD (Jeste and Geschwind, 2014), specific common genetic variants seem to regulate how the ASD phenotype manifests in response to the social environment. Two examples of these common variants involved genes coding for the serotonin transporter (*5-HTTLPR*) and dopamine receptor (*DRD4*), which have

been linked to social ASD-related phenotypes [e.g., (Camara et al., 2010; Drabant et al., 2012; Meyer-Lindenberg and Tost, 2012)] and are known to play a role in neural networks related to the salience of social environments (i.e., “social salience”). Polymorphisms related to *5-HTTLPR* and *DRD4* critically modulated the sensitivity of the social phenotype of ASD patients to either low or high levels of parental care (Caplan et al., 2021). These findings therefore support the “differential susceptibility” model of G×E, while refute the hypothesis of a biological constraint effect in ASD, positing that ASD children may be less susceptible to the influences of social environments due to their “inborn limited social information processing” (van Ijzendoorn et al., 2007). Importantly, these results alternatively suggest that the biological (and genetic) variability within ASD patients may be an important indicator of their susceptibility to social environmental influences (Caplan et al., 2021).

It is important to highlight that this G×E study focused exclusively on the social phenotype of ASD patients, overlooking other behavioral alterations that are commonly associated with the complex autistic symptomatology, e.g., stereotypies, attentional or sensory-motor abnormalities. This strategy is interesting, and is in line with other studies on ASD, incorporating the Research Domain Criteria (R-DoC) paradigm [e.g., (Foss-Feig et al., 2016)]. Initiated by the National Institute of Mental Health, R-DoC is a methodological approach which associates psychiatric problems with symptoms (e.g., low social functioning) instead of psychiatric categories [e.g., ASD (Cuthbert, 2014)]. R-DoC should allow investigation into the causes of psychiatric problems to be liberated of the inaccuracies of diagnostic categorization, enabling research into the basic mechanisms of psychiatric disorders, transcending traditional psychiatric classification (Montalvo-Ortiz et al., 2016). This approach is therefore directly applicable to preclinical studies in animal models of ASD and social dysfunction, thus allowing the transversal evaluation of social dysfunction across multiple pathological conditions.

3. Gene-environment interactions and social behavior: animal studies

Animal studies may allow overcoming several limitations affecting human research on G×E. This includes the problems of false negative and false positive results mentioned before, since working with animals allows to easily increase the sample size of a study, and to reduce the number of candidate genes tested. More importantly, research on animal models allows to precisely control the genetic and environmental variables involved in the considered interactions (Will et al., 2004).

Animal studies indeed allows to standardize the genetic factors manipulated in a study, through the use of inbred genetic backgrounds and of mutations/variants that can be precisely controlled through the approaches that will be described in detail in section 3.2. Furthermore, the use of classical transgenic and knock-out genetic approaches, as well as of more recent CRISPR/Cas 9, optogenetic and pharmacogenetic techniques allow to manipulate the mouse genome in ways that

are unimaginable for human studies. The possibility of including both sexes in animal studies is an additional advantage as it allows to assess the sexual dimorphism known to characterize the behavioral impact of G×E interactions in both humans and animals (Ordovas, 2007; Torres-Reveron and Dow-Edwards, 2022).

Concerning the possibility of manipulating environmental variables, animal research also markedly overcomes human studies which are weakened by the high variability of environmental conditions of the subjects. Furthermore, as it will be described in detail in section 3.3, animal studies provide with the unique opportunity of precisely manipulate complex environmental components, e.g., physical activity, maternal care, the availability of social interactions, simply through variations of the housing conditions.

Finally, animal studies may offer an additional advantage when applied to the investigation of G×E on social dysfunction; they provide with more direct and objective measures of social behaviors, compared to the behavioral scales often obtained in human studies, which are often indirectly obtained, i.e., through the reports of teachers or family members, as in the case of ASD children. As it will be described, measures of social interest, communication and aggression are usually derived from direct observations of the animal behavior, or even automatically computed by dedicated software. These measures therefore increase the reliability and replicability of the social behavioral results obtained in animal models.

3.1. Testing social dysfunction in laboratory mice

Despite the long tradition of research on social behaviors using laboratory rats [recently reviewed and discussed in (Ben-Ami Bartal, 2024)], it is now widely accepted that mice are a highly social species, displaying a rich repertoire of social behaviors also in the laboratory settings (Berry and Bronson, 1992; Wills et al., 1983). Indeed, research on genetic preclinical models of aggression and ASD during the last decades has progressively become centred on the mouse species, because of its wider opportunities of sophisticated genetic manipulations. Social behaviors can be assessed in mice as early as postnatal days 8-10, using the homing test for mother-infant attachment (Ricceri et al., 2007). Later, the social drive of juvenile and adult animals can be assessed using automated social preference tasks, such as the 3-chamber test (Nadler et al., 2004). After a first habituation trial to the apparatus, the sociability of a tested animal is evaluated by measuring the time spent in the side compartment containing a conspecific versus the empty side; this sociability trial is often followed by the assessment of social novelty preference, by measuring the time spent in the side compartment containing a novel versus a familiar conspecific. The social interest of juvenile or adult mice can also be assessed through direct interaction tests, where the tested subject is allowed to get in social contact with a stimulus mouse (while in the 3-chamber test, direct contact is prevented by confining

the stimulus animal in a perforated transparent box). Depending on animals' sex and age, as well as on specific testing conditions, several behaviors may be evaluated in the direct social interaction test, including juvenile play, social interest, courtship/sexual behaviors, aggression (Crawley, 2004, 2007a; Crawley, 2007b). Hence, the development of social abilities and competencies may be also investigated in laboratory mice, an issue that is of critical translation relevance for human research.

During these direct interaction tests, social interest is typically measured: it is mostly derived from the duration and frequency of sniffing of the tested subject towards the conspecific, as olfactory exploration and recognition is of critical relevance to mouse social behavior (Terranova et al., 1993). In addition, following, allogrooming or other behaviors indicating social contact with the conspecific can be scored (Terranova et al., 1993). Videos are commonly scored manually by one or more observers, most often using specific softwares for behavioral analysis, although automatized (de Chaumont et al., 2012) and machine learning (Goodwin et al., 2020; Maisterrena et al., 2024; Pereira et al., 2022; Segalin et al., 2021) approaches have started to be applied to the analysis of mouse social behaviors. Most of the available social tests focus on dyadic interactions, in order to simplify behavioral analyses. Nonetheless, novel analysis tools have been recently developed to allow the evaluation of social interactions among grouped mice (de Chaumont et al., 2019), thus providing with a more complex description of social behaviors.

Aggressive behaviors typically emerge in laboratory male mice during adolescence, with a peak of ambivalent agonistic behaviors occurring around PND 35, corresponding to puberty (Terranova et al., 1998). Aggression in adult mice is often assessed using the resident-intruder test, i.e., inserting an unfamiliar animal in the home cage of the tested subject, which has been typically single housed during a certain period of time (Takahashi et al., 2012). Aggression in mice is most typically studied in males, where it can be induced by early social isolation (Miczek et al., 2001); in contrast, female mice only display aggressive tendencies when lactating and in presence of the pups, thus strongly limiting studies of female aggression in the mouse species (Been et al., 2019). Aggressive behavior is typically measured by the analysis of latencies to attack the intruder, but more extensive analyses can be performed, e.g., measuring the duration and frequencies of offensive/defensive postures, tail rattling, attacks and even the occurrence and severity of biting episodes.

Due to its translational relevance for ASD models (Caruso et al., 2020), social communication has also been largely assessed in laboratory mice, since they emit USVs in social contexts at multiple stages of their life (Wohr, 2014; Wohr and Scattoni, 2013). USVs are uttered upon social isolation to elicit maternal retrieval during the first post-natal days and they tend to decrease around the second post-natal week (Branchi et al., 2001; D'Amato et al., 2005). USVs also accompany adult social interactions, namely male-female and female-female encounters, often positively correlating with

social interest (Holy and Guo, 2005; Moles et al., 2007). The spectrographic analysis of USVs in mice has undergone an impressive evolution in the last years (Premoli et al., 2023), advancing from the initial measures of the number and mean duration of the call to the qualitative analysis of call types (Chabout et al., 2012; Holy and Guo, 2005; Kikusui et al., 2021; Roy et al., 2012). Furthermore, while the evaluation of adult USVs is still mostly performed in the context of dyadic interactions, recent advances have allowed the assessment of USVs in more complex social contexts, coupling their analysis with social interactions (de Chaumont et al., 2021; Ferhat et al., 2015). Interestingly, assessing the presence of deficits in social interest and ultrasonic communication is generally a well-accepted criterion to support the validity of a mouse model of ASD (Crawley, 2004, 2007a, 2023; Wohr and Scattoni, 2013).

3.2. Research strategies to assess the impact of genetic factors on social dysfunction in mice

The genetic control of social behaviors, as well as of other behavioral domains, can be investigated in animal studies by multiple approaches (van der Staay, 2006), e.g., strain comparisons and selective breeding strategies. The first approach is based on the fact that animals of the same inbred strain are genetically identical and that therefore between-strain differences in a specific behavior show the existence of genetic influences on individual differences in this behavior. Selective breeding is based instead on the observation that the offspring of animals with a desired quality, e.g., high aggression, are more likely to demonstrate that quality than the progeny of random individuals. Usually, animals are bred for opposite directions of the behavior of interest, e.g., “low aggression” and “high aggression” lines.

The next step after the demonstration of the genetic control of a given behavior in animals is the identification of the specific genes involved, using either whole genome searches or candidate gene approaches. The candidate gene approach is the most widely used, and it can be based on two main strategies. The first is similar to the one used in classical human association studies and it consists in making use of naturally occurring variants of the genes of interest, e.g., the BTBR mouse line to model ASD. The second strategy is to actively manipulate the gene in question by its inactivation (KO models) or insertion of extra copies (transgenic lines). Comparing the behavior of genetically-modified animals with that of the wild type (WT) ones having the intact gene can help to deduce the function of the gene and determine its effects on the trait under investigation.

Concerning the genetic control of aggression, the selective breeding approach has been extensively applied. Three pairs of mouse lines bidirectionally selected for intermale aggression have been most commonly used: the Finnish Turku Aggressive and Non Aggressive lines (TA and TNA) (Lagerspetz et al., 1968; Nyberg et al., 2004; Nyberg et al., 2003), the Dutch Short and Long Attack Latency lines (SAL and LAL) (Oliveira et al., 2024; Sluyter et al., 2003; van Oortmerssen and Bakker, 1981), and the American North Carolina 900 and 100 lines (NC900 and NC100) (Cairns et al., 1983;

Hood and Quigley, 2008). These studies have contributed to advance our understanding of the genetic and molecular bases of pathological aggression or ASPD, since male mice from these high aggression lines are not inhibited by submission signals and may even attack females, thus showing persistent, indiscriminate and thus maladaptive forms of aggression which are very relevant for the study of deviant human aggressive behaviors. Close findings to human data have been also generated by studies using KO and transgenic approaches (Jager et al., 2018); as expected from human results previously summarized, *MAOA*-KO mice displayed for instance increased aggression in the resident-intruder test and maladaptive social behaviors (Bortolato and Shih, 2011; Kolla and Bortolato, 2020; Scott et al., 2008), as well as mice deficient for *COMT* (Gogos et al., 1998), dopamine transporter (Rodríguez et al., 2004) and adrenoceptors (Sallinen et al., 1998). The strain approach has also provided with candidate mouse models: the BALB/cJ strain has been for instance identified for its high aggression levels (Mondragon et al., 1987) and general maladaptive social behaviors, including lower social approach (Brodkin et al., 2004; Burket et al., 2011; Moy et al., 2007) and lack of conditioned social place preference compared to other inbred strains such as the most widely used C57Bl/6 (B6) strain (Panksepp and Lahvis, 2007). The DBA/2J strain has also been proposed to study intermale aggression, since DBA/2J males showed shorter attack latencies than B6 individuals (Crawley et al., 1997). In contrast to BALB/cJ mice, the DBA/2J strain showed normal sociability levels (Bolivar et al., 2007; Moy et al., 2007), thus providing an interesting tool to study the dissociation between aggressive and sociability abnormalities.

As reviewed in several articles (Banerjee et al., 2014; Bey and Jiang, 2014; Ellegood and Crawley, 2015; Moy et al., 2006), a huge variety of mouse models for ASD have been proposed in the last decades, based on very different approaches. One strategy is based on identifying mouse strains that spontaneously present some major ASD-like symptoms, such as low sociability or poor communication abilities. The best-known example of this approach is the BTBR strain (Bolivar et al., 2007; McFarlane et al., 2008; Meyza et al., 2013; Moy et al., 2007), widely employed in ASD research and proposed as a tool to identify novel genes involved in the control of social behaviors. The main disadvantages of this strain approach are (i) the problem of identifying an appropriate control strain and (ii) the possibility that strain-specific phenotypes of emotionality or locomotor activity may explain the supposed ASD-like behavioral profiles (Oddi et al., 2013b).

Another approach consists of manipulating the mouse genome to import in the animal model some of the genetic alterations associated with ASD. This experimental strategy has generated the *Shank3*, *Neurolegin* and *Syntaxin* models, only to mention few examples; nonetheless, its validity is undermined by the high heterogeneity of the genetic alterations known to be somehow involved in ASD, as already mentioned (Abrahams and Geschwind, 2008). Hence, another approach to model ASD in mice, is based on the paradoxical finding that, although the etiopathogenesis of ASD is the

result of concomitant mutations in multiple loci, there is a growing list of genes whose single disruption is sufficient for the whole autistic phenotype to occur. Based on such evidence, mouse models of single gene mutations may carry a great deal of information concerning the underlying mechanism(s) leading to ASD (Ey et al., 2011; Oddi et al., 2013a).

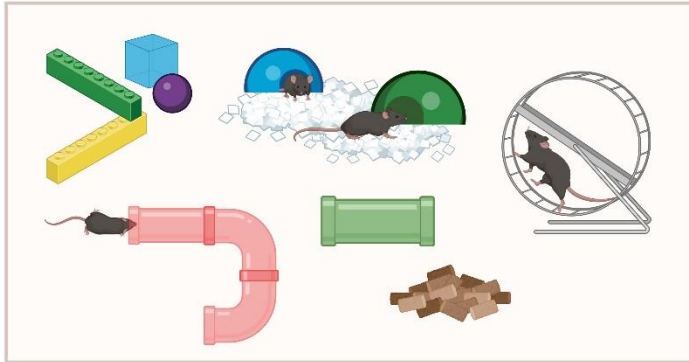
Hence, mouse models of ASD have been created by focusing on other developmental pathologies featuring ASD-like traits, but having a defined, single genetic cause. An example of this approach is provided by the *Fmr1*-KO mouse line, modelling the most common monogenic cause of ASD, i.e., Fragile X syndrome (FXS). These KO mice displayed several ASD-like phenotypes, including altered social interactions, reduced social interest and preference for social novelty, as well as alterations in ultrasonic communication (Bernardet and Crusio, 2006; Kat et al., 2022; McNaughton et al., 2008; Pietropaolo et al., 2011).

3.3. Experimental tools to investigate the impact of environmental factors on social dysfunction in mice

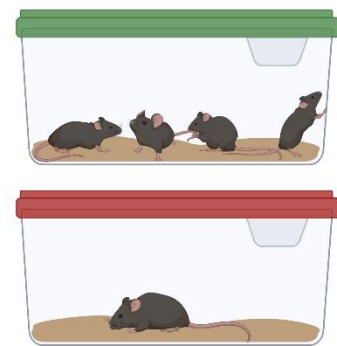
The behavioral impact of environmental factors can be studied in laboratory mice by a variety of manipulations of animals' housing and breeding conditions, allowing to modify several components of the rearing environment, in either a combined or independent manner. Here we will focus on those environmental manipulations which were employed in mouse studies on GxE and social dysfunction. These manipulations are illustrated in Fig.2 and intend to model the manipulations of the physical, social and parental environment investigated in human studies on GxE interactions and social pathologies (see also Fig. 1). The effects of environmental stimulation are often investigated in laboratory mice through environmental enrichment/physical exercise (fig.2-A), or through earlier strategies of maternal enrichment or cross-fostering (Fig. 2-C). Environmental adversity is instead commonly modelled in mouse studies through maternal separation (Fig. 2-C), social isolation (Fig. 2-B) or stress exposure (Fig. 2-D).

The impact of these environmental factors in laboratory mice has been investigated on several behavioral domains, including social interactions, encompassing the analysis of short- and long-term effects, with multiple duration of the environmental exposure (spanning from one day to several months) starting at pre-natal, adolescent, adult or more advanced ages. Here we provide a brief description of the behavioral effects of these environmental interventions in laboratory mice.

A. Environmental enrichment/physical exercise



B. Social isolation



C. Cross fostering, maternal enrichment/separation



D. Stress



Fig.2: Examples of environmental manipulations commonly used to study G×E effects on social dysfunction in laboratory mice. Changes in housing and breeding conditions allow to manipulate the physical (A) and social (B) environment where laboratory mice are reared, as well as their levels of maternal care (C). Environmental enrichment, physical exercise (A) and stimulation of maternal care (C) are commonly used to model positive experiences and beneficial environmental stimulation in mice. Conversely, social isolation (B), maternal separation (C) and exposure to stressors (e.g., restraint stress, D) are largely employed to induce environmental adversity in mouse studies on G×E and social dysfunction. All these environmental interventions can be implemented at different phases of the prenatal or post-natal development. Created with BioRender.com.

3.3.1 Environmental enrichment and physical exercise

Animal studies investigating the mechanisms underlying the behavioral effects of environmental manipulations were originally inspired by the research of the group of Mark Rosenzweig at Berkeley University, carrying out a series of experiments exploring the effects of environmental stimulation on brain development and cognitive abilities in rats (Renner and Rosenzweig, 1987). These studies provided the model for the standardized enriched environment (EE) that is still most commonly used in rodent research, i.e., providing enhanced possibilities of both physical and social stimulation.

In these initial experiments enriched housing conditions consisted of group-housing animals at weaning in large cages with various toys and running wheels, and the brain and behavioral characteristics of enriched animals were compared to those of impoverished controls, i.e., reared in social isolation in standard cages (Renner and Rosenzweig, 1987). Subsequent studies have kept the

original enrichment settings, but they have compared enriched animals with those housed in standard grouped conditions.

The typical example of EE (see also Fig.2-A) therefore includes a combination of social and physical environmental complexity, as well as the opportunity of performing physical exercise, provided by the presence of running wheels (Smith et al., 2024). Wheel running activity has indeed been proposed as one of the key elements of the enriched environment, since both manipulations produced similar effects on brain and behavior (van Praag et al., 2000). Indeed, wheel running activity alone is able to exert cognitive effects that were comparable to those of environmental enrichment (Harburger et al., 2007; Lambert et al., 2005). Nonetheless, the majority of the available studies demonstrating marked effects of wheel running activity have invariably employed control conditions in which no wheel was installed. When locked-wheel controls were instead adopted, the cognitive effects of wheel running did not clearly emerge in rats (Gobbo and O'Mara, 2005), mice (Pietropaolo et al., 2006) or in mouse models of Alzheimer disease (AD) (Nichol et al., 2007; Pietropaolo et al., 2008b)). It is indeed possible that the presence of a locked wheel *per se* is able to induce some enrichment-like effects, i.e., attenuating the cognitive deficits of AD mice (Nichol et al., 2007).

Research on EE, as well as on physical exercise, has largely been focused on the protective effects of this manipulation in the context of neurodegenerative disorders and cognitive dysfunction [e.g., (Caston et al., 1999), (van Dellen et al., 2000) (Arendash et al., 2004; Jankowsky et al., 2005), (Adlard et al., 2005; Nichol et al., 2007; Pietropaolo et al., 2014; Pietropaolo et al., 2008b; Wolf et al., 2006), especially after the discovery of its ability to promote adult neurogenesis in the hippocampus [reviewed in (van Praag et al., 2000)]. Nonetheless, the effects of EE on mouse social behavior have also been investigated: a large part of these studies focused on inter-male aggression, in order to assess the potential implication of enriched housing conditions on the welfare of laboratory mice (Van Loo et al., 2004; Van Loo et al., 2003). Interestingly, EE was mostly found to exacerbate the aggressive behavior of adult male mice, and this effect seemed to be mainly due to the difficulty of keeping stable adult dominance relationships within the dynamic EE (Haemisch and Gartner, 1997; Haemisch et al., 1994; McQuaid et al., 2012; Mesa-Gresa et al., 2013). In fact, EE promoted instead more adaptive aggressive behaviors in adult male mice when the enriched exposure was limited to the adolescent period (Pietropaolo et al., 2004), i.e., during a critical phase for the development of agonistic behaviors in mice. Furthermore, EE increased social interest and social interaction in laboratory mice outside the context of aggressive behavior testing (Abramov et al., 2008; Burrows et al., 2017; Cabrera-Munoz et al., 2022; Hendershott et al., 2016; McQuaid et al., 2018), an effect that was especially evident in female mice (Cabrera-Munoz et al., 2022). Although similar pro-social effects were observed also following wheel-running activity alone, they seemed less robust than

those exerted by EE (Calpe-Lopez et al., 2022b; Salam et al., 2009) and more dependent on the type of available exercise (Dubreucq et al., 2015).

Hence, despite its limited applicability in mouse studies on anti-social personality and aggressive disorders, exposure to EE could be employed to assess the potential therapeutic effects of environmental stimulation on the social deficits observed in genetic mouse models of ASD and NDDs with social dysfunction. These mouse studies may have important implications to understand the mechanisms underlying G×E interactions in the context of ASD, in particular in terms of the effects of behavioral stimulation in ASD patients, as it will be described in detail later.

3.3.2 Manipulations of maternal care

Despite its wide applications, one of the problems affecting the use of EE in mouse studies on G×E is related to its little applicability to early post-natal phases, since the exploitation of cages equipped with toys and running wheels is strongly limited in mouse pups by their motor and sensorial immaturity. In fact, the exposure of laboratory mice to the classical type of EE before weaning does not entail the neurobiological effects that are typically induced by the same post-weaning intervention (Kohl, 2002). Nonetheless, providing enhanced environmental stimulation during the early post-natal periods is of obvious critical relevance to the translational validity of preclinical studies on mouse models of ASD and related NDDs.

As the main component of the environment of an infant laboratory mouse is represented by its mother, a useful alternative strategy to promote early environmental enrichment consists of stimulating mother-infant interactions. This approach, by focusing on parent-infant relationships, may model more closely than classical EE the early behavioral interventions applied to children with NDDs (Dawson, 2008). This type of early environmental enrichment can be achieved by stimulating mouse pups by housing two lactating dams and their litters together, a procedure also known as “communal nesting” which induces long-lasting beneficial brain and behavioral effects in WT mice (Branchi, 2009). Among these, increased social interest and improved inter-male aggressive behaviors were described in adult mice following communal nesting (Branchi et al., 2006; D'Andrea et al., 2007), thus supporting the translational value of early enrichment as a therapeutic approach. In order to avoid the nutritional confounding factor intrinsic to the communal nesting paradigm, the maternal enrichment (ME) approach has been proposed as an alternative model of early EE. In this case, mouse pups are housed only with an additional non-lactating female from birth until weaning (D'Amato et al., 2010), thus receiving enhanced maternal care, but unaltered nutritional support (D'Amato et al., 2010; Heiderstadt et al., 2014). This ME has also shown to exert long-term neurobehavioral effects in WT mice (D'Amato et al., 2010).

Another strategy to manipulate the early maternal environment, is cross-fostering (CF), i.e., the procedure based on pairing mouse pups to a different mother than the natural one. This procedure has been often used to differentiate the role of pure genetic factors from those related to the maternal environment; for instance, several studies on strain behavioral differences have investigated their persistence after CF with dams of a different strain, and the same approach has been adopted to identify the genetic origins of the behavioral phenotypes of selected mouse models of ASD, e.g., the BTBR (Yang et al., 2007) or the *Fmr1*-KO (Zupan and Toth, 2008) lines. When repeatedly applied during the first post-natal days, cross-fostering has also been used to model early exposure to stress/environmental adversity, since it produces long-term behavioral impairments in WT mice (Di Segni et al., 2019; Lo Iacono et al., 2021; Luchetti et al., 2021; Luchetti et al., 2015; Ventura et al., 2013).

Similarly, disrupting mother-infant interactions through periods of maternal separation (MS) is known to induce dramatic long-term behavioral effects in rodents (Millstein and Holmes, 2007; Szyf et al., 2007; Tractenberg et al., 2016). MS, typically implemented by 3h/day pup separation during the first two post-natal weeks, is also able to reduce social interactions and to induce social withdrawal in adult rodents (Franklin et al., 2011; Maciag et al., 2002; Niwa et al., 2011), although some discrepancies were reported across studies (Calpe-Lopez et al., 2022a; Giachino et al., 2007; Hulshof et al., 2011; Toth and Neumann, 2013; Tsuda et al., 2011). Similarly, MS stimulated aggressive behaviors in adult female (Veenema et al., 2007) and male (Kim et al., 2023) mice, but the promoting effects on mouse intermale aggression were not consistently observed (Reshetnikov et al., 2020; Tsuda et al., 2011; Veenema et al., 2007).

3.3.3 Social isolation

The lack of social stimulation/interactions is known to represent a major component of environmental adversity and a precipitating factor in a variety of neuropsychiatric disorders. An impressive number of studies have investigated the effects of social isolation (SI) in laboratory rodents across the last decades; most of this research work has implemented SI starting at weaning age (at 3 weeks of age), typically for at least 4-6 weeks (Geyer et al., 1993; Pietropaolo et al., 2008a; Weiss and Feldon, 2001), thus allowing to exclude confounding manipulations of mother-infant interactions and to include the adolescent phase, which is critical for the development of social behaviors and the related brain mechanisms in rodents (Laviola and Terranova, 1998; Spear, 2000, 2004; Terranova et al., 1993; Terranova et al., 1998).

In comparison to group-housed controls, SI produces a range of brain and behavioral changes in mice [commonly referred to as the “isolation syndrome” (Valzelli, 1973)], that may be linked to clinically relevant human psychopathological traits. The latter included hyperactivity (Abramov et al.,

2004; Benton and Brain, 1981), enhanced sensitivity to amphetamine (Wilmot et al., 1984), deficits in sensorimotor abilities (Varty et al., 2006) and social withdrawal (Bouet et al., 2011); since these behavioral alterations were accompanied by an hyperdopaminergic brain profile (Wilmot et al., 1986) and they resembled some of the alterations observed in schizophrenia, SI has been for a while proposed as an environmental model of this NDD (Van den Buuse et al., 2003).

Besides its traditional use in schizophrenia research, SI is obviously a powerful modulator of social behaviors and has therefore been commonly used to induce social stress in rodent models of neuropsychiatric disorders. SI affects for instance social interest, inducing increased social motivation at short-term and social withdrawal at long-term (Arakawa, 2018; Bouet et al., 2011). SI also modified social communication, e.g., altering the qualitative characteristics of USVs emitted by adult male mice as well as their association with social exploration (Chabout et al., 2012; Keesom et al., 2017), without effects on adult USVs in female mice (Screven and Dent, 2019). Finally, social isolation increased aggression especially in male mice, an effect that has been among the first to be described within the SI syndrome and that seems related to the territoriality and neuroendocrine changes induced by SI (Brain et al., 1971; Ely and Henry, 1974; Harding and Leshner, 1972; Sofia, 1969; Valzelli, 1973; Weltman et al., 1968). Furthermore, the lack of social experiences with male conspecifics seems a critical factor for the SI effects on intermale aggression: indeed, male mice housed from juvenile age with a female had the same aggressive profile of SI males, while 1-month housing with a male mouse was able to prevent the SI-induced hyper-aggressiveness (Crawley et al., 1975). Indeed, SI is commonly employed as a standard experimental procedure to test intermale aggression in laboratory mice (Miczek et al., 2001); although most studies have applied 3-4 weeks of pre-testing SI, short SI, even limited to 24hs, are sufficient to induce a resident state in male mice, and therefore to allow measuring aggressive behaviors towards an intruder (Thurmond, 1975).

3.3.4. Stress exposure

Environmental adversity in human studies commonly coincides with exposure to stressors or stressful experiences. Hence, a common experimental approach to model environmental adversity in laboratory rodents consists of the unpredictable stress exposure [UMS, (Mineur et al., 2006; Mineur et al., 2003; Willner, 2005)]. This procedure, combining multiple stressors of different nature (e.g., wet litter, inclined home cage, light cycle disruption, restraint stress, predator odor), seems the most suitable to model human stressful experiences and has the advantage to minimize habituation and exclude pain or nutritional effects (Campos et al., 2013; Imbe et al., 2006). Nonetheless, other studies have employed protocols of chronic stress based on the repeated occurrence of the same stressor, commonly restraint [for a discussion on the comparison between the two procedures, see for example (Campos et al., 2013; Imbe et al., 2006)].

Several lines of research have investigated the effects of chronic stress exposure when applied during early phases, e.g., prenatally: in most existing preclinical studies [reviewed in (Sandi and Haller, 2015; Weinstock, 2008)] stress exposure was implemented during the last week of gestation of the dams, as this phase is a preferential target to induce long-term brain and behavioral modifications in the offspring, because of its high environmental and stress sensitivity (Enayati et al., 2012; Misdrahi et al., 2005). Prenatal stress is known to induce marked long-term behavioral alterations in wild-type rodents, including cognitive, emotional, motor and social abnormalities [reviewed in (Sandi and Haller, 2015; Weinstock, 2008)].

Nonetheless, the specific effects of prenatal or post-natal stress on social behaviors have often led to conflicting results, for instance, reporting reduced (Kiryanova et al., 2016) or increased (Reshetnikov et al., 2020) aggression in male mice or social avoidance/motivation in WT rodents of both sexes [reviewed in (Toth and Neumann, 2013)]. A large part of these discrepancies are due to methodological differences across studies, including the stress protocols, as well as the sex of the subjects. Several sex differences have indeed been described in the behavioral responsiveness to stress in rodents; these include differences in the severity of stress effects, but also in their specificity to selected behavioral domains (Sickmann et al., 2015; Sierksma et al., 2013; Weinstock, 2007).

3.4 The impact of gene x environment interactions on social dysfunction in mice

The effects of the environmental manipulations described so far have been evaluated in genetic mouse models of social dysfunction, such as aggressive and autistic-like behaviors (as summarized in Table 1). Here we reviewed preclinical evidence from research combining genetic and environmental manipulations, including only those studies where social behaviors (i.e., aggression, sociability, social interaction and ultrasonic communication) were assessed.

3.4.1 G×E in mouse models of aggression and anti-social personality disorder (ASPD)

As previously mentioned, several studies investigated the effects of environmental enrichment (EE) on intermale aggression in mice: some of these included the assessment of G×E by comparing different strains reared under enriched or standard conditions (Table 1). EE eliminated the strain differences in aggressive behavior displayed by 129/SVJ mice, displaying higher levels of aggression than B6 males (Abramov et al., 2008), in contrast to other non-social behaviors where inter-strain differences were instead accentuated by EE. This effect of EE was due to its tendency to decrease intermale aggression only in male 129/SVJ mice, thus suggesting that the effects of EE on aggression are strongly modulated by a genetic predisposition. This conclusion was supported by other studies showing that EE increased aggressiveness in inbred mouse strains typically considered among the most aggressive, i.e., the BALB (Giles et al., 2018), or the DBA/2J (Haemisch et al., 1994), but not in

docile ones, such as the ABG strain (Marashi et al., 2004). Furthermore, when the DBA/2J strain was directly compared to a less aggressive one, the CBA/J, EE increased aggressiveness in both strains, but changed the dominance relationships only in DBA/2J (Haemisch and Gartner, 1994). Following EE, the pattern of social organization shifted from groups with a single permanent dominant mouse typical of standard conditions to groups with a frequently changing dominant mouse and this EE effect was evident only in DBA/2J mice, where it was accompanied by an increase in corticosterone levels (Haemisch and Gartner, 1994).

The role of G×E in the expression of aggressive behaviors was confirmed by mouse models of anti-social personality disorder (ASPD) based on selective breeding approaches (Table 1). These studies demonstrated that social isolation (SI) was necessary to allow the expression of genetically-induced aggression, which was instead unaffected by the cross-fostering by non-aggressive mothers (Sluyter et al., 1995; Sluyter et al., 1996). When TA or TNA mice were group-housed from weaning until the age of 8 months, neither lines displayed aggression towards a submissive male; aggression emerged after one week of SI in the TA mice only, and increased exponentially during 8 weeks of adult isolation (Lagerspetz and Lagerspetz, 1971). Furthermore, when mice were given repeated encounters with a submissive male, the TNA lines were the only ones showing a time-dependent increase in fighting episodes, thus confirming that aggression can be learned, although within the limits which are genetically determined (TNA mice indeed did not reach at the last encounter the initial levels of TA animals). Interestingly, mice from the TNA lines were also the only one showing an increase in sexual behaviors across repeated encounters with a receptive female (Lagerspetz and Lagerspetz, 1971), suggesting that the expression of aggressive behaviors, shown by TA mice also in the sexual context, may represent an overall disadvantageous behavior. Interestingly, similar results were found when TA and TNA lines were exposed to mating mice during adolescence through a wire mesh placed within the home cage; indeed, this early exposure to odors/pheromones was able to increase aggression towards a receptive female later at adulthood, an effect that was more marked in TA mice (Sandnabba, 1994). Hence, these findings suggest that the genetic predisposition to develop anti-social behaviors can be modulated by both early and adult social experiences. Furthermore, they provide additional preclinical evidence to the hypothesis that sexual and aggressive behaviors may be inter-related and may be modulated by shared G×E (Zillman, 1984).

Finally, the role of G×E was investigated in a *MAOA* transgenic mouse line (Godar et al., 2016), characterized by the low expression of this enzyme and therefore closely mimicking the best identified genetic predisposition to develop ASPD in humans, as described in section 3.1. Early life stress, i.e., exposure to maternal separation combined with i.p. injections during the first 3 post-natal weeks, modelling parental neglect and physical abuse, increased aggression in the resident-intruder test in adult mutant mice only (Table 1). Interestingly, the first post-natal week seemed the most

critical to induce the G×E interactive effects on adult aggression; furthermore, early stress only during the first week was sufficient to induce increased home-cage aggression in adolescent mutants, again without effects on social interactions (Godar et al., 2016). While ineffective on aggressive behaviors, the mutation alone was able to decrease social approaches in the social interaction test both at adulthood and at adolescence, but this phenotype was unaffected by G×E (Godar et al., 2016). Hence, these findings provide with an example of a clear synergistic G×E, i.e., when the combination of the genetic factor with an environmental insult is necessary to induce the behavioral pathological phenotype, at least in its aggressive component; furthermore, these results suggest an intriguing potential dissociation between the social and aggression profiles of ASPD in terms of their modulation by G×E.

3.4.2 G×E in mouse models of ASD

Compared to ASPD, a large number of studies have investigated the impact of G×E on the pathological phenotypes of genetic mouse models of ASD (Table 1). These included modifications of the physical, social and maternal environment, which were combined with a variety of genetically-modified or strain-based mouse models (Table 1).

3.4.2.1 Environmental enrichment

Intermale aggression was again modulated by G×E, but this time in the *Dp(11)17/+* mouse model of Potocki–Lupski syndrome, a rare disorder caused by a duplication in 17p11.2 which is characterized in more than 80% of its cases by ASD symptoms. EE when applied at weaning, strongly mitigated adult aggression (Lacaria et al., 2012), i.e., a typical phenotype of this mutant line when raised in standard cages (Molina et al., 2008; Ricard et al., 2010). Furthermore, EE restored social novelty recognition in the 3-chamber test (and its variant, the partition test) in adult mutant mice, thus supporting the validity of “classical” forms of environmental stimulation in treating the ASD-like social phenotypes induced by the mutation (Lacaria et al., 2012). The behavioral effects of EE were accompanied by a rescue of the serotonergic imbalance found in selected brain areas of mutant mice, thus highlighting possible brain mechanisms involved in the observed G×E.

Opposite effects of EE on intermale aggression were described in another mouse model of ASD, i.e., *NL3(R451C)* mutant mouse line, carrying the autism-associated R451C mutation in the gene encoding the synaptic adhesion protein neuroligin-3 (*NL3*) (Burrows et al., 2020). EE enhanced sociability in the 3-chamber test in mice of both genotypes, as well as aggressive behaviors, without specifically affecting the aggressive phenotype displayed by *NL3(R451C)* mice. These findings therefore provide additional evidence supporting the view that both affiliative and aggressive social behaviors are overall vulnerable to changes in the physical environment (Burrows et al., 2020)

EE was also able to modulate the ASD-like phenotypes of an other mouse model of ASD, i.e., the *Pten* +/- mutant line, characterized by the haploinsufficiency of the Phosphatase and tensin homolog (*PTEN*) gene (Clipperton-Allen and Page, 2015). Loss-of-function mutations in this gene have been described in patients diagnosed with macrocephaly/autism syndrome (Buxbaum et al., 2007). EE, which was integrated with an additional daily session in a novel “play” arena containing objects, rescued the sociability deficits displayed by female mutants; male mutants did not show deficits in this test, but EE induced a lack of social preference in WT male mice (Clipperton-Allen et al., 2021). In the habituation/dishabituation task, consisting in the repeated presentation of the same social stimulus (habituation) followed by a novel one (dishabituation), male mutant mice showed a dishabituation deficit which was rescued by EE (Clipperton-Allen et al., 2021). Again, EE induced a dishabituation deficits in WT male mice. These data suggest that EE can rescue the deficits in social approach in female and social recognition in male *Pten* +/- mice. Interestingly, EE appears to alter normal patterns of social behavior in male WT mice, decreasing social interest and impairing social recognition. The authors hypothesized that the “detrimental” effects of EE in WT male mice may be related to the increased social instability potentially experienced in the enriched settings, but experimental data to support this hypothesis are missing. Interestingly, in females, EE also rescued the altered expression of pre-synaptic proteins vGluT1 (excitatory) and vGAT (inhibitory) observed in in the *Pten* +/- frontal cortex, thus restoring the excitatory/inhibitory (E/I) balance (Clipperton-Allen and Page, 2015). Additional data from males would be necessary to evaluate the potential sex-specificity of these brain effects of EE in mutant mice, thus supporting their role in underlying the behavioral results.

An exception to the efficacy of classical EE in rescuing ASD-like social deficits was provided by a study on NKO mice, i.e., brain-specific *Uba6* knock-outs. *Uba6* is a gene involved in ubiquitase activation, which is responsible for the selective degradation of abnormal proteins and play a critical role in brain development (Lee et al., 2015). EE was not able to rescue the sociability deficits displayed by NKO mice, while being housed in pairs with WT littermates did. The behavioral effects of paired housing were accompanied by epigenetic changes, i.e., alteration of histone acetylation in the amygdala of mutant mice. Nonetheless, the study did not include all proper control conditions, thus preventing for drawing definitive conclusions about the precise efficacy of the social versus physical enrichment components. Furthermore, the effects of pair housing were detected when this manipulation was started at PND 7, but not at adolescence (i.e., PND 28). Since social interactions are minimal at one week of age, it is possible that a sort of maternal enrichment/cross fostering procedure may instead have played a major role (Kim et al., 2019).

Therapeutic effects of EE were again observed in a mouse model of ASD based on strain differences rather than KO approaches, i.e., the BTBR mouse line. EE started at weaning was able to

increase sociability in adult BTBR mice, but not their lack of social novelty recognition in the 3-chamber test (Queen et al., 2020). Interestingly these effects were observed only in male mutants, when they were accompanied by increased BDNF hypothalamic expression, while both behavioral and brain effects were absent in females. Unluckily this study did not allow to fully assess the impact of G×E on BTBR ASD-like neurobehavioral phenotypes, because of the lack of comparison with sociable controls (e.g., B6 mice). Nonetheless, it supports the therapeutic impact of the stimulation of the physical environment in this mouse model of ASD; in this respect, the sex specific effect may not forcedly represent a limitation for the face validity of the model, because of the well-known higher occurrence of ASD in the male sex (Rapin, 1991).

In contrast to EE, physical exercise alone starting from the juvenile age was not able to rescue the adult social phenotypes of the BTBR mouse model. The availability of a running wheel during the juvenile phase indeed did not rescue the sociability deficits in the 3-chamber test displayed by adult BTBR mutants of both sexes, while it was effective on their altered nociception (Fairburn et al., 2022). However, it should be noted that in this study the control group was housed in the presence of partial cage enrichment, i.e., a plastic igloo, which could have played a critical role in reducing the effects of physical exercise. More importantly, the sample size of this study was rather low (n=4), and could have limited the emergence of behavioral effects of exercise, as well as sex differences. Further studies are therefore needed to better characterize the effects of wheel running on ASD-like social phenotypes in the BTBR mouse model.

Another type of EE, slightly different from the more typical paradigm used by Queen and co-workers (2020), was employed in another study on the BTBR strain (Binder and Bordey, 2023); this EE included not only the typical EE elements of wheel running and objects, but also an additional home cage providing a “family unit” where two dams (of the same genotype, BTBR versus B6) could raise together their pups until adolescence. Thus, this type of EE included a form of communal nesting and was meant to provide mice from birth until adolescence with a semi-naturalistic environment which may fulfill the “natural needs” of mice during their developmentl better than standard housing conditions. In this EE, mice were indeed found to gradually leave the original housing unit with age, thus mimicking the natural dispersal of juvenile mice observed in natural conditions. EE during the first 2 post-natal weeks did not affect the USV phenotypes of BTBR mice, but reduced USV duration, peak and fundamental frequencies in B6 pups (Binder and Bordey, 2023). EE rescued the sociability deficits displayed by BTBR mice the 3-chamber test at adolescence, i.e., PND 25, without inducing effects in B6 controls. All effects of EE were equally detected in mice of both sexes (Binder and Bordey, 2023); hence these data, compared to the previous ones by Queen et al. (2020), suggest that an early period of exposure may be critical for the effects of EE on female BTBR social phenotypes. Furthermore, the findings obtained from the semi-naturalistic EE environment suggest that the

meaning of the terms “standard housing” or “enriched environment” may need to be reconsidered. The standard (control) housing conditions applied to laboratory mice may indeed be considered as impoverished when compared to the dynamic and complex environments where wild mice live in. The latter conditions may therefore be more closely modelled by EE in laboratory mice, and enriched conditions in mice may better reflect the complex environment typical of human lifestyle. Binder and Bordey (2023) therefore suggest that standard conditions with their low environmental complexity may exaggerate or even induce the sociability deficits in BTBR mice, which may be genetically more sensitive to environmental deprivation than controls. It could be therefore hypothesized that standard housing conditions may lead to misinterpretations of the behavioral phenotypes of certain mouse models; therefore enriching the environment may simply correct a behavioral artifact rather than a true phenotypic feature of a mouse model (Binder and Bordey, 2023).

This hypothesis was not confirmed by the analysis of the social phenotypes of BTBR mice when housed in the Visible Burrow System (VBS) (Bove et al., 2018). The VBS also represents a semi-naturalistic environment, with male and female rodents of the same genotype housed together in an enclosure where a large open arena is connected to a continuously dark burrow system. The analysis of home-cage social behaviors demonstrated that BTBR mice performed less social behaviors and have a preference for non-social behaviors compared to B6 mice (Bove et al., 2018). Nonetheless, in this study the behavioral analyses were performed within the VBS and without comparison with standard housing controls, in contrast to the study by Binder and Bordey (2023). Another difference between these two studies on the effects of semi-naturalistic environments on BTBR social phenotypes is the age and duration of the exposure, since one study housed mice in the VBS at adulthood for 8 days (Bove et al., 2018), while the other from birth during almost 4 weeks (Binder and Bordey, 2023). Interestingly, when mice were housed in the VBS differences in their ASD-like brain phenotypes were also confirmed, with reduced GABA and increased glutamate concentrations detected in brain prefrontal cortex and amygdala regions of the BTBR mice compared to B6 controls, thus supporting the use of VBS to study deficits in social behavior and E/I imbalances in this ASD mouse model (Bove et al., 2018).

Furthermore, these findings suggest that the social deficits displayed by BTBR mice at adulthood and typically measured through their sociability towards a stimulus control mouse can be confirmed in social groups of the same genotype. This was not the case for another genetic mouse model of ASD, i.e., the *Fmr1*-KO line. This model recapitulates the X-linked mutation observed in FXS, and has been increasingly employed as a mouse model of ASD, since a strong link between these NDDs has emerged (Budimirovic and Kaufmann, 2011; Wang et al., 2010). *Fmr1*-KO mice showed ASD-like social phenotypes, e.g., reduced social recognition in the 3-chamber test, and deficits in

social interaction in direct tests with WT stimulus mice (Bernardet and Crusio, 2006; Kat et al., 2022; McNaughton et al., 2008; Pietropaolo et al., 2011). A recent study has analysed the behavior of adult *Fmr1*-KO mice within same-genotype colonies housed in a complex environment containing plastic igloos and found a markedly different social phenotype than the one observed in standardized behavioral tests (Giua et al., 2023). *Fmr1*-KO male mice indeed displayed higher levels of social interaction characterized by an increased tendency to physical contact, although with different social dynamics. However, with time and acclimation to the new environment, this behavior normalized, returning to levels similar to the control WT groups (Giua et al., 2023).

3.4.2.2 Social isolation

The effects of the social context on the behavioral ASD-like phenotype of the *Fmr1*-KO mouse model have been studied further by Heitzer and colleagues (2013). In this study, *Fmr1*-KO mice single housed from weaning until the age of 5-7 months displayed deficits in social recognition in a modified version of the 3-chamber test compared to their WT littermates. According to the authors' interpretation, these findings may suggest that SI does not differentially impact the behavioral phenotype of *Fmr1*-KO mice, since they displayed social deficits as in previous studies under grouped housing conditions. Furthermore, the authors hypothesized that SI may allow to detect more robust social deficits in adult *Fmr1*-KO male mutants, suggesting that inconsistencies across previous studies on the social behavioral phenotype of these mutants may be due to the variability induced by social grouping (Heitzer et al., 2013). Nonetheless, the lack of group-housed controls in this study strongly limits the strength of these conclusions.

The quality of social interactions, and not only their availability *per se*, seems to be a critical factor affecting the impact of the social environment on the social phenotypes of mouse models of ASD, as it has been demonstrated in the BTBR line. When BTBR mice of both sexes were housed from weaning until adulthood with B6 cagemates, their sociability deficits typically displayed when housed with cagemates of the same genotype became undetectable (Yang et al., 2011). Interestingly, these « therapeutic » effects of social grouping with B6 conspecifics were equally observed after 20 or 40 days, thus suggesting that the inclusion of the adolescent period, instead of the duration of the exposure, is a critical factor to induce the rescuing effects of this type of social enrichment on the social phenotype of BTBR mice. The effects of social grouping with B6 mice were observed on the sociability deficits displayed by adult BTBR mice, but not on their enhanced levels of self-grooming (Yang et al., 2011), thus supporting the view that social and repetitive domains may be independently modulated in ASD (Ronald et al., 2006). Intriguingly, both behavioral domains were unaffected by the maternal genotype, since both the low sociability and high-self grooming levels displayed by BTBR mice were unaltered by cross fostering with B6 dams (Yang et al., 2007). Interestingly, B6 mice

reared by BTBR dams did not display altered sociability, thus supporting the view that ASD-like social phenotypes are genetically determined, as previously described for ASPD mouse models (Sluyter et al., 1995; Sluyter et al., 1996).

When SI was applied in the BTBR mouse model of ASD, differential behavioral effects emerged on selected social phenotypes of BTBR and B6 controls. While social isolation increased scent marking behavior in male B6 mice in the absence of any social stimulus and reduced it in the presence of a different strain conspecific, in BTBR mice isolation did not induce any effect on scent marking. Scent marking was overall increased in BTBR mice already in the absence of social stimuli, but was unaffected by the presence of different social stimuli (Higuchi et al., 2023). These data indicate that male BTBR mice were less responsive to the presentation of social stimuli and the expression of social signaling responses, which was paralleled by blunted c-Fos responsivity and morphological changes in vasopressin neurons in selected brain areas (Higuchi et al., 2023). Hence, while adult male B6 mice adjusted their scent marking responses to the social characteristics of confronted opponents, BTBR males showed a poor ability to modulate their responses to encountered social conditions and this may be linked to altered functionality of the brain circuits involved in social recognition. It should be noted that social isolation was implemented here two weeks before testing, so at adulthood and not at weaning, as more typically done. Furthermore, the high levels of scent marking displayed by BTBR animals under grouped conditions may have prevented the detection of social isolation effects in these mice. Hence, further studies are needed to investigate the effects of SI on scent marking and other social behaviors in BTBR mice.

A more typical SI paradigm was applied to the *NL3(R451C)* mouse model of ASD (Burrows et al., 2017), previously described for its use in studies with EE (Burrows et al., 2020). Here, SI was applied starting at weaning until behavioral testing, occurring at 13-19 weeks of age. SI increased the social interest towards a receptive female in mice of both genotypes, while it did not affect mounting behavior (Burrows et al., 2017). Mutant mice displayed more mounting and aggression towards a female, and reduced exploration of female urines; the latter behavior was rescued by SI (Burrows et al., 2017). Overall, these results suggest a partial effect of SI in rescuing the pathological phenotypes of *NL3* mutant mice, although it seems especially effective on behaviors related to olfactory and pheromone communication.

3.4.2.3 Stress exposure

Besides social deprivation that can be preclinically modelled by SI, environmental adversity in mouse studies on G×E and ASD has been widely implemented through the unpredictable mild stress procedure (UMS), previously described in detail in section 4.3.4.

The behavioral effects of this procedure at adulthood have been evaluated and compared to those of simple restraint stress in the *Fmr1*-KO mouse model of ASD. In this study, 2 week-exposure to restraint stress at adulthood (but not to UMS) reduced social interaction in WT mice, without affecting the social deficits displayed by *Fmr1*-KO mice (Lemaire-Mayo et al., 2017). The behavioral unresponsiveness of KO animals to adult stress could be explained by some specific neurobiological abnormalities of these mutants: a previous study showed for instance an altered brain distribution of gluco-corticoid receptors in these mutants, with a drastic reduction in their hippocampal dendritic expression (Miyashiro et al., 2003). This may contribute to a marked reduced responsiveness to stress, in the presence of circulating corticosterone levels similar to those of the WT. Indeed, the same study on adult chronic stress showed no evidence for altered long-term hormonal response to stress in *Fmr1*-KO mutants (Lemaire-Mayo et al., 2017), in agreement with previous studies (Nielsen et al., 2009; Qin and Smith, 2008; Qin et al., 2011). It is also possible that the unresponsiveness to stress of *Fmr1* mutant mice may be related to a deficit in experience-dependent plasticity, leading to the absence of an adaptive response to stressors. This hypothesis, suggested also by previous authors (Qin et al., 2011), was supported by evidence showing that chronic stress induced changes in dendritic branching and morphology in brain areas crucial for behavioral control, i.e., the amygdala, in WT, but not in *Fmr1*-KO mice (Qin et al., 2011).

In line with this view, the social phenotype of *Fmr1*-KO mice was not affected by stress exposure even when applied prenatally, i.e., during a critical period for neurobehavioral development. Indeed, UMS applied one week before birth did not markedly alter the social interaction and USV phenotypes of mutant mice at either juvenile (Petroni et al., 2022) or adult ages (Petroni et al., 2022). The lack of short- and long-term effects of prenatal stress on the behavior of the offspring was instead mirrored by several effects on the behavior of the stressed dams (Subashi et al., 2023). Stress indeed decreased maternal care, drastically reducing especially licking/grooming of the pups (Petroni et al., 2022) and affected social interaction, but not USVs, in *Fmr1* mutant and WT dams (Subashi et al., 2023).

3.4.2.4 Manipulations of maternal care

The importance of maternal care in the expression of later social behaviors has been further investigated by studies applying maternal enrichment (ME) in mouse models of ASD. To our knowledge, the most widely used paradigm of ME used in this field of research has been so far the one adding one non-lactating female to the dam with its mutant and WT pups until weaning of the offspring. The first evidence of the therapeutic effects of this type of ME has been obtained from the *Fmr1*-KO mouse model (Oddi et al., 2015): as expected, this procedure strongly increased the maternal care received by all pups, and was able to induce a plethora of short- and long-term

neurobehavioral effects. While *Fmr1*-KO mice did not display deficits in USVs production at infancy, ME was able to reduce USVs in mice of both genotypes, thus suggesting a possible reduction in animals' overall emotional distress. Furthermore, ME rescued the social deficits displayed by *Fmr1* mutants at adulthood, a therapeutic effect that was confirmed on their altered hippocampal and amygdala dendritic spine phenotype (Oddi et al., 2015).

The effects of ME have been investigated also in another monogenic mouse model of ASD, i.e., in the μ -opioid receptor knock-out mouse line (*Oprm1*^{-/-}) (Garbugino et al., 2016), showing deficits in social behavior and communication starting from infancy (Becker et al., 2014; Moles et al., 2004). ME reduced USVs in all mice, in line with the hypothesis of reduced emotional reactivity to maternal separation, and did not rescue the USV deficits displayed by *Oprm1*-KO pups (Garbugino et al., 2016). At the juvenile age, ME rescued instead the sociability deficits displayed by mutant mice, and at adulthood increased the dishabituation in a social recognition task only in WT mice. These effects were equally observed in mice of both sexes; when mice were tested in a variant of the 3-chamber test measuring their preference for a WT versus a KO mouse, all mice avoided the mutant animal, and this effect was observed only in male mice, since females did not show any preference/avoidance (Garbugino et al., 2016). Hence, these findings underline the importance of the characteristics of the stimulus subject to assess intermale social behaviors, highlighting the aversive impact of social interactions between mutants mice, as confirmed by other results from the BTBR model (Higuchi et al., 2023).

Taken together, these findings from ME in mouse models of ASD suggest that increasing maternal-like physical contact is sufficient to strongly stimulate the pups, exerting several short- and long-term effects. These results agree with human data emphasizing the importance of maternal contact in early child stimulation: studies in pre-term babies have shown, for example, a correlation between maternal involvement and the infants' cognitive development during the first year of life (Wijnroks, 1998). Hence, ME represents a powerful tool to apply early stimulation in preclinical models of ASD and potentially other NDDs.

4. Critical discussion and conclusive remarks

Here we reviewed the available preclinical data from mouse models of ASPD and ASD showing the effects of G×E on social behaviors. As summarized in Table 1, overall these findings confirm that social interactions, either of affiliative or aggressive nature, are strongly modulated by G×E effects in mouse models as observed in humans. Nonetheless, animal data allow to investigate whether certain environmental components, e.g., social versus physical complexity, may have a differential impact on genetically-induced specific social alterations. Although differences in the type, duration and starting age of the environmental manipulations can be detected across the considered studies and different

manipulations were rarely applied in the same genetic model (Table 1), there are some common considerations that can be drawn concerning G×E impact on social dysfunction in mice.

An overview of the data suggests for instance that manipulating the physical environment through environmental enrichment (EE) allowed to strongly modulate genetically-induced social deficits in mouse models of ASD, with an overall therapeutic impact in multiple mouse lines. These effects seem somehow magnified by increasing the complexity of EE, as demonstrated by studies in the semi-naturalistic settings. The therapeutic effects of EE seemed related to the combination of exercise and increase object/environment exploration, although further studies comparing multiple housing conditions would be needed. Furthermore, social interactions are modified in the EE, as it has been shown specifically for inter-male aggression in male mice. EE in fact did not exert therapeutic effects in mouse models of ASPD, as it mostly exacerbated the occurrence of fighting episodes in male mice, probably due to the increased social instability of the enriched environment. These findings may actually highlight a limitation in the translational value of mouse studies on aggression, due to the high territorial nature of mouse species (Blanchard et al., 2003). The effects of EE on social interactions may represent a potential confounding factor; nonetheless, this limitation may affect almost all the environmental manipulations mentioned here, since changes in social interactions among cage mates may occur also following exposure to stressors, physical exercise or maternal enrichment. Hence, “secondary” modifications of social interactions in group-housed mice should be considered as an intrinsic characteristic of all most commonly used manipulations of the rearing environment of laboratory mice.

Social isolation (SI) appeared instead as the most powerful modulator of aggression, as it was the necessary condition for the expression of aggressive behaviors in certain mouse models, e.g., the TA lines and *MAOA* mutants. SI was instead less effective in modulating social phenotypes in mouse models of ASD, maybe because of the higher importance of the quality of social interactions which seems reduced within mutant groups and could therefore reduce the impact of social deprivation. Findings from the BTBR, *Orp1*-KO and *Uba6*-NKO mouse lines have indeed underlined the different relevance of social interactions among mutant versus WT mice, also suggesting the therapeutic impact of housing mutants with WT cage mates. This issue highlights an additional level of complexity of G×E interactions on social dysfunction, as it has been already suggested (Esposito et al., 2018). Several studies on ASD have supported the view that genetic mutations may induce an individual to engage in specific social behaviors that would additionally modify the surrounding environment. This so-called pathological self-generated environment can in turn induce, enhance or reduce the negative impact of the environment on the individual’s behavior (Esposito et al., 2018). For example, introverted subjects pursue less socially stimulating environments as compared to individuals who are more extroverted, thus in turn exacerbating the environmental impact on their

social phenotypes. This concept of self-generated environment may explain the effects of same-genotype social interactions in mouse models of ASD, and play an important role in G×E effects in ASD mouse models as in human studies (Esposito et al., 2018).

From another point of view, these results highlighted the relevance of social stimulation alone (through positive interactions with WT individuals) as a potential therapeutic approach to treat social ASD-like phenotypes. These effects of social stimuli seemed magnified when applied during early post-natal phase, as supported by the results showing the long-term positive effects of maternal enrichment (ME) on monogenic mouse models of ASD (Table 1). Hence, mouse data strongly support the need of early interventions focusing on physical and social stimulation to treat social dysfunction in ASD and related NDDs, an approach that is increasingly promoted in clinical practice. A developmental approach should indeed be encouraged in G×E studies of mouse models of social dysfunction: this research strategy, which is especially relevant to ASD preclinical models, should include also assessing the development of social behavior, encompassing the ontogeny of social behavioral patterns across infancy and adolescence.

Finally, these findings provide partial support to certain theories about G×E mentioned in initial sections of our review. For instance, the impact of SI on aggression in the MOAO and TA models supports a two-hit model for ASPD, since both genetic and environmental insults were necessary for the expression of the aggressive phenotype. The differential susceptibility hypothesis instead did not find a precise confirmation in the preclinical findings reviewed here, since few models were investigated in combination with both a stimulant and aversive environmental manipulation (Table 1). When this happened, as in the case of the *Fmr1*-KO mouse line, the obtained results did not demonstrate an enhanced sensitivity of mutant mice to both the positive and aversive environmental interventions, since ME rescued the social deficits, but prenatal stress did not affect them. Nonetheless, more studies on stress in other mouse models are necessary to support this conclusion.

The little availability of data assessing the impact of multiple environmental manipulations in the same or closely related mouse models of ASD represents indeed a major problem of preclinical studies on G×E on social dysfunction. This issue is especially evident for stress studies (Table 1), where only one mouse model of ASD was assessed, and is rather surprising, considering the importance of modelling environmental adversity in these type of preclinical research. Additional studies investigating the effects of stress, maternal separation, SI or EE indeed have been carried out in several mouse models of ASD, but they did not include the evaluation of social behaviors, focusing instead on emotional or cognitive phenotypes, and could therefore not be included in the present review. Future studies should therefore carefully avoid this major limitation, since social phenotypes

are well recognized as core identifying symptoms of ASD in mouse models, as in the clinical population (Crawley, 2007a).

Future mouse studies on G×E should also systematically include both sexes; the overview of the results provided in Table 1 clearly shows the overall limited use of female mice in studies on G×E and social dysfunction. The preferential use of male mice is somehow intuitive for studies on ASPD because of the specific focus on inter-male aggression; nonetheless, more data on female aggressive phenotypes will be needed to compare the role of G×E in this behavior which is highly relevant in the human population. Similarly, male mice have been most often employed in studies on ASD (with the exception of the BTBR strain, see Table 1), because of the higher prevalence of ASD in the male sex (Ferri et al., 2018). Nonetheless, human studies have suggested that the impact of G×E on social behaviors may significantly differ between sexes (Kendler et al., 2001; Kessler et al., 1985; Kim-Cohen et al., 2006; Kolla and Bortolato, 2020). A clear sexual dimorphism in the impact of G×E on behavioral expression in general has also emerged from human and animal findings (Torres-Reveron and Dow-Edwards, 2022). Converging lines of research therefore provide convincing evidence supporting the hypothesis that the interplay between genes, sex, and environmental factors may modulate disease susceptibility. Hence, further mouse studies are needed to assess the impact of Sex × G×E interactions on social dysfunction, as these will be of critical translational value to advance our understanding of the complex modulation of social behaviors.

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Table 1: Summary of mouse studies assessing the impact of GxE on social behaviors

Genetic manipulation			Environmental manipulation				Behavioural tests	Results	References	
Modelled disorder	Mouse model	Sex	Manipulated component	Description	Starting age	Duration				
ASPD	129/SVJ or B6	♂	Physical environment	Enriched environment (EE = SG+ NM + RW+ OBJ)	Weaning	7 w	Resident-intruder	EE reduced aggression only in 129/SVJ mice	Haemisch and Gartner 1994	
	DBA/2J or CBA/J	♂		Enriched environment (EE = complex space)	Adult	6 w	Resident-intruder+ home-cage aggression	EE increased aggression in both strains, but changed dominance and CORT levels only in DBA/2J	Haemisch and Gartner 1994	
	TA and TNA mouse lines	♂	Social environment	Social isolation (SI)	Adult	1, 2, 3, 6 or 8 w	Aggressive behaviour towards a submissive male	SI increased aggression only in TA mice	Lagerspetz and Lagerspetz 1971	
				Direct mating/fighting experience	Adult	5 encounters with either a submissive male or a receptive female	Sexual/aggressive behaviours towards a female or submissive male	Only TNA showed "social learning", i.e., increased aggressive and sexual behaviors following experience		
				Indirect mating experience	Weaning	10 daily exposure sessions	Sexual/aggressive behaviours at adulthood towards a female	Indirect experience enhanced aggression especially in TA mice	Sandnabba et al. 1994	
MAOA transgenic mice	♂	Maternal care/Stress	Early life stress (ELS = Maternal separation + daily IP)	PND 1	1, 2 or 3 w 1 w	Resident-intruder + social interaction Home-cage aggression at adolescence	ELS increased aggression in mutants, no effect on social exploration	Godar et al. 2019		
ASD	Dp(11)17/+	♂	Physical environment	Enriched environment (EE = SG+ NM + RW+ OBJ)	Weaning	5-9 w	Social dominance tube + 3-chamber (sociability) + partition test	EE rescued the altered aggression and sociability displayed by mutants and their brain serotonergic imbalance	Lacaria et al. 2012	
	NL3 (R451C)	♂		Enriched environment (EE = SG+ NM + RW+ OBJ) + explorative session in novel arena	Weaning	5- 9 w	3- chamber (sociability + social novelty) + resident intruder	EE increased sociability and aggression in both WT and NL3 mice	Burrows et al. 2017	
	Pten-KO	♂♀		Enriched environment (EE = SG+ NM + RW+ OBJ) + daily explorative sessions	Weaning	5 w	3-Chamber (sociability) + Social habituation/dishabituation	EE rescued sociability deficits in female mutants and social recognition abnormalities in males. In females, EE rescued the E/I cortical imbalance	Clipperton-Allen et al. 2021	
	Uba6-NKO	♂♀		Physical environment	Enriched environment (EE = SG + RW+ OBJ) / SG with WT mice	Not defined	Not defined	3-Chamber (sociability)	No effect of EE on social deficits in mutant mice	Kim et al. 2019
						PND 7	7-8 w		SG rescued social deficits	
						Juvenile	4-5 w		No effect of SG	
	BTBR	♂♀		Social environment	Enriched environment (EE = SG+ NM + RW+ OBJ)	Juvenile	17 w	3-Chamber (sociability + social novelty)	EE increased sociability, but not social novelty preference and hypothalamic BDNF in male BTBR mice.	Queen et al. 2020
					physical exercise (RW)	Juvenile	5 w	3-Chamber (sociability + social novelty)	RW did not rescue the sociability deficits of BTBR mice	Fairburn et al. 2022
					Semi-naturalistic enriched environment (EE = SG+ NM + RW+ OBJ) + ME	Birth	25 d	USVs (PND 6 and 12), 3-Chamber (sociability, PND 25)	EE altered USVs only in B6, rescued sociability deficits in BTBR mice of both sexes	Binder and Bordey 2023
					VBS (SG + complex space)	Adult	8 d	Home-cage monitoring	BTBR showed social deficits compared to B6 mice in the VBS	Bove et al. 2018
	Fmr1-KO	♂		Social environment	Complex environment	Adult	60 h	Home-cage monitoring	Increased social interaction in mutant mice compared to WT, with altered social dynamics in the complex environment	Giua et al. 2023
	Fmr1-KO	♂			Social isolation (SI)	Weaning	4-6 m	3-Chamber (sociability + social novelty)	Social novelty deficits in KOs compared to WT reared in SI	Heitzer et al. 2013
	BTBR	♂♀			SG with WT mice	Weaning	20d or 40d	3-Chamber (sociability)	BTBR reared with B6 cagemates from weaning did not show sociability deficits when adults	Yang et al. 2011
	BTBR	♂			Social isolation (SI)	Adult	2 w	Scent marking	Scent marking was increased by SI in B6, but not in BTBR mice	Higuchi et al. 2023
	NL3 (R451C)	♂			Social isolation (SI)	Juvenile	10- 16 w	Social interaction with a receptive female + test with female urines	SI increased social interaction in both WT and NL3 mice, rescued the deficits in female urine sniffing displayed by NL3 mutants	Burrows et al. 2017
Fmr1-KO	♂ ♂♀ ♂ ♀ dams	Stress	Unpredictable mild stress (UMS)		Unpredictable mild stress (UMS)/ restraint alone	Adult	2 w	Social interaction test + USVs	UMS reduced social interaction only in WT mice. No effect on KO social deficits	Lemaire-Mayo et al. 2017
					Prenatal (GD 14)	1 w	At juvenile age: Social interaction test + USVs	UMS did not affect the social phenotypes of KO mice, but modulated social interaction in WTs.	Petroni et al. 2022a	
					Prenatal (GD 14)	1 w	At adult and old ages: Social interaction test + USVs	No major effect of UMS in WT or KOs	Petroni et al. 2022b	
					Prenatal (GD 14)	1 w	Maternal behavior + Social interaction test + USVs	UMS reduced maternal care and modulated social interaction in WT and KO dams	Subashi et al. 2023	
Fmr1-KO	♂	Maternal care	Maternal enrichment (ME)		Prenatal (GD 14)	4 w	SI + USVs	ME Reduced USV number and duration in WT and KO pups; ME rescued social interaction deficits in adult KOs	Oddi et al. 2015	
Oprm1-KO	♂♀				Prenatal (GD 16)	4 w	pup USVs + 3-chamber test (sociability) + habituation/dishabituation	ME reduced USVs in all mice, rescued sociability deficits of KOs, increased social recognition only in WT	Garbugino et al. 2016	

ASPD = anti-social personality disorder; ASD = Autism Spectrum Disorder; Dp(11)17/+ =17p(11).2 duplication; Pten = Phosphatase and tensin homolog; Oprm1 = Opioid Receptor Mu 1; NL3= Neuroligin-3; R451C=Arginine to cysteine residue 451 substitution ; SG= social grouping; NM = nesting material; RW = Running wheel; OBJ = objects; i.p.= intraperitoneal injection; VBS = Visible burrow system; Weaning = 3 weeks; Juvenile = 4-6 weeks; Adult = older than 2 months; GD = gestational day; PND = post-natal day; USVs = ultrasonic vocalizations.

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