Abstract

This study examined the hypothesis that environmental enrichment (EE) would reduce autistic-like symptoms on three behavioral tasks in BTBR mice, an inbred strain used as a genetic model for autism. Based on our previous work with adversity induced symptoms of mental disorder in an outbred mouse strain, we predicted that EE would 1) increase preference for social stimuli in the 3-chamber apparatus, 2) enhance preference for home nest odors versus clean familiar shavings on the odor preference test, and 3) reduce anxiety-like behavior on the elevated plus maze. We found that EE 1) increased BTBR preference for a stranger mouse enclosure versus an empty enclosure, 2) did not influence BTBR scores on the odor preference test, and 3) did not influence anxiety scores for BTBR mice on the elevated plus maze. However, BTBR mice spent less time than CD-1 outbred controls on the open arm of the elevated plus maze, a finding that is consistent with evidence that anxiety is frequently comorbid with autism in humans. These results imply that different neural mechanisms underlie different autistic symptoms, since environmental intervention does not influence all symptoms equally.

Environmental Enrichment Improves Sociability in BTBR Mice, a Rodent Model for Autism

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Introduction

Autism Spectrum Disorder: Symptoms and Causes

Autism spectrum disorder (ASD) is a neurodevelopmental disorder that affects 1 in 59 (1.7%) individuals in the US (Baio, 2014). A diagnosis of autism is based upon behavioral abnormalities that include deficits in social behavior and communication as well as restricted, repetitive or inflexible interests or activities (American Psychiatric Association, 2013). The financial cost ASD is estimated to be $35 billion annually, and $3 million per case for a lifetime of care, with most of the cost resulting from adult care and lost productivity (Ganz, 2007). Treatment for cases of autism that can improve prosocial behaviors and communication could reduce the high costs of living with ASD by bolstering autonomy and productivity. However, the development of a comprehensive treatment has not yet been achieved largely due to the heterogeneity of behavioral symptoms in ASD diagnoses, as well the lack of identified biomarkers (Worley & Matson, 2012).

Research suggests that there are a variety of both genetic and environmental mechanisms underlying ASD pathology (Homberg et al., 2016). For instance, Sonuga-Barke et al. (2017) found that of the orphans that had been sent to the UK for adoption after experiencing extreme social and physical deprivation as infants while in the care of Romanian institutions for over six months, 20% met the diagnostic threshold for ASD later in childhood, compared to 2-11% of UK adoptee controls, raised under adequate physical conditions. Berg et al. (2016) found that in non-institutional settings, individuals with ASD were more likely to experience “1-3” and “4+” adverse childhood experiences (ACEs) – which includes traumatic maltreatment or familial stressors early in development – and less likely to have never experienced an ACE than a control group without any reported condition. In the same study, the authors found an association

between a greater severity of ASD symptoms (i.e., mild vs. moderate/severe) and an elevated risk of experiencing an ACE. The concept of environmental influence on mammalian development is receiving institutional support, in a technical report by the American Academy of Pediatrics, Shonkoff and Garner (2012) propose an "ecobiolodevelopmental framework" for academic and medical professionals that emphasizes the impact of early environmental experiences on epigenetic modification and down-stream effects on brain structure; as well as an emphasis on the impact of toxic stress on the development of learning and behavior impairments and disorders.

In terms of genetic underpinnings, Rosenberg et al. (2009) found a concordance rate of autism diagnoses in 81% of monozygotic twins and 31% of dizygotic twins; and Sandin et al. (2014) found elevated rates of concordance for both maternal and paternal half-sibling's, as well as cousins, versus a non-related control. There are also several dozen rare gene mutations that are concordant in 10-20% of ASD diagnoses (Geschwind, 2011). While there is no universal biomarker that has been discovered for ASD, there is evidence for them in the form of salivary micro-ribonucleic acid (miRNA); an epigenetic regulatory mechanism (Galiana-Simal et al., 2018). A team at SUNY Upstate tested saliva samples from individuals with and without a diagnosis of ASD and found 14 miRNA's (among hundreds) that significantly correlated with ASD diagnoses, and that when the target miRNA were used as a screening measure, the salivary measure performed with nearly twice the specificity of the current gold-standard questionnaire (Hicks et al., 2016). While these results are preliminary, the team is currently in the process of collecting more data and refining the salivary test itself (UpstateOnline).

Usefulness of Animal Models

Because the manipulation of the genome and environment of a human crosses ethical/legal boundaries, lines of inquiry are often pursued using non-human animal models.

Mice (*mus musculus*), are suited for this role due to comparable neurobiological organization (Vandamme, 2014). In addition to biological similarities, mice display complex social behavior, and psychological studies utilizing mice have investigated phenomena such as stress (Wang & Wu, 2005), anxiety (Peng, Hsieh, Lee, Lin, & Liao, 2000), neurodevelopmental disorders (Peça et al., 2011; Sigurdsson, Stark, Karayiorgou, Gogos, & Gordon, 2010), and neurodegenerative disorders (Jackson-Lewis & Przedborski, 2007).

The present experiments examined whether physical, sensorimotor enrichment of BTBR T+ tf/J (BTBR) strain mice, a genetic mouse model for autism, would influence autistic-relevant behaviors in that strain, namely responses to stimuli and to anxiety-producing situations, using wild-type CD-1 mice as a control strain. This design builds on previous work from our lab in which early-life adversity was produced by three hours of daily separation from the mother for the first two weeks of life in CD1 mice (Cornwell et al., 2018). Furthermore, two weeks of postweaning environmental enrichment (EE) prevented the deficits. However, the separation procedure did not increase anxious behavior, although enrichment reduced it (Diamond & Cornwell, 2019). We reasoned that even though the underlying mechanisms that produced the symptoms differed in the adversity versus genetically manipulated situations, environmental enrichment might prove to be an effective remedy for the genetically-related social deficits, because that had been the result for the adversity-induced procedure. In contrast, we predicted that strain and housing effects on anxious behavior might follow a different pattern, since adversity had not influenced this type of behavior in our previous work with CD-1 mice.

There have been only two studies of environmental intervention to remedy symptoms of autism in genetic animal models, both have used the BTBR strain. Reynolds, Urruela, and Devine (2013), found that 30 days of physical enrichment for adult BTBR mice significantly reduced the

time spent self-grooming versus a BTBR control group. The second study by Yang, Perry, Weber, Katz, and Crawley (2011), found that BTBR mice who were placed in home cages at weaning with same-sex C57BL/6J (or B6) mice and tested during adolescence demonstrated a significant preference for stimuli produced by novel conspecifics on the 3-chamber apparatus for both male and female mice. This preference was not observed in standard reared BTBR control groups. This social enrichment is distinct from physical enrichment since it includes more animals per cage as well as cross-weaning with more sociable strains. The current study focused solely on physical enrichment. This type of environmental intervention has not been used previously to examine responses to social stimuli in animal models for ASD.

The present study used the same tasks as our previous early-life deprivation experiments i.e., the 3-chamber apparatus to test sociability, a two-choice situation to test social odor preferences, and the elevated-plus task to test anxiety-like behaviors. In our previous work, CD-1 mice that received maternal separation (MS) did not show a preference for a potentially helpful stranger mouse on the 3-chamber apparatus, similar to the BTBR strain (Moy et al., 2007). Environmental enrichment following maternal separation resulted in scores similar to CD-1 control mice on this task (Cornwell et al., 2018). We therefore predicted that enriched, but not normally reared BTBR animals would display a preference for the stranger's enclosure.

In mice and other rodents, social communication is in part accomplished though odor discrimination (Crawley, 2007). In our previous experiments, CD-1 mice that were subject to maternal separation did not show a preference for nest odors versus clean hardwood shavings on the two-choice odor preference test; while mice exposed to maternal separation and subsequent enrichment demonstrated a preference for nest odors, similar to CD-1 control mice (Cornwell et al., 2018). These results seem similar to data from a study in which BTBR mice were unable to

discriminate between own nest and other nest shavings (Yang et al., 2012). On the basis of these previous findings, we predicted that BTBR mice reared under standard conditions would not demonstrate a preference for nest odors over clean hardwood shavings, but that enriched BTBR mice and CD-1 controls would demonstrate a preference for nest odors.

Anxiety symptoms and disorders are not diagnostic of ASD, but are comorbid in 40-84% of ASD cases (Muris, Steerneman, Merckelbach, Holdrinet, & Meesters, 1998; van Steensel, Bögels, & Perrin, 2011). In previous work from our lab (Diamond & Cornwell, 2019), maternal separation did not influence open arm time scores on the elevated plus maze for CD-1 mice that had received maternal separation versus standard-reared controls. Therefore maternal separation resulted in deficits specific to sociability and communication, and not a broader anxiety phenotype. An unpredicted result was that enrichment of both maternally separated and standard control groups significantly decreased anxiety-like behavior (Diamond & Cornwell, 2019). We therefore predicted that BTBR animals will react similarly to CD-1 mice on the elevated plus maze, and that enrichment would reduce anxiety scores for both strains.

Genetic Approaches to Animal Models of Disease

In general, genetic models of pathology are advantageous in experimental paradigms because genetic variability can be constrained, and are derived from either inbred or transgenic paradigms. The BTBR strain is a result of inbreeding via the forward genetics approach, by which mice are selectively bred and behaviorally tested until a target abnormality is observed and can then be investigated to a greater extent (Takahashi, Pinto, & Vitaterna, 1994). Transgenic strains are obtained via the opposite mechanism using reverse genetics, where the

genome is manipulated directly with the goal that there will be a development of particular abnormality (Takahashi et al.,1994).

There are limitations to the reverse genetics approach, as well as certain advantages in implementing an inbred strain in research. For example, to start a colony of BTBR mice costs roughly $600 (Jackson Laboratory, 2018); furthermore, to maintain said colony requires that offspring are subsequently able to be inbred from three-to-six months of age, and so on. Conversely, creating a transgenic colony requires not only complex equipment and training to generate a genome of interest, but also costly genotyping procedures to effectively sort the offspring by their genetic makeup. An alternative solution could include requesting the creation of a particular transgenic strain through the University of Pennsylvania's Perlman School of Medicine (specifically, the Transgenic and Chimeric Mouse Facility), which prices "standard transgenic services" at upwards of $6,000 per strain (Charge for Services, n.d.). This is in addition to the risks observed in developing mice, which have been noted to include sickly animals and animals that begin to die before or during adolescence (Han et al., 2012), making it difficult to track pathological symptoms and treatments into adulthood and old age. One could also make the argument that mouse models for autism that are sickly and/or have a severely attenuated lifespan do not meet the first type of validity needed for an appropriate animal model (i.e., face validity) as described by Chadman and Guariglia (2012); because while a diagnosis of autism is associated with a reduced lifespan (roughly 62 years for males, and 61 years for females), said individuals are expected to live well into adulthood (International Economic, 2015; Shavelle, Strauss, & Pickett, 2001).

BTBR as a Model for Autism

The BTBR is an inbred mouse strain that has gained popularity as a model for autism over the last 20 years. BTBR mice were first utilized in studies of obesity due to an increased likelihood of rapid weight gain during a specific developmental period (Chadman & Guariglia, 2012). Despite an increased susceptibility to obesity in cases of ASD, the BTBR strain was not considered as a potential model for autism until it was included in a study by Moy et al. (2007), who tested 10 inbred strains on assays of sociability, preference for social novelty, and rigidity of spatial learning abilities. Moy and colleagues selectively found deficits in sociability, a core feature of ASD, in BTBR mice; concluding that it was most appropriate candidate for an inbred model for autism of the 10 strains included in the study. On the basis of these tests and later studies, Chadman and Guariglia (2012) note that BTBR mice match the three major types of validity that are necessary for an animal model; 1) face validity - or similar diagnostic and comorbid behaviors, 2) construct validity - or similar pathological backgrounds, and 3) predictive validity - or the ability for treatment effects to be reproduced across species. BTBR behavioral abnormalities that support these conclusions are described below.

BTBR: behavioral features

1. Social Behavior

Impairments in sociability behaviors is a diagnostic feature of ASD and analogous impairment is seen in BTBR behavior. Moy et al. (2007) found that BTBR mice did not show a preference for a stranger mouse enclosure on the 3-chamber apparatus. When compared to B6 mice, McFarlane et al. (2008) noted that juvenile BTBR mice display fewer social behaviors such as "social grooming, nose-to-nose sniffing, and push over/crawl under". Similarly, when Defensor et al. (2011) (as cited in Chadman and Guariglia, 2012) tested adult B6 and BTBR mice, pairs of BTBR mice demonstrated interactive behaviors to a lesser extent than pairs of B6

mice. Based on previous work, we predicted that environmental enrichment would increase sociability behavior on the 3-chamber apparatus for BTBR mice.

2. Communication

Olfactory deficits have been identified in some cases of ASD, as well as with the BTBR strain. However, olfaction is an essential aspect of social communication in rodents and therefore disruption of the olfactory system of a mouse model is disproportionately more consequential to features of social communication than is the case with humans (Bennetto, Kuschner, & Hyman, 2007; Chadman & Guariglia, 2012). the BTBR stain does not display general anosmia, Moy et al. (2007) found that BTBR mice were able to find buried food pellets with similar efficacy as other inbred strains. However, on the olfactory habituation-dishabituation test Yang et al. (2012) found that while habitation to non-social odors was similar to a B6 control, BTBR mice were not able to discern odors from different mouse cages. The delayed onset of social communication is diagnostic of ASD (American Psychiatric Association, 2013). Mice aurally communicate using ultrasonic vocalizations, there is evidence that BTBR mice, both juvenile and adult, exhibit a narrowed frequency range or less frequent utterances compared to B6 mice (Scattoni,Gandhy, Ricceri, & Crawley, 2008; Scattoni et al., 2011). Based on our maternal separation work with CD-1 mice, we predicted that BTBR mice would show deficits in social odor preferences that environmental enrichment would prevent.

3. Repetitive Behaviors

Restricted, repetitive or inflexible cognition and behavior is a diagnostic criterion of ASD (American Psychiatric Association, 2013). In mouse models this autistic criterion is met by excessive repetitive self-grooming (Reynolds et al., 2013). Reynolds et al. (2013) found that

BTBR mice preformed more self-grooming behavior than B6 control and that post-weaning environmental enrichment significantly reduced this behavior. The current hypothesis of this paper was that would reduce the other two core diagnostic symptoms of this genetic model for ASD.

4. Anxious Behavior

Anxiety symptoms and/or disorders are not a diagnostic of ASD but are comorbid in 40% cases (Van Steensel, F. J., Bögels, S. M., & Perrin, S., 2011). BTBR animals have shown inconsistent results in that they display hypo-anxious behavior on the elevated plus maze and the 'light-dark box test' but evidence of an increased reaction to predator stress (Chadman, 2011; Chadman & Guariglia, 2012). The overall inconsistency in defining anxiety behavior of the BTBR mouse could potentially be due to the control strain it is compared to, which is discussed below.

5. Cognitive Abilities

Intellectual disability (ID) is comorbid in 50-70% of autism cases, and consists of impairments to learning and memory systems (American Psychiatric Association, 2013; Matson & Shoemaker, 2009). In general, BTBR mice tend not to display learning impairments on simple tasks compared a B6 control, although there is evidence that BTBR do preform worse on complex tasks involving higher-order executive function (Chadman & Guariglia, 2012). However, a comprehensive characterization of BTBR learning and memory features has not been reached and should receive further investigation.

6. Sensory/Motor Abilities

BTBR mice show sensory impairment such as reduced sensitivity to a hot surface, leading to altered performances on tasks that require cued or contextual fear conditioning (Chadman & Guariglia, 2012; Silverman, Tolu, et al., 2010). This sensory abnormality will not create a confound for any of our behavioral tests. It is also a noteworthy analog to symptoms experienced by individuals with ASD, such that cases are highly comorbid with sensory integration issues (Myles et al., 2004).

Compared to several inbred controls, BTBR strain mice were observed to show to reduced latency to falling on the rotarod task which is postulated to be due to uncoordinated motor movements. Additionally, the BTBR strain did demonstrate heightened locomotion in open field task, indicative of hyper-activity. Regardless of these motor deficits, BTBR mice are generally thought to be capable of adequate performance on behavioral tests involving physical exploration (Chadman & Guariglia, 2012). Furthermore, these motor characteristics represent a feature of face validity for the BTBR model. The prevalence of comorbidities involving hyperactivity are seen in roughly one- third of ASD diagnoses (Simonoff et al., 2008). Also, uncoordinated motor movements due to atypical gait has been noted in ASD (Rinehart et al., 2006).

BTBR: neruo-anatomical and -physiological features

The BTBR strain is noted for a complete absence of the corpus collosum as well as a greatly reduced hippocampal commissure (Wahlsten, Metten, & Crabbe, 2003). These morphological distinctions are a result from an X-linked dominant inheritance, a commonality to other known X-linked disorders in humans that result in an autistic phenotype,

such as Rett and Fragile-X syndromes (Amir et al., 1999; Chadman & Guariglia, 2012; Verkerk et al., 1991). Although these BTBR-specific abnormalities are not consistently observed in individuals diagnosed with ASD (namely the complete absence of the collosum), there is considerable evidence that human cases of the disorder present a corpus collosum that are smaller in size and malformed at sublocations (Casanova et al., 2011; Egaas, Courchesne, & Saitoh, 1995).

In rodent and human brains alike, neurogenesis is observed in the sub granular zone of the hippocampus throughout the lifespan (Kempermann, Song, & Gage, 2015; Song et al., 2016). Reduced hippocampal neurogenesis is noted in BTBR mice (Stephenson et al., 2011). In humans, low rates of hippocampal neurogenesis have been shown to impact cognitive function as well as exacerbate depressive and anxiety symptoms, all of which are comorbid symptoms of ASD (Sahay & Hen, 2007; Trejo, Llorens-Martin, & Torres-Alemán, 2008). there is also evidence that neurogenesis deregulation occurs in the hippocampus as well as other localities in the brains of individuals diagnosed with ASD, although more research is needed in this area (Wegiel et al., 2010).

BTBR: neuroendocrinological features

Counterintuitive to their reported hypo-anxious affect, the BTBR mouse produces elevated concentrations of the primary stress hormone, corticosterone (or CORT) (Silverman, Tolu, et al., 2010). Chadman and Guariglia (2012) offer that the high CORT levels but low anxiety behaviors could be due to a disruption in the information feedback loop of the hypothalamic-pituitary-adrenal (HPA) axis which regulates the physical response to perceptual stress, but it is only speculative. Within ASD research, there are mixed findings in regard to

cortisol (the human equivalent of corticosterone) production. Levine et al. (2012) found that cortisol levels of children with autism were near baseline after a socially stressful task, but had significantly increased for a typically developing control group. Although the case is opposite for BTBR mice, Levine et al. (2012) does concur that the effect could nonetheless be due to dysregulation of the HPA-axis.

BTBR: psychoneuroimmunological features

Elevated CORT (which often have an anti-inflammatory effect) in BTBR mice upregulate the production of typically pro-inflammatory cytokines of the immune system, resulting in severe inflammation of brain tissue (Careaga, Schwartzer, & Ashwood, 2015; Sorrells & Sapolsky, 2007). Chadman and Guariglia (2012) argue that this may in-part be responsible for atypical behavior of BTBR mice. In ASD, "widespread changes" are observed in the immune system, and inflammation is observed in the brain as well as the periphery; there is also evidence that cytokine presence (and therefore inflammation) positively and consistently correlates with the severity of behavioral impairment in subjects with ASD, as well as existing in significantly higher concentrations than control subjects (Ashwood et al., 2008, 2011; Careaga et al., 2015).

Environmental Enrichment: background & rationale

Environmental enrichment has been studied using rodents since the mid-twentieth century and observed to influence an array of behavioral and biological modalities. Beginning with an experiment by Donald Hebb in 1947 (of Hebbian plasticity notoriety) and utilizing learning tasks (via maze learning) on lab-reared vs. home-reared rats, Hebb found that early life enrichment, in this case home-rearing of rats, resulted in improved scores on maze learning tasks

in adult mice (Brown & Milner, 2003). Brown and Milner (2003) conclude that, regarding enrichment:

> "[Hebb's] ideas formed the basis of one of the most powerful concepts in developmental psychology, leading to the establishment of 'early start' [programs] to enrich the experiences of underprivileged children in reading, writing and mathematical abilities, and in music, sports and art... [Hebb's ideas] still influence research today."

From there, Marian Diamond and a team from UC Berkeley spent some decades detailing behavioral effects of enrichment on rat models (Diamond, Johnson, & Ingham, 1975; Diamond, Krech, & Rosenzweig, 1964; Globus, Rosenzweig, Bennett, & Diamond, 1973).

Contemporary research efforts involving physical enrichment are broad and abundant in terms of the species being examined. For example, enrichment effects have been observed in species such as rats, mice, and array of captive (ex., chimpanzees, gorillas, leopards) and domestic (ex., cows, cats, chickens) animals. (Benaroya-Milshtein et al., 2004; Lazarov et al., 2005; Leggio et al., 2005; Newberry, 1995; Wells, 2009). There is also literature detailing clinical enrichment efforts specific to ASD. Woo et al., (2015) found that a treatment of sensorimotor enrichment for children with a diagnosis of ASD led to improved scores on cognitive and sensory integration tasks. The paradigm used by Woo et al. (2015) was directly inspired by enrichment effects on BTBR mice from Reynolds et al. (2013), involving the effect of physical enrichment on repetitive behaviors in BTBR mice. While initial results from ASD enrichment protocols appear promising, translational research is still in its infancy. Examining enrichment effects on sociability, social communication and anxiety behaviors using the BTBR model for autism may provide evidence for further clinical investigation.

Environmental enrichment is the topic of an ongoing discussion regarding its role in research protocols that is outlined in the Science Magazine article, "The Happiness Project" (2018). While one camp of researchers including Joseph Garner, a behavioral scientist at the Stanford Medical Center, believes that animals are being controlled to the point where they are "no longer useful", and argues that, “If we want animals to tell us about stuff that’s going to happen in people, we need to treat them more like people” (Grimm, 2018). The view from the other camp can be encapsulated by statements made by John Crabbe, a behavioral geneticist at the Oregon Health & Science University who does not think that environmental enrichment should not be the new standard environment for mice because its benefits cannot yet be generalized for all pathologies: “If you show it works in tumor studies, I have no trouble with it being the guideline for tumor studies ... but don’t generalize it to psychiatric disease” says Crabbe (Grimm, 2018). Evidence to support our experimental hypothesis would help to broaden the psychiatric applicability of environmental enrichment.

Environmental Enrichment: behavior

In addition to enrichment effects on sociability observed previously in our lab, Pietropaolo et al. (2004) found that physically enriching wild-type CD-1 mice resulted in reduced aggressive social interaction behavior versus both a control condition and a social enrichment condition. Furthermore, in a study by Morley-Fletcher, Rea, Maccari, and Laviola (2003), prenatal stress of wild-type rats resulted in lowered social play behavior and that early life environmental enrichment following prenatal stress was able to rescue social play deficits.

Hendershott, Cronin, Langella, McGuinness, and Basu (2016) investigated anxiety-like behaviors in response to enriched vs. standard housing using a B6 mouse. They found that mice

who had received environmental enrichment demonstrated lower anxiety scores on the elevated plus maze, in terms of a reduced latency to enter the open arm well as more frequent entries into the open arm. Using wild-type rats, Francis, Diorio, Plotsky, and Meaney (2002) found that maternal separation resulted in heightened anxiety scores on the open field test, and that subsequent enrichment was able to lower anxious behavior to that of controls.

Environmental Enrichment: neurobiology

As noted earlier, BTBR mice display reduced hippocampal neurogenesis. Kempermann, Kuhn, and Gage (1997) found that female B6 mice that received enrichment demonstrated hippocampal neurogenesis at nearly twice the rate as a control condition that was housed in standard conditions. In the same study, the group found that the volume of the hippocampi of enriched mice were significantly greater than those of the control group. Olson, Eadie, Ernst, and Christie (2006) conclude that, in adult humans, environmental enrichment has "consistently been shown to increase adult hippocampal neurogenesis and improve spatial learning ability".

In addition, The BTBR strain displays a hippocampus that is both displaced and malformed as a result of agenesis of the corpus collosum, which may impact their ASD- like phenotype (Stephenson et al., 2011). Furthermore, a diagnosis of ASD been associated with a reduction in hippocampus size (Raymond, Bauman, & Kemper, 1995; Saitoh, Karns, & Courchesne, 2001). Research has shown that environmental enrichment using B6 strain mice resulted in hippocampi that were significantly more dense and larger by volume compared to control mice reared in standard caging (Faherty, Kerley, & Smeyne, 2003).

N-methyl-D-asparate receptors (NMDAR) are heavily implicated in tasks of learning and

memory, and one study found that creating a transgenic NMDAR-knockout mouse model produced an ASD-like phenotype (Saunders et al., 2013). Another study utilizing a similar NMDAR-knockout model found that mice who had undergone environmental enrichment displayed a higher density of dendritic spines in the pyramidal cells of the hippocampus than knockout mice raised in standard conditions (Rampon et al., 2000).

Environmental Enrichment: neuroendocrinology & immunology

Aspects of autistic behavior, both in model organisms as well as human diagnoses, is thought to be impacted by the neuroendocrine and immune systems. As noted in the rationale, both ASD and autism models have been observed to display abnormal CORT levels, as well as increased inflammation due to CORT-cytokine feedback. Furthermore, said inflammation is greater in individuals with ASD vs. non-ASD controls, and correlates with degree of behavioral impairment (Ashwood et al., 2011; Careaga et al., 2015; Chadman & Guariglia, 2012). This is in addition to the observation that chronic elevation of CORT itself can be toxic, typically damaging cells in the hippocampus due to metabolic dysregulation (Sapolsky, 1986). Both elevated levels of CORT and inflammation are noted in the BTBR strain, which is thought to mediate some of their abnormal behaviors (Chadman & Guariglia, 2012). Environmental enrichment has been shown to reduce levels of CORT to normative levels in wild-type rats after early life maternal separation, concomitant with a reduction in anxiety-like behaviors on the elevated plus maze (Francis et al., 2002). This also suggests that inflammation may have also been reduced after enrichment, although only speculatively. Shilpa, Bhagya, Harish, Bharath, and Rao (2017) demonstrated that wild-type male rats that were subject to chronic immobilizing stress (CIS) resulted in reduction of glucocorticoid receptors (i.e., CORT receptors) in the hippocampus, therefore dysregulation of the HPA-axis and increased anxiety-like behavior on the elevated plus

maze and open field tests; and that subsequent enrichment was able to significantly reduce anxiety scores on both assays as well as restore glucocorticoid receptor concentrations to that of the control conditions. Although our experiments do not include measurements of CORT or cytokine levels directly, one could speculate that a reduction in anxiety-like behavior as a function of environmental enrichment would lend evidence to CORT and/or inflammation being influenced in a protective way.

Use of CD-1 as a control.

The CD-1 strain is an outbred, wild-type strain with a greater degree of genetic and behavioral variability than inbred strains, making it useful in the representation of phenotypic diversity that is typical of human populations. Despite the ecological validity of outbred strains as controls, studies involving BTBR mice use inbred B6 mice as controls (McFarlane et al., 2008; Scattoni, Ricceri, & Crawley, 2011; Silverman, Tolu, Barkan, & Crawley, 2010). B6 mice are popular in part due to their status as an inbred strain while retaining relatively stable similarities to wild-type strain behaviors; meaning a greater constraint of variability on behavioral tasks, leading to a reduction of the necessary sample size needed to observe some treatment effect. Hsieh and colleagues (2017) did find this to be the case when comparing CD-1 and B6 on sociability tasks. While the study found that B6 scores resulted in a greater Cohen's D value than those of CD-1 scores, as well as greater statistical power, both constituted large effect sizes (d>1) and the authors concluded that CD-1 mice are just a suitable as B6 for control purposes on tests with a social context. The expected differences in behavioral variation between the strains on each task is addressed in the "Results" section.

While B6 mice have been observed to preform normally on tests of sociability, the strain does not completely match the characteristics of a wild-type strain. As previously noted, B6 mice average 10% of elevated plus time in the open arm, while the time outbred mice strains in general is 25% (File & Baldwin, 1989). The B6 strain mice also demonstrates increased levels of anxiety versus the DBA/2 mouse, another inbred strain that is often used as a control (Podhorna & Brown, 2002). In fact, the B6 genome is often used as springboard to develop strains specifically with the purpose of altered anxiety behavior (Belzung & Griebel, 2001). Such a characteristic could compromise data from both our anxiety measure, and less obviously our sociability measure; which itself can induce stress due to the novelty of the environment and therefore represents an extraneous variable. For these reasons, the present study used CD1 mice as controls, a strain whose behavior on the plus maze is species-typical (Holmes, 2000)

Methods

Twenty-nine (n=16 female) BTBR mice from four litters, and 32 (n=16 female) CD-1 mice from four litters were tested on either the elevated plus maze or the 3-chamber apparatus and odor preference tests. CD-1 stock was acquired from Charles River Laboratories (www.criver.com), and BTBR stock was acquired from Jackson Laboratoies (www.jax.org).

All animals were housed at the 621 Skytop research facility throughout the experiments, in a vivarium room at a constant temperature of 22.5±2°C, humidity of 42%, food and water available *ad libitum*, and kept on a 12-hour light cycle (lights off at 6am). Breeding was done according to a split litter design (appendix a) to account for genetic variability of CD-1 mice. Prospective dams were housed in cages with two-to-three similar strain males for seven days, after which males were removed from breeding cages and females were left for another seven days, then finally isolated to birthing cages. On the day of birth (or PND-0), each litter was

culled by a lab member to include four male and four female neonates. On PND-21 litters were weaned into either enriched or standard caging until the time of testing. All behavioral testing was performed during wakeful hours (6am-6pm).

Animals that were not utilized for anatomical purposes were otherwise euthanized after behavioral testing by Laboratory Animal Resources (LAR) personnel. Because there are no chemical treatments involved in our experiments, all euthanized CD-1 mice were eligible for donation to wildlife rehabilitation centers for animal feed.

Risk to researchers and technicians was mitigated by the use of gloves, lab coats, and ventilation masks that were incorporated during all interactions with the animals. All procedures were approved by the University's Institutional Animal Care and Use Committee (IACUC), though the Office of Research Integrity and Protections (ORIP). Funding was attained through allocations from the Psychology Department, the Dean's Office (via First-Year Forum), and the Ronald E. McNair Program.

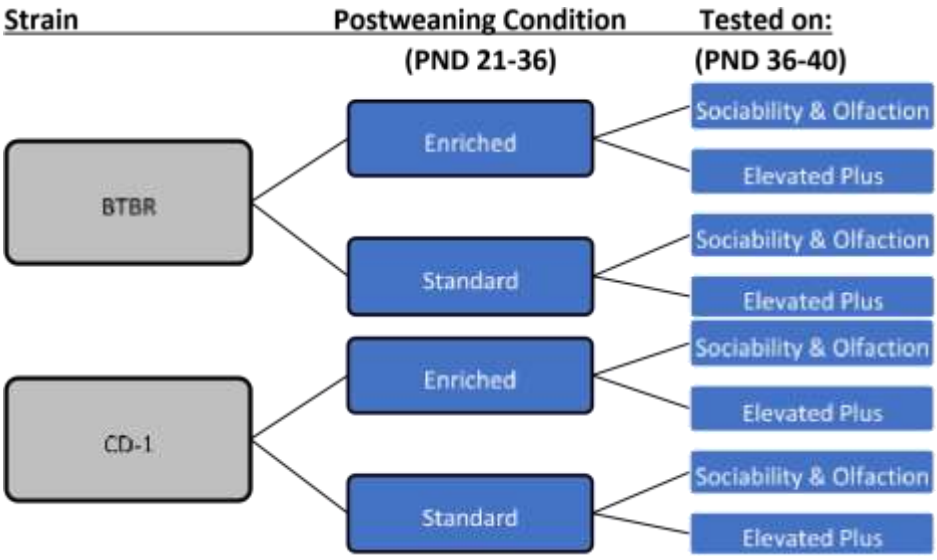


Figure 1. A flow diagram of our experimental paradigm

Beginning on PND-21 and extending until the time of behavioral testing (PND 36-40), both CD-1 and BTBR mice were assigned to either enriched or standard housing conditions. Standard cages consisted of a Plexiglass cage (45 X 24 X 15cm), holding approximately 2.2L of nest bedding as well as a 5.05cm^2 Nestlet. Enriched housing conditions included a cage that was 25% larger-by-volume (45 X 24 X 20cm) compared to the standard caging and was equipped with a set of five stimuli (i.e., a running wheel, plastic tube, ball, cup, and ring) in addition to nest bedding and a Nestlet. The stimuli varied in shape, size, and function, and were replaced and rearranged every other day during the enrichment period. On the day of testing, two males and one female from each litter were tested on either the 3-chamber apparatus and odor preference tests, or the elevated plus maze.

Figure 2. An example of a post-weaning enriched caging environment (left) with assorted enrichment stimuli and Nestlet, and standard caging environment (right) with a Nestlet.

Behavioral Tests

All behavioral trials were video recorded and data collection sheets were coded by the author, such that there was a blind control measure in the reporting of the raw data by research assistants before being analyzed by the author. Specifically what was encoded was the post-weaning condition of each mouse. The limitation to this method involves coding for strain due to the easily discernible differences in appearance between CD-1 and BTBR mice (see appendix b).

3-Chamber Apparatus: 16 (n=9 female) BTBR mice from four litters and 14 (n=7 female) CD-1 mice from four litters were tested. The 3-chamber apparatus (fig.3.a) is a test of sociability for mice consisting of a Plexiglas box (62 X 40cm), partitioned into three chambers (each 20 X 40cm) with a door on each partition that allow access to the entirety of box, and in each side chamber is an enclosure (Cornwell, 2017).

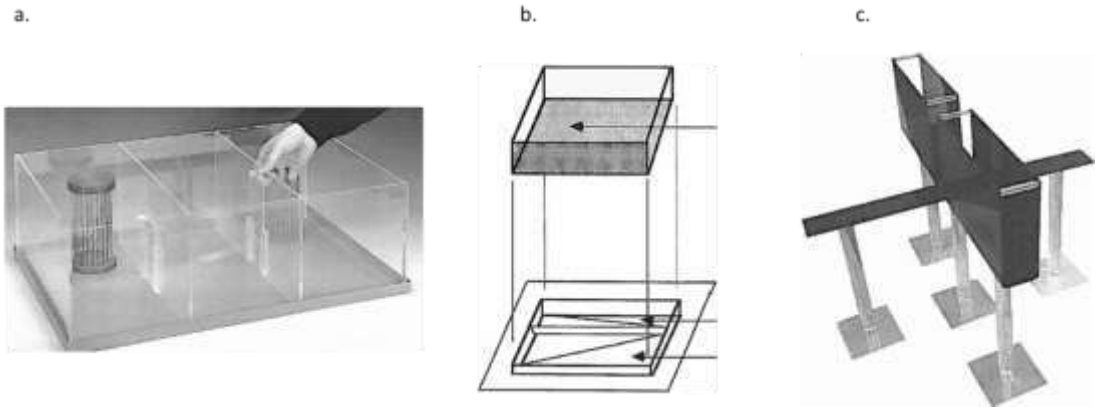


Figure 3. Images of the (a.) 3-chamber apparatus, (b.) odor preference test, and (c.) elevated plus maze, which assay sociability behavior, social odor preference, and anxiety-like behavior, respectively (Cornwell, 2017).

The trial begins with a 10-minute habituation period, where the test mouse is placed in the apparatus and left to explore the empty chambers. The time of exploration is recorded for

each chamber with the expectation that there is no preference for either side. The test mouse is then removed, and a novel same-sex conspecific mouse is placed randomly in one of the side enclosures. The test mouse is reintroduced to the center chamber and left to explore for another 10-minute period. The amount of time spent exploring either the empty-enclosure chamber or the enclosure containing the conspecific, or "stranger" mouse is recorded. What is typically observed during a trial using a wild-type strain is a significant preference for the enclosure holding the stranger mouse versus the empty side chamber (Kaidanovich-Beilin, Lipina, Vukobradovic, Roder, & Woodgett, 2011).

Odor preference test: 16 (n=9 female) BTBR mice from four litters and 16 (n=8 female) CD-1 mice from four litters were tested. The odor preference test (fig.3.b) consists of a 6X8 gridded platform (22 x 29cm) with a "V" shape that breaks the grid into three sections. Placed to one side of the "V" is soiled bedding from the home cage of the animal being tested, to the other side is placed clean hardwood bedding, and the middle section is left empty. A sturdy mesh-wire screen is placed directly over the grid, and a test mouse is placed on the screen and left to explore for 180-seconds. Raw data is collected regarding the amount of time spent over each type of bedding as well as tracing the locomotion of the test mouse throughout the apparatus (Cornwell, 2017). Normally-reared rodents spend more time above a familiar odor, as opposed to an unfamiliar one (Cornwell-Jones, Stephens, & Dunston, 1982), while infant maternally separated mice show development deficits on this task. The assumption is that a normative mouse will prefer to spend time above a familiar odor, as opposed to an unfamiliar one (Thomas, Fonken, LeBlanc, & Cornwell, 2010).

Elevated plus maze: 13 (n=7 female) BTBR mice from four litters and 16 (n=8 female) CD-1 mice from four litters were tested. The elevated plus maze (fig.3.c) is used to assay the

unconditioned response to a potentially dangerous environment, by inducing anxiety via the fear of falling juxtaposed with a rodent's natural tendency to explore a novel environment (File & Baldwin, 1989). It is composed of four alternating open and closed arms (each arm 50 X 10cm; enclosed walls 40cm tall) and elevated above a flat surface. Animals are brought to a dimly lit and sound attenuated testing room and left to habituate for 30-minutes. Once habituated a test animal is place on the central square of the plus, facing towards an open arm, and left to explore for300-seconds. Raw data is collected reflecting the amount of time spent on the open arm and the number of open arm entries during the trial. As mentioned, a normal rodent will spend approximately 25% of the trial exploring the open arm (File & Baldwin,1989). Enrichment increased time on the open arm for both maternally separated and normally reared CD-1 mice (Diamond & Cornwell, 2019).

Statistical Analysis

Both R-Studio and JASP software were used to analyze data and construct figures for these experiments. (JASP Team, 2018; RStudio Team, 2016). Omnibus significance testing was accomplished using ANOVAs, and all planned or post-hoc comparisons we set to an alpha threshold accounting for Bonferroni corrections for multiple comparisons. Due to strain differences, Levene's test of equal variance was used to compare between-condition data for each task. For any task data that met the threshold for significant differences in variance, statistical models were adjusted so that the output would not reflect an assumption of equal variance.

Results

Sociability

Data from the 3-chamber apparatus (Fig.4) were analyzed using 2 (sides) x 2 (strains) x 2 (rearing conditions) repeated measures ANOVA. On the habituation trial, a Levene's test found evidence to reject equal variance for both the left ($F=4.31$, $p=0.01$) and right ($F=3.63$, $p=0.03$) side chambers. There was a within subjects effect of time spent in the side chambers [$F(1,26)=5.06$, $p=0.03$], as well as a between subjects effect of strain on chamber time [$F(1,26,)=4.31$, $p=0.01$]. Post-hoc paired sample t-tests found that CD-1 standard, BTBR standard, and BTBR enriched mice spent more time in the right chamber versus the left, $t(5)=3.90$, $t(6)=3.56$, $t(8)=2.87$, $p<0.025$, respectively (Appendix C).

On the sociability trial, a Levene's test did not find evidence to reject the assumption of equal variance for either the stranger side ($F=0.30$, $p=0.82$) or empty side ($F=2.18$, $p=0.11$) within-subject metrics. We found no significant difference in time spent in either enclosure side [$F(1,26)=0.46$, $p=0.51$], nor did we find an effect of treatment on enclosure time [$F(1,26)=0.49$, $p=0.49$]. However, we did observe a significant effect of strain on enclosure time [$F(1,26)=5.83$, $p=0.02$]. Planned 1-tail paired samplest-tests found that BTBR animals reared in standard housing did not show a preference for the stranger enclosure, $t(6)=1.72$, $p>0.025$, but BTBR animals that had been enriched displayed a significant preference for exploring the stranger side, $t(8)=2.35$, $p<0.025$.

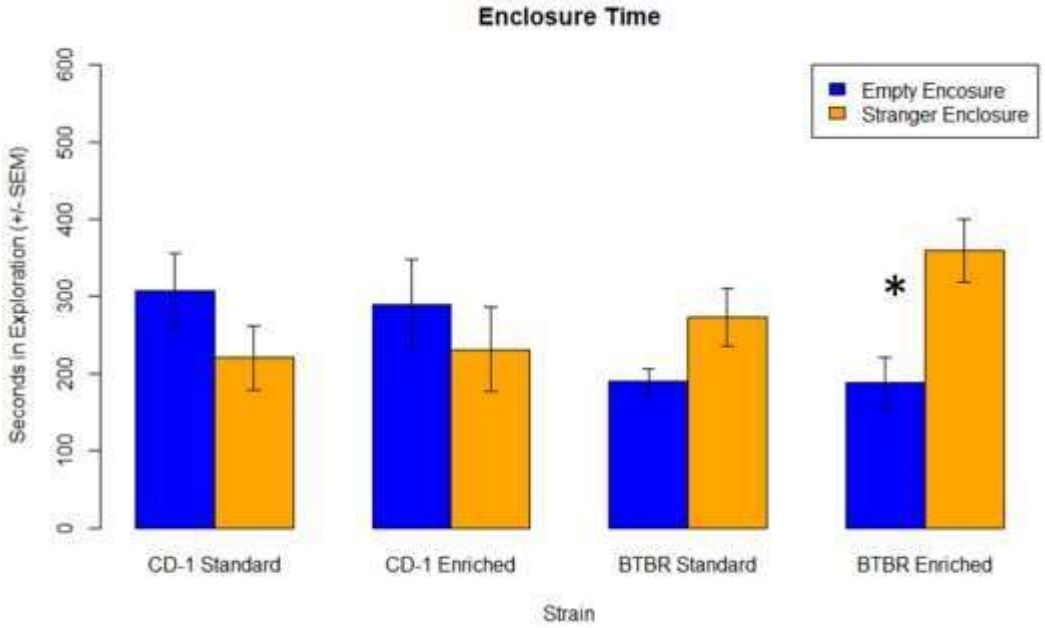


Figure 4. Results from the 3-chamber apparatus test of sociability. Typically sociable mice prefer exploring the chamber housing a potentially helpful same-sex conspecific versus an empty enclosure. As expected, the BTBR-Standard condition did not show a significant preference for the stranger mouse. However, BTBR mice that had been enriched significantly preferred exploring the stranger enclosure. Asterisks represent a significant side preference after a planned 1-tail paired sampled t-test with an alpha level of 0.025 for multiple comparisons.

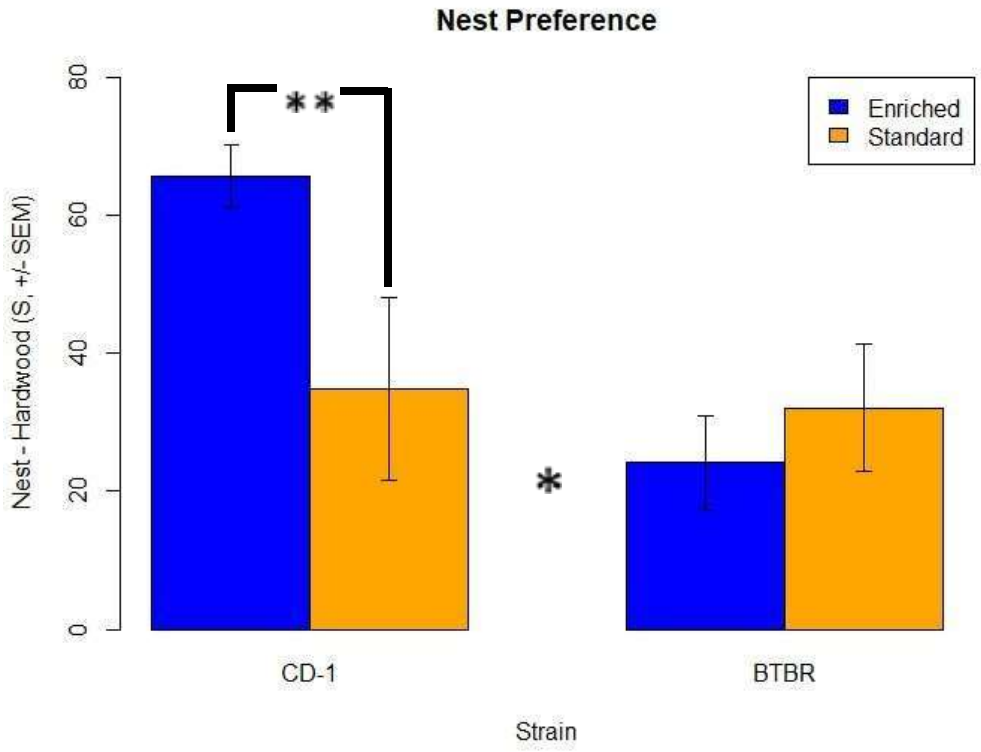


Figure 5. Results from the social odor preference test. Typically sociable mice prefer to spend time over familiar odors when placed in the novel environment. Enrichment increased time over nest odors for CD-1 but not BTBR mice. Dark asterisk represents a main effect of strain on nest preference (p=0.02); double asterisks represent a significant difference between histograms (p<0.025); light asterisks represent a significant difference from zero (no preference), after a Bonferroni correction for four comparisons (p<.01).

Data from the odor preference test (Fig.5) were analyzed by performing a 2 (strains) x 2 (rearing conditions) ANOVA, for mean time over nest minus hardwood. An effect of strain [F(1,28)=6.10, p=0.02] indicated that CD-1 mice spent significantly more time over nest odors compared to BTBR mice. Although there was no main effect of treatment [F(1,28)=1.64,

p=0.21], a significant interaction effect was obtained[F(1,28)=4.68, p=0.04]. A Leven's test did detect evidence for unequal variance in our nest preference data (F=4.62, p=0.01), therefore statistical models for analyzing nest preference data did not assume equal variance. post-hoc 1tail independent samples t-tests found that CD-1 mice that were enriched displayed significantly greater preference than standard reared controls for nest odors t(15)=2.21, p<0.025, but this treatment effect was not observed for BTBR mice, t(15)=0.69, p=0.5.

Additionally, planned 1-tail independent sample t-tests were used to compare the mean of each condition to no a score of zero (no preference for either odor). We found that both BTBR-Standard and BTBR-Enriched mice showed a significant preference for nest odors, t(6)=3.50, and t(8)=3.54, p<.01, respectively. CD-1 mice who had received post-weaning enrichment did significantly prefer nest odors to fresh hardwood shavings, t(7)=14.26, p<0.025, although this was not the case for CD-1 standard animals, t(7)=2.64, p>0.025.

Anxiety

To analyze anxiety results from the elevated plus maze (Fig.6), data was subjected to a 2 (strains) x 2 (rearing condition) ANOVA, comparing mean scores of percent open arm time by strain and treatment. There was a significant effect of strain on percent open arm time [F(1,25)=4.69, p=0.04], but not for treatment [F(1,25)=0.18, p=0.70]. The strain effect indicated that BTBR mice spent a lower percentage of time on the open arm than CD-1 mice regardless of housing condition (Figure 5). We did not observe significant evidence to reject percent open arm scores as having equal variance (F=2.92, p=0.06). Planned 1-tail independent samples t-tests were used to compare the mean of each condition to a score of 25% (typically stress reactive). We found that both CD-1 standard and enriched mice were found to perform within the typical range, t(7)=1.79 and t(7)=0.68, p>0.01, respectively. BTBR animals that received enrichment

also scored within the typical range, t(5)=0.65, p>0.01, but BTBR animals reared in standard conditions performed significantly below the typical score, t(6)=-4.01, p<0.01.

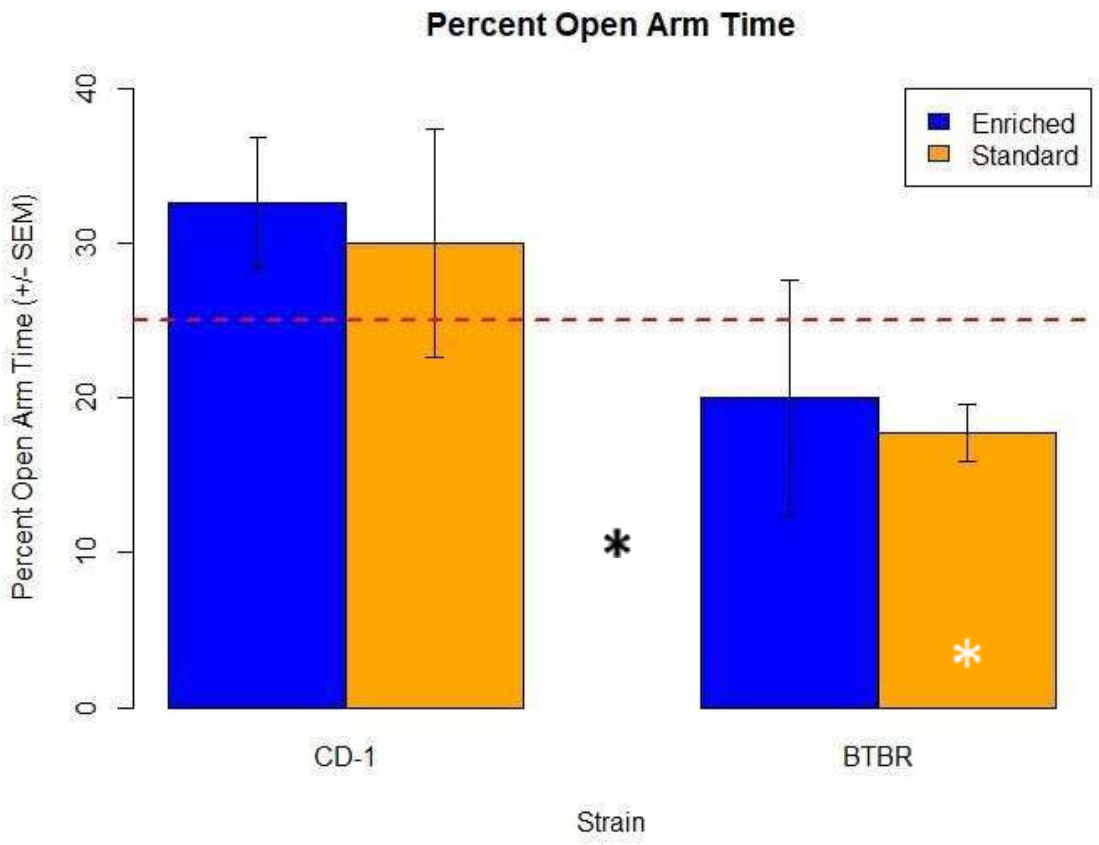


Figure 6. Results from the elevated plus. Typically stress reactive mice prefer to spend around 25% of the trial on the open arm. Our results indicate enrichment did not reduce anxiety scores for either strain. However, CD-1 mice were typically responsive while BTBR mice appeared to display heightened anxiety-like behavior. Dark asterisk represents a main effect of strain on open arm time; light asterisk represents a significant difference from 25% open arm time after a Bonferroni correction for four comparisons.

Limitations

Due to an unforeseen issue with animal care facilities there was a backup of live CD-1 mice due to a freezer malfunction. We surmise that the mixing of odors from different cages resulted in odors from separate cages becoming familiar instead of novel. This abnormality could have led to the atypical behavior we observed from CD-1 control conditions on the 3-chamber apparatus. This situation would not have influenced the distinction between familiar nest shavings and clean hardwood shavings on the odor preference test, not the ability to perceive distance cues on the elevated plus maze.

Discussion

On the test 3-chamber apparatus BTBR-strain mice housed in standard conditions did not show a preference for an enclosure housing a stranger mouse versus an empty enclosure, but following postweaning environmental enrichment BTBR mice displayed a significant preference for exploring an enclosure holding a stranger mouse. This is evidence that early developmental intervention in the form of physical, sensorimotor enrichment can bolster responsiveness to social stimuli in a strain that is characterized by abnormal social patterns. This finding is consistent with work by Reynolds et al. (2013), indicating that environmental enrichment reduces another core symptom of ASD in the same strain. It is also consistent with enrichment effects on CD-1 mice after prenatal exposure to the antiepileptic drug Valproic acid (VPA), an environmental model for ASD through the mechanism of a teratogen. Yamaguchi et al. (2017) found that VPA exposure resulted in significantly less sniffing behavior on the social interaction test versus a saline control, and that VPA exposed CD-1 mice that had received enrichment demonstrated sniffing behavior similar to a CD-1 control group.

The present work compliments evidence that environmental enrichment can decrease autistic-like behaviors in an adversity-induced mouse model for ASD (Cornwell et al., 2008). Additionally, environmental enrichment was shown to reduce hyperactivity and enhance cognitive function in a rat model for ADHD (on the open field test and y-maze, respectively) as well as a medley of effects relating to the reduction of addiction-related behaviors in mouse and rat models (Botanas et al., 2016; Solinas et al., 2010). In relation to the "Happiness Project" article featured in a 2018 article of Science Magazine, this is further support for the role of enrichment for models of psychiatric disorders addition to physical diseases such as tumors.

This finding on sociability behavior may also be relevant to attempts to translate sensorimotor enrichment results from mice into a protocol to treat symptoms for individuals with ASD. As mentioned earlier in the paper, Woo et al. (2015) were partially inspired to conduct research on humans by physical enrichment's reduction of repetitive behaviors in BTBR mice (Reynolds, Urruela, & Devine, 2013). Woo and colleagues found that sensorimotor enrichment of children ages 3-12 with a diagnosis of ASD (consisting of olfactory, tactile, and auditory stimuli, as well as exercise and balance training), in addition to standard care, resulted in statistically higher scores on a nonverbal IQ test, improved sensory responses, language performance, and reduced severity of ASD symptoms compared to an age- and condition-matched group that received standard care only (2013;2015). In light of the findings from this experiment there may evidence to investigate potential pro-social benefits of sensorimotor enrichment for those diagnosed with ASD.

On the odor preference test, enrichment increased attraction to nest odors for CD-1, but not BTBR mice. This stands in contrast to our previous results using an adversity model, whereby environmental enrichment served to improve home nest preference for maternally

separated CD-1 mice. We propose that differences in strain responses to enrichment on this task were due to differing neural mechanisms; meaning that the limbic system of CD-1 mice may have been disrupted by the maternal separation procedure and rescued by enrichment, the BTBR animals may display different or more extensive extensive impairments to the network due to their genetic inheritance, making enrichment alone an inadequate treatment. However, BTBR mice of both treatment conditions displayed a significant preference for familiar nest odors, suggesting that their performance was not due to an ability to respond selectively. While Yang et al. (2011) found that BTBR mice did not display a preference between own nest odors and other nest odors, our data indicate that the strain can successfully discriminate between odors in a two-choice situation.

Environmental enrichment did not influence behavior for either strain on the elevated plus maze. These findings are in contrast with our previous data (Diamond & Cornwell, 2019), in which enrichment reduced anxious behavior in the adversity-induced model for ASD, as well findings from Yamaguchi et al. (2017), who found that mice exposed to VPA demonstrated increased anxiety behavior on the elevated plus maze, and this deficit was rescued by enrichment. However, Hulbert, Bey, and Jiang (2018) recently found that environmental enrichment of the Shank3 transgenic model for ASD increased anxiety behavior in this testing situation; suggesting that this treatment may work differently between environmental and genetic models for ASD.

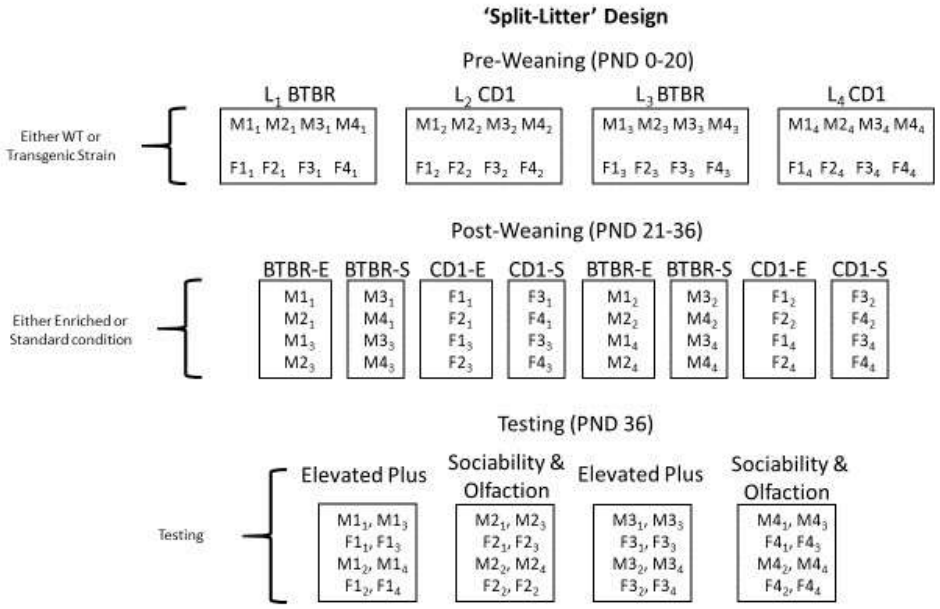
Strain influenced open arm time, with CD-1 mice spending a greater percentage of time in the open arm than BTBR mice. Both groups of CD-1 animals scored with the normal range for typically behaving Mice. In contrast, BTBR animals reared in standard conditions scored significantly lower than the typical range. These results dispute the claim that the BTBR may

display reduced anxiety behavior on the elevated plus maze (Chadman & Guariglia, 2012), and highlights the importance of employing an outbred control strain on tests of anxiety.

It is possible that the enrichment housing situation induces social patterns in BTBR groups that differ from those seen in CD-1 mice given enrichment tools. Informal observations of living groups suggest that BTBR animals didn't utilize the running wheel with the same frequency as the CD-1 mice. One way to investigate this would be by combining the social enrichment paradigm used by Yang et al. (2011), housing BTBR with same-sex outbred mice (in our case CD-1 mice) together at weaning in a physically enriched environment. The outbred CD-1 mice might "teach" their BTBR cage mates to take advantage of enrichment, resulting in broader effects on BTBR ASD-like symptoms than those achieved in the present study. We could also extend the length of enrichment for BTBR mice to examine whether additional exposure would have more of an effect on their behavior.

Appendix A

Figure A1. Schematic of split-litter breeding paradigm.

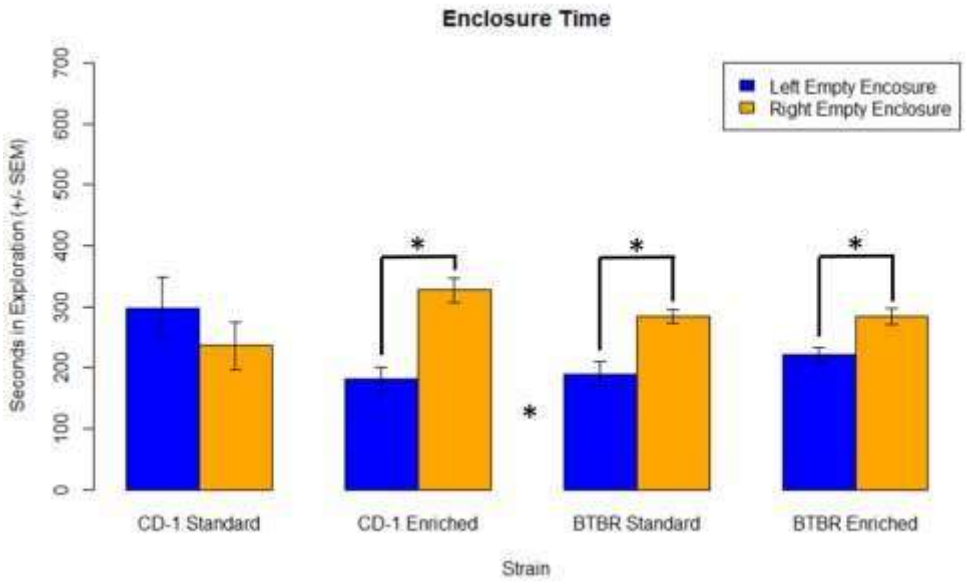


Appendix B

Figure B1. Stock images of an adult (a.) CD-1 and (b.) BTBR strain mice (Charles River Laboratories, 2018; Jackson Laboratory, 2018)

Appendix C

Figure C1. Results from the 3-chamber apparatus sociability trial. Top asterisks represent a significant within subject effect of time spent in either enclosure after a Bonferroni correction. Bottom asterisk represents a significant between subject effect of strain on time spent in either enclosure.



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Education

2022† Ph.D., Syracuse University, Cognitive Psychology

- Concentration in Neuroscience
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2019† M.S., Syracuse University, Psychology

2017 M.S., Pace University. Mental Health Counseling

2015 B.A., Pace University. Applied Psychology (*magna cum laude*)

Appointments

2018 Future Professoriate Program (FPP), Syracuse University

2018-2021 Institutional Animal Care and Use (IACUC) Committee Member, Syracuse University

2018 Instructor, Department of Psychology, Syracuse University

2018-2019 Teaching Assistant/Recitation Instructor, Department of Psychology, Syracuse University

2017-2018 Teaching Assistant/Recitation Instructor, Department of Psychology, Syracuse University

2017- Research Assistant, Laboratory in Behavioral Neuroscience, Syracuse University, PI: Catherine Cornwell

2016-2017 Laboratory Coordinator, Department of Psychology, Pace University

2015-2017 Research Assistant, Trauma, Resilience, and Social Processes (TSPR) Lab, Pace University, PI: Anthony Mancini

Teaching

2018 PSY 382, Health Psychology Syracuse University

Teaching Assistant & Recitation Instructor

2017-2019 PSY 205, Foundations of Human Behavior Syracuse University

Supervision & Mentorship

2019	Ailene Casado, PRIDE Student	Syracuse University
2018	Sarina Wallace, PRIDE Student	Syracuse University
2017	Khemia Burke, PRIDE Student	Syracuse University

- Psychology Research Initiative for Diversity Enhancement

Selected Honors and Awards

2019	Certificate in University Teaching, Syracuse University
2017	Ph.D. Studentship, Syracuse University
2016-2017	Graduate Academic Scholarship, Pace University
2012-2015	Undergraduate Academic & Athletic Scholarships, Pace University

Skills

R, Jasp Statistics, LaTeX, Excel, Word, Blackboard, Sona Systems, SPSS, Qualtrics, Web Design, Perfusion Fixation

Funding

2019	Summer Research Fellowship, Department of Psychology, Syracuse University ($2,400)
2019	Neuroscience Graduate Travel Grant, Department of Psychology, Syracuse University ($500)
2018	Departmental Master's Thesis Funding, Department of Psychology, Syracuse University ($600)
2017-2018	Graduate Student Organization Travel Grant, Syracuse University ($350)

Professional Memberships

American Psychological Society (APS), Eastern Psychological Association (EPA), Cognitive Neuroscience Society (CNS), Psy Chi Honor Society

Contributed Presentations

Wallace, S.A., Loeb, K., Burke, K., Allawh, C., **Diamond, B.**, Cornwell, C.A. (2019) Environmental

Enrichment Reveals Social Odor Preference Deficits in BTBR Mice, an Animal Model for Autism. *26th Annual Poster Session and Awards Ceremony, Department of Psychology, Syracuse University*. Syracuse, NY.

Diamond, B., Cornwell, C.A. (2019) Environmental Enrichment Prevents Autistic-like Behavior after Maternal Separation in CD-1 Mice. *Eastern Psychological Association*. New York, NY.

Wallace, S.A., Cornwell, C.A., **Diamond, B.** (2018). The Effects of Environmental Enrichment on Anxiety and Self-Grooming in Adolescent CD-1 Mice on the Open Field Apparatus. *Louis Stokes Alliance for Minority Participation (LSAMP) Research Symposium, Syracuse University.* Syracuse, NY.

Cornwell, C., **Diamond, B**., Klabuhn, K., Burke, K., Allwah, C., Mustafa, N. (2018). Environmental Enrichment Prevents Autistic-like Behaviors in Maternally Separated Mice. *International Conference on Learning and Memory*. Irvine, CA.

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Allawh, C., Tan, X., Mustafa, N., **Diamond, B.**, Cornwell, C. (2018) Anxiety-related Behaviors Are Influenced by Environmental Enrichment but not Maternal Separation in CD-1 Mice. *25th Annual Poster Session and Award Ceremony, Department of Psychology, Syracuse University*. Syracuse, NY.

Mustafa, N., Allawh, C., Tan, X., **Diamond, B**., Cornwell, C. (2018) Environmental Enrichment Reduces Anxiety-like Behavior in Maternally Separated Mice. *Fourth Annual Neuroscience Research Day, Department of Biology, Syracuse University.* Syracuse, NY.

Mancini, A., **Diamond, B**., Shevorykin, A., John, G., Veith, S., Bonaviso, L., Marino, C. Bloom, R., Pitcher, S., Caiola, J. (2017). Cumulative Lifetime Adversity and Memory for Aversive Stimuli: An Experimental Investigation. *Poster presented at the 123rd Annual Convention for the Association for Psychological Science.* Boston, MA.

Mancini, A., **Diamond, B**., Risler, J., Tirado, A. (2016). Subjective Bonding with Others Moderates the Impact of Shared Aversive Experience. *Poster presented at the 122rd Annual Convention for the Association for Psychological Science.,* Chicago, Ill.

Publications

Diamond, B., Cornwell, C.A. (2019). *Environmental Enrichment and Autistim-relevant Behavior in BTBR Mice*. [Manuscript in Preparation]

Cornwell, C., **Diamond, B.**, LeMon, J., Burke, K., Allawh, C. (2019). *Autistic-like Behavior Following Early-Life Stress is Prevented by Environmental Enrichment in a Wild-type Mouse Strain.* [Manuscript in Preparation]