Although the etiology of autism is unclear, disruptions of the dopaminergic and serotonergic systems have been associated with the disorder. Based upon behavioral differences observed in the BALB/c strain of mice in comparison to other strains, notably, C57BL/6J mice, it has been suggested that the BALB/c strain may serve as an animal model of autism. However, to date, most work investigating neural and behavioral abnormalities in this strain has been performed in adult animals. Therefore, experiment 1 was conducted to examine the development of the central dopaminergic and serotonergic systems of BALB/c mice as compared to C57BL/6J mice. Levels of dopamine, serotonin, and their metabolites in several different brain regions and at three ages during development were measured. Alterations in both monoaminergic systems associated with age and strain were detected across brain regions indicating that there are neurochemical differences between these strains early in life. However, despite these differences in the development of brain monoaminergic systems, it remains difficult to
declare this strain as a valid model of autism. Glutathione is an endogenous antioxidant, and gene mutations affecting glutathione have been linked to autism. One such gene mutation involves the altered expression of glutathione-S-transferase M1 (GSTM1). An animal model of autism incorporating this genetic mutation may be useful in studying the disorder. Therefore, experiment 2 was performed to investigate the neurochemical development of GSTM1 wildtype and knockout animals. Like experiment 1, dopamine, serotonin, and their metabolites were measured in several brain regions at three developmental time points. Neurochemical analysis revealed alterations in both dopaminergic and serotonergic systems associated with age and genotype. An understanding of these mice may help to further develop this animal model of autism.
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INTRODUCTION

Overview of Autism:

Autism is a neurodevelopment disorder characterized by impaired social interactions and communication, as well as stereotypic and sometimes self-injurious behaviors. These symptoms typically appear before the age of three and persist throughout the lifetime of the individual. They also vary greatly in intensity, ranging from mild to severely debilitating deficits (Rapin, 1997). Although the cause of autism remains elusive, there appear to be a number of factors that play a role in its etiology, including genetic and environmental influences.

As mentioned earlier, the symptoms of autism vary in severity. Thus, individuals with autism are considered to have one of a group of disorders referred to in the DSM-IV as pervasive developmental disorders; they are sometimes called autism-spectrum disorders (ASDs) as well. Rapin (1997) provides definitions for these disorders. For example, individuals with Asperger's disorder have deficient social skills and a narrow range of interests, but are not mentally retarded. On the other hand, those with autistic disorder show severe deficits in social interaction, language, communication, and play; they also show stereotypies, perseveration, and a narrow range of interests and activities. Another type is disintegrative disorder, also known as Heller's syndrome, in which children undergo a massive regression between the ages of two and ten, resulting in severe autism, usually including the loss of cognitive abilities. Rett's disorder, another pervasive developmental disorder, is specific to girls who show infantile regression, microcephaly, stereotypic hand movements, and severe retardation, along with other
neurological deficits. It is also possible for an individual to have an ASD but not fall under one of these specific categories.

The Center for Disease Control's Autism and Developmental Disabilities Monitoring Network released a report in December of 2009 that addressed the prevalence of ASDs in the United States during the 2006 reporting period. They found that among children aged 8 years, across 11 reporting sites in the United States, that 9.0 per 1,000 children were diagnosed with an ASD. This is equivalent to approximately one child in every 111. In addition, they reported an increased prevalence in males, with the ratio of males to females diagnosed with an ASD being 4.5 to 1 (CDC, 2009).

Although the neurobiology of autism is not well understood, individuals with autism appear to have disruptions in dopaminergic and serotonergic activity, and these disruptions could play a part in mediating some of the behavioral symptoms of the disorder.

Dopamine in Autism:

Dopamine is a catecholamine that is synthesized from tyrosine, a dietary amino acid. Tyrosine is first hydroxylated by tyrosine hydroxylase into L-dihydroxyphenylalanine (L-DOPA) which is then converted to dopamine by DOPA decarboxylase (Lam et al., 2006). There are three primary dopaminergic pathways that contribute to the wide range of dopamine-mediated behaviors. The nigrostriatal pathway, which is primarily involved in movement, has cell bodies located in the substantia nigra that project to the neostriatum. The mesolimbic pathway, which projects from the ventral tegmental area to a number of limbic regions, plays an important role in reinforcement.
The third major dopaminergic pathway is the mesocortical. This pathway projects from the ventral tegmental area to the prefrontal cortex, an area that is crucial for higher order functions such as planning (Lam et al., 2006).

With respect to the symptoms of autism, dopamine antagonists alleviate hyperactivity, stereotypies, aggression, and self-injurious behavior that are often associated with the disorder while, in contrast, drugs that increase dopamine activity exacerbate those symptoms (Volkmar, 2001). Collectively, these pharmacological observations may indicate that autistic individuals have dopaminergic overactivity (Lam et al., 2006). In addition to the pharmacological evidence in support of dopamine's role in autism, mothers of autistic children are more likely to have a 19-base pair sequence deletion in one or both alleles of the gene coding for the dopamine-beta-hydroxylase enzyme, resulting in high maternal levels of dopamine (Robinson et al., 2001). In an examination of dopamine transporter binding using positron emission tomography, Nakamura et al. (2010) found that autistic individuals 18 to 26 years old showed significantly increased binding in the orbitofrontal cortex compared to age- and IQ-matched controls. However, despite this evidence, dopamine's role in autism still remains unclear. Studies of urinary dopamine and homovanillic acid (HVA), a metabolite of dopamine, have revealed little evidence to suggest differences in peripheral indices of dopaminergic activity between autistic individuals and control subjects (Lam et al., 2006). Similarly, the examination of cerebrospinal fluid (CSF) HVA levels in individuals with autism have provided limited support for increased dopamine turnover in autism. However, a few studies have reported increased CSF HVA in autistic subjects (Gillberg et al., 1983; Gillberg and Svennerholm, 1987), and others have shown that
autistic children with more severe stereotypies and hyperkinesis tend to have increased CSF HVA levels (Cohen et al., 1974; Cohen et al., 1977).

Serotonin in Autism:

The evidence supporting the involvement of serotonin in autism is far more convincing than that of dopamine. Serotonin is an indolamine derived from the amino acid tryptophan. Tryptophan is hydroxylated by tryptophan hydroxylase to form 5-hydroxytryptophan (5-HTP), which is then converted to serotonin by 5-HP decarboxylase (Lam et al., 2006). The serotonergic cell bodies are found primarily within the raphe nuclei of midbrain, pons, and medulla, and project diffusely throughout the brain. Serotonin plays a role in controlling mood, eating, thermoregulation, arousal, and sexual behavior, among other important functions and behaviors (Lam et al., 2006).

As mentioned earlier, serotonin's involvement in autism is much better defined than dopamine's role. About 30% of the individuals with autism have platelet hyperserotonemia (Schain and Freedman, 1961); more than 25 studies have confirmed this platelet hyperserotonemia which appears in roughly one third of all individuals diagnosed with autism (Lam et al., 2006). In autistic individuals that have hyperserotonemia, the platelet serotonin is approximately 50% higher than in control subjects (McBride et al., 1998). Studies examining a genetic basis of autism have also linked serotonin activity to the disorder. Several autism susceptibility genes that have been identified code for proteins that are known to be involved in the regulation of serotonin transport (SLC6A4 and 5-HTTLPR) or serotonin receptors (HTR2A) (Guhathakurta et al., 2009).
Despite the fact that one third of the individuals with autism have platelet hyperserotonemia, there has been no evidence to suggest that there are increases in brain levels of serotonin. In fact, several pieces of evidence suggest that individuals with autism may actually have decreased central serotonergic activity. McDougle et al. (1996) have shown that an acute depletion of tryptophan, the precursor of serotonin, leads to an increase in autistic symptoms. In addition, the most commonly prescribed treatment for autistic symptoms are the serotonin selective reuptake inhibitors which have been shown to reduce repetitive thoughts and actions, aggressive behavior, and improve some elements of social behavior (Brodkin et al., 1997; West et al., 2009). Furthermore, some individuals with autism have been shown to have altered serotonin synthesis capacity as compared to nonautistic children (Chugani et al., 1999). Children without autism showed relatively high levels of 5-HT synthesis between the ages of 2 and 5, which subsequently decreased toward normal adult levels as they aged. Autistic children, on the other hand, did not show this trend. Rather, they had significantly lower serotonin synthesis capacity between the ages of 2 and 5, which then increased slightly with age. Other studies, though, do not provide support for brain hyposerotonemia in autism. For example, measuring cerebrospinal fluid for levels of 5-hydroxyindoleacetic acid (5-HIAA), a metabolite of serotonin, has been used to assess central serotonergic function in autistic and control subjects (Gillberg et al., 1983; Cohen et al., 1977), and results from these studies do not suggest a widespread change of serotonin turnover in the brains of autistic individuals. This does not, however, rule out the possibility of regional alterations in serotonin activity.
BALB/c as a Model of Autism:

Through the use of animal models, some insight into the biological basis of the behavioral deficits associated with autism may be ascertained. The use of the BALB/c mouse strain could be valuable, as it has been asserted that, relative to other strains, these mice exhibit behavioral characteristics similar to those seen in autism. For example, using a social conditioned place preference paradigm, Panksepp and Lahvis (2007) demonstrated that BALB/c mice are less responsive to social contact than several other inbred mouse strains, including C57BL/6J mice. Similarly, Southwick and Clark (1968) found that, of 14 inbred mouse strains, BALB/c mice showed the least amount of social grooming. Differences in sexual behavior, as well as maternal behavior, may also be indicative of decreased social interactions in this strain. Shoji and Kato (2006) showed that BALB/c mothers had reduced nursing posture, pup licking, and slower time to retrieve pups than CBA/CA inbred mice. Additionally, in a review of mouse social behavior by Crawley et al. (1997), BALB/c mice exhibited the lowest amount of male copulatory behaviors with estrus females. Finally, BALB/c mice also exhibit other features that resemble autism including high levels of aggression and anxiety, large brain size, underdevelopment of the corpus callosum, and low adult levels of brain serotonin (Brodkin, 2007).

Experiment 1 Objective:

Because BALB/c mice exhibit behavioral deficits seen in autism, and monoamine disruption may have a role in mediating those deficits, an understanding of the neurochemistry of BALB/c mice may shed light on the neuropathology of this disorder.
Therefore, the objective of this study was to determine if there are differences between BALB/c and C57BL/6J mice in the development of brain serotonergic and dopaminergic systems. It was hypothesized that analysis of the neurochemistry of the BALB/c mice, relative to that of C57BL/6J mice, would reveal alterations indicative of an “autistic” strain. That is, evidence of dopaminergic hyperactivity and/or serotonergic hypoactivity was expected.

GSTM1 in Autism:

Glutathione is an endogenous thiol-containing tripeptide which is produced in all organs, and plays an important role in our antioxidant defense system. Specifically, it is involved in the cellular defense against xenobiotics and naturally occurring deleterious compounds, such as free radicals and hydroperoxides (Pastore et al., 2003). Glutathione gene mutations have been implicated in autism (Ming et al., 2010; Williams et al., 2007; Buyske et al., 2006). One such mutation is glutathione-S-transferase M1 (GSTM1) allele deletions. Glutathione-S-transferases are a family of enzymes that catalyze the conjunction of glutathione with harmful compounds, and therefore are crucial to their biotransformation and detoxification (Das et al., 1981). Buyske et al. (2006) suggests that there is an association of the homozygous GSTM1 deletion genotype with an increased risk of autism. Because of the importance of glutathione activity in cellular antioxidant defense, individuals of the homozygous GSTM1 deletion genotype likely have a compromised antioxidant defense system and may be more vulnerable to environmental insult that results in oxidative damage. Although the population frequency
Experiment 2 Objective:

Because GSTM1 gene mutations have been linked to autism, an animal model of autism that incorporates this genetic influence may be a useful tool to study the disorder. As posited by Yochum et al. (2010), animals that have deficits in glutathione, when exposed to an environmental insult at a critical developmental time point, may show behavioral and neurochemical deficits that model those of autism. To that end, the objective of this study was to investigate the neurochemical development of both GSTM1 knockout and wildtype mice. This information will be useful in the further development of this animal model of autism.
MATERIALS AND METHODS

Experiment 1:

Animals:

Breeding colonies of BALB/c and C57BL/6J were established (original breeding pairs obtained from Jackson Laboratories, Bar Harbor, Maine). All animals were maintained under standard vivarium conditions, with free access to food and water and a 12:12 hour light:dark cycle. All procedures were approved by the Animal Care Committee and are in accordance with AAALAC guidelines. Non-sibling mice of the same strain were housed together in pan cages (3 females and 1 male per cage) and allowed to breed. Mice were monitored and the day pups were born was recorded as postnatal day 0 (P0). A total of 115 mice were used in this experiment (BALB/c, \( n = 63 \); C57BL/6J, \( n = 52 \)).

Brain Chemistry:

Male and female BALB/c and C57BL/6J mice pups were sacrificed on post-natal days 3, 10, or 30. Cerebellum, hippocampus, striatum, and frontal cortex regions were dissected, frozen in liquid nitrogen, and stored until homogenization in 0.3 ml of 0.4 N perchloric acid with 0.1 mM EDTA. Homogenized samples were centrifuged at 20,000 x g for 20 min at 4°C and the supernatant was frozen in liquid nitrogen until analyzed. Supernatant was assayed for dopamine, serotonin, and their metabolites using HPLC-electrochemical detection (Bioanalytical System, West Lafayette, Indiana). Samples were delivered through a high pressure (Rheodyne) valve fitted with a 20 µl sample loop onto a Biophase ODS C-18 reverse-phase column (5 mm, 250 x 4.6 mm i.d.), and
oxidized with a +.72 V potential between the glassy carbon electrode and the Ag/AgCl reference electrode. The mobile phase consisted of 0.1375 M sodium phosphate (dibasic), 0.0625 M citric acid, 5.0mg EDTA, and 14% methanol with a flow rate of 0.7ml/min. Quantification was measured against external standards injected between every six samples.

Statistical Analysis:

All data was analyzed using Statview statistical software. Outliers more than three standard deviations from the mean were removed from analysis. ANOVAs for strain and age were performed. Fisher's PLSD post hoc tests were performed on statistically significant main effects. $P$ values < 0.05 were considered statistically significant.

Experiment 2:

Animals:

The GSTM1 knockout and wildtype genotypes were established in the manner described by Yochum et al. (2010). A murine GSTM1 genomic clone was obtained from BAC/PAC Genomics Resource Center (CHORI). An 11 kb fragment containing all 8 exons of GSTM1 was amplified and subcloned in MC1TK-containing vector. A loxP-neo-Lox P cassette was inserted to replace exons 1–5, and final construct was obtained in Bluescript vector. The vector was linearized and electroporated into 129SVEv x C57BL/6 F1 hybrid ES cells. ES cell clones, which had undergone homologous recombination with the GSTM1 target vector, were selected on G418 (250 µg/ml) and
gancyclovir (2 µM)-containing medium. Gene-targeted mouse ES cells were injected into blastocysts and transferred to pseudopregnant females. Chimeric pups were born, germline transmission was confirmed for at least 3 animals, and colonies of the homozygous mutant animals have been established. Homozygous GSTM1 mice appeared to be normal and fertile. These GSTM1 colonies were maintained under the same conditions as the BALB/c and C57/BL6J colonies in experiment 1. A total of 156 mice were used in this experiment (Wildtype, $n = 80$; Knockout, $n = 76$)

Brain Chemistry:

Male and female GSTM1+/+ and GSTM1−/− mice pups were sacrificed on post-natal days 3, 10, or 30. The procedures for the neurochemical assay are the same as in experiment 1. Please note that the data for experiment 2 was collected during the establishment of the GSTM1 colony at a date prior to the completion of experiment 1. At that time, we were not confident in our ability to dissect hippocampal and striatal regions on P3. Therefore, data from these regions on P3 are not included.

Statistical Analysis:

All data was analyzed using the same statistical software and in the same manner as in experiment 1.
RESULTS

Experiment 1:
Cerebellum:

Neurochemical analysis of the cerebellum revealed a significant effect of age as well as a strain by age interaction on dopamine levels \( F(2, 105) = 21.487, p < .0001, \) and \( F(2,105) = 5.926, p = .0036, \) respectively (Figure 1; Table 1 A). With respect to age, post hoc analysis revealed that cerebellar concentrations of dopamine in both strains decreased as the animals matured. Specifically, in BALB/c mice, dopamine concentrations declined significantly on P10 and P30 as compared to the concentrations observed on P3. Likewise, in C57BL/6J mice, dopamine concentrations declined on P30 as compared to P3. With respect to strain, post hoc analysis revealed that BALB/c mice had significantly more cerebellar dopamine on P3 as compared to C57BL/6J mice. Neurochemical analysis of DOPAC levels revealed no changes over age or strain. However, HVA analysis revealed significant effects of age and strain \( F(2,105) = 6.612, p = .002, \) and \( F(1,105) = 5.926, p = .0.0443, \) respectively (Figure 2; Table 1A). Post hoc tests indicated that in C57BL/6J mice, HVA concentrations decreased significantly on P30 as compared to both P3 and P10. In BALB/c mice, HVA levels increased significantly on P10 from concentrations on P3 and decreased significantly on P30 as compared to P10. With respect to strain, post hoc analysis revealed that BALB/c mice had significantly less HVA on P3 than C57BL/6J mice. As for turnover rates, cerebellar DOPAC/DA turnover showed a significant effect of age \( F(2,105) = 7.644, p = .0008 \) (Figure 3; Table 1A), as turnover increased significantly on P30 for both strains, as compared to both P3 and P10. Neurochemical analysis of HVA/DA turnover, on the
other hand, did not show an effect of age, but did reveal an effect of strain \( F(1,105) = 4.468, p = .0369 \) (Figure 4; Table 1A). *Post hoc* analysis showed that BALB/c mice had a significantly lower HVA/DA turnover than C57BL/6J mice on P3.

Neurochemical analysis of the cerebellum also revealed significant effects of age and strain on serotonin levels \( F(2, 105) = 15.20, p < .0001 \) and \( F(1, 105) = 5.16, p = .02 \), respectively] (Figure 5; Table 1B). With respect to age, animals of both strains had significantly less serotonin at both P10 and P30 compared to P3. With respect to strain, *post hoc* analysis revealed that on P10, BALB/c pups had significantly less serotonin than C57BL/6J pups. However, by P30, BALB/c and C57BL/6J pups no longer had statistically different levels of serotonin. There was also a significant age effect for 5-HIAA \( F(2, 105) = 33.751, p < .0001 \) (Figure 6; Table 1B), with 5-HIAA levels decreasing with age. BALB/c mice showed a statistically significantly decrease in 5-HIAA at each age, while 5-HIAA levels in C57BL/6J mice only showed a significant decrease between P10 and P30. Finally, there were significant strain and age effects for serotonin turnover \( F(1,105) = 8.325, p = .004 \) and \( F(2,105) = 25.538, p < .0001 \), respectively] (Figure 7; Table 1B). *Post hoc* analysis revealed that BALB/c mice had a significantly lower turnover on P30 than on both P3 and P10. In C57BL/6J mice, there was a significant increase in turnover from P3 to P10, which then decreased by P30 to a level significantly lower than at both P3 and P10. As for differences between strains, BALB/c pups had significantly higher serotonin turnover than C57BL/6J pups on P30.

Hippocampus:
Neurochemical analysis of the hippocampus revealed a significant effect of strain for dopamine \( [F(1,104) = 4.492, p = .0364] \) (Table 2A). Although hippocampal levels of dopamine were higher in BALB/c animals at each age, producing a significant main effect, post hoc tests did not reveal statistically significant results at a particular time point. Analysis of DOPAC levels revealed no changes over sex or strain. HVA analysis, however, showed a significant effect of age \( [F(2,104) = 3.455, p = .0353] \) (Figure 8; Table 2A). Post hoc analysis indicated that in C57BL/6J mice, HVA increased significantly on P10 compared to P3, and then decreased significantly on P30 compared to P10. In addition, neurochemical analysis of DOPAC/DA turnover revealed no changes over sex or strain, but analysis of HVA/DA turnover showed a significant effect of age \( [F(2,104) = 5.905, p = .0037] \) (Figure 9; Table 2A). Post hoc analysis revealed that in BALB/c mice, there was a significant increase in HVA/DA turnover on both P10 and P30, when compared to P3. As for C57BL/6J mice, there was a significant increase on P10 compared to P3 and then a significant decrease from P10 to P30.

Neurochemical analysis of serotonin levels in the hippocampus revealed a significant effect of age, as serotonin increased with age in both strains \( [F(2,104) = 35.86, p < .0001] \) (Figure 10; Table 2B). Post hoc tests showed that in BALB/c mice, there was significantly more serotonin in the hippocampus at P30, than at both P3 and P10. The same effect was seen in the C57BL/6J mice, but there was also a significant increase in serotonin from P3 to P10. Analysis of 5HIAA revealed a significant effect of age as well, as 5-HIAA levels increased with age \( [F(2,104) = 23.641, p < .0001] \) (Figure 11; Table 2B). At P30, animals of both C57BL/6J and BALB/c strains, had significantly more serotonin than at P3 and P10. Neurochemical analysis of 5-HIAA/5-HT turnover
revealed significant effects of strain, age, and strain by age interaction \[F(1,104) = 12.358, p = .0007, F(2,104) = 6.142, p = .0030, \text{ and } F(2,104) = 4.022, p = .0208, \] respectively] (Figure 12; Table 2B). Post hoc analysis revealed that with respect to age BALB/c mice showed a significant decrease in turnover at P10 and P30, compared to P3. These age differences were not seen in C57BL/6J animals. Additionally, with respect to strain, BALB/c pups had significantly higher serotonin turnover ratios on P3 and P10 as compared to C57BL/6J pups. However, on P30, BALB/c and C57BL/6J pups had similar serotonin turnover ratios.

Striatum:

Neurochemical analysis of the striatum revealed a significant effect of strain, age, and strain by age interaction for dopamine levels \[F(1,106) = 8.322, p = .0047, F(2, 106) = 228.3, p < .0001, \text{ and } F(2,106) = 5.546, p = .0051, \] respectively] (Figure 13; Table 3A). Post hoc analysis revealed that in both strains, with respect to age, there was a significant increase in dopamine at P10 and P30, as compared to P3. Additionally, dopamine levels at P30 were significantly different than at P10. With respect to strain, BALB/c pups had significantly less striatal dopamine on P30 than C57BL/6J pups. Analysis of DOPAC levels indicated that there was an effect of both strain and age \[F(1,106) = 8.292, p = .0048, F(2,106) = 32.205, p < .0001, \] respectively] (Figure 14; Table 3A) Post hoc analysis revealed that with respect to age, DOPAC levels in BALB/c mice increased significantly from P3 to P10 and increased again from P10 to P30. In C57BL/6J mice, DOPAC levels increased significantly on P30, as compared to both P3 and P10. With respect to strain, BALB/c pups had significantly less DOPAC than C57BL/6J pups.
starting on P10 and this difference increased by P30. There was an effect of age on HVA levels as well \[F(2,106) = 60.314, p < .0001\] (Figure 15; Table 3A). Further analysis showed that in BALB/c pups, HVA levels significantly increased on P10 as compared to P3, and then significantly increased again from P10 to P30. In C57BL/6J mice, HVA levels were significantly higher at P30 than at both P3 and P10. As for turnovers, neurochemical analysis revealed no changes in DOPAC/DA turnover, but did show an effect of age on HVA/DA turnover \[F(2,106) = 3.290, p = .0411\] (Figure 16; Table 3A). Both strains showed a significant increase in turnover on P10 compared to P3.

Neurochemical analysis of the striatum revealed a significant effect of age on serotonin \[F(2,105) = 160.099, p < .0001\] (Figure 17; Table 3B). Post hoc tests showed that BALB/c mice have significantly more serotonin on P30 than at P3 and P10. Additionally, post hoc tests showed that in C57BL/6J mice, serotonin increased significantly from P3 to P10 and then again from P10 to P30. Analysis of 5-HIAA revealed an effect of both strain and age \[F(1,105) = 6.936, p = .0097, \text{ and } F(2,105) = 75.549, p < .0001, \text{ respectively}\] (Figure 18; Table 3B). With respect to age, both BALB/c and C57BL/6J mice showed significant increases in 5HIAA from P3 to P10 and then again from P10 to P30. As for strain differences, BALB/c pups had significantly less 5-HIAA at P10 than their C57BL/6J counterparts. In addition, there was also a significant effect of age on 5-HIAA/5-HT turnover \[F(2,105) = 23.586, p < .0001\] (Figure 19; Table 3B). Post hoc tests revealed that in BALB/c pups turnover was significantly higher on P10 than P3, and then decreased to a level significantly lower than at both P3 and P10. As for C57BL/6J animals, there was significantly higher turnover on
P10 as compared to P3, and then turnover decreased significantly on P30 as compared to P10.

Frontal Cortex:

Neurochemical analysis of the frontal cortex revealed a significant effect of age on dopamine, as dopamine levels increased with age [$F(2, 109) = 22.324, p < .0001$] (Figure 20; Table 4A). Post hoc analysis revealed that both BALB/c and C57BL/6J pups had significantly more dopamine on P30 than on both P3 and P10. Additionally, there was a significant effect of age on DOPAC [$F(2, 109) = 7.190, p = .0012$] (Figure 21; Table 4A). Like dopamine, DOPAC levels increased with age. In BALB/c mice, DOPAC levels were significantly greater on P30 as compared to P3. In C57BL/6J mice, DOPAC levels on P30 were significantly greater than on both P3 and P10. There was also a significant effect of both strain and age on HVA [$F(1, 109) = 6.360, p = .0131$, and $F(2, 109) = 13.836, p < .0001$, respectively] (Figure 22; Table 4A). Post hoc analysis revealed that, with respect to age, BALB/c pups had significantly more HVA on P30 than at P3. As for C57BL/6J mice, there was a significant increase in HVA from P3 to P10 and then again from P10 to P30. With respect to strain, BALB/c mice had significantly more HVA than C57BL/6J mice on P10 and P30. Neurochemical analysis revealed no changes in either DOPAC/DA turnover or HVA/DA turnover in the frontal cortex.

Analysis revealed a significant effect of age on serotonin levels in the frontal cortex [$F(2, 109) = 12.134, p < .0001$] (Figure 23; Table 4B). Post hoc tests showed that in BALB/c animals there was significantly more serotonin on P30 than on P3. As for C57BL/6J mice, there was a significant increase in serotonin on P30 as compared to both
P3 and P10. Neurochemical analysis showed no significant effects on 5-HIAA. However, it did reveal a significant effect of age on 5-HIAA/5-HT turnover \( [F(2, 109) = 12.549, p < .0001] \) (Figure 24; Table 4B). Post hoc analysis showed that in BALB/c mice, there was a significant increase in turnover on P10 as compared to P3. On P30, however, 5-HIAA/5-HT turnover was significantly lower than on both P3 and P10. With regards to C57BL/6J pups, there was significantly lower turnover on P30 as compared to P3.

Experiment 2:
Cerebellum:

Neurochemical analysis of the cerebellum revealed a significant effect of age and a significant age by genotype interaction for dopamine levels \( [F(2,140) = 10.731, p < .0001, \text{ and } F(2,140) = 3.606, p = .0297, \text{ respectively}] \) (Figure 25; Table 5A). Post hoc tests showed that for both genotypes there was significantly less dopamine on P30 as compared to P3. Additionally, analysis revealed that this decrease in dopamine occurred sooner in wildtype mice than knockout mice, as there was significantly less dopamine on P10 than P3 in wildtype animals. With respect to genotype, knockout animals had significantly more dopamine than their wildtype counterparts on P30. Neurochemical analysis also revealed a significant effect of age on DOPAC \( [F(2,139) = 16.488, p < .0001] \) (Figure 26; Table 5A). Post hoc analysis indicated that for both genotypes, DOPAC levels were significantly greater on P30 than on either P3 or P10. As for HVA, analysis showed that there was a significant effect of age, as well as a significant age by genotype interaction \( [F(2,138) = 9.781, p = .0001, \text{ and } F(2,138) = 3.499, p = .0329, \text{ respectively}] \).
respectively] (Figure 27; Table 5A). For wildtype mice, there was a significant decrease in HVA levels in the cerebellum on P30 compared to both P10 and P3. For knockout animals, this decrease on P30 is only significantly different from levels on P10. In addition, post hoc tests revealed that wildtype mice had significantly more HVA than knockout animals on P3, but this genotypic difference no longer remained on P10. Neurochemical analysis also uncovered significant effects of age and genotype interaction for DOPAC/DA turnover \( F(2,137) = 116.569, p < .0001, \) and \( F(2,137) = 6.512, p = .0014, \) respectively] (Figure 28; Table 5A). Post hoc analysis revealed that with respect to age, mice of both genotypes showed a significant increase in DOPAC/DA turnover from P3 to P10 and then again from P10 to P30. There was also a significant effect of genotype on P30, as wildtype animals had higher turnover than knockout mice. Like DOPAC/DA turnover, analysis of HVA/DA turnover also showed significant effects of age and genotype interaction \( F(2,134) = 16.773, p < .0001, \) and \( F(2,134) = 7.147, p = .0308, \) respectively] (Figure 29; Table 5A). Both genotypes showed a significant decrease in turnover on P30 as compared to both P3 and P10. Additionally, with respect to genotype, wildtype mice had significantly higher turnover on P3 and significantly lower turnover on P30 than knockout mice.

Neurochemical analysis of the cerebellum revealed significant effects of age, genotype, and age by genotype interaction for serotonin \( F(2,142) = 78.194, p < .0001, \) \( F(1,142) = 4.017, p = .0469, \) and \( F(2,142) = 5.645, p = .0044, \) respectively] (Figure 30; Table 5B). With respect to age, both wildtype and knockout animals showed a significant decrease in serotonin on P10 and P30 relative to P3. However, only wildtype mice had a significant decrease from P10 to P30. As for genotype, there were significant
differences between the two genotypes at every age. Wildtype mice had significantly more serotonin than knockout mice on P3 and P10, but had less serotonin on P30. Like serotonin, there were significant effects of age, genotype, and age by genotype interaction for 5-HIAA levels \( F(2,140) = 138.237, p < .0001, F(1,140) = 7.947, p = .0055, \) and \( F(2,140) = 3.607, p = .0297, \) respectively] (Figure 31; Table 5B). 5-HIAA levels significantly decreased with age from P3 to P10 and then again from P10 to P30 in both genotypes. Wildtype mice had significantly more 5-HIAA on P3 and P10 than knockout animals. Analysis revealed a significant effect of age for 5-HIAA/5-HT turnover \( F(2,139) = 37.710, p < .0001 \) (Figure 32; Table 5B). Both genotypes showed a significant increase in turnover from P3 to P10 and then a significant decrease from P10 to P30. Additionally, turnover on P30, for both genotypes, was significantly less than turnover on P3.

Hippocampus:

Neurochemical analysis of the hippocampus did not reveal any significant effects on dopamine or DOPAC levels. There was, however, a significant effect of age on HVA \( F(1,90) = 48.007, p < .0001 \) (Figure 33; Table 6A). Post hoc analysis uncovered a significant decrease in HVA from P10 to P30 for both genotypes. There was also significant effect of age on DOPAC/DA turnover \( F(1,88) = 5.400, p = .0024 \) (Figure 34; Table 6A). Wildtype mice showed a significant increase in DOPAC/DA turnover from P10 to P30. Similarly, there was a significant effect of age on HVA/DA \( F(1,87) = 88.751, p < .0001 \) (Figure 35; Table 6A). Post hoc tests showed that for both genotypes, HVA/DA turnover decreased significantly from P10 to P30.
Neurochemical analysis of the hippocampus revealed significant effects of age and genotype on serotonin levels $[F(1,89) = 149.229, p < .0001$, and $F(1,89) = 7.732, p = .0066$, respectively] (Figure 36; Table 6B). Post hoc tests revealed that serotonin increased significantly from P10 to P30 for both genotypes. In addition, wildtype animals had significantly less serotonin at P30 than their knockout counterparts. As for 5-HIAA levels in the hippocampus, there was a significant effect of age $[F(1,90) = 19.760, p < .0001]$ (Figure 37; Table 6B). Both genotypes showed an increase in 5-HIAA with age, as there was significantly more 5-HIAA on P30 than on P10. Like 5-HIAA, there was a significant effect of age on 5-HIAA/5-HT turnover $[F(1,88) = 60.350, p < .0001]$ (Figure 38; Table 6B). Post hoc analysis showed that turnover significantly decreased from P10 to P30 for both genotypes.

Striatum:

Neurochemical analysis of the striatum revealed a significant effect of age on dopamine $[F(1,87) = 30.625, p < .0001]$ (Figure 39; Table 7A). Post hoc tests indicated that dopamine levels significantly increased from P10 to P30 in both genotypes. As for DOPAC levels in the striatum, analysis showed significant effects of age and age by genotype interaction $[F(1,86) = 20.714, p < .0001, and F(1,86) = 4.218, p = .0430$, respectively] (Figure 40; Table 7A). With respect to age, there was a significant increase in DOPAC levels in knockout mice from P10 to P30. Despite the significant age by genotype interaction, post hoc tests did not reveal any significant effects of genotype. There were also significant effects of age and genotype on striatal HVA $[F(1,86) = 15.426, p = .0002, and F(1,86) = 3.962, p = .0497$, respectively] (Figure 41; Table 7A).
Both wildtype and knockout animals showed a significant increase in HVA from P10 to P30. In addition, wildtype mice had significantly less HVA than knockout mice on P30. Neurochemical analysis did not reveal any significant effects of DOPAC/DA turnover, but there was an effect of age on HVA/DA turnover [$F(1,82) = 9.537, p = .0027$] (Figure 42; Table 7A). *Post hoc* analysis showed that there was a significant decrease in HVA/DA turnover from P10 to P30 in wildtype animals.

Neurochemical analysis of the striatum revealed a significant effect of age, as well as a significant age by genotype interaction for serotonin levels [$F(1,86) = 67.045, p < .0001$, and $F(1,86) = 5.468, p = .0217$, respectively] (Figure 43; Table 7B). *Post hoc* tests indicated that both genotypes showed a significant increase in serotonin from P10 to P30. With respect to genotype, wildtype animals had significantly less serotonin on P30 than knockout mice. As for striatal 5-HIAA levels, analysis indicated that there was a significant age by genotype interaction [$F(1,86) = 7.333, p = .0082$] (Figure 44; Table 7B). *Post hoc* analysis showed, with respect to age, that 5-HIAA levels decreased significantly from P10 to P30 in wildtype mice. As for genotypic differences, wildtype mice had significantly less 5-HIAA on P30 than their knockout counterparts. Neurochemical analysis also revealed a significant effect of age on 5-HIAA/5-HT turnover [$F(1,84) = 387.903, p < .0001$] (Figure 45; Table 7B). Both genotypes show a significant decrease in turnover from P10 to P30.

Frontal Cortex:

Neurochemical analysis of the frontal cortex revealed a significant effect of age on dopamine levels [$F(2,138) = 9.297, p = .0002$] (Figure 46; Table 8A). Both genotypes
showed a significant decrease in dopamine from P3 to P10. Although dopamine levels increased from P10 to P30 in both genotypes, the increase was only significant in wildtype animals. Like dopamine, there was also a significant effect of age on DOPAC levels in the frontal cortex \[ F(2,140) = 5.093, p = .0073 \] (Figure 47; Table 8A). Post hoc analysis indicated that DOPAC levels at P30, in knockout animals, were significantly higher than on both P3 and P10. Neurochemical analysis did not uncover any effects on cortical HVA levels, but did reveal an effect of age on DOPAC/DA turnover \[ F(2,135) = 29.410, p < .0001 \] (Figure 48; Table 8A). DOPAC/DA turnover increased with age in both genotypes. In wildtype animals, post hoc tests showed that turnover was significantly higher on P30 than on both P3 and P10. In knockout mice, DOPAC/DA turnover increased significantly from P3 to P10 and remained significantly higher than P3 on P30. There was also a significant effect of age on HVA/DA turnover \[ F(2,133) = 4.680, p = .0109 \] (Figure 49; Table 8A). In knockout animals, there was a significant increase in turnover from P3 to P10, and then a significant decrease from P10 to P30.

Neurochemical analysis of the frontal cortex revealed a significant effect of age and an age by genotype interaction on serotonin \[ F(2,138) = 9.598, p = .0001, \text{ and } F(2,138) = 4.176, p = .0174, \text{ respectively} \] (Figure 50; Table 8B). Post hoc tests showed that with respect to age, knockout animals had significantly more cortical serotonin on P30 as compared to P3 and P10. With respect to genotype, wildtype animals had significantly more serotonin than knockout animals on P3 and significantly less serotonin on P30. There were no significant effects on 5-HIAA levels, but there was an effect of age on 5-HIAA/5-HT turnover \[ F(2,134) = 5.407, p = .0322 \] (Figure 51; Table 8B). Post
hoc analysis revealed that in wildtype mice turnover was significantly lower on P30 than on P3 and P10.
DISCUSSION

Experiment 1:

Although the neuropathology of autism is not well understood, a number of studies have suggested that there may be alterations in the cerebellum, hippocampus, striatum and/or frontal cortex of individuals with autism as compared to age-matched controls (Bauman and Kemper, 2005; Langen et al., 2009; Amaral et al., 2008). Results of the present study reveal regional differences in development of the brain monoaminergic system across both age and strain in these regions. Most notably, in the cerebellum it was found that both dopamine and serotonin levels decrease with age and that the BALB/c mice tend to have higher levels of serotonin in this brain region as compared to C57BL/6J mice. In the hippocampus, it was found that serotonin levels increase with age in both strains and that serotonin turnover is elevated in BALB/c mice as compared to the C57BL/6J mice. In the striatum, increases in both dopamine and serotonin concentrations over age were observed, as well as a significant decrease in dopamine levels apparent in BALB/c mice as compared to C57BL/6J mice. Finally, the same strong increase in dopamine and serotonin levels over age was observed in the frontal cortex, but this region exhibited no differences in levels of either neurotransmitter with respect to strain.

As noted, it has been asserted that the BALB/c strain of mice may serve as an "animal model" of autism (Crawley et al., 1997; Brodkin, 2007). These observations have been based on behavioral and anatomical observations comparing the BALB/c mice with other strains, notably C57BL/6J mice (Crawley et al., 1997; Brodkin, 2007; Panksepp and Lahvis, 2007). To date, these comparisons have been made predominately
in adults. The present study examined the maturation of the dopaminergic and serotonergic systems in these two strains and found significant alterations associated with age and strain. Of interest, these alterations appear in brain regions that have been linked to autism. It had been hypothesized that the BALB/c mice would show decreased serotonergic activity and/or increased dopaminergic activity relative to the C57BL/6J pups. However, only some of the observed neurochemical differences between BALB/c and C57BL/6J mice were in the hypothesized direction. Evidence of dopamine overactivity in the BALB/c animals was limited to increased cerebellar dopamine on P3, as well as increased HVA on P10 and P30 in the frontal cortex. Decreases in cerebellar serotonin on P10 and striatal 5-HIAA on P10 may indicate decreased release of serotonin. Considering the changes are fleeting and limited to a few brain regions, these observed differences in neurochemistry provide limited, if any, support for using BALB/c mice as a model of autism.

Our hypothesis, that BALB/c mice would show decreased serotonergic activity and/or increased dopaminergic activity was based on the assumption that BALB/c mice might serve as a valid model of autism. Specifically, with respect to serotonin, we expected that the decreased brain serotonin that has been observed in frontal cortex and striatum of 8-week old BALB/c mice (Brodkin, 2007) might be present during early development. However, we did not detect a decrease in serotonin in either region by P30. It is possible that this change occurs at an age older than 30 days.

Whitaker-Azmitia (2005) suggests a mechanism by which the blood hyperserotonemia observed in some autistic individuals can result in serotonergic depletion in the brain, and ultimately behavioral deficits. The hypothesis proposed by
Whitaker-Azmitia (2005) states that high levels of blood serotonin at early stages of development may enter the brain prior to the formation of the blood-brain barrier and lead to a loss of serotonin terminals through negative feedback mediated by the 5-HT1A receptor. If BALB/c mice exhibit higher levels of serotonin in their blood, we might expect to see increased serotonin content in the brain prior to the formation of blood-brain barrier, which occurs at approximately 20 days of age in rodents (Whitaker-Azmitia, 2005), and decreases in serotonin once it is fully formed. However, analysis of the BALB/c neurochemistry did not support this hypothesis. This suggests that BALB/c mice do not model Whitaker-Azmitia blood-brain barrier hypothesis. Conversely, this does not preclude the hypothesis from accurately describing serotonin activity in humans with blood hyperserotonemia.

Despite the fact that the BALB/c strain displays similarities to the autism phenotype, such as antisocial, anxious, and aggressive behavior (Brodkin, 2007; Crawley et al., 1997), our results suggest that this strain, without any additional treatment, does not adequately model the monoaminergic deficits associated with autism. An animal model of autism that encompasses factors in addition to strain may provide a more appropriate and comprehensive model. For example, environmental insult appears to play an important role in the development of autism (Kern and Jones, 2006; Rodier and Hyman, 1998) and it is likely that gene alterations render some individuals particularly sensitive to such insult. A model that accounts for these multiple factors may provide a better representation of both the behavioral and neurochemical deficits that accompany the disorder (e.g. Yochum et al., 2008; Yochum et al., 2010). In these studies, an environmental toxicant is administered to genetically-compromised animals at a critical
time of brain development, producing behavioral and neural deficits that model those observed in autism.

In summary, we observed early developmental neurochemical alterations that may be associated with both the behavioral and anatomical differences identified in BALB/c mice. However, for the most part, these differences alone do not support the notion that BALB/c mice provide a strong representation of the neurochemical abnormalities associated with autism. An animal model that includes genetic, age, and environmental factors might provide a better model of the disorder.

Experiment 2:

Like the first experiment, the results of experiment 2 reveal regional differences in neurochemical development across both age and strain in the cerebellum, hippocampus, striatum and frontal cortex. In the cerebellum it was found that both dopamine and serotonin levels decrease with age. Additionally, wildtype mice show a number of differences in dopaminergic and serotonergic activity as compared to the knockout animals. For example, there are differences in dopamine turnover, and wildtype mice exhibit early increases in serotonin and 5-HIAA. In the hippocampus, serotonin was found to increase with age, and wildtype mice had less serotonin than knockout mice in this region. In the striatum, there were increases in both dopamine and serotonin levels with age. Like in the previous regions, it was found that wildtype and mice had differences in serotonergic activity, as wildtype mice had less serotonin and 5-HIAA than knockout animals. Finally, in the frontal cortex, we again observed age related effects on dopamine and serotonin, as well genotypic differences in serotonergic
activity. Specifically, wildtype mice showed an early increase in serotonin relative to knockout animals. However, wildtype animals later showed a decrease in serotonin levels as compared to the knockout mice.

It is interesting that there were so many differences in neurochemical development between the two genotypes, as the deletion of GSTM1 was not expected to result in neurochemical changes. It is unclear why this genetic alteration resulted in these changes. On the other hand, had these animals been treated with a toxicant that results in oxidative damage, we might expect neurochemical differences to appear between the genotypes. Yochum et al. (2010) treated GSTM1 homozygous wildtype and knockout mice with either sodium valproate (VPA) or saline on P14. VPA is a toxicant known to cause neural and behavioral deficits in developing animals, and its toxicity is believed to be mediated, at least partly, by oxidative stress. Although VPA treatment produced neurochemical changes in the hippocampus and cerebellum, genotype did not appear to alter VPA’s effect on neurochemistry. However, genotype did have an effect on apoptosis in those brain regions, as VPA-treated wildtype females had significantly fewer apoptotic cells than any other VPA-treated animals. Additionally, VPA-treated knockout animals, as compared to wildtype mice, showed a significant decrease in crawl-unders, a measure of social behavior. Despite the fact that there was not an effect of genotype on neurochemistry in VPA-treated mice, the wildtype mice did appear partially protected from the deleterious effects of VPA as evidenced by the apoptosis and behavioral data.

The work of Yochum et al. (2010) demonstrates the utility of a GSTM1 mouse model of autism. Specifically, this model attempts to capture the dynamic interaction of age, environmental, and genetic factors in the disorder. The present study provides
insight into the neurochemical development of these mice and will be useful in the further
development of this animal model of autism.
REFERENCES

Brodkin, E.S., 2007. BALB/c mice: low sociability and other phenotypes that may be relevant to autism. Behav Brain Res. 176, 53-65.


TABLE LEGENDS

Table 1: Cerebellar Neurochemistry for BALB/c and C57BL/6J Pups on P3, P10, and P30. Values are mean µg/g of tissue. SEM provided in parentheses. All values were rounded to two decimal places.

+ indicates effect of age compared to P3, within strain \((p < 0.05)\).

^ indicates effect of age compared to P10, within strain \((p < 0.05)\).

* indicates effect of strain at that age \((p < 0.05)\).

Table 2: Hippocampal Neurochemistry for BALB/c and C57BL/6J Pups on P3, P10, and P30. Values are mean µg/g of tissue. SEM provided in parentheses. All values were rounded to two decimal places.

+ indicates effect of age compared to P3, within strain \((p < 0.05)\).

^ indicates effect of age compared to P10, within strain \((p < 0.05)\).

* indicates effect of strain at that age \((p < 0.05)\).

Table 3: Striatal Neurochemistry for BALB/c and C57BL/6J Pups on P3, P10, and P30. Values are mean µg/g of tissue. SEM provided in parentheses. All values were rounded to two decimal places.

+ indicates effect of age compared to P3, within strain \((p < 0.05)\).

^ indicates effect of age compared to P10, within strain \((p < 0.05)\).

* indicates effect of strain at that age \((p < 0.05)\).
Table 4: Frontal Cortex Neurochemistry for BALB/c and C57BL/6J Pups on P3, P10, and P30. Values are mean µg/g of tissue. SEM provided in parentheses. All values were rounded to two decimal places.
+

indicates effect of age compared to P3, within strain (p < 0.05).

^indicates effect of age compared to P10, within strain (p < 0.05).

*indicates effect of strain at that age (p < 0.05).

Table 5: Cerebellar Neurochemistry for GSTM1 Wildtype and Knockout Pups on P3, P10, and P30. Values are mean µg/g of tissue. SEM provided in parentheses. All values were rounded to two decimal places.
+

indicates effect of age compared to P3, within genotype (p < 0.05).

^indicates effect of age compared to P10, within genotype (p < 0.05).

*indicates effect of genotype at that age (p < 0.05).

Table 6: Hippocampal Neurochemistry for GSTM1 Wildtype and Knockout Pups on P10 and P30. Values are mean µg/g of tissue. SEM provided in parentheses. All values were rounded to two decimal places.

^indicates effect of age compared to P10, within genotype (p < 0.05).

*indicates effect of genotype at that age (p < 0.05).

Table 7: Striatal Neurochemistry for GSTM1 Wildtype and Knockout Pups on P10 and P30. Values are mean µg/g of tissue. SEM provided in parentheses. All values were rounded to two decimal places.
Table 8: Frontal Cortex Neurochemistry for GSTM1 Wildtype and Knockout Pups on P3, P10, and P30. Values are mean µg/g of tissue. SEM provided in parentheses. All values were rounded to two decimal places.

+ indicates effect of age compared to P3, within genotype ($p < 0.05$).

^ indicates effect of age compared to P10, within genotype ($p < 0.05$).

* indicates effect of genotype at that age ($p < 0.05$).
Table 1: BALB/c and C57BL/6J Cerebellar Neurochemistry

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Table 2: BALB/c and C57BL/6J Hippocampal Neurochemistry

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Table 3: BALB/c and C57BL/6J Striatal Neurochemistry

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Table 4: BALB/c and C57BL/6J Frontal Cortex Neurochemistry

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Table 5: GSTM1 Wildtype and Knockout Cerebellar Neurochemistry

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Table 6: GSTM1 Wildtype and Knockout Hippocampal Neurochemistry

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Table 7: GSTM1 Wildtype and Knockout Striatal Neurochemistry

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Table 8: GSTM1 Wildtype and Knockout Frontal Cortex Neurochemistry

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FIGURE LEGENDS

Figure 1: Cerebellar dopamine of BALB/c and C57BL/6J mice sacrificed on P3, P10, or P30. Values are mean µg/g of tissue. Error bars represent SEM.
+ indicates effect of age compared to P3, within strain (p < 0.05).
* indicates effect of strain at that age (p < 0.05).

Figure 2: Cerebellar HVA of BALB/c and C57BL/6J mice sacrificed on P3, P10, or P30. Values are mean µg/g of tissue. Error bars represent SEM.
+ indicates effect of age compared to P3, within strain (p < 0.05).
^ indicates effect of age compared to P10, within strain (p < 0.05).
* indicates effect of strain at that age (p < 0.05).

Figure 3: Cerebellar DOPAC/DA turnover of BALB/c and C57BL/6J mice sacrificed on P3, P10, or P30. Values are mean µg/g of tissue. Error bars represent SEM.
+ indicates effect of age compared to P3, within strain (p < 0.05).
^ indicates effect of age compared to P10, within strain (p < 0.05).

Figure 4: Cerebellar HVA/DA turnover of BALB/c and C57BL/6J mice sacrificed on P3, P10, or P30. Values are mean µg/g of tissue. Error bars represent SEM.
* indicates effect of strain at that age (p < 0.05).

Figure 5: Cerebellar serotonin of BALB/c and C57BL/6J mice sacrificed on P3, P10, or P30. Values are mean µg/g of tissue. Error bars represent SEM.
+ indicates effect of age compared to P3, within strain ($p < 0.05$).

^ indicates effect of age compared to P10, within strain ($p < 0.05$).

* indicates effect of strain at that age ($p < 0.05$).

Figure 6: Cerebellar 5-HIAA of BALB/c and C57BL/6J mice sacrificed on P3, P10, or P30. Values are mean $\mu g/g$ of tissue. Error bars represent SEM.

+ indicates effect of age compared to P3, within strain ($p < 0.05$).

^ indicates effect of age compared to P10, within strain ($p < 0.05$).

Figure 7: Cerebellar 5-HIAA/5-HT turnover of BALB/c and C57BL/6J mice sacrificed on P3, P10, or P30. Values are mean $\mu g/g$ of tissue. Error bars represent SEM.

+ indicates effect of age compared to P3, within strain ($p < 0.05$).

^ indicates effect of age compared to P10, within strain ($p < 0.05$).

* indicates effect of strain at that age ($p < 0.05$).

Figure 8: Hippocampal HVA of BALB/c and C57BL/6J mice sacrificed on P3, P10, or P30. Values are mean $\mu g/g$ of tissue. Error bars represent SEM.

+ indicates effect of age compared to P3, within strain ($p < 0.05$).

^ indicates effect of age compared to P10, within strain ($p < 0.05$).

Figure 9: Hippocampal HVA/DA turnover of BALB/c and C57BL/6J mice sacrificed on P3, P10, or P30. Values are mean $\mu g/g$ of tissue. Error bars represent SEM.

+ indicates effect of age compared to P3, within strain ($p < 0.05$).
^ indicates effect of age compared to P10, within strain ($p < 0.05$).

Figure 10: Hippocampal serotonin of BALB/c and C57BL/6J mice sacrificed on P3, P10, or P30. Values are mean $\mu$g/g of tissue. Error bars represent SEM.
+ indicates effect of age compared to P3, within strain ($p < 0.05$).
^ indicates effect of age compared to P10, within strain ($p < 0.05$).

Figure 11: Hippocampal 5-HIAA of BALB/c and C57BL/6J mice sacrificed on P3, P10, or P30. Values are mean $\mu$g/g of tissue. Error bars represent SEM.
+ indicates effect of age compared to P3, within strain ($p < 0.05$).
^ indicates effect of age compared to P10, within strain ($p < 0.05$).

Figure 12: Hippocampal 5-HIAA/5-HT turnover of BALB/c and C57BL/6J mice sacrificed on P3, P10, or P30. Values are mean $\mu$g/g of tissue. Error bars represent SEM.
+ indicates effect of age compared to P3, within strain ($p < 0.05$).
* indicates effect of strain at that age ($p < 0.05$).

Figure 13: Striatal dopamine of BALB/c and C57BL/6J mice sacrificed on P3, P10, or P30. Values are mean $\mu$g/g of tissue. Error bars represent SEM.
+ indicates effect of age compared to P3, within strain ($p < 0.05$).
^ indicates effect of age compared to P10, within strain ($p < 0.05$).
* indicates effect of strain at that age ($p < 0.05$).
Figure 14: Striatal DOPAC of BALB/c and C57BL/6J mice sacrificed on P3, P10, or P30. Values are mean µg/g of tissue. Error bars represent SEM.

+ indicates effect of age compared to P3, within strain ($p < 0.05$).

^ indicates effect of age compared to P10, within strain ($p < 0.05$).

* indicates effect of strain at that age ($p < 0.05$).

Figure 15: Striatal HVA of BALB/c and C57BL/6J mice sacrificed on P3, P10, or P30. Values are mean µg/g of tissue. Error bars represent SEM.

+ indicates effect of age compared to P3, within strain ($p < 0.05$).

^ indicates effect of age compared to P10, within strain ($p < 0.05$).

Figure 16: Striatal HVA/DA turnover of BALB/c and C57BL/6J mice sacrificed on P3, P10, or P30. Values are mean µg/g of tissue. Error bars represent SEM.

+ indicates effect of age compared to P3, within strain ($p < 0.05$).

Figure 17: Striatal serotonin of BALB/c and C57BL/6J mice sacrificed on P3, P10, or P30. Values are mean µg/g of tissue. Error bars represent SEM.

+ indicates effect of age compared to P3, within strain ($p < 0.05$).

^ indicates effect of age compared to P10, within strain ($p < 0.05$).

Figure 18: Striatal 5-HIAA of BALB/c and C57BL/6J mice sacrificed on P3, P10, or P30. Values are mean µg/g of tissue. Error bars represent SEM.

+ indicates effect of age compared to P3, within strain ($p < 0.05$).
^ indicates effect of age compared to P10, within strain (p < 0.05).
* indicates effect of strain at that age (p < 0.05).

Figure 19: Striatal 5-HIAA/5-HT turnover of BALB/c and C57BL/6J mice sacrificed on P3, P10, or P30. Values are mean µg/g of tissue. Error bars represent SEM.
+ indicates effect of age compared to P3, within strain (p < 0.05).
^ indicates effect of age compared to P10, within strain (p < 0.05).

Figure 20: Frontal cortex dopamine of BALB/c and C57BL/6J mice sacrificed on P3, P10, or P30. Values are mean µg/g of tissue. Error bars represent SEM.
+ indicates effect of age compared to P3, within strain (p < 0.05).
^ indicates effect of age compared to P10, within strain (p < 0.05).

Figure 21: Frontal cortex DOPAC of BALB/c and C57BL/6J mice sacrificed on P3, P10, or P30. Values are mean µg/g of tissue. Error bars represent SEM.
+ indicates effect of age compared to P3, within strain (p < 0.05).
^ indicates effect of age compared to P10, within strain (p < 0.05).

Figure 22: Frontal cortex HVA of BALB/c and C57BL/6J mice sacrificed on P3, P10, or P30. Values are mean µg/g of tissue. Error bars represent SEM.
+ indicates effect of age compared to P3, within strain (p < 0.05).
^ indicates effect of age compared to P10, within strain (p < 0.05).
* indicates effect of strain at that age (p < 0.05).
Figure 23: Frontal cortex serotonin of BALB/c and C57BL/6J mice sacrificed on P3, P10, or P30. Values are mean µg/g of tissue. Error bars represent SEM.

+ indicates effect of age compared to P3, within strain ($p < 0.05$).

^ indicates effect of age compared to P10, within strain ($p < 0.05$).

Figure 24: Frontal cortex 5-HIAA/5-HT turnover of BALB/c and C57BL/6J mice sacrificed on P3, P10, or P30. Values are mean µg/g of tissue. Error bars represent SEM.

+ indicates effect of age compared to P3, within strain ($p < 0.05$).

^ indicates effect of age compared to P10, within strain ($p < 0.05$).

Figure 25: Cerebellar dopamine of GSTM1 wildtype and knockout mice sacrificed on P3, P10, or P30. Values are mean µg/g of tissue. Error bars represent SEM.

+ indicates effect of age compared to P3, within strain ($p < 0.05$).

* indicates effect of strain at that age ($p < 0.05$).

Figure 26: Cerebellar DOPAC of GSTM1 wildtype and knockout mice sacrificed on P3, P10, or P30. Values are mean µg/g of tissue. Error bars represent SEM.

+ indicates effect of age compared to P3, within strain ($p < 0.05$).

^ indicates effect of age compared to P10, within strain ($p < 0.05$).

Figure 27: Cerebellar HVA of GSTM1 wildtype and knockout mice sacrificed on P3, P10, or P30. Values are mean µg/g of tissue. Error bars represent SEM.

+ indicates effect of age compared to P3, within strain ($p < 0.05$).
^ indicates effect of age compared to P10, within strain ($p < 0.05$).

* indicates effect of strain at that age ($p < 0.05$).

Figure 28: Cerebellar DOPAC/DA turnover of GSTM1 wildtype and knockout mice sacrificed on P3, P10, or P30. Values are mean µg/g of tissue. Error bars represent SEM.

+ indicates effect of age compared to P3, within strain ($p < 0.05$).

^ indicates effect of age compared to P10, within strain ($p < 0.05$).

* indicates effect of strain at that age ($p < 0.05$).

Figure 29: Cerebellar HVA/DA turnover of GSTM1 wildtype and knockout mice sacrificed on P3, P10, or P30. Values are mean µg/g of tissue. Error bars represent SEM.

+ indicates effect of age compared to P3, within strain ($p < 0.05$).

^ indicates effect of age compared to P10, within strain ($p < 0.05$).

* indicates effect of strain at that age ($p < 0.05$).

Figure 30: Cerebellar serotonin of GSTM1 wildtype and knockout mice sacrificed on P3, P10, or P30. Values are mean µg/g of tissue. Error bars represent SEM.

+ indicates effect of age compared to P3, within strain ($p < 0.05$).

^ indicates effect of age compared to P10, within strain ($p < 0.05$).

* indicates effect of strain at that age ($p < 0.05$).

Figure 31: Cerebellar 5-HIAA of GSTM1 wildtype and knockout mice sacrificed on P3, P10, or P30. Values are mean µg/g of tissue. Error bars represent SEM.
+ indicates effect of age compared to P3, within strain (p < 0.05).

^ indicates effect of age compared to P10, within strain (p < 0.05).

* indicates effect of strain at that age (p < 0.05).

Figure 32: Cerebellar 5-HIAA/5-HT turnover of GSTM1 wildtype and knockout mice sacrificed on P3, P10, or P30. Values are mean µg/g of tissue. Error bars represent SEM.

+ indicates effect of age compared to P3, within strain (p < 0.05).

^ indicates effect of age compared to P10, within strain (p < 0.05).

Figure 33: Hippocampal HVA of GSTM1 wildtype and knockout mice sacrificed on P10 or P30. Values are mean µg/g of tissue. Error bars represent SEM.

^ indicates effect of age compared to P10, within strain (p < 0.05).

Figure 34: Hippocampal DOPAC/DA turnover of GSTM1 wildtype and knockout mice sacrificed on P10 or P30. Values are mean µg/g of tissue. Error bars represent SEM.

^ indicates effect of age compared to P10, within strain (p < 0.05).

Figure 35: Hippocampal HVA/DA turnover of GSTM1 wildtype and knockout mice sacrificed on P10 or P30. Values are mean µg/g of tissue. Error bars represent SEM.

^ indicates effect of age compared to P10, within strain (p < 0.05).

Figure 36: Hippocampal serotonin of GSTM1 wildtype and knockout mice sacrificed on P10 or P30. Values are mean µg/g of tissue. Error bars represent SEM.
^ indicates effect of age compared to P10, within strain ($p < 0.05$).

* indicates effect of strain at that age ($p < 0.05$).

Figure 37: Hippocampal 5-HIAA of GSTM1 wildtype and knockout mice sacrificed on P10 or P30. Values are mean $\mu$g/g of tissue. Error bars represent SEM.

^ indicates effect of age compared to P10, within strain ($p < 0.05$).

Figure 38: Hippocampal 5-HIAA/5-HT turnover of GSTM1 wildtype and knockout mice sacrificed on P10 or P30. Values are mean $\mu$g/g of tissue. Error bars represent SEM.

^ indicates effect of age compared to P10, within strain ($p < 0.05$).

Figure 39: Striatal dopamine of GSTM1 wildtype and knockout mice sacrificed on P10 or P30. Values are mean $\mu$g/g of tissue. Error bars represent SEM.

^ indicates effect of age compared to P10, within strain ($p < 0.05$).

Figure 40: Striatal DOPAC of GSTM1 wildtype and knockout mice sacrificed on P10 or P30. Values are mean $\mu$g/g of tissue. Error bars represent SEM.

^ indicates effect of age compared to P10, within strain ($p < 0.05$).

Figure 41: Striatal HVA of GSTM1 wildtype and knockout mice sacrificed on P10 or P30. Values are mean $\mu$g/g of tissue. Error bars represent SEM.

^ indicates effect of age compared to P10, within strain ($p < 0.05$).

* indicates effect of strain at that age ($p < 0.05$).
Figure 42: Striatal HVA/DA turnover of GSTM1 wildtype and knockout mice sacrificed on P10 or P30. Values are mean µg/g of tissue. Error bars represent SEM. ^ indicates effect of age compared to P10, within strain (p < 0.05).

Figure 43: Striatal serotonin of GSTM1 wildtype and knockout mice sacrificed on P10 or P30. Values are mean µg/g of tissue. Error bars represent SEM. ^ indicates effect of age compared to P10, within strain (p < 0.05). * indicates effect of strain at that age (p < 0.05).

Figure 44: Striatal 5-HIAA of GSTM1 wildtype and knockout mice sacrificed on P10 or P30. Values are mean µg/g of tissue. Error bars represent SEM. ^ indicates effect of age compared to P10, within strain (p < 0.05). * indicates effect of strain at that age (p < 0.05).

Figure 45: Striatal 5-HIAA/5-HT turnover of GSTM1 wildtype and knockout mice sacrificed on P10 or P30. Values are mean µg/g of tissue. Error bars represent SEM. ^ indicates effect of age compared to P10, within strain (p < 0.05).

Figure 46: Frontal cortex dopamine of GSTM1 wildtype and knockout mice sacrificed on P3, P10, or P30. Values are mean µg/g of tissue. Error bars represent SEM. + indicates effect of age compared to P3, within strain (p < 0.05).
Figure 47: Frontal cortex DOPAC of GSTM1 wildtype and knockout mice sacrificed on P3, P10, or P30. Values are mean µg/g of tissue. Error bars represent SEM.

+ indicates effect of age compared to P3, within strain (p < 0.05).

^ indicates effect of age compared to P10, within strain (p < 0.05).

Figure 48: Frontal cortex DOPAC/DA turnover of GSTM1 wildtype and knockout mice sacrificed on P3, P10, or P30. Values are mean µg/g of tissue. Error bars represent SEM.

+ indicates effect of age compared to P3, within strain (p < 0.05).

^ indicates effect of age compared to P10, within strain (p < 0.05).

Figure 49: Frontal cortex HVA/DA turnover of GSTM1 wildtype and knockout mice sacrificed on P3, P10, or P30. Values are mean µg/g of tissue. Error bars represent SEM.

+ indicates effect of age compared to P3, within strain (p < 0.05).

^ indicates effect of age compared to P10, within strain (p < 0.05).

Figure 50: Frontal cortex serotonin of GSTM1 wildtype and knockout mice sacrificed on P3, P10, or P30. Values are mean µg/g of tissue. Error bars represent SEM.

+ indicates effect of age compared to P3, within strain (p < 0.05).

^ indicates effect of age compared to P10, within strain (p < 0.05).

* indicates effect of strain at that age (p < 0.05).

Figure 51: Frontal cortex 5-HIAA/5-HT turnover of GSTM1 wildtype and knockout mice sacrificed on P3, P10, or P30. Values are mean µg/g of tissue. Error bars represent SEM.
† indicates effect of age compared to P3, within strain ($p < 0.05$).

^ indicates effect of age compared to P10, within strain ($p < 0.05$).
Figure 1: BALB/c and C57BL/6J Cerebellar Dopamine

**µg of DA / g of tissue**

<table>
<thead>
<tr>
<th>Post-natal Day</th>
<th>C57BL/6J</th>
<th>BALB/c</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td><strong>2.0</strong></td>
<td>1.5</td>
</tr>
<tr>
<td>10</td>
<td>1.0</td>
<td><strong>+</strong></td>
</tr>
<tr>
<td>30</td>
<td><strong>+</strong></td>
<td><strong>+</strong></td>
</tr>
</tbody>
</table>

* Indicates significant difference between C57BL/6J and BALB/c at the indicated post-natal day.
Figure 2: BALB/c and C57BL/6J Cerebellar HVA

![Graph showing HVA levels for BALB/c and C57BL/6J over post-natal days 3, 10, and 30.](image_url)

* C57BL/6J
+ BALB/c

**µg of HVA / g of tissue**

**Post-natal Day**

3 10 30
Figure 3: BALB/c and C57BL/6J Cerebellar DOPAC/DA Turnover
Figure 4: BALB/c and C57BL/6J Cerebellar HVA/DA Turnover
Figure 5: BALB/c and C57BL/6J Cerebellar Serotonin

- µg of 5-HT / g of tissue
- Post-natal Day
- C57BL/6J
- BALB/c

* ++ ^
+ +

0.00  0.02  0.04  0.06  0.08  0.10  0.12  0.14  0.16  0.18  0.20

0.00  0.02  0.04  0.06  0.08  0.10  0.12  0.14  0.16  0.18  0.20

3  10  30
Figure 6: BALB/c and C57BL/6J Cerebellar 5-HIAA

![Graph showing 5-HIAA levels in BALB/c and C57BL/6J mice at different post-natal days.](image-url)
Figure 7: BALB/c and C57BL/6J Cerebellar 5-HIAA/5-HT Turnover
Figure 8: BALB/c and C57BL/6J Hippocampal HVA
Figure 9: BALB/c and C57BL/6J Hippocampal HVA/DA Turnover
Figure 10: BALB/c and C57BL/6J Hippocampal Serotonin

![Graph showing hippocampal serotonin levels for BALB/c and C57BL/6J mice at post-natal days 3, 10, and 30. The graph displays µg of 5-HT/g of tissue, with C57BL/6J shown in black and BALB/c in grey. Significant differences are indicated by symbols above the bars.](image-url)
Figure 11: BALB/c and C57BL/6J Hippocampal 5-HIAA
Figure 12: BALB/c and C57BL/6J Hippocampal 5-HIAA/5-HT Turnover
Figure 13: BALB/c and C57BL/6J Striatal Dopamine

µg of DA / g of tissue

Post-natal Day

C57BL/6J
BALB/c
Figure 14: BALB/c and C57BL/6J Striatal DOPAC

![Graph showing the striatal DOPAC levels of BALB/c and C57BL/6J mice across different post-natal days. The x-axis represents post-natal days (3, 10, 30), and the y-axis represents micrograms of DOPAC per gram of tissue. The graph displays significant differences (*) and trends (^) between the two strains at different time points.]
Figure 15: BALB/c and C57BL/6J Striatal HVA
Figure 16: BALB/c and C57BL/6J Striatal HVA/DA Turnover

![Graph showing BALB/c and C57BL/6J Striatal HVA/DA Turnover over post-natal days 3, 10, and 30.](image-url)
Figure 17: BALB/c and C57BL/6J Striatal Serotonin
Figure 18: BALB/c and C57BL/6J Striatal 5-HIAA

Post-natal Day

µg of 5-HIAA / g of tissue

0.0 0.1 0.2 0.3 0.4

C57BL/6J BALB/c

3 10 30
Figure 19: BALB/c and C57BL/6J Striatal 5-HIAA/5-HT Turnover
Figure 20: BALB/c and C57BL/6J Frontal Cortex Dopamine

![Graph showing the comparison of dopamine levels in BALB/c and C57BL/6J mice across post-natal days 3, 10, and 30. The graph indicates a significant increase in dopamine levels in C57BL/6J mice compared to BALB/c mice on post-natal day 30.](image-url)
Figure 21: BALB/c and C57BL/6J Frontal Cortex DOPAC

The graph shows the concentration of DOPAC (µg of DOPAC / g of tissue) over post-natal days. The y-axis represents the concentration, while the x-axis shows post-natal days. The black bars represent C57BL/6J, and the gray bars represent BALB/c. The graph indicates a significant increase in DOPAC concentration for both strains as post-natal days increase, with a particular peak on post-natal day 30 for BALB/c.
Figure 22: BALB/c and C57BL/6J Frontal Cortex HVA

![Graph showing HVA levels in BALB/c and C57BL/6J frontal cortex across post-natal days 3, 10, and 30.](image-url)
Figure 23: BALB/c and C57BL/6J Frontal Cortex Serotonin
Figure 24: BALB/c and C57BL/6J Frontal Cortex 5-HIAA/5-HT
Figure 25: GSTM1 Wildtype and Knockout Cerebellar Dopamine

µg of DA / g of tissue

<table>
<thead>
<tr>
<th>Post-natal Day</th>
<th>Knockout</th>
<th>Wildtype</th>
</tr>
</thead>
<tbody>
<tr>
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<td>+</td>
</tr>
<tr>
<td>10</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>30</td>
<td>+</td>
<td>*</td>
</tr>
</tbody>
</table>
Figure 26: GSTM1 Wildtype and Knockout Cerebellar DOPAC

<table>
<thead>
<tr>
<th>Post-natal Day</th>
<th>Wildtype</th>
<th>Knockout</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>0.10</td>
<td>0.10</td>
</tr>
<tr>
<td>10</td>
<td>0.15</td>
<td>0.15</td>
</tr>
<tr>
<td>30</td>
<td>0.20</td>
<td>0.20</td>
</tr>
</tbody>
</table>

µg of DOPAC / g of tissue

- ^: Significance at P < 0.05
Figure 27: GSTM1 Wildtype and Knockout Cerebellar HVA
Figure 28: GSTM1 Wildtype and Knockout Cerebellar DOPAC/DA Turnover
Figure 29: GSTM1 Wildtype and Knockout Cerebellar HVA/DA Turnover
Figure 30: GSTM1 Wildtype and Knockout Cerebellar Serotonin
Figure 31: GSTM1 Wildtype and Knockout Cerebellar 5-HIAA

- µg of 5-HIAA / g of tissue
  - Knockout
  - Wildtype

Post-natal Day

3 10 30
Figure 32: GSTM1 Wildtype and Knockout Cerebellar 5-HIAA/5-HT Turnover
Figure 33: GSTM1 Wildtype and Knockout Hippocampal HVA
Figure 34: GSTM1 Wildtype and Knockout Hippocampal DOPAC/DA Turnover
Figure 35: GSTM1 Wildtype and Knockout Hippocampal HVA/DA Turnover
Figure 36: GSTM1 Wildtype and Knockout Hippocampal Serotonin

![Graph showing the concentration of 5-HT in µg/g of tissue for GSTM1 Wildtype and Knockout groups on post-natal days 10 and 30.](image-url)

- **Wildtype**
  - Post-natal Day 10: ~0.3 µg/g of tissue
  - Post-natal Day 30: ~0.6 µg/g of tissue

- **Knockout**
  - Post-natal Day 10: ~0.3 µg/g of tissue
  - Post-natal Day 30: ~0.6 µg/g of tissue

*Statistical significance indicated by asterisks (*).
Figure 37: GSTM1 Wildtype and Knockout Hippocampal 5-HIAA

[Graph showing the comparison of 5-HIAA levels in Wildtype and Knockout groups on Post-natal Day 10 and 30.]
Figure 38: GSTM1 Wildtype and Knockout Hippocampal 5-HIAA/5-HT Turnover
Figure 39: GSTM1 Wildtype and Knockout Striatal Dopamine
Figure 40: GSTM1 Wildtype and Knockout Striatal DOPAC

![Bar chart showing the comparison of GSTM1 Wildtype and Knockout Striatal DOPAC levels.](chart.png)

- **X-axis**: Post-natal Day
- **Y-axis**: µg of DOPAC / g of tissue

**Legend**:
- **Black**: Knockout
- **Gray**: Wildtype

**Key**:
- ^: Significant difference

**Data**
- Post-natal Day 10: Wildtype ~ 0.6, Knockout ~ 0.4
- Post-natal Day 30: Wildtype ~ 1.0, Knockout ~ 1.2
Figure 41: GSTM1 Wildtype and Knockout Striatal HVA

![Bar graph showing the comparison of HVA levels between Wildtype and Knockout in post-natal days 10 and 30.](image-url)
Figure 42: GSTM1 Wildtype and Knockout Striatal HVA/DA Turnover
Figure 43: GSTM1 Wildtype and Knockout Striatal Serotonin

![Graph showing GSTM1 Wildtype and Knockout Striatal Serotonin levels on post-natal day 10 and 30. The graph displays the concentration of 5-HT in µg per gram of tissue.](image-url)
Figure 44: GSTM1 Wildtype and Knockout Striatal 5-HIAA

![Graph showing GSTM1 Wildtype and Knockout Striatal 5-HIAA levels across post-natal days.](image-url)
Figure 45: GSTM1 Wildtype and Knockout Striatal 5-HIAA/5-HT Turnover
Figure 46: GSTM1 Wildtype and Knockout Frontal Cortex Dopamine

![Graph showing the comparison of GSTM1 Wildtype and Knockout Frontal Cortex Dopamine levels on post-natal days 3, 10, and 30. The y-axis represents micrograms of DA per gram of tissue, and the x-axis represents post-natal day. The graph includes error bars for each data point.]
Figure 47: GSTM1 Wildtype and Knockout Frontal Cortex DOPAC

![Graph showing DOPAC levels across post-natal days 3, 10, and 30 for Wildtype and Knockout groups.](image-url)
Figure 48: GSTM1 Wildtype and Knockout Frontal Cortex DOPAC/DA Turnover

![Graph showing DOPAC/DA Turnover over Post-natal Days 3, 10, and 30 for Wildtype and Knockout groups.](image)
Figure 49: GSTM1 Wildtype and Knockout Frontal Cortex HVA/DA Turnover
Figure 50: GSTM1 Wildtype and Knockout Frontal Cortex Serotonin

![Bar chart showing the comparison of serotonin levels between Knockout and Wildtype groups on post-natal days 3, 10, and 30.](chart.png)

µg of 5-HT / g of tissue vs Post-natal Day

- **Knockout**
- **Wildtype**

* indicates a significant difference.
Figure 51: GSTM1 Wildtype and Knockout Frontal Cortex 5-HIAA/5-HT Turnover