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Effort-Related Decision Making in COMT Variant Mice:
Pharmacological Studies and Genetic Susceptibility to Motivational Dysfunction.

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Abstract

Effort-related decision making tasks in animals can model motivational symptoms in humans, which are a set of symptoms spanning a multitude of neuropsychiatric disorders, such as major depressive disorder and the negative symptoms of schizophrenia. The present studies aimed to evaluate the effort-related effects of the Val158Met polymorphism of human catechol-methyltransferase (COMT), by testing mice carrying either the human COMT Val (n=8) or Met allele (n=8) with Wild-Type control mice (n=15) by using concurrent FR2 and FR4/pellet choice tasks in a touchscreen operant conditioning apparatus. The Val158Met polymorphism has been repeatedly associated with neuropsychiatric disorders, and the Val allele has been associated with negative symptoms of schizophrenia. Additionally, the effort-related effects of the dopamine D₂ antagonist, haloperidol, a drug used to treat positive symptoms of schizophrenia, but often inducing motivational side effects, was assessed in these transgenic mice. Haloperidol (0.05-0.15 mg/kg IP) decreased selection of the high effort/high reward option by reducing panel pressing across all genetic groups for both fixed ratio tasks. Furthermore, with the human COMT Val allele had significantly reduced panel pressing compared to Wild-Type mice. This study further validates the role of dopaminergic transmission in effort-related decision making, and supports the idea that the human COMT Val allele may be involved in negative symptoms of schizophrenia.

1. Introduction

The public health impact of diseases and psychiatric disorders with motivational deficits, such as major depressive disorder (MDD), schizophrenia, cancers, Parkinson's (Nunes et al. 2014; Salamone & Correa 2012; Dantzer et al. 2012) have grown over time (Maes et al. 2009), and it has become apparent that improving the quality of life for these patients requires further exploration of the pathophysiology of motivational symptoms. Motivational symptoms, including psychomotor retardation, fatigue, and anergia, are disabling and are related to problems with social function, employment, and treatment response (Stahl 2002; Yohn et al. 2016). MDD is the fourth leading cause of disability worldwide (Maes et al. 2009). However, the most common course of treatment for MDD, selective serotonin reuptake-inhibitors (SSRIs), do not alleviate motivational symptoms. Approximately 30 – 40% of patients in one study were not responsive to a sufficient dose and duration of SSRI/SNRI treatment (Trivedi et al. 2006). Despite decades of research, the underlying causes of depression and related disorders is still poorly understood, and the treatment of motivational dysfunction needs to be improved.

Current animal models of motivational symptoms include measures of effort-related choice behavior, such as operant tasks (Nunes et al. 2014; Randall et al. 2012) and T-maze procedures (Salamone et al. 1994; Pardo et al. 2012; Mott et al. 2009). In rodents, effort-related decision making tasks provide a choice between a more valued reinforcer that can only be obtained by a high degree of effort versus a low effort/low reward option (Salamone & Correa 2012; Salamone et al. 2007). Human studies of effort-related decision making demonstrated that patients with MDD (Treadway et al. 2012) and schizophrenics with a high preponderance of negative symptoms (Gold et al. 2013; Barch et al. 2014; Farvaha et al. 2013; Treadway et al. 2015) have reduced selection of high effort/high reward options.

Motivational symptoms and effort-related choice behavior are controlled by neuronal circuits involving mesolimbic and striatal dopamine (Salamone & Correa 2012; Salamone et al. 1997, 2007). Past research has shown that depletion or antagonism of mesolimbic dopamine, regardless of the task used, shifts choice behavior by decreasing selection of the high effort option and increasing selection of the lower effort alternative (Randall et al. 2012; Nunes et al. 2014; Salamone et al. 2014; Yohn et al. 2016; Salamone & Correa 2012). One method used for interfering with dopamine transmission is through intraperitoneal injections of a dopamine antagonist drug, such as haloperidol. Haloperidol is an antipsychotic drug used to treat positive symptoms of schizophrenia (Salamone et al. 2014), but often causes an induction of negative symptoms in humans (Artaloytia et al. 2006; Morrens et al. 2008). The dopamine D2 antagonist haloperidol has been studied extensively with effort-related choice procedures and has been shown to induce motivational deficits in rats (Salamone et al. 1991, 1994, 1996; Mott et al. 2009; Pardo et al. 2012; Randall et al. 2012).

Catechol-O-methyltransferase (COMT) is an important enzyme in the metabolism of catecholamines such as dopamine and norepinephrine (Risbrough et al. 2014). COMT is particularly important for the clearance of dopamine from the prefrontal cortex, where COMT mRNA is highly expressed and dopamine transporters have low expression; the striatum has relatively low COMT expression, but dopamine levels are still effected by the enzyme (Matsumoto et al. 2003). The gene encoding for COMT is located on chromosome 22q11.2, and has been implicated as a candidate gene for the pathogenesis of neuropsychiatric disorders (Risbrough et al. 2014). The human COMT gene is one of the genes deleted in 22q11.2 deletion syndrome, a disease in which patients have a high risk for developing multiple psychiatric disorders, such as schizophrenia, anxiety and mood disorders (Murphy et al. 1999; Gothelf et al.

2005). A single nucleotide polymorphism (SNP) of the human COMT gene, resulting from a missense mutation of Valine to Methionine at codon 158, may be associated with a variety of psychiatric disorders (Lachman et al. 1996). The Met allele has been shown to cause a 40% decrease in enzymatic activity of COMT in the prefrontal cortex, compared to the Val allele (Lachman et al. 1996; Chen et al. 2004). The role of the COMT gene in schizophrenia has been unclear, with many contradictory findings, and meta-analyses finding no clear association (Hori et al. 2014). Although the COMT gene may not be associated with the whole disease phenotype, the gene is being evaluated for its association to specific symptomology. In schizophrenia, the Met allele has been associated with mood disorders (Drabant et al., 2006), while the Val allele has been linked to negative symptoms (Wang et al. 2010; Pelayo-Teran et al. 2011; Mao et al. 2016), although there are some conflicting data (Goghari & Sponheim 2008). Therefore, it is reasonable to hypothesize that the Val allele could shift effort related choice behavior towards the low-effort/low-reward option in an effort-related choice behavior task.

The present study uses two different operant schedules: concurrent FR2/choice and FR4/choice tasks utilizing a touch screen apparatus for mice. Mice were used instead of rats, because of the ability to use transgenic mice carrying humanized versions of the COMT gene. The study aimed to (1) examine the effects of the COMT Val158Met polymorphism in effort-related decision-making tasks, and (2) investigate the effects of Val158Met on the pathogenesis of motivational deficits through systemic haloperidol administration. It was hypothesized that (1) the Val/Val group would show a behavioral shift to the lower-effort alternative as compared to the Met/Met and wild type groups and (2) the Val158Met polymorphism would show genetic susceptibility to haloperidol-induced motivational deficits through reductions in dopaminergic transmission. Furthermore it was expected that haloperidol would not improve selection of the

high-effort panel pressing in Val/Val animals because typical antipsychotics such as haloperidol generally fail to improve negative symptoms, and in fact tend to exacerbate them (Morrens et al., 2008).

2. Materials and Methods

2.1 Animals

31 adult male mice of mixed S129 and C57BL6J background (Jackson Laboratories, Bar Harbor, ME) were purchased at four to five weeks of age and housed separately at 23° with 12-h light/dark cycles (lights on at 0:700 h). There were 15 wild-type mice, 8 Val (<https://www.jax.org/strain/027990>) and 8 Met (<https://www.jax.org/strain/027993>). Mice were left undisturbed for seven days following arrival to allow habituation to the environment before introducing human handling. Mice weighed 20-30 g at the beginning of the study, and were initially food deprived to 85% of their free-feeding body weight for training. Mice were fed supplemental chow to maintain weight throughout the study, with water available ad libitum in the home cages. Despite food restriction, mice were allowed modest weight gain throughout the experiment. All animal protocols were approved by the University of Connecticut Institutional Animal Care and Use Committee, and followed NIH guidelines.

2.2 Pharmacological Agents and Dose Selection

Haloperidol was obtained from (Sigma-Aldrich) and was dissolved in a stock solution of 0.3% tartaric acid solution and then diluted with physiological saline; saline also served as the vehicle control. The doses of haloperidol were selected based on pilot studies conducted on mice with a S129 background to determine if the dose range used would induce motivational deficits. Haloperidol was administered intraperitoneally (IP).

2.3 Apparatus

All experiments and training were performed in standard mouse Bussey-Saksida touchscreen chambers (Campden Instruments Ltd., Loughborough, UK; Heath et al. 2015). The chamber consisted of Fiberglas trapezoidal walls opening to a touchscreen, with a stainless steel holed floor with a removable tray underneath. The touchscreen measured 12.1 inches with a 800 x 600 resolution screen. There are infrared (IR) beam arrays located 5 mm away from the touch screen to ensure that the mice do not have to apply pressure to have a detected response. Across from the touchscreen is a reward liquid dispenser, attached to a pump, which would deliver 20 μ L of milkshake (Strawberry Ensure) reward for the correct amount of touchscreen presses. An LED would light up upon delivery of award to cue the mouse to collect delivery, and would turn off after reward collection. Additionally, during reward delivery, the touchscreen would turn off until the reward was collected. These touchscreen operant chambers are each housed within sound-attenuating chambers equipped with fans to minimize background noise and offer ventilation.

2.4 Behavioral Procedures

For two days preceding the start of behavioral training, a small dish containing the liquid reward (Strawberry Ensure) used in the concurrent fixed ratio/pellet choice procedure was introduced to each cage to minimize neophobia (Horner et al. 2013). First, mice were trained on a magazine training/continuous reinforcement schedule, in which 20 μ L of milkshake was delivered every 30 seconds, to train them to obtain the reward from the liquid dispenser. Any panel presses during magazine training reset the time and delivered 60 μ L of milkshake. Second, mice were trained on an FR1 schedule, in which one panel press would equate to delivery of reward, for thirty minute sessions, 5 days a week, with a touchscreen panel near the floor, to train the mice to press the touch screen for a reward. Third, the touch screen panel was raised on the FR1 schedule, to

make the task more difficult. The schedule was then raised to FR2 or FR4 and mice were trained until they reached baseline levels of panel pressing (panel presses did not vary very much for each individual mice for a week). Finally, mice were trained on the concurrent FR2/pellet choice or FR4/pellet choice procedure, in which pre-weighed amounts of 45 mg pellets (Bio-serv, Frenchtown, NJ), which typically weighed around 6 g in total, were concurrently available in the touchscreen chamber during the session (30 minutes). Pellets were put in a small Petri dish, on the bottom of the touchscreen chamber, between the touchscreen and the liquid dispenser. Therefore, mice were given the choice of a low-effort option: consuming the less-preferred pellets, or the high-effort/high-reward option: panel pressing for liquid reward. The mice were loaded into their touchscreen chambers, the soundproof box was shut, and the fixed ratio program was started using the computer program, Whisker Server. At the end of the 30-minute session, mice were removed from the touchscreen chamber, panel pressing was recorded from the program, ABET II Touch, and the amount of pellets consumed was calculated from weighing the pellets left in the petri dish and spillage left in the touchscreen chamber's removable tray. The same groups of mice were used for both experiments.

2.5 Experimental Procedures

On drug test days, all animals (n=31) received IP injections of the following doses of haloperidol; saline vehicle, 0.05, 0.10, 0.15 mg/kg. This experiment used a within-groups design, with all mice receiving all drug treatments in a random varied order (one treatment per week). Baseline training, or non-drug, sessions were conducted four additional days per week, and behavioral performance on these days was unaffected by the previous injections. All injections were given 50 minutes before the beginning of the testing session. Mice were then put into their respective, prepared, touchscreen chambers, the soundproof box was closed, and the FR2 or FR4

schedule was loaded and started on the computer program ABET II Touch. At the end of the 30-minute session, mice were removed from the operant box, panel pressing was recorded, and the amount of pellets consumed was calculated from weighing the pellets and spillage left in the touchscreen chamber. Baseline, or nondrug, training sessions were conducted 4 days per week. Drug administration and testing was completed on the fourth day. Half the animals were on an FR2 schedule while the other half were on an FR4 schedule. All doses were completed for every animal, to complete the first part of the experiment. Then, the mice were switched to the other fixed ratio schedule they had previously not been on, trained on that new schedule, and the experiment was repeated with all drug doses in a within group design. Therefore, all animals had been tested with all doses of drug on both a concurrent FR2/pellet choice and FR4/pellet choice procedure.

2.6 Statistical Analyses

Number of panel presses and gram quantity of pellet intake from the thirty-minute sessions in experiments 1-2 were analyzed with repeated measures of analysis of variance (ANOVA), using the computer program SPSS. A 3 x 4 factorial ANOVA was used, with a between-subjects factor of gene group, and a within-subject factor of the drug treatment. Planned comparisons were made with the overall error term to compare the haloperidol treatment to the vehicle control group.

3. Results

3.1 Experiment 1: Effects of systemic administration of haloperidol on concurrent FR2/pellet choice procedure in wild type and humanized mice carrying COMT158 Met/Val alleles.

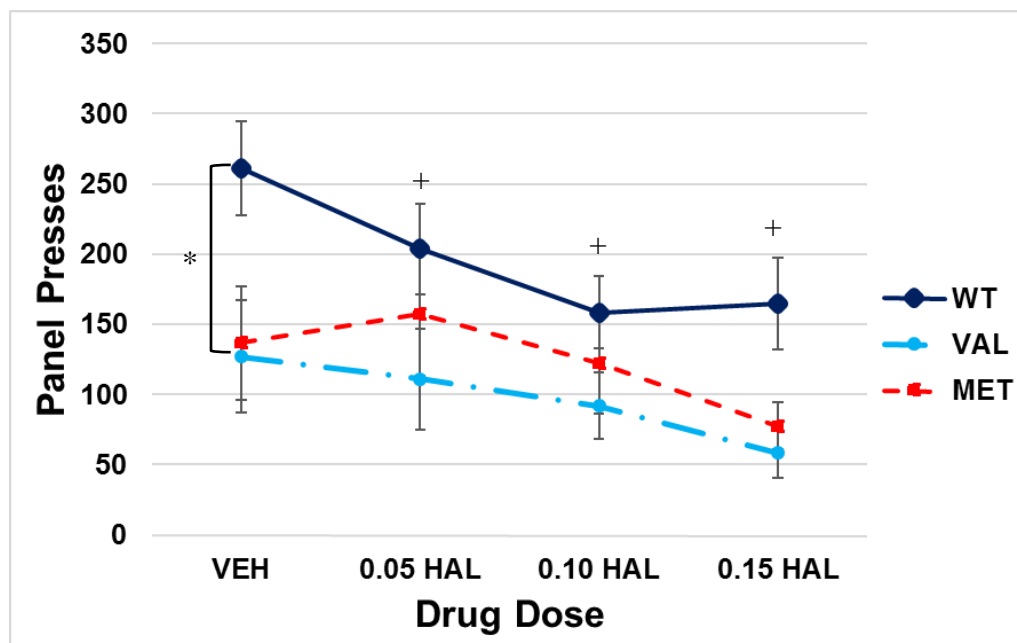


Figure 1. Effect of haloperidol (HAL) on FR2 panel pressing for three COMT variant groups [WT group (n=16), VAL group (n=8), and MET group (n=8)]. Mean (\pm SEM) number of panel presses after treatment with vehicle (VEH) and various doses of HAL. * $p < 0.05$, different from WT; * $p < 0.05$, different from vehicle treatment for all gene groups

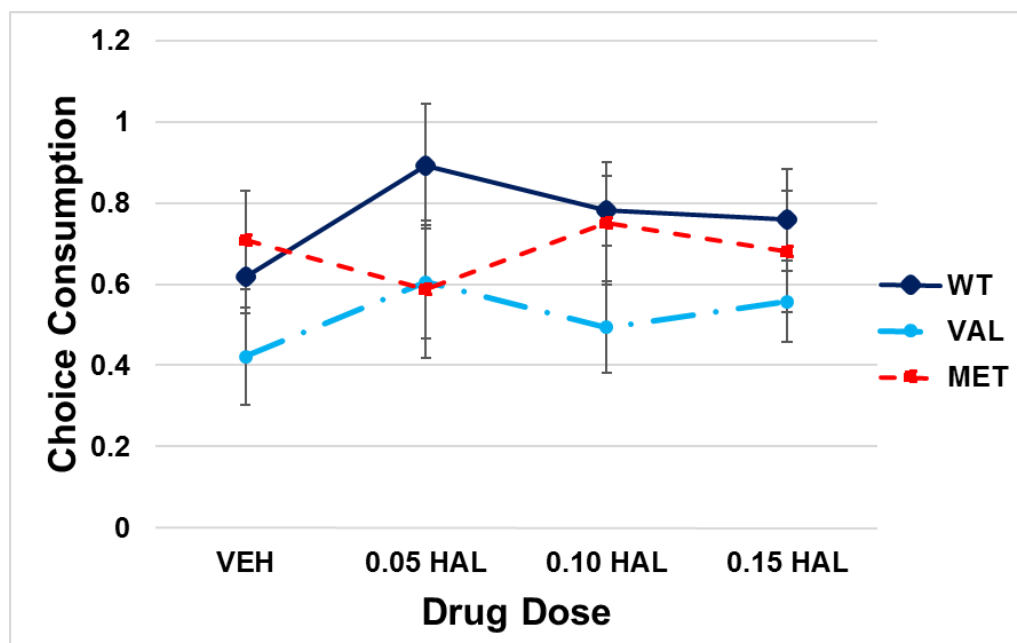


Figure 2. Effect of haloperidol (HAL) on FR2 pellet intake for three COMT variant groups [WT group (n=16), VAL group (n=8), and MET group (n=8)]. Mean (\pm SEM) pellet intake after treatment with vehicle (VEH) and various doses of HAL. There were no overall significant effects for HAL or COMT gene group on pellet intake for the concurrent FR2/pellet choice procedure.

The effects of haloperidol administration on panel pressing by COMT gene group is shown in Figure 1. There was an overall significant effect of haloperidol on panel pressing for the concurrent FR2/pellet choice procedure, $F(3,84)=5.300$, $p < 0.05$. Post hoc comparisons were conducted across gene groups, and showed that panel pressing was suppressed by 0.05, 0.10, and 0.15 mg/kg HAL compared to vehicle ($p < 0.05$). Repeated measures ANOVA of between subjects effects revealed that there was an overall significant effect of COMT gene group on panel pressing for the concurrent FR2/pellet choice procedure, $F(2,28)=3.921$. There was no significant effect of the haloperidol dose x gene group interaction. The effects of haloperidol administration on pellet intake by COMT gene group is shown in Figure 2. The overall effects of haloperidol, COMT gene group, and the Haloperidol x gene group interaction on pellet intake were not significant.

3.2 Experiment 2: Effects of systemic administration of haloperidol on concurrent FR4/pellet choice procedure in wild type and humanized mice carrying COMT158 Met/Val alleles.

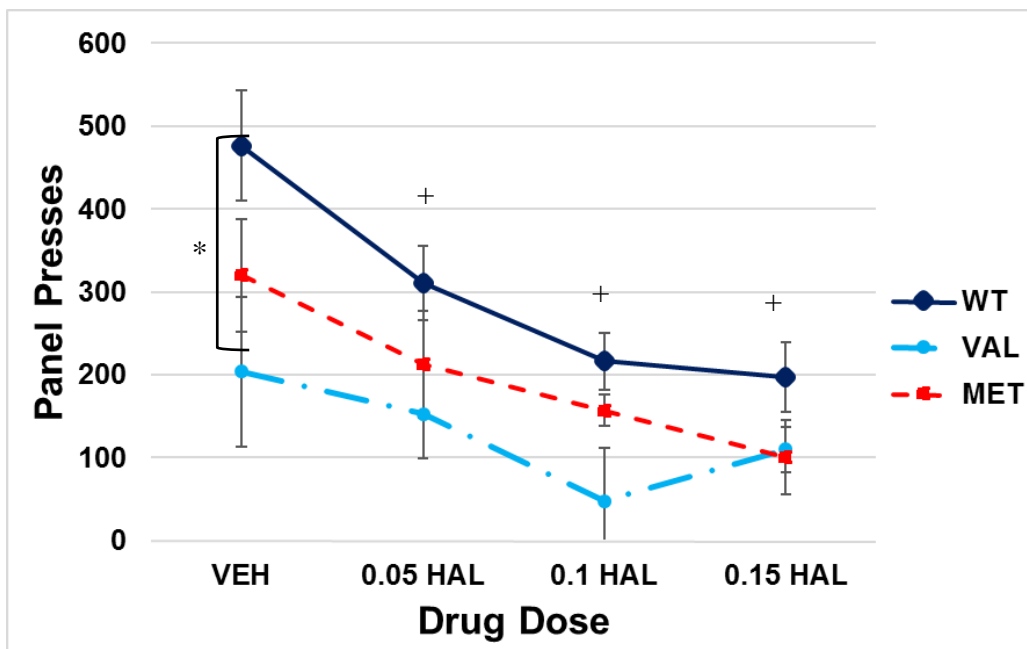


Figure 3. Effect of haloperidol (HAL) on FR4 panel pressing for three COMT variant groups [WT group (n=16), VAL group (n=8), and MET group (n=8)]. Mean (\pm SEM) number of panel presses after treatment with vehicle (VEH) and various doses of HAL. * $p < 0.05$, different from WT; + $p < 0.05$, different from vehicle treatment for all gene groups

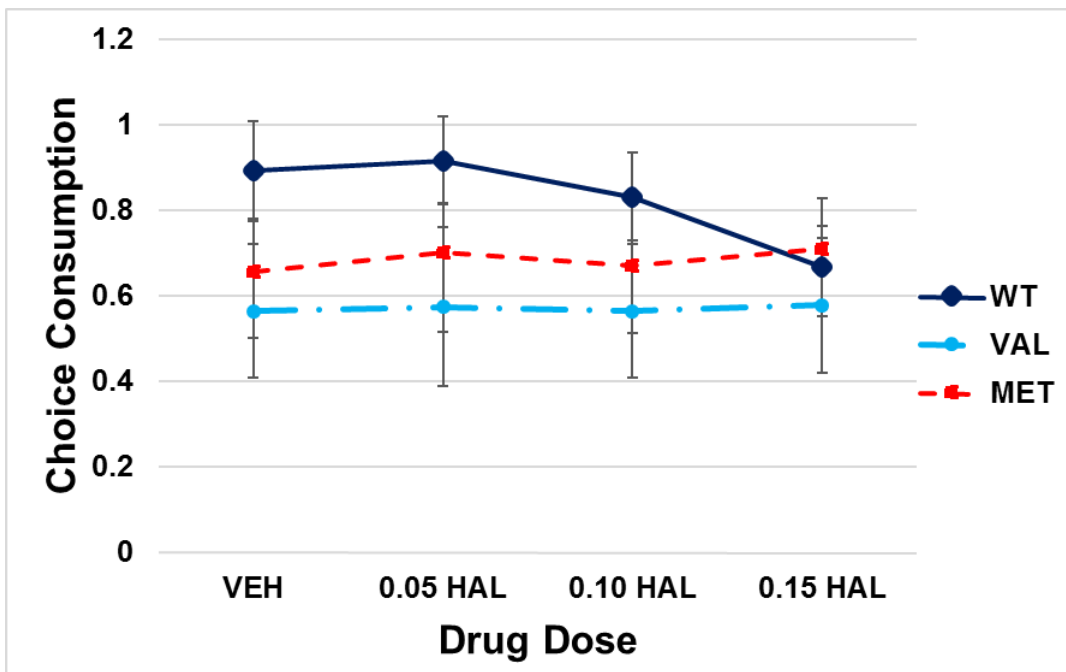


Figure 4. Effect of haloperidol (HAL) on FR4 pellet intake for three COMT variant groups [WT group (n=16), VAL group (n=8), and MET group (n=8)]. Mean (\pm SEM) pellet intake after treatment with vehicle (VEH) and various doses of HAL. There was no overall significant effect of HAL or COMT gene group on pellet intake for the concurrent FR4/pellet choice task.

The effect of haloperidol administration on panel pressing by COMT gene group is shown in Figure 3. There was an overall significant effect of haloperidol on panel pressing for the concurrent FR4/pellet choice procedure, $F(3,84)=16.525$, $p < 0.001$. Post hoc comparisons were conducted across gene groups, and showed that panel pressing was suppressed by 0.05, 0.10, and 0.15 mg/kg HAL compared to vehicle ($p < 0.05$). Repeated measures ANOVA of between subjects effects revealed that there was an overall significant effect of COMT gene group on panel pressing, $F(2,28)=3.895$, $p > 0.05$. The effect of haloperidol administration on pellet intake by COMT gene group is shown in Figure 4. There was no significant effect of the haloperidol dose x gene group interaction. The overall effects of haloperidol, COMT gene group, and the haloperidol x gene group interaction on choice food consumption were not significant.

4. Discussion

The present study investigated the effects of the COMT Val158Met polymorphism on its own and with pharmacological manipulations on effort-related motivational symptoms in transgenic mice. In the past, the dopamine D₂ antagonist, haloperidol, was shown to effort-related decision making in rodents by shifting behavior from the high-effort/high-reward option to the low-effort/low-reward option. This drug's effects on effort-related decision making has been extensively validated with rats (Salamone et al. 1991, 1994, 1996; Mott et al. 2009; Randall et al. 2012), and more recently has been studied in mice (Pardo et al. 2012). The present study demonstrated that haloperidol significantly reduced panel pressing for all genetic groups for both FR2 and FR4 schedules. Doses of haloperidol that clearly affect panel pressing appear to have little effect on pellet intake, indicating that all types of food-related behaviors were not equally affected by dopamine antagonism. This further validates the use of haloperidol to alter effort-related decision making in mice.

Effort-related decision making paradigms, such as the touchscreen apparatus for mice, could be useful as animal models of motivational symptoms. This is supported by human studies of effort-related decision making, which show a shift in effort-related choice behavior from the high effort/high reward option towards the low effort-/low reward option in patients with major depressive disorder (Treadway et al. 2012) and schizophrenia patients with a preponderance of negative symptoms (Gold et al. 2013; Barch et al. 2014; Farvaha et al. 2013; Treadway et al. 2015). Mice are a useful tool for studying models of human disease, including studies that involve using transgenic mice, such as studying the human COMT Val158Met polymorphism. An animal model of the Val and Met alleles of the human COMT gene in an effort-related decision making task can be helpful for evaluating the link between the Val158Met

polymorphism to neuropsychiatric disorders. The experiments demonstrated that the Wild-Type group's panel pressing was significantly higher than the COMT Val allele group panel pressing for both FR2 and FR4 schedules. Additionally, as COMT gene variants may affect cognition (Hori et al. 2014), it is important to note that there were no significant differences in acquisition or the concurrent FR1/pellet choice task, a task which does not highlight differences in effort-related decision making between groups. The genetic variation of the Val group reduced effort-related decision making. This is consistent with past studies linking the Val allele to negative symptoms of schizophrenia (Wang et al, 2010; Pelayo-Teran et al. 2011; Mao et al. 2016). The Val allele has increased enzymatic activity, compared to the Met allele, which has 40% reduced enzymatic activity. Thus, a likely mechanism for the effect of the Val allele would be that increased enzymatic activity in animals with the Val allele would lead to a reduction in mesolimbic dopaminergic transmission, leading to increased motivational symptoms, as would occur with negative symptoms of schizophrenia. Perhaps more significant differences between the Val and Met groups were not seen because the COMT enzyme mainly works in the prefrontal cortex, with an overall reliance on the dopamine transporter, DAT, in the striatum (Risbrough et al. 2014; Matsumoto et al. 2003). Mice with a COMT knockout have shown a significant rise in levels of prefrontal cortex dopamine, without significant changes of dopamine level in the striatum. (Gogos et al. 1998).

There were several limitations of this study. First, the mixed backgrounds of the mice (S129 and C57BL6J) may have affected the results, as this adds variability to the background genetics. Second, the use of the touchscreen apparatus and the fixed ratio procedures for mice are still relatively new, and should be validated with continuing studies using the procedure. These experiments showed that in terms of the suppression of panel pressing, the concurrent FR4/pellet

choice procedure yielded the cleanest data compared to the concurrent FR2/pellet choice procedure, and will most likely be used in future experiments. Nonetheless, this study validated the use of the touchscreen apparatus for studying effort-related decision making in mice. The results obtained were similar to the extensively validated studies conducted in rats and mice, where haloperidol administration will shift behavior away from the high effort/high reward option (Salamone et al. 1991, 1994, 1996; Mott et al. 2009; Pardo et al. 2012; Randall et al. 2012). This paradigm will be a useful tool in the future for studying other genetic models of schizophrenia or major depressive disorder.

To summarize, haloperidol altered effort-related decision making as measured by the concurrent FR2 and FR4/pellet choice procedures in the touchscreen apparatus for mice. Additionally, the Val allele of the human COMT gene altered effort-related decision making by significantly reducing panel pressing as compared to Wild-Type mice. Together with other studies, the present research further validates tests of effort-related decision making in rodents for their usefulness as a model of motivational symptoms in humans. This study also further supports the compiling evidence that the COMT gene may be involved in the pathogenesis of multiple psychiatric disorders, and that the Val allele can be associated with negative symptoms of schizophrenia. Additionally, this study falls along the thought process of the Research Domain Criterion (RDoC) approach, which prioritizes studying psychiatric symptoms and their associated neural circuits, instead of traditional whole diagnostic categories of disorders (Cuthbert & Insel 2013). Future directions include further testing the validity of the touchscreen apparatus as a test of effort-related decision making in mice. Additionally, further studies will include transgenic mouse models of other genes with interact with the dopamine system or

COMT, such as dopamine receptor D4 (DRD4) and serotonin transporter promotor region (5-HTTLPR) (Benjamin et al. 2000; Strobel et al. 2003).

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