Salience Attribution Differences by Dopamine Transporter Genotype

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Abstract

Encoding of salient information is believed to be a key attentional process that facilitates learning by devoting cognitive resources to the most relevant sensory information. This study examined the relationship between a variation of the dopamine transporter (DAT) gene, which modulates dopamine transporter expression in the striatum, and performance on two measures of salience, the Salience Attribution Task (SAT) and Learned Irrelevance (LIrr) task. The SAT measures implicit and explicit learning of information made salient by monetary rewards, whereas the LIrr task measures the learning of information made salient by stimulus-response associations. Subjects were either homozygous (10/10) or heterozygous (9/10) for the 10-repeat allele of the DAT genotype. On the SAT, implicit adaptive salience was numerically higher in 9/10 carriers relative to 10/10 carriers, although this result did not achieve statistical significance. Aberrant salience did not differ by genotype. On the LIrr task, both groups exhibited similar amounts of learned irrelevance. These genotypic differences in performance on reward-based behavior but concomitant similarities in stimulus-response association learning indicate that individual differences in DAT activity had differential effects on encoding of salient information selective to motivational function.
Introduction

Salience can be defined as “a process whereby objects and representations [are] attention-grabbing and capture thought and behavior” (Jensen and Kapur, 2009). Salience is believed to be a key attentional procedure that facilitates learning by devoting cognitive resources to the most relevant sensory information. Examples of salient stimuli might include: feature contrast (e.g. a bright light flashing in a dark room), novelty (e.g. a new object in a familiar environment), and emotional/motivational association (e.g. pairing a stimulus with reward or punishment). As such, evaluative judgments and predictions of salience are useful in guiding behavior (O’Doherty, 2004). Two tasks which explore the construct of salience are the Salience Attribution Task (SAT) and the Latent Inhibition (LI) / Learned Irrelevance (LIrr) measure.

The SAT measures implicit and explicit reward learning related to task-relevant and task-irrelevant stimuli, and quantifies adaptive salience (the correct assignment of salience) and aberrant salience (the erroneous assignment of salience to external objects and internal representations). Previous studies have shown that presentation of a reinforced stimulus (S+) has been shown to increase the speed of responding relative to the presentation of a nonreinforced stimulus (S-) (Wyvell & Berridge, 2000). This effect is termed “motivational salience”, meaning that a neutral stimulus acquires an emotional quality due to its association with primary reinforcement (such as a monetary reward), and consequently can influence behavior and command attention (Berridge & Robinson, 1998; Milstein & Dorris, 2007). The SAT calculates implicit adaptive salience, also termed reward learning, using reaction times from reinforced and nonreinforced stimuli, whereas explicit reward learning was calculated using a Visual Analogue Scale (VAS). Further results from the SAT suggest that the measures of Learned Irrelevance (LIrr) and implicit adaptive salience might be based on similar underlying processes, which are
dissociable both from implicit aberrant salience and explicit measures of salience (Schmidt and Roiser, 2009).

Latent inhibition (LI) and LI-related paradigms measure processes not on a reflex but rather on an attentive and cognitive level. Latent inhibition refers to the hindrance of learning an association between two stimuli after the subject witnesses non-reinforced preexposure of these stimuli; that is, LI reflects the ability of normal individuals to ignore irrelevant, inconsequential stimuli (Orosz et al., 2008). For example, if a stimulus that is predictive of a target is repeatedly preexposed without reinforcement, then the ability to learn the association between predictor and target is delayed. Therefore, LI is realized as a delay in associative learning due to the subject’s prior familiarity with the stimulus. This means that individuals with reduced LI learn the familiar-stimulus/unfamiliar-stimulus association faster than normal controls.

Related to LI, the learned irrelevance (LIrr) task tests a similar effect, which is thought to reflect the ability to ignore irrelevant stimuli (Gal et al., 2005). One consequence of deficient information processing is the inability to filter out irrelevant stimuli, which leads to stimulus overload. (Orosz et al., 2008). LIrr is a measure of information processing, specifically, the ability of normal individuals to ignore irrelevant internal and external stimuli in order to protect themselves from stimulus overload. The LIrr paradigm measures salience via a visual target-detecting task in which subjects respond to a target, represented by the letter X. This target letter is always preceded by a predictor letter, and predictor letters are presented according to the schedules of three different conditions: non-preexposed (NPE), preexposed (PE), and random (R). In addition to target and predictor letters, the LIrr task also includes “filler” letters, which serve as intervals between predictor-target constructs.
In the PE condition, preexposed “filler” letters serve as target predictors. In a PE block, the target is preceded by the same PE letter every time. In the R blocks, the targets appeared after a random PE letter, i.e. each time by a different PE predictor letter. Thus, preexposure to the PE letters takes place in the R blocks as well as during filler letter presentations, where the subjects learned that a consonant is not necessarily followed by the target. In contrast, a NPE predictor letter is never seen previously in the task. Therefore, in both the NPE and PE blocks, there was reliable prediction of the target, while in R blocks, there was none. Furthermore, because the predictor letter in NPE blocks it novel, the predictive relationship is more salient than in PE blocks. (Orosz et al., 2007).

The difference between LI and LIrr is that in the LIrr paradigm, both the predictor and the target are preexposed. In the LIrr task, it is of critical importance that the predictor and the target are presented in an explicitly unpaired manner in order to prevent associative learning in the preexposure phase (Orosz et al., 2008). In the random blocks as well as with filler letter presentations, subjects learn that the target does not necessarily follow a certain consonant. The LIrr task is believed to have a greater power than previous LI tasks, for in contrast to former LI paradigms, the predictor-target contingency is previously presented in an unpaired manner.

These measures of salience have been utilized in subjects diagnosed schizophrenia and schizotype disorders (Schmidt et al., 2009), since two positive symptoms of this disorder are disrupted salience and reward learning, driven by dysregulated dopamine transmission. Studies have shown that dopaminergic neurochemical aberration usurps the normal process of contextually driven salience attribution and leads to aberrant assignment of salience to external objects and internal representations (Kapur, 2003). One of the most frequently cited deficits is a selective attention dysfunction, conceptualized as an inability to ignore irrelevant or unimportant
stimuli. Consequently, in the L1rr task, healthy controls showed faster acquisition of novel compared to preexposed-target association, indicating the presence of L1rr; in contrast, patients in an acute phase of their first psychotic episode showed similar acquisition times for the association of the novel- and preexposed-target characters, indicating L1rr disruption (Orosz et al, 2008).

Both the positive symptoms of schizophrenia and Attention-deficit Hyperactivity Disorder (ADHD) are characterized by distractibility and difficulties maintaining focus of attention. The role of dopaminergic dysfunction in ADHD has long been supposed and is still being investigated. A major area of examination includes the administration of psychostimulants, such as methylphenidate (Ritalin), acting on dopaminergic transmission. These pharmacological drugs exert their effects in part by inhibiting the dopamine transporter, keeping a greater quantity of dopamine active in the synaptic cleft for a longer period of time (Amara and Kuhar 1993). The administration of these psychostimulants has been shown to reduce impulsiveness and inattentiveness, pointing to a deficit in dopaminergic transmission associated with ADHD (Solanto, 1998). Several genetic studies of ADHD have focused on genes that are involved in dopaminergic function because of the central role of dopamine in reward-seeking behaviors (Waldman, 1998). One such gene of interest is the dopamine transporter (DAT1) gene, as the ADHD diagnosis in children has been associated with allelic variations of genes encoding DAT (Cook et al., 1995; Gill et al., 1997). The dopamine transporter (DAT) is a protein that is largely responsible for the reuptake of dopamine from the synaptic cleft. Accordingly, it regulates the duration of the cellular actions of dopamine and the extent to which dopamine diffuses in the extracellular space. It is expressed most abundantly in the striatum, and is the primary means of removing extracellular dopamine from the synaptic cleft in the striatum.
One area of genetic research into the role of dopamine as a modulator of attention focuses on a region in the 3’-untranslated region (3’-UTR) of the gene (SLC6A3) coding for the dopamine transporter (DAT) (Madras, Miller, and Fischman, 2002). The 3’-UTR of this gene varies in length due to a range of variable number tandem repeats (VNTR); the range varies from three to eleven copies of a 40-base unit (Madras, Miller, and Fischman, 2002). Behavioral patterns characteristic of ADHD have been shown to be more prevalent in homozygous carriers of the 10-repeat allele (10/10) relative to heterozygous carriers (9/10) (Cook et al., 1995; Waldman et al., 1998). In one study, 9/10 carriers had a mean 22% reduction in DAT protein availability in the putamen compared with 10/10 carriers (Heinz et al., 2000). This corroborates the hypothesis that symptoms associated with ADHD could be due in part to elevated levels of the DAT protein, and thus lower amounts of available dopamine in the synaptic cleft.

These aforementioned salience tasks (SAT and LIrr), which have been used in studies involving schizotypal subjects, are also important in the context of Attention-deficit Hyperactivity Disorder (ADHD), since difficulties with attention, impulsiveness, or hyperactivity, as well as abnormal salience processing, are characteristic of ADHD (Madras, Miller, and Fischman, 2002). Additionally, both schizophrenia and ADHD are characterized by distractibility and difficulties maintaining focus of attention. Direct comparisons made in studies of at-risk samples indicate that children prone to developing schizophrenia or those already exhibiting features of psychosis have much overlap with ADHD-diagnosed children in their performance on experimental tests of attention (Barr, 2001).

Nevertheless, neither the SAT or LIrr tasks have been used to study implicit and explicit salience attribution in persons genetically predisposed to ADHD. Because ADHD and schizotypal disorders share many attention related cognitive impairments, it is important to generate data
using the SAT and LIrr in this population. In this study, implicit and explicit salience attribution, both adaptive and aberrant, was measured using the two aforementioned tasks (SAT and LIrr) in normal adults (heterozygous carriers of the 10-repeat allele, i.e. 9/10) and adults genetically predisposed to ADHD (homozygous carriers of the 10-repeat allele, i.e. 10/10). It is predicted that the SAT will show increased adaptive salience for controls (9/10), and increased aberrant salience for persons genetically predisposed to ADHD (10/10). Furthermore, it is believed that the LIrr task will show that learned irrelevance will be intact in 9/10 carriers, but disrupted in 10/10 carriers.

Method

Subjects

Twenty-eight volunteers (7 male, 21 female) were recruited through the Georgetown University Research Volunteer Program. Ten subjects (8 female) were carriers of the 9/10 genotype, whereas 18 subjects (13 female) were carriers of the 10/10 genotype. The genotype groups did not differ in age (Mean = 20.24 years, S.D. = 1.10). Subjects were presented with a complete description of the study and test procedures. Thereafter, a written informed consent was obtained from each subject. Subjects were compensated with a $10 payment for their time (appointments lasted about an hour) and all subjects won a $5 gift card as part of their earnings in the Salience Attribution Task. This study was approved by the Georgetown Institutional Review Board.

Procedure

Subjects completed the cognitive test battery described below. The order of administration of these tasks was counterbalanced across subjects. Subjects had the opportunity to take a break between measures and were able to win money on the Salience Attribution Task.
Salience Attribution Task (SAT)

On the SAT, subjects responded to the onset of a probe (a black square) in order to earn money. Pictures that appeared just before the onset of the probe signaled the probability that the subject would win money on a given trial. However, subjects were not informed of the contingencies between the different pictures and reward. Subjects could earn a minimum of $3.35 and a maximum on $16.75 on the test.

Prior to the main task, subjects completed a computerized tutorial. The tutorial consisted of two practice sessions, which familiarized subjects with the test and provided a measure of baseline response time (RT). Subjects were instructed to try to respond as quickly as possible, and before the black square disappeared. On these practice sessions, a fixation cross appeared at the beginning of each trial. Following a variable interval (minimum 0.5 s, maximum 1.5 s) the probe (black square) appeared, and subjects responded by pressing the keyboard space bar as quickly as possible. During the first practice session, the probe was on the screen for randomized variable periods, with a minimum duration of 0.5 s, a maximum of 1.5 s, and a mean of 1.0 s. Visual feedback was provided after 2 s as “Good” if the subject responded before the probe disappeared, “Try to respond faster” if they responded after the probe disappeared, “Too early” if they responded before the probe appeared on-screen, and “No key pressed” if no response was made. On the second practice session, the mean probe duration was set according to the subject’s RTs on the first practice session. This guaranteed that subjects were responding as quickly as possible, and yoked task difficulty to individual performance. The standard deviation of the fastest half of the trials (SDF) from the first practice session was calculated, and was used to set the minimum and maximum probe durations for the second practice session. For the main test,
minimum and maximum probe durations were calculated from the second practice session in the same way.

After the tutorial, subjects completed two blocks of 64 trials on the main test, where a reward (money) was available on 50% of the trials. The likelihood that money was available on a trial was signaled by one of four stimuli that appeared at the top and bottom of the screen before the onset of the probe. Stimuli varied on two different visual dimensions: color (blue or red) and shape (animal or household object). Therefore, there were four different types of stimuli: blue animals, red animals, blue household objects, and red household objects (Table 1). One of these dimensions (e.g. color) was task-relevant so that one level of the dimension was reinforced on 28 out of 32 (87.5%) of the trials while only 4 out of 32 (12.5%) trials of the other level were reinforced. For example, if color was the task-relevant dimension and blue the reinforced level, 14 out of 16 blue animals and 14 out of 16 blue household objects would be reinforced, while only 2 out of 16 red animals and 2 out of 16 red household objects were reinforced. The other dimension, in this example shape, was task-irrelevant, such that 16 out of 32 (50%) of both levels (animal and household object) were reinforced. At the end of the block, subjects were presented with a Visual Analogue Scale (VAS), and asked to judge, on a sliding 0% to 100% scale, how often they received money for each of the four types of stimuli (blue pictures, red pictures, pictures of animals, and pictures of household objects). This VAS scale served as a measure of explicit salience. The contingencies were identical on the first and second blocks of the task. Subjects were not informed of the contingencies, but instead learned them over the course of the task.

The main test consisted of two blocks of 64 trials. At the beginning of each trial, a fixation cross appeared; after 1 s, while the fixation cross remained on-screen, one of the four
stimuli was displayed at the top and bottom of the screen until the end of the trial (Figure 1).

After a variable period of time (between 0.5 s and 1.5 s) the probe appeared and subjects attempted to respond before the probe disappeared. The probe duration was calculated according to the subject’s response times (ms) on the second practice block, as described above. After 2.25 s, visual feedback was presented for 1.5 s. If the trial was not reinforced, the message “Sorry – no money available” was displayed. If the trial was reinforced, subjects won between 5 and 25 cents, depending on the quickness of their response. On reinforced trials were subjects made either no response or responded after the probe had disappeared, the message “Missed: 5 cents” was displayed. If subjects responded before the onset of the probe, the message “Too early: 5 cents” was displayed. On reinforced trials where subjects responded before the probe disappeared, but slower than their mean response time (RT), the message “Hit – good: 10 cents” was displayed. When subjects responded more quickly than their mean RT, the message “Quick – very good: X cents” was displayed (for responses up to 1.5 SDFs faster than their mean RT) and “Very quick – excellent: X cents” (for responses faster than their mean RT by at least 1.5 SDFs). The reward was scaled according to $X = 10 + (0.15 \times (\text{mean RT} - \text{trial RT})/(3 \times \text{SDF}))$, up to a maximum of 25 cents. The money won on each trial was added to the subject’s running total of reward money, which was displayed underneath the feedback at the end of each block.

Four different versions of the SAT were used, each with a different stimulus level (blue, red, animal, or household object) that was task-relevant and reinforced with high probability. Each subject was administered the same version for both blocks of the SAT. These four versions of the task were counterbalanced across subjects.

Learned Irrelevance (LIr)
The Learned Irrelevance (L Irr) paradigm involved a visual target detecting task in which the subjects were instructed to press the keyboard space bar as soon as the target, represented by the letter X, appeared on the screen. In addition to the target, there were 10 different letter characters occurring in the test. These non-target characters were capital letters that were divided into two groups, namely preexposed (PE) and non-preexposed (NPE). The five vowels (A, E, I, O, and U) were assigned to the NPE group, while a selection of five consonants (B, D, P, T, and Z) comprised the PE group. All characters were colored yellow and presented on a gray background, and all were presented in the same size (Courier New font, Bold, 32 pt.) in the center of the screen (Figure 2). They appeared one after the other in a 1 s rate without any interstimulus interval. A test session involved 450 letters: 75 targets and 375 non-target letters.

The target and non-target letters (PE and NPE) were presented according to the schedules of three different conditions: non-preexposed (NPE), preexposed (PE), and random (R). The three conditions, in turn, were segmented in five sections each; after each section, subjects received a short break. R, PE, and NPE blocks were presented in a fixed order and a test session always started with an R block. There were never two successive blocks of the same condition. Regardless of the condition, each block contained 30 characters: 5 targets, 5 target predictor letters which were presented immediately before the target, and 20 filler letters consisting of characters of the PE group. Filler letters served to “fill” the intervals between the predictor letter-target contingencies. On average, there were four filler letters between the target and predictor letters, with a range between one and eight letters; filler letters never predicted the target. There were three blocks to each section: one R block, one PE block, and one NPE block. In total, the L Irr task consisted of five sections, resulting in a total 450 characters (75 targets, 75 predictor letters, and 300 filler letters.)
In the R blocks, the targets randomly appeared after any consonant letter, which also served as PE letters. Actually, the five targets of a block were preceded once by each of the five PE letters. Therefore, the target could not be predicted in an R block at all. In NPE blocks, the target letter was preceded by the same vowel letter for all five targets in the block. Each vowel acted as a target predictor in one particular NPE block and was not presented before or later in the test session. Thus, vowels reliably predicted the target and enabled full prediction of the target letter. In a PE block, the target was preceded five times by the same preexposed letter. However, PE letters were preexposed throughout the test in the R blocks and as random, inconsequential filler letters; these filler letters constituted the major part of the LIrr test (300 filler letters out of a total 450 letters). Therefore, in a PE block the target could only partly be predicted. According to the degree of prediction, the response time (RT) to the target was expected to be the lowest (i.e. fastest) in NPE blocks, somewhat higher in PE blocks, and highest (i.e. slowest) in R blocks. In the case of the LIrr task, the average RT in the PE block is expected to be significantly higher than in the NPE block.

Prior to the test session, subjects were given the following instructions: “This is a reaction time test which lasts about 8 minutes. Watch the screen, and when an ‘X’ appears, press the space bar as quickly as you can. You may find that the other letters help you to predict when the ‘X’ is going to appear, but do not worry if you do not. Try not to make mistakes, but do not worry if you do.”

Results

All data were analyzed using the Statistical Package for the Social Sciences (SPSS), version 16 (SPSS Inc., Chicago, IL, USA).
For each subject, mean reaction times (RTs) were calculated for each block, as well as for each stimulus type (animals, blue pictures, objects, and red pictures). Only valid responses (those made during the appearance of the probe) were included in analysis. Reaction times that were lower than 100 ms or greater than 1000 ms were excluded from analysis, on the grounds that they are implausibly fast and slow responses, respectively. Additionally, for each subject, the mean VAS rating for each stimulus type was calculated. Two measures of motivational salience were calculated for each block. Adaptive salience was defined in two ways (implicit and explicit). RT adaptive salience (implicit) was defined as the speeding of reaction time on high-probability-reinforcement trials relative to low-probability-reinforcement trials, and VAS adaptive salience (explicit) was defined as the increase in probability rating for high-probability-reinforcement trials relative to low-probability-reinforcement trials. For RT, adaptive salience was computed as low-reinforcement-probability mean RT – high-reinforcement-probability-mean RT. For VAS, adaptive salience was computed as high-reinforcement-probability VAS rating – low-reinforcement-probability VAS rating. This calculation was performed separately for each block. Aberrant salience was defined as the absolute difference in RT (implicit) or VAS rating (explicit) between the two levels of the task-irrelevant stimulus dimension. Since aberrant salience is defined as any deviation from reaction time or VAS rating for the two levels of the task-irrelevant stimulus dimension, the sign is unimportant. Therefore, aberrant salience was always positive, whereas adaptive salience could be positive or negative.

Reaction times (ms) and VAS ratings were analyzed using repeated measures ANOVA; five separate ANOVAs were conducted, with block (1st block, 2nd block), RT adaptive salience (high-reinforcement, low-reinforcement), RT aberrant salience (task-irrelevant condition 1, task-irrelevant condition 2), VAS adaptive salience (high-reinforcement, low-reinforcement), and
VAS aberrant salience (task-irrelevant condition 1, task-irrelevant condition 2) as the within-subjects factors, and genotype (9/10, 10/10) as the between-subjects factor for each of the five ANOVAs.

Behavioral data are presented in Table 2. There was a main effect of block, as subjects responded more quickly to trials in the second block relative to the first block [main effect of block, $F(1, 26) = 2.943, p < 0.10$]. There was no significant main effect of genotype [$p > .11$]. The trial type X genotype interaction was not significant [$p > .63$]; therefore, as the pattern of block differences did not differ by DAT, we collapsed RT across blocks for the remaining ANOVAs.

For RT adaptive salience, as predicted, subjects responded more quickly to high-probability-reinforced trials than low-probability-reinforced trials, indicating significant adaptive salience [main effect of trial type, $F(1, 26) = 12.479, p < .005$]. There was no significant main effect of genotype [$p > .11$]. The trial type X genotype interaction was not significant, indicating that the amount of adaptive salience did not differ by genotype [$p > .19$] (Figure 3). As we had predicted a difference between DAT groups, we tested for it with an independent samples $t$-test comparing RT adaptive salience (low-reinforcement-probability mean RT – high-reinforcement-probability-mean RT) between DAT groups; this difference was not significant ($p > .12$).

For RT aberrant salience, subjects’ RTs differed between the two levels of the task-irrelevant dimension [main effect of trial type, $F(1, 26) = 39.88, p < .001$], indicating significant aberrant salience. There was no significant main effect of genotype [$p > .10$]. There was no significant interaction between DAT group and RT aberrant salience [$p > .30$] (Figure 4), indicating both DAT groups exhibited similar amount of aberrant salience. Chi-square tests
revealed that no one stimulus dimension resulted in significantly greater RT aberrant salience attribution ($p > .90$).

For VAS adaptive salience, there was a main effect of trial type, as subjects rated high-probability-reinforced trials as more likely to produce reward relative to low-probability-reinforced trials [main effect of trial type, $F(1, 22) = 139.8, p < .001$]. There was no significant main effect of genotype [$p > .74$]. The trial type X genotype interaction was not significant, indicating that the explicit encoding of the rewarded dimension did not differ by genotype [$p > .76$] (Figure 5).

For VAS aberrant salience, there was a main effect of trial type [$F(1, 26) = 52.555, p < .001$], indicating significant aberrant salience. There was no significant main effect of genotype [$p > .58$]. There was no significant interaction between DAT group and VAS aberrant salience [$p > 0.79$], indicating both DAT groups exhibited similar amount of aberrant salience (Figure 6).

Chi-square tests revealed that no one stimulus dimension resulted in significantly greater VAS aberrant salience attribution ($p > .90$).

**Learned Irrelevance Task**

Only subjects who successfully responded to at least 80% of target hits (60 of the total of 75) were included in the analyses. This criterion, which was met by all subjects, indicated that subjects understood and followed the given instructions. Mean reaction times (ms), i.e. the time measured between the target onset and the pressing of the keyboard space bar, were calculated. Reaction times that were lower than 100 ms or greater than 1000 ms were excluded from analysis, on the grounds that they are implausibly fast and slow responses, respectively. These mean RTs were analyzed using repeated measures analysis of variance (ANOVA), with condition (R, PE, NPE) as the within-subjects factor and genotype (9/10, 10/10) as the between-
subjects factor. A Bonferroni correction \((p < .05)\) was applied to comparisons of means by trial type. Additionally, a repeated measures ANOVA was conducted with block as the within-subjects factor and genotype group as the between-subjects factor. Only the RTs of the last three trials (the 3rd, 4th and 5th target) of each block were used for analysis. This was based on the expectation that implicit associative learning might start to express itself after two CS-US pairings. Additionally, non-target hits (responses to filler letters or target predictors) and missed targets were counted per condition (R, PE, and NPE), and were considered errors. Accuracy was defined as \((\# \text{ of Targets} - \# \text{ of Missed Targets}) / (\# \text{ of Targets}) - (\# \text{ of Errors/} \# \text{ of Non-Targets})\). An independent samples t-test was conducted to compare accuracy between DAT groups. Furthermore, a repeated measures ANOVA was conducted with accuracy for each condition (R, PE, NPE) as the within-subjects factor and genotype group as the between-subjects factor.

Across DAT groups, subjects exhibited a main effect of block on response time \([F(4,23) = 5.365, p < .01]\), with response times in each successive block becoming increasingly slower. However, there was no significant interaction between block and DAT group \([p > .27]\). There was a significant main effect of condition (R, PE, NPE) \([F(2, 25) = 16.97, p < .001]\). Post-hoc analysis using the Bonferroni adjustment for multiple comparisons revealed that there was a significant difference in response time to NPE targets compared to PE targets \([p < .001]\) and R targets, such that RTs to NPE targets were significantly faster than RTs to both R and PE targets \([p < .001]\), as well as a significant difference in RT between R and PE targets, such that RTs to PE targets were significantly faster than RTs to R targets \([p < .05]\) (Figure 7). Thus, learned irrelevance is observed, since RTs were fastest for NPE blocks, and progressively slower for PE and R blocks, respectively. However, there was no main effect of DAT group \([p > .87]\). There was no significant interaction between condition and DAT group \([p > .44]\), indicating that both
DAT groups showed equally adept learned irrelevance. There was no significant main effect of DAT group on mean response time \([p > .80]\). Finally, there was no significant difference in the total accuracy scores between DAT groups \([p > .11]\). Furthermore, there was no main effect of condition (R, PE, NPE) on accuracy \([p > .16]\), indicating that accuracy did not differ significantly on each condition. There was no significant interaction between accuracy for each condition and DAT group \([p > .41]\), indicating that both DAT groups showed equal accuracy on each condition.

**Discussion**

Two measures of salience, the SAT and LIrr task, were implemented in subjects varying by DAT genotype. In the SAT, both genotype groups implicitly learned the to attribute salience to reward-related stimuli. However, these two genotype groups did not significantly differ in the amount of implicit adaptive salience they attributed to reinforced stimuli. Additionally, both genotype groups exhibited significant aberrant salience, such that both groups believed there was a reward contingency between stimuli to which no reward probability was attributed. However, there was no significant genotype by trial type interaction, indicating that neither group exhibited significantly greater aberrant salience than the other group. Subjects successfully and explicitly learned the stimulus-reward contingencies, such that subjects in both genotype groups associated reinforced stimuli with reward. However, neither genotype group exhibited significantly greater explicit adaptive salience than the other group. Finally, subjects in both genotype groups exhibited significant explicit aberrant salience, such that subjects erroneously attributed a difference in reward probability to stimuli in which no contingency was present. However, neither genotype group exhibited significantly greater explicit aberrant salience than the other group. For the LIrr task, across both genotype groups, response times were fastest for NPE.
blocks, and slower for PE and R blocks, as expected. Post-hoc analyses revealed significant differences in RTs between all three conditions. However, neither genotype group exhibited significantly greater learned irrelevance than the other group.

Though these data have not yet provided significant differences between DAT groups in the attribution of salience, there are already emerging trends that indicate important differences in task performance by genotype. For instance, the 9/10 genotype group exhibited greater implicit adaptive salience than the 10/10 group, and though this interaction was not significant, the low p value for this interaction indicates that with greater sample sizes, this interaction may likely approach significance. This is especially important given the high amount of variance in RT within each DAT group. An independent samples t-test was conducted as a follow-up measure, and these results support the emerging data trend that the 9/10 genotype group exhibited greater implicit adaptive salience than the 10/10 group. For implicit aberrant salience, interestingly, the 9/10 group showed greater implicit aberrant salience than the 10/10 group. However, statistical analyses indicate that this trend, even with greater sample sizes, may not prove to be significant.

Additionally, for explicit adaptive salience, both DAT groups successfully and explicitly learned the stimulus-reward contingencies, indicating that the learning of these contingencies was not impossible. However, there was no significant difference in explicit adaptive salience scores between genotype groups. For explicit aberrant salience, both groups erroneously decided that one task-irrelevant stimulus was more likely to predict reward than another task-irrelevant stimulus; however, there was no significant interaction between explicit aberrant salience and genotype, indicating that both DAT groups exhibited similar explicit aberrant salience. Finally, chi-square tests revealed that no stimulus type (animal, blue, object, or red) was attributed a
significant amount of aberrant salience. This confirms that there were no visual features of the images themselves that would significantly alter the distribution of attention. In essence, this ensures that the regulation of attention is goal-directed and not stimulus-driven. This finding was also replicated in a previous study (Rosier et al., 2009), corroborating the finding that participants did not reliably respond more quickly in the context of any particular stimulus feature relative to the others.

It is especially interesting that there was no significant interaction between explicit adaptive salience and genotype, in light of that finding that the implicit measure, RT adaptive salience, showed a weak trend towards an interaction. These differences in learning (as measured by VAS score) and motivated behavior (as measured by mean RT) might be due to the small sample size. It is possible that the differential effect of explicit salience between genotype groups is weaker than the implicit effect; a larger sample size might elicit this fact, and the effect of explicit salience might also approach significance.

Alternatively, these differences in learning and motivated behavior might be due to the differential roles of dopamine in the striatum. Dopamine is a neurotransmitter that has important functions involved with motivated behavior and learning in the striatum, hippocampus, and prefrontal cortex. Dopamine signaling in the nucleus accumbens, located in the ventral striatum, has been shown to be a key modulator of behavioral activation, attention, and responsiveness to conditioned stimuli (Salamone and Correa, 2005). Furthermore, it has been shown that these motivational processes are distinct and dissociable from the functions that underlie learning (Salamone et al., 2002). Previous research in rats has shown that interference with DA in the nucleus accumbens can impair acquisition on various learning procedures, though these impairments are not necessarily dependent upon deficits in motivation (Kelley, 2004).
Additionally, fMRI research in human subjects has highlighted a distinct difference in the functioning of dopaminergic projections to the dorsal and ventral striatum; the former is associated with the learning of stimulus-response associations, while the latter is implicated in reward and motivation (O’Doherty et al., 2004). These findings of dissociable contributions of the dorsal and ventral striatum may help explain why differences in implicit adaptive salience between DAT groups were greater than differences in explicit adaptive salience. Dopamine availability, as predicted by DAT genotype, may likely differ between the dorsal and ventral striatum, such that DAT activity has a greater effect in the ventral striatum, resulting in greater differences in measures of reward-induced motivation. Remarkably, previous fMRI research has shown that reduced ventral striatal activation during reward anticipation is correlated with impulsivity and hyperactivity (Scheres et al., 2007), and that adults with ADHD showed reduced ventral striatal activation when compared to controls (Strohle et al., 2008). Another study in children diagnosed with ADHD reported that treatment with methylphenidate (MPH), a psychostimulant that increases dopamine levels in the brain, increased the children’s motivation to perform an ongoing task in which they received a monetary reward (Chelonis et al., 2010). These results implicate the role of dopamine signaling in the ventral striatum in modulating reward-based behavior and impulsivity.

For the LIrr task, there was a main effect of block, such that response times on each successive block were significantly greater than the previous block. This may be due to fatigue effects, as subjects are exposed to 90 letters in as many seconds, and then repeat this measure four more times. Understandably, after 8 minutes of consecutive and repetitive letter exposure, subjects would exhibit fatigue. Furthermore, there was no interaction between block and genotype, indicating that these effects were consistent regardless of DAT group. Finally, a t-test
showed that there was no significant difference in accuracy scores between DAT groups, as both achieved high levels (greater than 96%) of performance on this task.

As predicted, there was a significant main effect of condition, such that response times were fastest for NPE blocks, and slower for PE and R blocks. Post-hoc analyses revealed significant differences in RTs between all three conditions. This indicates that across DAT groups, novel, non-preexposed vowel letters were better predictors of the target than a single preexposed consonant or a random preexposed consonant. In effect, both DAT groups exhibited successful learned irrelevance. However, there was no genotype by condition interaction, indicating that neither DAT group exhibited significantly greater learned irrelevance than the other group. It is possible that the effect of genotype group on learned irrelevance is relatively weak, and with larger sample sizes, a significant difference in learned irrelevance between genotype groups will appear.

On the other hand, this finding may also be related to the aforementioned dissociation between dorsal and ventral striatal processes, i.e. that the dorsal striatum is involved in the learning of stimulus-response associations, while the ventral striatum is implicated in reward and motivation (O’Doherty et al., 2004). As previously discussed, subjects showed differential motivational behavior despite a similar explicit rating of stimulus-reward learning. Likewise, because the LIrr task simply involves a stimulus-response association, and does not contain any motivational or rewarding outcomes, current research would suggest that this task recruits mostly dorsal striatal mechanisms of activation. Results from the SAT also indicate that DAT genotype might not have a significant effect on activities that are associated with dorsal striatal activation, but does have a near-significant effect on components that involve ventral striatal activation. Accordingly, these data show no significant interaction between LIrr condition and genotype,
indicating that behaviors that activate dorsal striatal pathways are not significantly affected by DAT genotype.

Though these data suggest that DAT genotype has a differential effect on behaviors that recruit dorsal and ventral striatal activation, it is still unclear whether this effect is necessarily due to a differences in synaptic dopamine levels. Though previous research has shown that behavioral patterns characteristic of ADHD have been shown to be more prevalent in carriers of the 10/10 allele relative to 9/10 carriers (Cook et al., 1995; Waldman et al., 1998), that adults with ADHD showed reduced ventral striatal fMRI activation when compared to controls (Strohle et al., 2008), and that subjects with ADHD showed greater striatal DAT density relative to controls (Larisch et al., 2006), there is no data in this study which directly elucidates the effect of varying dopamine levels or ventral striatal activation on task performance.

In conclusion, these results indicate a trend towards differential motivational behavior, as measured by implicit salience attribution, between carriers of the 9/10 and 10/10 DAT allele. Furthermore, differences in reward-based behavior between genotype groups and concomitant similarities in stimulus-response association learning between genotype groups indicates that DAT activity, as predicted by DAT genotype, might have differential effects in the dorsal and ventral striatum.
References


Author Note

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Table 1

Task Design Example: Red is the Reinforced Condition

<table>
<thead>
<tr>
<th>Shape (Task–Irrelevant)</th>
<th>Color (Task-Relevant)</th>
<th>Measures Adaptive Salience</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High-Reinforcement</td>
<td>Low-Reinforcement</td>
</tr>
<tr>
<td>No Difference in</td>
<td>Red Animals</td>
<td>Blue Animals</td>
</tr>
<tr>
<td>Reinforcement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Red Animals</td>
<td></td>
<td>Blue Animals</td>
</tr>
<tr>
<td>Red Objects</td>
<td></td>
<td>Blue Objects</td>
</tr>
</tbody>
</table>
**Table 2**

SAT Behavioral Data

<table>
<thead>
<tr>
<th>Condition</th>
<th>Mean (S.D)</th>
<th>Mean (S.D.)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DAT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT Adaptive Salience (ms)</td>
<td>12.93 (6.07)</td>
<td>5.82 (14.94)</td>
</tr>
<tr>
<td>RT High-Reinforcement</td>
<td>246.36 (18.83)</td>
<td>231.39 (28.77)</td>
</tr>
<tr>
<td>RT Low-Reinforcement</td>
<td>259.29 (22.82)</td>
<td>237.21 (34.27)</td>
</tr>
<tr>
<td><strong>VAS Adaptive Salience (%)</strong></td>
<td>52.25 (15.03)</td>
<td>49.47 (23.86)</td>
</tr>
<tr>
<td>VAS High-Reinforcement</td>
<td>73.65 (8.20)</td>
<td>71.19 (18.28)</td>
</tr>
<tr>
<td>VAS Low-Reinforcement</td>
<td>21.40 (8.82)</td>
<td>21.72 (13.83)</td>
</tr>
<tr>
<td><strong>RT Aberrant Salience (ms)</strong></td>
<td>10.52 (5.08)</td>
<td>7.55 (7.16)</td>
</tr>
<tr>
<td>RT Irrelevant 1</td>
<td>247.53 (21.65)</td>
<td>230.51 (29.16)</td>
</tr>
<tr>
<td>RT Irrelevant 2</td>
<td>258.06 (19.89)</td>
<td>238.05 (32.79)</td>
</tr>
<tr>
<td><strong>VAS Aberrant Salience (%)</strong></td>
<td>17.70 (15.70)</td>
<td>19.00 (10.83)</td>
</tr>
<tr>
<td>VAS Irrelevant 1</td>
<td>54.60 (16.02)</td>
<td>57.28 (9.95)</td>
</tr>
<tr>
<td>VAS Irrelevant 2</td>
<td>36.90 (12.48)</td>
<td>38.28 (10.09)</td>
</tr>
</tbody>
</table>
Figure Caption

Figure 1. Progression of a single trial on the SAT

Figure 2. Overview of the LIrr task

Figure 3. RT adaptive salience by DAT genotype

Figure 4. RT aberrant salience by DAT genotype

Figure 5. VAS adaptive salience by DAT genotype

Figure 6. VAS aberrant salience by DAT genotype

Figure 7. Mean RT for LIrr condition grouped by DAT genotype

Figure 8. Accuracy score by DAT genotype
Figure 1

- **Fixation**: 1000 ms
- **Conditioned stimulus**: 1000–2000 ms
- **Quick response**: 2250 ms
- **Feedback**: 1500–2500 ms

10 cents
<table>
<thead>
<tr>
<th>Block</th>
<th>Letter sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>R₁</td>
<td>B X T D Z B Z T D X Y D Y Z X T B T Y X Z B D B Y T X Z D Y</td>
</tr>
<tr>
<td>PE₁</td>
<td>D X B T Y Z T B D X Y B Z Y T D X B Z D X Y T B Z T D X Y Z</td>
</tr>
<tr>
<td>NPE₁</td>
<td>T I X D B Y Z D Y I X T Y I X B D Z B T I X Y Z D I X Z B T</td>
</tr>
</tbody>
</table>
Figure 3

Adaptive Salience (ms)

DAT Genotype

9/10

10/10
Figure 5

![Bar chart showing the adaptive salience of DAT genotype 9/10 and 10/10. The y-axis represents adaptive salience in percentage, ranging from 0 to 60%. The x-axis represents DAT genotype, with 9/10 on the left and 10/10 on the right. There are error bars indicating variability.]
Figure 7
Figure 8

![Bar chart showing accuracy for different DAT genotypes. The chart indicates that the 10/10 genotype has higher accuracy compared to the 9/10 genotype.](chart.png)