EFFECTS OF DOPAMINE AND SALIENCE MANIPULATIONS ON MAGICAL THINKING

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by

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The undersigned, appointed by the dean of the Graduate School, have examined the thesis entitled

Effects of Dopamine and Salience Manipulations on Magical Thinking

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and hereby certify that, in their opinion, it is worthy of acceptance.

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I dedicate this thesis to my family, especially my husband for his endless support and love. I also dedicate it to my brother, for his encouragement and support.

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ABSTRACT

Although delusional and magical thinking is associated with both increased dopamine and aberrant salience, it is unknown whether dopamine manipulations cause increased magical thinking on non-clinical measures or whether salience manipulations cause an increase in magical thinking. The current research investigated whether experimental manipulations of dopamine and salience cause an increase in magical thinking as measured by a lab task in college students (n = 252). Magical thinking was measured behaviorally by throwing darts at either a highly positive baby face or a neutral smiley face. Dopamine levels were manipulated by whether or not participants performed a high reward gambling task. Salience levels were manipulated by whether the baby face stimulus was novel or had been seen frequently on an earlier task. Dopamine functioning was measured with a reversal learning task. Trait magical thinking was measured with the Magical Ideation Scale. As expected, performance on the magical thinking behavioral task was associated with both the dopamine reversal learning task and increased trait magical thinking. In addition, the dopamine manipulation affected performance on the dopamine reversal learning task. Most importantly, we found that both the dopamine manipulation and the salience manipulation caused an increase in magical thinking on the behavioral task (i.e., less accurate in throwing at baby face than at smiley face). Overall, the current research provides evidence that experimental increases in dopamine and salience cause increased magical thinking.

EFFECTS OF DOPAMINE AND SALIENCE MANIPULATIONS ON MAGICAL THINKING

Chapter 1

Magical thinking can be conceptualized as the attribution of a causal relation to otherwise random events (Meehl, 1964), and can range from delusions to relatively common irrational beliefs (Brugger & Graves, 1997; Eckblad & Chapman, 1983). Previous research has indicated that approximately one quarter of Americans believe in some form of magical thinking, such as astrology, clairvoyance, ghosts, or communication with the dead (Vyse, 1997). Measures of magical thinking have been shown to reliably predict future psychosis (Chapman et al., 1994). Two potentially related mechanisms that have been implicated in psychotic magical thinking are increased striatal dopamine and aberrant salience (Kapur, 2003; Kester et al., 2006; Morrison & Murray, 2009; Sass, 1992). Although theories of magical thinking posit causal mechanisms, much research in psychopathology is correlational and does not test causation (Sher & Trull, 1996). For example, no previous study has examined whether manipulating aberrant salience causes an increase in magical thinking. The current research examined whether experimental manipulations of dopamine and salience cause an increase in magical thinking in college students.

Magical thinking has often been measured using questionnaires or interviews. However, in examining whether manipulations cause increases in magical thinking, there are potential problems with both questionnaire and interview measures. A potential problem with questionnaire measures is that they ask about previous beliefs and experiences and therefore might not be sensitive to short-term changes in magical thinking. For example, consider an item from the Magical Ideation Scale (Eckblad &

Chapman, 1983): “I have occasionally had the silly feeling that a TV or radio broadcaster knew I was listening to him.” If someone experienced a short-term increase in magical thinking in the lab, it would not be expected to affect someone’s answer to this question about past thinking. For interview measures, a potential problem is that they require trained interviewers, can be time consuming, and can be challenging to rate reliably (Hunsley & Mash, 2008; Ross, Swinson, Doumani, & Larkin, 1995). Moreover, given that interviews contain items not designed to measure transient psychotic symptoms, reports do not always fit precisely into categories of delusional thinking (Pomarol-Clotet, 2006). Therefore, it is necessary to have measures of magical thinking that are sensitive to short term changes in magical thinking.

An alternative way to measure magical thinking is to use behavioral lab tasks. These tasks appear to be sensitive to short-term changes in magical thinking (e.g., Berenbaum, Boden, & Baker, 2009; King, Burton, Hicks, & Drigotas, 2007). At the same time, they are relatively easy to administer and score without requiring trained interviewers. Therefore, behavioral lab measures appear to be useful for relatively large sample research examining short-term changes in magical thinking. Ultimately, the development and validation of behavioral magical thinking measures might provide performance measures useful for measuring psychosis risk. However, like interview measures, there is also limited evidence supporting the validity of behavioral lab tasks for measuring short-term changes in magical thinking. For example, previous research to our knowledge has not examined whether higher trait levels of magical thinking is associated with behavioral measures of magical thinking. Hence, an important goal of the current

research is to examine whether behavioral lab tasks appear to be valid measures of magical thinking.

Another important goal of the current research is to examine whether experimental manipulations of dopamine cause an increase in magical thinking on a behavioral lab task. Based on at least 50 years of research, changes in dopamine is the most strongly implicated mechanism of psychotic symptoms (Howes & Kapur, 20009). For example, all well-established antipsychotic drugs are dopamine receptor antagonists (Creese, Burt, & Snyder, 1976; Kapur & Seeman, 2001; Seeman, Chau-Wong, Tedesco, & Wong, 1975). More recently, imaging studies have revealed increased amounts of dopamine in both individuals with schizophrenia and individuals at risk for schizophrenia (Laruelle et al., 2003; Stone et al., 2010). At the same time, amphetamines that increase striatal dopamine have also been found to increase interview measures of psychotic symptoms including magical thinking (Brier et al., 1997; Laruelle et al., 1996). However, previous research has not examined whether experimental manipulations of dopamine cause an increase in behavioral lab measures of magical thinking.

The current study will examine whether increasing levels of dopamine through performing a rewarding gambling task causes an increase in magical thinking. While many previous studies regarding dopaminergic increases have relied on pharmacological increases in dopamine (e.g., Angrist & Gershon, 1970; Brier et al., 1997), due to the cost, extensive exclusionary criteria, and length of time associated with administering pharmacological increases in dopamine, the present study used a rewarding task in order to increase dopamine (Knecht et al., 2004; Schultz, 2007; Tomasi et al., 2009). Imaging studies have shown that rewarding tasks lead to increases in striatal dopamine (Abler,

Herrnberger, Gron, & Spitzer, 2009; Cools et al., 2009). Although previous research has shown that increases in dopamine lead to increases in psychotic symptoms, the current study examined whether increases in dopamine, caused by performing a rewarding gambling task, resulted in increases in magical thinking. Relatedly, the current study aimed to further validate whether performing a rewarding task appears to cause an increase in baseline dopamine by using a reversal learning task found to be sensitive to dopamine levels (Cools et al., 2009; Swainson et al., 2000). Furthermore, the current study also examined whether performance of a behavioral task thought to reflect increased dopamine levels is associated with increased scores on a self-report measure of trait magical thinking, which previous research has not investigated.

In addition to examining the effects of increases in dopamine, another important goal of the current research was to examine whether increased salience causes an increase in magical thinking. As hypothesized by many psychosis researchers (e.g., Heinz & Schlagenhauf, 2010; Howes et al., 2009; Kapur, 2003), a key psychological mechanism in the development of magical thinking is aberrant salience, or an increases in salience resulting in the incorrect assignment of significance to neutral environmental stimuli. There are at least three pieces of evidence supporting a role of aberrant salience in magical thinking. First of all, patient case studies provide evidence that during initial experiences with psychosis, patients' experience a sense that otherwise irrelevant stimuli are somehow more significant (Bowers, 1973; MacDonald, 1960). In addition, it has been proposed that increased striatal dopaminergic leads to the aberrant assignment of salience to environmental stimuli in psychosis-prone individuals (Kapur, 2003). Lastly, a questionnaire measuring aberrant salience, the Aberrant Salience Inventory, has been

found to be related to both trait magical thinking and history of a psychotic disorder (ASI: Cicero, Kerns, & McCarthy, 2010). However, previous research has not investigated whether increasing an individual's perceived salience causes an increase in lab measured magical thinking.

One method of increasing salience is through the use of novel stimuli. Viewing novel images, as opposed to previously seen images, have been shown to result in increases in perceived salience and in striatal dopamine (Amso et al., 2005). However, previous research has not examined whether an increase in perceived salience causes an increase in magical thinking. Furthermore, previous research has not investigated the relationship between lab measures of magical thinking and trait aberrant salience. Therefore the current study examined whether manipulating the salience of an image is related to increases in lab measured magical thinking, as well as whether performance on the lab measure of magical thinking is related to trait aberrant salience, as measured by the Aberrant Salience Inventory (Cicero, Kerns, & McCarthy, 2010).

The current study aimed to investigate the causes and correlates of magical thinking, through examining the relationships between magical thinking, dopamine, and salience. It was hypothesized that manipulating dopamine levels through a rewarding gambling task will result in increases in a lab measure of magical thinking. As a manipulation check, it was also expected that the dopamine manipulation would also affect performance on a separate task sensitive to dopamine levels. It was also hypothesized that participants with greater trait magical thinking would exhibit heightened performance on this dopamine sensitive task. Similarly, it was expected that increasing salience through manipulating the novelty of an object would also result in

increases in magical thinking. The current study also examined whether individual differences in magical thinking, dopamine, and aberrant salience were related to a behavioral lab measure of magical thinking. It was hypothesized that participants with greater trait magical thinking, heightened performance on a task sensitive to dopamine, and greater trait aberrant salience would exhibit increased magical thinking on a behavioral lab task.

Chapter 2

Methods

Participants

Participants were college students recruited from a large Midwestern public university who received credit from an introduction to psychology course for their participation. I recruited 253 college students to participate in this study (56% female; mean age = 18.71, *SD* = .88, 81% Caucasian, 9.8% African-American, 3.4% Asian-American, 3.9 Latino/Latina, 1.5% Biracial). Following previous research, participants (*n* = 18) were excluded due to Chapman infrequency scores of 3 or greater (Chapman & Chapman, 1983). Participants were randomly assigned, using a Latin square, to one of four groups. They were assigned to either: the high salience and low dopamine condition, high salience and high dopamine condition, low salience and low dopamine condition, or low salience and high dopamine condition. Each participant was asked to report their age, gender, and ethnic background.

Materials

Magical thinking behavioral lab tasks. Participants completed a modified version of King et al's (2007) Dart Throwing Task. Participants were told that this part of the study concerns manual dexterity at common tasks, and that they would throw darts at a dart board. Participants were given six practice throws. They were then told that to make the task more interesting, they would be throwing the darts at different shapes. For all participants, the first shape was a face-sized smiley-face in black ink. The image was tacked (at the corners) to the dart board over the bull's eye. After the participants

completed throwing darts at the smiley face, the experimenter attached a second "shape" to the dartboard, this time a photograph of a baby that was the same size as the smiley face. This photograph of a baby was either an image previously seen in an image viewing task, or it was a novel picture of a baby. For each trial, whether the dart hit the bulls-eye, as well as the distance (in centimeters) between the hole made by each dart and the target center was recorded by an experimenter who was blind to both the hypotheses of the study and the condition of the participant.. Magical thinking scores on the Dart Throwing Task were calculated as the extent to which people were less accurate throwing images at the baby image than at the smiley face. For the Dart Throwing Task, difference scores were calculated for each subject, with the average distance of the darts from the smiley face image minus the average distance of the darts from the baby image, which I will refer to as the *dart throwing difference score*. Larger scores for the dart throwing difference score indicate larger distance for the baby image as opposed to the smiley image, indicating greater magical thinking. Following the experiment, participants were asked to report how much they liked each image (i.e., the smiley face and baby), as well as how much they liked throwing darts at each image, on a 10-point Likert scale (with 0 being not at all and 9 being extreme like). This was in order to gauge whether participants in the low salience condition, who were previously exposed to the image, evidenced higher magical thinking scores due to liking the image of the baby (due to the mere exposure effect, thus potentially making making them less accurate on the Dart Throwing Task, which as will be seen below was not the case). Difference scores were calculated for liking the image of the baby by subtracting how much they liked the smiley face from how much they liked the baby image.

In addition to the Dart Throwing Task, participants also completed the Preference Ratings Task, which included three sets of preference ratings. These tasks were derived from the work of Rozin, Millman, & Nemeroff (1986), and Berenbaum, Boden, & Baker (2006), and were given in order to provide a second measure assessing state magical thinking. For each of these three sets within the Preference Ratings Task, participants rated the degree to which they prefered one of the stimuli over the other by making a pencil mark on a 100-mm scale labeled "definitely prefer A" on one end and definitely prefer B" at the other end. Participants were informed that they would actually sample the stimulus that they prefered. Individuals in the low salience condition were informed about the nature of the Preference Ratings Task and the fact that none of the stimuli were real at the beginning of the experiment. It was thought that this might result in the novelty and salience of the task to wear off, although ideally this would also have involved greater exposure to stimuli before making preference ratings, but this turned out not to be feasible. Individuals in the high salience condition were given this same information just minutes before completing the tasks, hence this information should still have been novel and salient to participants.

For the first set of the Preference Ratings Task, participants were presented with two new plastic cups. The participant then poured water into each cup. The experimenter then placed a plastic cockroach in one cup and a plastic candle holder in the other cup. The order of which cup received which stimulus was alternated between participants. The participant rated how much they would like to take a sip from each of the two cups of water. Following this rating, the participant took a sip from the preferred cup.

The second set of the Preference Ratings Task consisted of two pieces of the same fudge, each on its own separate paper plate. One piece was shaped in the form of a square, and the other piece was in the shape of dog feces. The order of the fudge pieces was alternated between participants. The pieces were approximately the same size. The subjects rated their desire to eat each of the pieces of fudge, and indicated which they would prefer. They then took a bite of the piece of fudge that they preferred.

On the third set of the Preference Ratings Task, participants rated two 500 ml chemical bottles, each one-quarter filled with white powder (sugar). One bottle was labeled “Sucrose (table sugar)”, and the other was labeled “Sodium Cyanide”. The experimenter then set out two plastic cups, and poured water into both. Then the experimenter placed half a spoonful of powder (sugar) from the first bottle into a cup. Then the experimenter placed half a spoonful from the other bottle into the second cup. The order of the bottles and the cups was alternated between participants. The participant then rated how much they would like to drink from each of the cups, and stated a preference between the two cups. The participant then took a sip from the preferred cup.

For each of these sets in the Preference Ratings Task, magical thinking scores were calculated as the extent to which participants preferred the three normal items (the candle holder, the square-shaped fudge, and the “Sucrose” drink) to the three magical thinking items (the roach, the feces-shaped fudge, and the “Sodium Cyanide” drink). With the Preference Ratings Task, difference scores were also calculated with the rating for the normative objects (sucrose, square shaped fudge, and the candle holder) minus the rating for the magical ideation objects (sodium cyanide, poop shaped fudge, and the roach). Larger scores for the Preference Ratings Task difference score indicate greater

preference for the normal items as opposed to the magical thinking items, indicating greater magical thinking.

Dopamine Manipulation: Gambling versus Non-gambling Tasks. Before participants completed the magical thinking behavioral lab task, they performed one of two tasks to manipulate dopamine levels. Participants in the high dopamine condition completed a gambling task. I used a modified version of the gambling task used by Eisenegger et al. (2010). Participants completed a total of 50 trials of the gambling task, in which participants were presented with an array of 10 closed boxes on a computer screen. Subjects had the chance to open as many boxes as they wished. They were told that nine of the boxes contained monetary rewards, while one box contained a loss. This loss would make them lose all of their winnings for the current trial (and ending that trial). After each opened box, participants had to decide whether to continue opening boxes or terminate the trial to avoid a loss. Since this was the high dopamine condition task, rewards were fixed to ensure that each participant was receiving a high number of rewards, as rewards increase striatal dopamine (Abler, Herrnberger, Gron, & Spitzer, 2009; Cools et al., 2009). Thus, unbeknownst to the participant, the reward trials were fixed, so that participants won 50% of the first ten trials, 60% of the second ten trials, and 70% of the third ten trials, 80% of the fourth ten trials, and 90% of the last ten trials. For reward trials, a smiley face, a "+100" sign, and a positively-valenced sound were presented as feedback. For punishment trials, a sad face, a "-100" sign, and the negatively-valenced sound were presented as feedback. During the task, participants also saw their total amount of points and they were told that the goal was to accumulate as

many points as possible. Therefore, participants in the high dopamine condition completed a total of 50 gambling task trials.

Participants in the low dopamine condition performed a non-gambling syntactic judgment task modeled after the task used by Ni et al. (2000). In this task, participants were asked to judge whether a series of 60 sentences were grammatically correct. It was determined through piloting the task that the time it took to grammatically judge 60 sentences was comparable to the time it took to complete the gambling task. Sentences were presented on a computer screen, one at a time, whereby the participant was prompted to judge whether or not the sentence was grammatically correct. There was no time limit for the completion of each trial. Stimuli were presented using E-prime. We did not provide participants' with feedback regarding their performance, in order to ensure that this was not a rewarding task, and therefore was appropriate as a low reward/low dopamine task. Thus, while this task still required that the participants made choices (as in the gambling task), these choices did not lead to reward.

Salience Manipulation: Image Viewing Task. Salience was manipulated in the Dart Throwing magical thinking behavioral task by first having participants perform an earlier image viewing task. On the Image Viewing Task, all participants occasionally saw a picture of a baby. Then in the subsequent Dart Throwing Task, in the high salience condition, participants threw darts at the image of a novel baby not previously seen. In the low salience condition, participants threw darts at the image of the baby previously seen in the Image Viewing Task. On the Image Viewing Task, visual images were chosen from the International Affective Picture System (IAPS; Lang, Bradley & Cuthbert, 1995). Participants viewed six neutral images featuring inanimate objects, as well as six images

featuring animate objects, including a photograph of a baby. Each image was presented ten times. During each trial, a fixation cross was presented for 1-s on a computer screen, followed by a 2-s presentation of an image. The participant was instructed to judge whether the object was an animate or inanimate object, and responded with a keyboard press. The task was presented using E-prime (Psychology Software Tools, Inc., 2002). In the low salience condition, the photograph of a baby seen during this Image Viewing Task was used as the image participants threw a dart at during the Dart Throwing Task. Since participants in the low salience condition had previously seen the image in the Dart Throwing Task, participants had presumably habituated to the image, and it was no longer a novel and salient image as, in comparison to novel images, previously seen images are less salient (Amso et al., 2005).

Trait Magical Thinking. Participants completed the Magical Ideation Scale (Eckblad & Chapman, 1983). The questionnaire is a 30-item true–false questionnaire designed to measure "beliefs in forms of causation that by conventional standards are invalid" (Eckblad & Chapman, 1983, p. 215). For example, "I have worried that people on other planets may be influencing what happens on Earth." The Magical Ideation Scale has been shown to have good test-retest reliabilities for males and females, with correlation coefficients of .80 and .82, respectively (Chapman, Chapman, & Miller, 1982). Previous research has shown that high scores on the Magical Ideation Scale are at increased risk for future psychosis (Gooding, Tallent, & Matts, 2005). We found an internal consistency comparable to the Cronbach's alpha reported by Eckblad & Chapman (1983; Cronbach's alpha = .80).

Magical thinking was also assessed using the Peters et al. (1999) Delusions Inventory (PDI). The PDI is a 40-item yes-or-no questionnaire designed to measure delusional ideation in a nonclinical population. This questionnaire was included in order to determine whether trait magical thinking has been measured reliably. This questionnaire assesses delusional beliefs such as, "Do you ever feel as if you have been chosen by God in some way?" Each endorsed belief is subsequently rated on a 5-point Likert scale for the distress, preoccupation, and conviction associated with the delusional belief. We found a Cronbach's alpha of .79 for this scale. This questionnaire has been used to measure delusional ideation in community samples (Peters, Joseph, & Garety, 1999).

Dopamine behavioral tasks. To assess individual differences in dopamine, participants completed two tasks that are thought to be affected by striatal dopamine levels. The first dopamine task was a Reversal Learning Task (Cools et al., 2009). For reversal learning tasks, participants first learn that one stimulus is rewarded and another stimulus is "punished," and then subsequently the associations with reward and punishments are switched and participants have to learn the new associations, with this pattern repeating through a number of reversals.

There are two trial types that are most important for this task: (1) unexpected reward trials, where a stimulus that was associated with punishment on the previous trials is now switched and associated with reward; and (2) unexpected punishment trials, where a stimulus that was associated with reward on the previous trials is now associated with punishment. It is thought that heightened dopamine activity should facilitate a more rapid learning of stimulus-reward associations. In particular, given its role in reward learning, it

is thought that increase dopamine is associated with better reversal or new learning on unexpected reward trials than on unexpected punishment trials. Consistent with this, recent imaging studies have found that individual differences in striatal dopamine are associated with performance on this Reversal Learning Task (Cools et al., 2009; Schonberg, Daw, Joel, & O'Doherty, 2007). Thus, larger reversal learning scores are thought to be associated with high levels of striatal dopamine, wherein larger reversal learning scores reflect better learning from unexpected reward than punishment. After a "reversal"(i.e., a change in reward vs. punishment stimulus mapping), the stimulus highlighted on the first trial after the reversal (when participants would make an error) would also remain highlighted on the second trial after the reversal. The second trial after the reversal is used to calculate reversal learning scores, with increased dopamine associated with greater accuracy after unexpected reward and worse accuracy after unexpected punishment. The number of accurate trials was transformed into a proportional score using the total number of reversal trials completed (because the number of reversal trials completed varied by participant as a function of performance). These proportions of accurate responses were then arcsine transformed (2 x arcsine ($\sqrt{x}$), as has been done in previous research using this task (Cools et al., 2006; 2008). In addition, reversal learning scores were calculated with reaction times, with slower reaction times (RTs) after unexpected punishments and faster RTs after unexpected rewards (with higher reversal learning scores reflecting better learning after unexpected reward than after unexpected punishment). Both the accuracy reversal learning scores (ACC) and the reaction time reversal learning scores (RT) were included in analyses.

On the Reversal Learning Task, on each trial two vertically adjacent stimuli were presented together: one face and one scene. The location of each image was randomized. On each trial, one of the two stimuli was highlighted with a black border. The participant predicted whether the highlighted stimulus would lead to a reward or a punishment on each trial. The participant's self-paced response was followed by an interval of 1000 ms, after which the outcome was presented for 500 ms. If the participant responded to the highlighted stimulus correctly, a green smiley face, a "+$100" sign and a high-frequency jingle tone was presented. If the participant incorrectly responded to the highlighted stimulus, a red sad face, a "-$100" sign and a single low-frequency tone was presented. Through trial and error, participants learn which image is associated with reward or with punishment.

First, each subject performed one practice block. The practice block included one reversal, following which participants had to get 20 (not necessarily consecutive) trials correct before moving on to the experimental blocks. This criterion was imposed in order to ensure that participants became acclimated to the task (Cools et al., 2009). Following the practice block, participants completed four experimental blocks, with a total of 120 trials per block. The reward vs. punishment associations would change after the participant got a random number of trials correct (between 5 and 9 trials; in order to prevent the participant from predicting when the reward vs. punishment stimulus associations would change).

In the current study, the Reversal Learning Task was completed relatively close in time to the Gambling Task (following performance of the Gambling Task, Dart Throwing Task, and then the Preference Ratings Task). Hence, it was expected that performance of

the Reversal Learning Task not only assessed individual differences in striatal dopamine levels but that it also functioned as a manipulation check on the extent to which the Gambling Task produced an increase in dopamine levels. However, it is also possible that increases in dopamine levels could be fleeting and that dopamine levels could return to baseline by the time participants completed the Reversal Learning Task.

Participants also completed a second possible dopamine task, the Finger Tapping Test (Reitan 1969), which has been shown to index striatal dopamine functioning (e.g., Yang et al., 2003). Conversion to psychosis in people at high risk is predicted by movement abnormalities (Mittal et al., 2008) and there is evidence for overactivation of subcortical regions, including the basal ganglia, in untreated individuals with schizophrenia during the Finger Tapping Test (Muller, Roder, Schuierer, & Klein, 2002). This task was comprised of four repeats of 5-s blocks alternating between the dominant and non-dominant hand, during which participants were asked to 'tap' the space-bar of a keyboard as fast as possible. The mean and SD of taps (in order to assess both the number of taps, as well as the variability of taps) across trials were calculated as indexes of dopamine functioning.

Trait salience. Trait aberrant salience was assessed using the Aberrant Salience Inventory (ASI; Kerns, Cicero, & McCarthy, 2010). The ASI is composed of 29 yes-or-no items and was designed to assess pre-psychotic experiences thought to be indicative of aberrant salience, specifically increased attribution of salience to stimuli, sharpened senses, general feelings of significance, heightened emotionality, and heightened cognition (feeling as if a part of something important). The ASI includes items such as, "Do certain trivial things ever suddenly seem especially important or significant to you?"

Previous research has found that the ASI is strongly correlated with other measures of psychosis-proneness and that people with a history of psychosis had a higher score on the questionnaire than people without psychosis (Cicero, Kerns, & McCarthy, 2010). Furthermore, the questionnaire was also shown to have good internal reliability with a Cronbach's alpha of .83 for the current sample.

Current Mood. Current mood was assessed using the Positive and Negative Affect Schedule (PANAS: Watson, Clark, & Tellegen, 1988). This scale consists of two 10-item mood scales, which separately assess positive and negative affect. Participants rated each of twenty emotions on a scale from 1 to 5, in reference to how they were currently feeling. Cronbach's alphas for internal reliability were .76 for positive affect and .81 for negative affect (Watson et al., 1988). This scale has been used extensively in previous research to assess current mood (e.g., Gadea et al., 2005; Minnema & Knowlton, 2008; Vercammen et al., 2009).

Trait Extraversion.

Trait extraversion was assessed using the extraversion scale from the Mini-International Personality Item Pool (Mini-IPIP: Goldberg et al., 2006)m which includes four items. This measure of extraversion was included in order to investigate the relationships between extraversion, dopamine, salience, and magical thinking. It also acted as a test of discriminant validity for the magical thinking behavioral lab tasks, as previous research indicates that magical thinking is not related to extraversion (Kerns, 2006; Ross et al., 2002). Participants indicated how accurately each question described themselves on a scale ranging from 1 ("very inaccurate") to 5 ("very accurate"). The extraversion scale of the Mini-IPIP was also shown to have high internal reliability with

an average Cronbach's alpha of .81 for a college student sample (Cooper, Smillie, & Corr, 2010), whereas the current study had a Cronbach's alpha of .80 for the extraversion scale of the Mini-IPIP.

Procedure and Data Analyses

Participants were randomly assigned to one of four groups (high salience and low dopamine condition, high salience and high dopamine condition, low salience and low dopamine condition, or low salience and high dopamine condition). Following random assignment, participants completed the tasks in the following order: Demographic questionnaire (asking about the participant's age, gender, and ethnicity), image viewing task, gambling task or syntactic judgment task, Dart Throwing Task (using either the previously seen image or the novel baby image), PANAS, Preference Ratings Task, reversal learning task, finger tapping task, Magical Ideation Scale, ASI, and Peters et al. Delusions Inventory.

In order to analyze the results, I used a 2 (dopamine condition: high vs. low) x 2 (salience condition: high vs. low) repeated measures ANOVA. In reporting effect sizes, I used partial eta-square for the omnibus tests. In addition, I also used Pearson correlations to test whether the state levels of magical thinking (as assessed by the Dart Throwing Task and the Preference Ratings Task) were associated with increased trait levels of magical thinking, aberrant salience, and/or performance of tasks thought to reflect dopamine functioning.

Chapter 3

Results

Correlations between magical thinking and dopamine behavioral tasks

First, I examined correlations between performance on the dopamine and magical thinking behavioral lab tasks. As can be seen in Table 1, there was not a significant relationship between the two magical thinking tasks, dart throwing and preference ratings. Hence, it appears that these two tasks might not be measuring the same construct. At the same time, there was also not a significant relationship between the two putative dopamine tasks, reversal learning and finger tapping, suggesting that these tasks might not measure the same construct. However, there was a positive correlation between the dart throwing difference score and performance on the reversal learning task. Hence, there was some evidence that performance on this magical ideation lab task was related to performance on a dopamine behavioral task.

Dopamine behavioral tasks

Next, I examined whether the reward manipulation affected performance on the dopamine behavioral tasks. If the reward manipulation actually increased dopamine, then it was expected that the high and low dopamine groups would differ in their performance on both the Reversal Learning Task and the Finger Tapping Task. For the Reversal Learning Task, as can be seen in Figure 1 and Table 2, the high dopamine group exhibited better learning from reward than from punishment (as assessed by the reversal learning accuracy rates), $F\,(1, 231) = 12.62$, $p < .001$, $d = .46$. In addition, for the reversal learning reaction times, as can be seen in Figure 2, there were similar results, there was a trend for the high dopamine group to exhibit the expected better learning

from reward than from punishment compared to the low dopamine group, [F (1, 231) = 2.95, p = .09]. In contrast, for the Finger Tapping Task, as can be seen in Table 3, there were no significant differences between the high and low dopamine groups, F (1, 231) = 1.29, p = .26 (although numerically at least the results are in the expected direction). However, recall that these dopamine tasks were administered roughly 20 minutes after the reward manipulation, being administered after the magical thinking tasks, with the reversal learning task administered before the finger tapping task. It is possible that the dopamine manipulation might have dissipated by the time participants completed these tasks. At the same time, as already discussed, performance on these two putative dopamine tasks was not correlated with each other. Hence, overall, there was partial support for the reward manipulation affecting performance on dopamine tasks, as there was evidence that the reward manipulation affected reversal learning accuracy scores on the Reversal Learning Task (and a trend for the reward manipulation to affect reversal learning reaction times on the Reversal Learning Task).

Magical Thinking Behavioral Lab Tasks

Next, an ANOVA was conducted in order to test whether the dopamine and/or salience manipulation had a significant effect on performance of the Dart Throwing Task. As can be seen in Figure 3 and in Table 4, the high dopamine groups exhibited significantly greater behavioral evidence of magical thinking than the low dopamine groups on the dart throwing difference score, F (1, 231) = 15.38, $p < .001$, d =.50. Hence, the high dopamine group was significantly less accurate in throwing the dart at the baby than at the smiley face image compared to the low dopamine group. In addition, as can be seen in Figure 3, the high salience group also exhibited significantly greater behavioral

evidence of magical thinking than the low salience groups, F (1, 231) = 4.43, $p < .05$, d =.27. Hence, it appeared that the salience manipulation also increased magical thinking. However, there was not a significant interaction between salience and dopamine on the dart throwing difference score, F (1, 231) = 2.20, p = .14, d =.19.

Next, I examined whether how much people liked the baby image could account for the effect of the dopamine and salience manipulations on dart throwing. To examine this, a difference score assessing how much a participant liked the image of the baby minus how much the participant like the image of the smiley face was included as a covariate. In this analysis, both the dopamine manipulation and the salience manipulation were still significant predictors of the dart throwing difference score. Hence, it does not appear that how much people liked the baby image can easily account for the effects of the dopamine and salience manipulations on the dart throwing task. .

Next, I am examined the effects of the dopamine and salience manipulations on the Preference Ratings Task. In contrast to the Dart Throwing Task, as can be seen in Figure 4 and in Table 4, neither the high dopamine [F (1, 231) = 1.26, p = .25, d = .14], nor the high salience [F (1, 231) = 0.13, p = .72, d = .06] groups had larger difference scores for the Preference Ratings Task than the low groups. There was also not a significant interaction between dopamine and salience on the Preference Ratings Task, F (1, 231) = 0.01, p = .91, d =.00. Next, I examined whether the dopamine or salience manipulations had effects on any of the individual ratings (e.g., preference for the ”sucrose” drink over the “sodium cyanide” drink, preference for the square-shaped fudge over the feces-shaped fudge, and preference for the candle-holder cup over the roach cup). However, there were no significant differences between the dopamine or salience

groups for any of the difference scores for the individual preference ratings. Thus, none of the hypotheses regarding the main effects or interaction of dopamine and salience were confirmed for the Preference Ratings Task.

Positive Schizotypy Questionnaires

As can be seen in Table 1, as expected from previous research, the three positive schizotypy questionnaires were all significantly correlated with each other, although the magnitude of the correlations between the scales was far from unity. It was expected that the positive schizotypy questionnaires would be significantly correlated with both the magical thinking behavioral lab tasks and the dopamine behavioral tasks. For the Dart Throwing Task, there was a significant positive correlation between the dart throwing difference score and the Magical Ideation Scale. Hence, people who self-reported higher magical thinking exhibited greater magical thinking on the Dart Throwing Task. Dart Throwing Task performance was not significantly related to the other positive schizotypy scales. For the Preference Ratings Task, there was a significant relationship between magical thinking exhibited on this task and increased self-reported schizotypy on all three positive schizotypy measures.

Next, I examined correlations between the positive schizotypy questionnaires and the dopamine behavioral tasks. For the Reversal Learning Task, it was significantly correlated with the Magical Ideation Scale. Hence, people who self-reported higher baseline magical thinking exhibited behavioral performance consistent with increased dopamine. In addition, performance on the Reversal Learning Task was also associated with the Aberrant Salience Inventory. In contrast, the Finger Tapping Task was not significantly correlated with any of the positive schizotypy measures.

Extraversion and Mood Questionnaires

Lastly, I examined the relationship between extraversion and the other measures. In addition, I also examined the relationship between state positive mood and the other measures. There was a significant negative correlation between extraversion and performance on the dart throwing task. Hence, increased extraversion was associated with less magical thinking on the behavioral lab task. There was also a significant positive correlation between performance on the dart throwing task and state positive mood, suggesting that heighted positive mood was associated with more magical thinking on the Dart Throwing Task. However, there was not a significant effect of the dopamine manipulation on mood, F (1, 231) = 0.53, p = .47, d =.11. In addition, neither mood nor extraversion statistically accounted for the effect of the dopamine or salience manipulations on dart throwing task performance. Furthermore, neither personality nor mood was associated with performance on the reversal learning task or with positive schizotypy questionnaires. Finally, there was a significant negative correlation between the Finger Tapping Task performance and state positive mood, indicating that participants with increased positive mood had slower Finger Tapping Task performance.

Chapter 4

Discussion

The current study attempted to causally examine the relationships between dopamine, salience, and magical thinking in a non-invasive way. Overall, the current study found evidence consistent with the hypothesis that behavioral manipulations of dopamine and salience could cause an increase in state magical thinking. Hence, the current study provides further evidence for the role of dopamine and salience in magical thinking. In addition, we think the current research could have implications for future investigations into the nature of psychosis risk.

In the current study, there were multiple pieces of evidence consistent with the hypothesis that increased dopamine causes an increase in state magical thinking. First, a dopamine manipulation, performing a rewarding gambling task, caused an increase in state magical thinking, as measured by a behavioral measure of magical thinking (the Dart Throwing Task). Furthermore, there was a trend for participants in the dopamine manipulation groups to exhibit altered performance on another behavioral dopamine task, the Reversal Learning Task. This evidence is consistent with the idea that the dopamine manipulation resulted in increases in dopamine. Lastly, there was a significant correlation between performance on the dopamine Reversal Learning Task and the behavioral measure of state magical thinking. This correlation is consistent with the view that increased magical thinking on the Dart Throwing Task was the result of a temporary increase in dopamine.

Hence, the current study is consistent with the hypothesis that a non-invasive dopaminergic manipulation can cause increases in state magical thinking. To our knowledge, this is the first study to find that a behavioral dopamine manipulation can cause increased state magical thinking. This is consistent with previous research finding a relationship between increases in dopamine and increases in positive symptoms of schizophrenia (e.g., Howes et al., 2009; Laruelle, Kegeles, & Abi-Dargham, 2003). Moreover, while previous research has shown that dopamine manipulations cause an increase in clinical interview measures of psychotic symptoms that include magical thinking (Brier et al., 1997; Laruelle et al., 1996), this is the first study to demonstrate that a behavioral dopamine manipulation can cause an increase in magical thinking on a behavioral lab task. This suggests that behavioral measures have the potential to be sensitive measures of psychosis liability.

The current study also found that a salience manipulation caused an increase on the state magical thinking behavioral measure. Participants shown a novel image of a baby, in comparison to those who saw the image multiple times, subsequently threw darts more inaccurately at the image. This novel finding indicates that altering the salience of a stimulus is sufficient in causing an increase on a behavioral measure of magical thinking. Therefore, in the current study, the novelty of the baby image may have led to increases in dopamine (Bunzeck & Duzel, 2006; Fuitart-Masip et al., 2010), which in turn led to increased state magical thinking. These results are consistent with evidence that salience is related to magical thinking (Cicero, Kerns, & McCarthy, 2010; Corlett et al., 2009; Rosier et al., 2005). The current study is novel in that no other study to date has found that experimentally manipulating salience causes an increase in state magical thinking.

The current study also found novel evidence associating self-reported psychotic-like thinking with a dopamine behavioral task and with the magical thinking behavioral lab task. Although self-reported psychotic-like thinking on the Magical Ideation Scale has been found to predict future psychotic disorders, to our knowledge no previous study has found that higher scores on this measure is associated with a behavioral task thought to reflect increased dopamine levels. In the current study, the Magical Ideation Scale was also associated with increased behavioral evidence of magical thinking on the Dart Throwing Task. Hence, this result further supports the construct validity of the Dart Throwing Task as a behavioral measure of magical thinking. Therefore, the current study found that self-reported psychotic-like thinking is associated both with a dopamine behavioral task and with a magical thinking behavioral task.

Overall, the results of the current study further support the involvement of dopamine and salience in psychosis. For example, previous research regarding the relationship between salience and magical thinking has been correlational (e.g., Cicero, Kerns, & McCarthy, 2010). The current study provides evidence that increases in dopamine and salience could cause an increase in magical thinking. In addition, the current study suggests that increases in dopamine and/or in the perceived salience of stimuli can increase state magical thinking even in a non-clinical sample. Presumably, this increase is not enough to cause full-blown psychosis, but over time a persistent state of elevated dopamine and elevated aberrant salience could potentially result in delusions. Hence, the current evidence supporting for the links between phasic dopamine increases, aberrant salience, and trait magical thinking is consistent with the assertions of Kapur (2003) that increases in phasic dopamine lead to an inappropriate assignment of salience,

which in turn leads to the development of delusional ideation. In addition, we think an important issue for understanding psychosis and for detecting risk for psychosis is to identify reliable and valid indicators of psychosis onset and relapse risk presumably related to episodically elevated dopamine and/or aberrant salience. The current research suggests that quantitative behavioral measures such as the Dart Throwing Task could be useful in attempting to identify individuals at risk of psychosis.

Despite this support for the overall hypothesis of a relationship between dopamine, salience, and magical ideation, at the same time there were some results that were not consistent with my initial hypotheses. For instance, Preference Ratings Task (PRT) performance did not seem to be affected by either the dopamine or salience manipulations. For the salience manipulation, as discussed earlier, one possible explanation is that manipulating the timing of the instructions on the PRT did not constitute an effective salience manipulation. Another finding not consistent with my initial hypotheses is that, although the PRT was associated with all three measures of self-reported psychotic-like thinking, it was not associated with tasks that appeared to be related to or were influenced by dopamine, such as the dopamine Reversal Learning Task or the Dart Throwing Task (which was affected by the dopamine manipulation). At the same time, one measure of self-reported psychotic-like thinking, the Peters Delusion Inventory, was also not associated with tasks related to or influenced by dopamine.

One possible explanation for the overall pattern of results in the current study is that there might be two different mechanisms that contribute to magical thinking. One mechanism is presumably increased striatal dopamine which results in aberrant salience.

A second mechanism might be the influence of emotion on cognition and judgment. In our study, some measures might be related to only one or the other of these two factors.

In particular, potentially the PRT and the Peters Delusional Inventory might only be related to the influence of emotion on cognition and judgment, but not related to increased striatal dopamine. Consistent with this, previous research using the PRT has found that increased attention to emotion was related to increased magical thinking on this task (Berenbaum, Boden, & Baker, 2009). At the same time, previous research has found that higher scores on the Peters et al. Delusions Inventory is related to higher scores on emotionalizing, which is the tendency to become emotionally aroused by events, which presumably should increase the influence of emotion on cognition (Laroi, Van der Linden, & Aleman, 2008). Hence, an issue for future research would be to further examine the role of these two mechanisms in psychotic-like thinking and whether they are differentially associated with different measures of psychotic-like thinking.

Another issue for future research is to more directly manipulate dopamine levels. In the current study, we used a behavioral dopamine manipulation in the form of a rewarding gambling task. Although the current study provides evidence that a behavioral manipulation of dopamine was related to increases in dopamine, further support for this hypothesis is if a pharmacological manipulation of dopamine produced similar results. Along these lines, future research should also investigate the impact of progressively larger increases in dopamine on magical thinking in both the general population and at-risk samples.

A related additional issue for future research would be to more directly assess whether dopamine levels have been increased. In the current study, we used an indirect method of

assessing dopamine by using a behavioral dopamine task which has previously been found to be sensitive to dopamine levels (Cools et al., 2009). A more direct way to index dopamine levels is through neuroimaging (Knutson et al., 2000; Laruelle, Kegeles, & Abi-Dargham, 2003; Zald et al., 2004). Future research could more directly assess the influence of the performance of the rewarding gambling task on performance of the Reversal Learning Task using neuroimaging.

Future research should also continue to study the effect of salience manipulations on state magical thinking. In particular, future studies could investigate whether other salience manipulations also cause increases in state magical thinking. In addition, research could investigate the neural mechanisms of salience manipulations using neuroimaging, with both college students and at-risk samples.

One last issue for further research is to further investigate the relationship between self-report measures of psychotic-like thinking and experiences and behavioral measures of magical thinking. Along these lines, future research could investigate and validate other behavioral measures of psychotic-like thinking and experiences (King et al., 2009). For example, research could examine the effect of dopamine and salience manipulations on behavioral measures of perceptual aberrations associated with hallucinations and on reasoning biases, such as jumping to conclusions, found to be associated with delusions.

Chapter 5

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Chapter 6

Table 1

Correlations between Magical Thinking Behavioral Lab Tasks, Dopamine Behavioral Tasks, and Questionnaire Measures

	Magical Thinking Behavioral Lab Tasks		Dopamine Behavioral Tasks			Positive Schizotypy Questionnaires			Personality Questionnaires	
	DTT	PRT	RLT ACC	RLT RT	FTT	MIS	ASI	PDI	EXT	SPM
DTT	1									
PRT	0.09	1								
RLT ACC	0.19**	0.08	1							
RLT RT	0.14*	0.09	0.45**	1						
FTT	0.10	0.02	0.09	0.05	1					
MIS	0.21**	0.18*	0.23**	0.18*	0.09	1				
ASI	0.12	0.13*	0.20**	0.18*	-0.02	0.57**	1			
PDI	0.08	0.20**	0.07	0.00	0.03	0.52**	0.43**	1		
EXT	-0.15*	-0.04	0.00	-0.03	-0.09	-0.10	-0.03	-0.10	1	

SPM	0.15*	0.11	0.12	-0.05	-0.28**	0.02	0.04	0.05	0.09	1

Note. DTT = Dart Throwing Task, PRT = Preference Ratings Task, RLT = Reversal Learning Task, ACC = accuracy, RT = reaction

Times, FTT = Finger Tapping Task, MIS = Magical Ideation Scale, ASI = Aberrant Salience Inventory, PDI = Peters Delusions

Inventory, EXT = Extraversion measure, BIS = Behavioral Activation Scale, SPM = State Positive Mood.

**p<.01, *p<0.05

Table 2

Means and Standard Deviations for the Reversal Learning Task

	ACC Scores[a]			RT (ms) Scores		
Group	Punishment	Reward	Difference	Punishment	Reward	Difference
Low Dopamine/ Low Salience	2.55 (0.15)	2.52 (0.13)	-0.03 (0.16)	765.13 (198.85)	755.48 (211.47)	9.65 (176.054)
Low Dopamine/ High Salience	2.56 (0.16)	2.52 (0.15)	-0.04 (0.17)	801.78 (326.54)	766.66 (267.38)	35.12 (152.78)
High Dopamine/ Low Salience	2.52 (0.12)	2.55 (0.12)	0.03 (0.12)	775.02 (244.78)	720.47 (213.87)	54.55 (123.43)
High Dopamine/ High Salience	2.54 (0.11)	2.58 (0.11)	0.04 (0.11)	748.97 (173.68)	691.65 (180.79)	57.32 (158.95)

Note. ACC= accuracy, RT= reaction time.

[a] Arcsine transformed accuracy scores.

Table 3

Means and Standard Deviations for the Finger Tapping Task

Group	Dominant Hand Average	Non-dominant Hand Average	Difference Score
Low Dopamine/ Low Salience	69.11 (11.64)	64.81 (12.52)	4.30 (11.78)
Low Dopamine/ High Salience	72.32 (13.44)	67.77 (13.55)	4.55 (14.64)
High Dopamine/ Low Salience	72.76 (10.87)	65.25 (10.18)	7.51 (10.32)
High Dopamine/ High Salience	71.26 (12.36)	66.18 (12.94)	5.08 (12.85)

Table 4

Means and Standard Deviations for the Magical Thinking Behavioral Lab Tasks

	Dart Throwing Task			Preference Ratings Task		
Group	Smiley Face Distance (inches)	Baby Face Distance (inches)	Difference Score	"Normal" Objects Average	"Magical Thinking" Objects Average	Difference Score
Low Dopamine/ Low Salience	2.28 (2.18)	2.03 (2.30)	-0.25 (0.86)	69.52 (13.68)	31.60 (20.74)	37.92 (21.85)
Low Dopamine/ High Salience	1.94 (2.55)	2.39 (1.58)	0.27 (1.25)	69.66 (15.51)	32.40 (20.31)	37.26 (21.22)
High Dopamine/ Low Salience	2.24 (0.74)	2.77 (1.08)	0.53 (0.95)	68.56 (16.67)	33.38 (22.54)	35.18 (21.74)
High Dopamine/ High Salience	1.77 (2.62)	2.57 (1.23)	0.62 (1.45)	65.59 (17.90)	31.69 (20.87)	33.90 (22.68)

Chapter 7

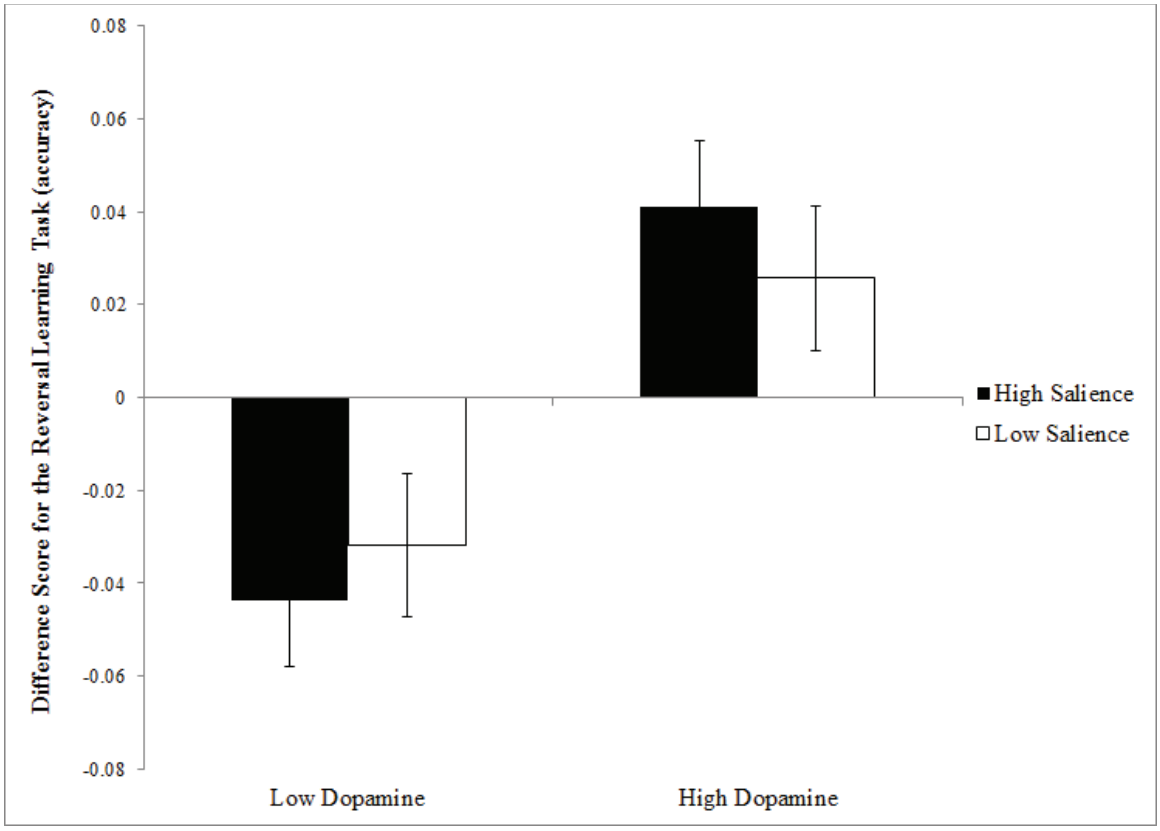

Figure 1. Group means on the Reversal Learning Task arcsin transformed accuracy scores.

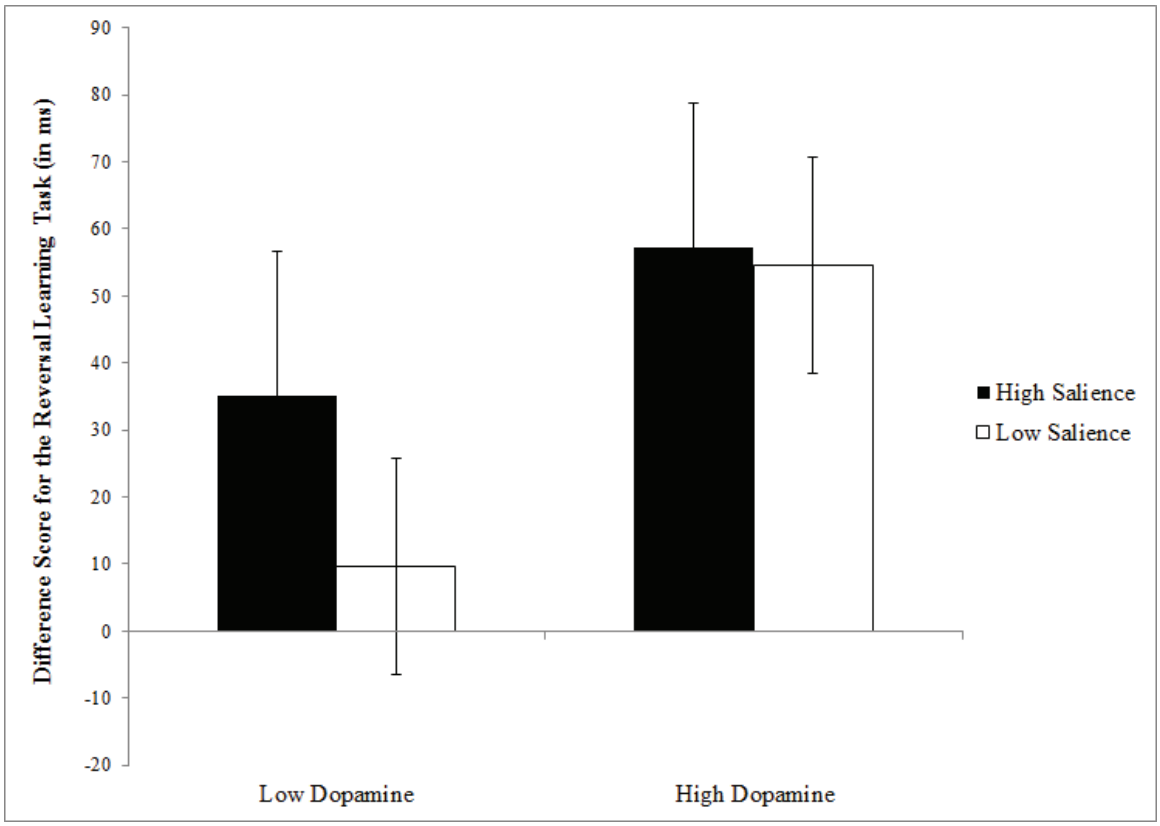

Figure 2. Group means on Reversal Learning Task reaction times.

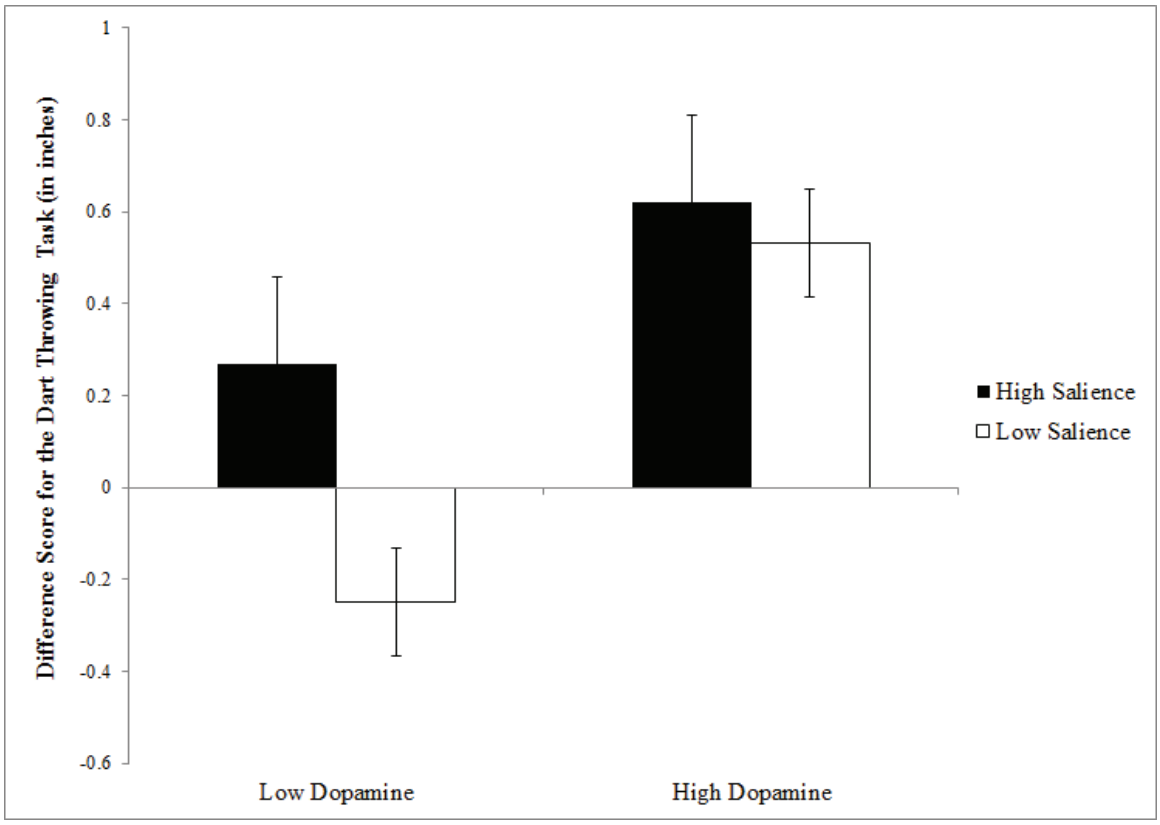

Figure 3. Group means on the Dart Throwing Task.

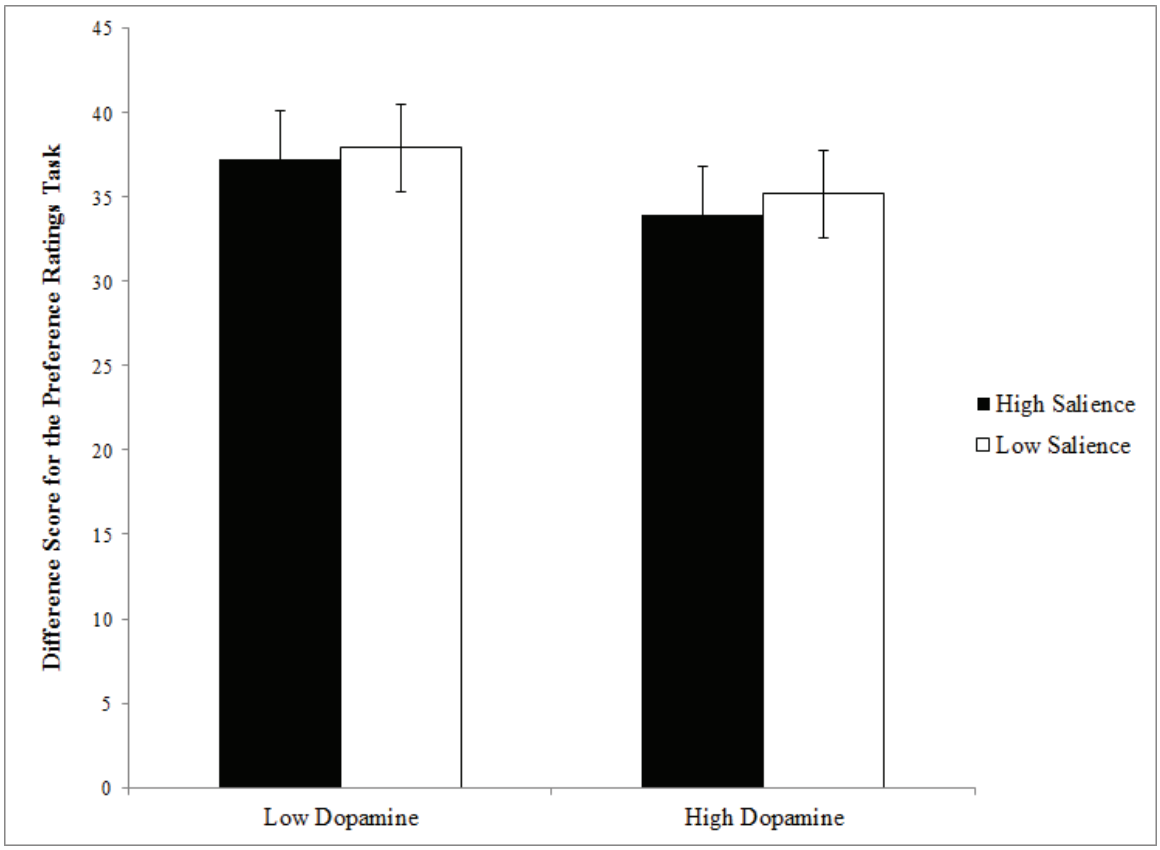

Figure 4. Group means on the Preference Ratings Task.

Appendix

"Annotated Bibliography":

Of all the hypotheses of the causes of schizophrenia, the dopamine dysfunction hypothesis is the most supported (e.g., Howes & Kupar, 2009). In its most basic form, the dopamine hypothesis is the idea that psychosis is associated with hyperactivity of dopamine transmission. Initial evidence for the dopamine hypothesis arose from the fact that antipsychotic medications are D_2 receptor antagonists (e.g., Seeman et al., 1975). Furthermore, there is evidence that second generation antipsychotic drugs bind preferentially to $D_{2/3}$ receptors in the intrastriatal associative regions (Grunder et al., 2006; Stone et al., 2005). Limited evidence also comes from the fact that dopamine enhancing drugs (i.e., amphetamine, cocaine) have psychotogenic effects (Lieberman et al., 1987). Since D_2 receptors are predominantly localized in the subcortical regions, such as the striatum, the dopamine hypothesis has focused on these areas. It is important to note that striatal dopamine elevation is unique to psychosis, as it has not been found in mania or depression (e.g., Howes et al., 2008). Although there were concerns that this hyperdopaminergic activity may be in part the result of exposure to antipsychotic medications, there is evidence for hyperdopaminergic functioning in drug naïve patients with schizophrenia (Abi-Dargham et al., 2009).

The majority of evidence for the dopamine hypothesis of schizophrenia comes from imaging studies. Evidence from such studies indicate that patients with schizophrenia exhibit elevated presynaptic dopamine synthesis, dopamine release, and moderate increases of dopamine $D_{2/3}$ receptor levels (e.g., Howes & Kapur, 2009; Laruelle, 1998; Meyer-Lindenberg, 2010). Of nine studies which investigated DOPA

uptake (levels of uptake reflect the activity of the enzyme dopa decarboxylase, which is believed to reflect the rate of presynaptic dopamine synthesis capacity) in schizophrenia patients, seven found increased accumulations of DOPA in the striatum of patients (Hietala et al., 1995; Hietala et al., 1999; Howes et al., 2008; Lindstrom et al., 1999; Meyer-Lindenberg et al., 2002; McGowan et al., 2004; Reith et al., 1994), one found non-significant elevation in synthesis capacity in patients with schizophrenia (Dao-Castellana et al., 1997), and one found a small reduction in capacity (Elkashef et al., 2000) . It should be noted that among those studies investigating dopamine synthesis in currently psychotic individuals, all found a significant increased dopamine synthesis (Howes et al., 2007). Furthermore, a PET study found evidence that drug-naïve schizophrenia patients are higher in dopamine release as well as baseline dopamine (Abi-Dargham et al., 2009). Lastly, there is some evidence that individuals in the prodromal phase exhibit elevated presynaptic dopamine synthesis capacity, and that striatal dopamine levels are related to the severity of prodromal symptoms (Howes et al., 2009; Fusar-Poli, McGuire, & Borgwardt, 2011).

Many recent imaging studies have found elevated hyperdopaminergic activity exclusively in the associative striatum in schizophrenia (e.g. Laruelle, 2006; Howes et al., 2009; Kegeles et al., 2010). The associative striatum, a part of the dorsal striatum, is associated with integrating information from different portions of the cortex, especially the dorsal lateral prefrontal cortex (for a review, see Balleine, Delgado & Hikosaka, 2007). This hyerdopaminergic activity in the associative striatum has been found to predate the onset of psychosis, as individuals with prodromal symptoms exhibit hyperdopaminergic activity in this area (Howes et al., 2009). It should be noted that

although there was a non-significant difference between the prodromal group and the patients with schizophrenia, the patients exhibited slightly increased dopaminergic activity than the prodromal group. These findings not only solidify evidence for a link between striatal dopamine and psychosis, but also suggest that elevated subcortical dopamine may impact the dorsolateral prefrontal cortex function (since the associative striatum is linked to the dorsolateral prefrontal cortex).

However, there is also evidence implicating dysfunctional dopaminergic activity in the ventral striatum. Evidence comes from the role of the ventral striatum in reward functions of the brain (Morris et al., 2011; Schultz et al., 1992). The ventral striatum has been implicated in learning both pleasant and unpleasant associations (e.g., Jensen et al., 2007; O'Doherty et al., 2004). Furthermore, Juckel and colleagues (2006) reported that patients with schizophrenia showed reduced activation in the ventral striatum during the presentation of reward-predicting cues. A recent fMRI study showed that in comparison to controls, patients had stronger ventral striatum activation in response to neutral stimuli than controls (Jensen et al., 2008). Therefore, it appears that there is reason to believe that the ventral striatum is involved in the reward circuitry in the brain, and this is impaired in individuals with schizophrenia. This line of research has major implications for the concept of aberrant salience, which is discussed later.

Other evidence for dopaminergic dysfunction in schizophrenia comes from amphetamine challenge studies. Although amphetamine challenge studies are not information in terms of baseline synaptic dopamine levels, these studies are able to measure change in synaptic dopamine transmission following a pharmacological induction. In amphetamine challenge studies, participants are scanned using PET or

SPECT to estimate the availability of striatal dopamine receptors before and after the administration of dopamine (e.g., Abi-Dargham et al., 2003; Martinez et al., 2004). In multiple studies investigating dopamine release following an amphetamine challenges, patients showed significantly greater amphetamine-induced dopamine release than controls (Laruelle et al, 1996; Breirer et al., 1997; Abi-Dargham et al., 1998). In addition, there is evidence for a positive relationship between amphetamine-induced dopamine release and baseline dopamine in schizophrenia patients but not in controls (Abi-Dargham et al., 2009). Furthermore, for patients with schizophrenia, the administration of amphetamine temporarily worsens positive symptoms (e.g., Laruelle, Kegeles, & Abi-Dargham, 2003). Lastly, there is some evidence that individuals with schizotypal personality disorder also exhibit increased dopamine release following an amphetamine challenge (Abi-Dargham et al., 2004).

It has been proposed that cortical functioning is regulated by means of cortico-striato-thalamo-cortical feedback loops (Alexander & Crutcher, 1990). It is proposed that there are five distinct loops (the motor circuit, ocularmotor circuit, dorsolateral prefrontal circuit, lateral orbitofrontal circuit, and anterior cingulate circuit), which are all centered around a separate part of the frontal lobe (Alexander & Crutcher, 1990). There is evidence that the anterior cingulate circuit projects to the ventral striatum, superior temporal gyrus and the hippocampus, which have been implicated in schizophrenia (e.g., Morris et al., 2011;Asami et al., 2012; Watson et al., 2012). Taken together, this provides evidence for a dysfunction anterior cingulated circuit, which may be the result of a dysfunctional dopaminergic system, leading to reduced activation in the areas implicated in the anterior cingulate circuit in schizophrenia.

Dopamine and Salience

Although the multitude of evidence links dopamine and psychosis, hyper-dopaminergic activity in and of itself does not explain the formation of positive symptoms. Research indicates that in general, dopamine neurons fire as a result of appropriate motivational salience, novelty, and reward (Berridge, 2007; van der Gaag, 2006). However, it is possible that as a result of a dysregulated hyper-dopaminergic system in schizophrenia, dopamine neurons fire stochastically (without motivational salience or reward). The result would be that individuals attribute salience to otherwise random or irrelevant objects or events. In other words, as a result of a dysfunctional dopaminergic system, individuals with schizophrenia may experience abnormal stimulus-reinforcement associations, by which otherwise neutral stimulus are reinforced, or deemed motivationally salient (Roisier et al., 2009; Waltz et al., 2007).

Evidence for this comes from studies showing deficits in learning stimulus-reinforcement associations coupled with reduced striatal responses (Juckel et al., 2006). Likewise, there are several studies indicating that individuals with schizophrenia have a deficits in adaptively responding to rewards, wherein patients are unable to properly assess the salience of a stimulus (Waltz and Gold, 2007; Waltz et al., 2009). Furthermore, individuals with positive symptoms show increased response to a neutral stimulus (Jensen et al., 2008; Romaniuk et al., 2010), indicating that they are attributing salience to otherwise irrelevant (neutral) stimuli. There is also limited imaging evidence that suggests that the anterior cingulate cortex (ACC) may be involved in salience attributions, whether that salience is cognitive or emotional in nature (Seeley et al., 2007; White et al., 2010). Relatedly, there is evidence that the ACC may be involved in a

related form of salience- self-relevance (Schmitz & Johnson, 2006). An fMRI study linked ACC activity with referential delusions (e.g., Menon et al., 2011), providing further support for the link between salience and delusional ideation. Although there is limited evidence for the role of aberrant salience in the formation of delusions and hallucinations, it is an elegant explanation for the role of dopamine in the formation of these positive symptoms.

Dopamine and Stress

The ventral hippocampus is thought to be the principle area in the hippocampus that is associated with response to stress (e.g., Herman & Mueller, 2006). Furthermore, there is evidence that the ventral hippocampus selectively regulates dopamine neuron activity (Lodge & Grace, 2006). For instance, during extremely salient (or significant) conditions, the ventral hippocampus may increase the number of active dopamine neurons, in order to increase attention to the stimulus (Lodge & Grace, 2011). Further evidence for a connection between dopamine and stress comes from a recent PET study showing that psychosocial stressors cause a significant release of dopamine in the ventral striatum (Pruessner et al., 2004). Furthermore, in a study investigating stress in adolescents, there was evidence of a daily stressors being related to increased positive (not not negative) prodromal symptoms (Tessner, Mittal & Walker, 2011). Relatedly, there is evidence for Hypothalamic-Pituitary-Adrenal Axis (HPA) dysfunction in schizophrenia (Walker, Mittal, & Tessner, 2008). The HPA axis facilitates both physiological as well as behavioral responses to stressors (Sapolsky, 2003). Research indicates that there is elevated baseline HPA activity in schizophrenia, which is related to hippocampal dsyfunction (Ganguli et al., 2002). This elevated HPA activity, as evidenced

by increased cortisol levels, has been found in both first-episode and chronic schizophrenia (for a review, see Bradley & Dinan, 2010). There is also evidence of a link between dopamine and the HPA. One study investigate dopamine and cortisol levels following a psychosocial stressor and found a positive correlation between ventral striatal dopamine release and cortisol levels (Pruessner et al., 2004).

Dopamine-glutamate interactions

It has been hypothesized that a specific class of glutamate receptor, the NMDA receptor, is decreased in schizophrenia (e.g., Olney & Farber, 1995). In addition, research indicates that glutamate can modulate dopamine release in the striatum (Mueller et al., 2004). While there is a growing body of evidence supporting a glutamate-dopamine interaction (e.g., Sesack, 2003), there is limited evidence that this interaction is linked to schizophrenia. It is proposed that glutamate hypoactivity could lead to enhanced subcortical dopaminergic activity (Brier et al., 1997; Meyer-Lindenberg et al., 2002). Furthermore, there is evidence from a small sample post-mortem tissue sample study for reduced glutamate transmission within the hippocampus of patients with schizophrenia (Gao et al., 2000). As previously mentioned, there is also evidence that glutamate neurons in the hippocampus are modulated by dopamine (David, Ansseau, & Abraini, 2005; Hatzipetros & Yamamoto, 2006). There is more substantial evidence that glutamate inputs regulate the firing of dopamine neurons (Kegeles et al., 2000; David et al., 2005). Evidence comes from a PET study in which individuals at risk for psychosis, but not controls, showed a significant negative relationship between hippocampal glutamate and striatal presynaptic dopamine synthesis, and there was evidence that this was related to later transition to psychosis (Stone et al., 2010). However, the picture is

not that simple, as there is also evidence that drugs that increase NMDA receptors primarily improve negative symptoms of schizophrenia, with no real benefit on positive symptoms (e.g., Javitt, 2006; Pilowsky et al., 2006). Overall, while the evidence points to a substantial role for dopamine in the development of psychosis, it is likely that there are multiple pathways to psychosis, which research suggests may involve the interaction of dopamine with salience attribution, stress, and glutamate (among others).

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