

BEHAVIORAL FUNCTIONS OF 5-HT_{1A} RECEPTORS IN ORBITOFRONTAL
CORTEX OF RATS

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Abstract

Cannula were implanted in the orbitofrontal cortex (OFC), a prefrontal region of the brain, of 17 rats. The behavior of these animals was observed after intracerebral infusion or intraperitoneal injection of 8-OH-DPAT, a serotonin- $1A$ agonist. Behavior paradigms used were the open field, social interaction, forced swim and prepulse inhibition tests. Intracerebral infusion of 8-OH-DPAT increased exploratory behavior, had a weak anxiety-reducing effect, and decreased social interaction of the rats, but did not affect depression like behavior or sensorimotor gating. Systemic injection of 8-OH-DPAT had an antidepressant-like effect. Results indicate a role of 5-HT $1A$ receptors in the OFC in regulating social and emotional behaviors, and may have implications for psychopathology.

Behavioral Functions of 5-HT_{1A} Receptors in Orbitofrontal Cortex of Rats

The prefrontal cortex appears to have a role in 'executive functions' in the brain, including coordinating perceptual input, predicting rewards and making goals, making decisions based on this input, inhibiting inappropriate responses, monitoring performance for errors, and focusing attention on tasks (Funahashi, 2001). Certain regions of the prefrontal cortex appear to be specialized for some of these tasks. The orbitofrontal cortex (OFC), also known as the agranular insular cortex, appears to be responsible for gauging rewards, for responding rapidly to outcomes in the environment, and for the emotional response to gains or losses (Krawczyk, 2002). In humans, the OFC may also be critical for memory formation (Frey & Petrides, 2002), and has been postulated to be involved in social cognitive skills such as 'mindreading,' or understanding intentions in other people (Baron-Cohen, 1995).

Abnormalities in the orbitofrontal cortex have been found in various psychiatric disorders, including depression, schizophrenia, social anxiety disorder, and obsessive-compulsive disorder. The volume of the orbitofrontal cortex has been found to be reduced in patients with major depression compared to healthy controls (Bremner et al., 2002). Physiological activity of the ventrolateral and orbital areas of the prefrontal cortex in depressed patients has been found to be abnormally high in some studies, and abnormally low in other studies (Davidson et al., 2002). In schizophrenic patients with high negative symptoms, reduced volume of white matter in the OFC has been noted (Sanfilippo et al., 2000). Another study found a similar effect, that smaller size of the OFC was correlated with more severe negative symptoms in schizophrenic patients (Baare et al., 1999). The orbitofrontal cortex is also suspected to be overly active in obsessive-compulsive disorder, possibly underlying the faulty determination of reward expectancy seen in that disorder (Graybiel & Rauch, 2000). The results of another study suggest that there may be overactivity of the frontolimbic system, especially the OFC, in social anxiety disorder (Veit et al., 2002). However, during public speaking, regional cerebral blood flow is

decreased in the OFC of people with social phobia compared to healthy comparison subjects (Tillfors et al., 2001). Thus, although the OFC is linked to social anxiety, discrepancies in these studies require further study.

Serotonin (5-hydroxytryptamine, or 5-HT), is an important neurotransmitter acting in the prefrontal cortex, and is known to have a role in regulating both behavior and mood. Abnormalities in the serotonergic system may underlie many symptoms of neuropsychiatric disorders. Delineating how these abnormalities contribute to psychiatric symptoms has proved difficult, due to the variety of 5-HT receptor subtypes and the differential distributions of these receptors. The most well studied 5-HT receptor is the 5-HT_{1A} receptor, which is located largely in the dorsal raphe nuclei, but is also found in the hippocampus and frontal cortex (Barnes & Sharp, 1999). In the raphe nuclei, 5-HT_{1A} receptors are auto-receptors found on the 5-HT neurons themselves, but in the forebrain regions, the receptors are found post-synaptic to 5-HT neurons; activation of 5-HT_{1A} receptors in either position by either 5-HT or agonists inhibits neuronal activity (Barnes & Sharp, 1999). Activation of the post-synaptic 5-HT_{1A} receptors increases dopamine release in the prefrontal cortex (Sakaue et al., 2000), which may indicate an indirect role of 5-HT in regulating working memory, as dopamine in the prefrontal cortex appears to be involved in working memory (Sawaguchi & Goldman-Rakic, 1991). Increase in noradrenaline release in the frontal cortex may be another effect of 5-HT_{1A} receptor activation (Barnes & Sharp, 1999).

The involvement of 5-HT_{1A} receptors in psychopathology is suggested by numerous studies. Administration of 5-HT_{1A} agonists has been found to have anxiolytic effects, though whether these effects are mediated by pre-synaptic or post-synaptic receptors remains unclear (Barnes & Sharp, 1999). Mice that are deficient in 5-HT_{1A} receptors show decreased exploratory behavior and increased avoidance of novel situations, suggesting that the receptor protects against anxiety; however, these mice also seem to be protected against depression-like behavior in a hopelessness test (Heisler et

al., 1998; Mayorga, Dalvi, Page, Zimov-Levinson, Hen & Lucki, 2001; Parks et al., 1998). In schizophrenic patients, the 5-HT_{1A} binding site density in the dorsolateral prefrontal cortex is significantly greater than in controls (Burnet, Eastwood & Harrison, 1996). Although this increase of 5-HT_{1A} density has also been observed in the OFC in other postmortem studies, an *in vivo* study failed to find altered levels of 5-HT_{1A} in the prefrontal cortex of schizophrenic patients (Gurevich & Joyce, 1997; Tauscher et al., 2002). Evidence suggests that the efficacy of serotonin-specific reuptake inhibitors in treating obsessive-compulsive disorder may be mediated by desensitization of 5-HT autoreceptors, including the 5-HT_{1A} receptor, in the orbitofrontal cortex (Bergqvist, Bouchard & Blier, 1999).

Studies on the roles of 5-HT_{1A} receptors in behavior have been made possible by the development of 8-hydroxy-2-(di-*N*-propylamino)tetralin (8-OH-DPAT), a selective and potent 5-HT_{1A} receptor agonist. The purpose of this study was to elaborate on the possible role of the OFC in psychopathology, and extend previous psychopharmacological findings, by examining the behavioral effects of administration of 8-OH-DPAT to the OFC in rats. To accomplish this, we used four behavioral tests that have been widely used as animal models of various symptoms of neuro-psychiatric disorders, including the open field, social interaction, forced swim, and pre-pulse inhibition tests.

The open field test takes advantage of ethological observations that rats avoid open spaces, and allows measurement of behavior that models symptoms observed in some anxiety disorders (Prut and Belzung, 2003). Previous studies using the open field and related tests have found that intracerebral administration of 8-OH-DPAT to the raphe nuclei produced anxiolytic effects, while injections into the hippocampus have produced ambiguous and sometimes conflicting results (Cervo, Mocaer, Bertaglia, & Samanin, 2000). In general, it appears that 5-HT_{1A} agonists have anxiolytic effects when operating on pre-synaptic receptors, and anxiogenic effects when acting on post-synaptic receptors

(File, Gonzalez & Andrews, 1996). Thus we predicted that delivery of 8-OH-DPAT to the OFC may increase anxiety-like behavior. The social interaction test detects changes in social behavior of rodents that may model deficits in social functioning observed in various disorders (see Appendix). If decreased social interaction models anxiety-behavior, then we predicted that, as in the open field test, the treatment would reduce social interaction in rats. The forced swim test employs the learned helplessness paradigm to model depression-like behavior; a broad variety of antidepressant drugs reduce immobility in response to the aversive environment in this test (Porsolt, Le Pichon & Jalfre, 1977). We suspected that delivery of 8-OH-DPAT to the OFC would increase depression-like behavior. Finally, the measurement of pre-pulse inhibition (PPI) in response to acoustic startle tests sensorimotor gating ability, which is deficient in schizophrenia. A previous St. Mary's Project (Chess, 2000) found that lesions of the OFC did not affect PPI in rats, suggesting that the area may not be a critical site of pathology in schizophrenia. However, another study found that systemic injection of 8-OH-DPAT, as well as direct administration of 8-OH-DPAT to the dorsal and medial raphe, reduced PPI in rats (Sipes & Geyer, 1995). We predicted a similar effect on PPI in this study.

Methods

Animals and Maintenance

Seventeen male Sprague-Dawley rats (Harlan, Indianapolis IN), 70-80 days old and weighing 300-350 grams at time of surgery, were used in this study. They were housed individually in plastic cages with bases of 26 cm x 40 cm, and a height of 18 cm. Animals had free access to water, and were fed 15-18 g rat chow daily. Animals were weighed periodically as a way to monitor health. The rats were housed in an animal colony maintained at constant temperature. This colony was maintained on a regular lighting schedule, with lights off beginning at 1400 and lights on at 200. All behavioral testing occurred between 1300 and 1750. Animals were treated humanely according to

APA guidelines; the IUCAC committee of St. Mary's College of Maryland approved protocols for this study.

Stereotaxic Surgery

After 3 weeks of habituation to the laboratory, all animals underwent surgery to implant guide cannulas in the OFC. Rats were anesthetized with intra-peritoneal (i.p.) injection of sodium pentobarbital (55 mg/kg; Nembutal, Abbott Laboratories, North Chicago, IL); heart rate was stabilized with an injection of Rubinol (0.02 mg/kg; A.H. Robins Company, Richmond VA). Rats were then placed in stereotaxic frame (Kopf Instruments), such that bregma and lambda were level. An incision in the scalp was made, and the dura mater pulled back to expose the skull. We drilled a hole in the skull and implanted the guide cannula (6.8 mm, 28 gauge, Plastics One) at coordinates AP: +3.8 mm, L: \pm 2.6 mm, V: -3.6 mm. Laterality of implantation was decided randomly. Two small mechanical screws were implanted in the skull to anchor the cannula. Dental cement was used to fix the cannula in place. We then sutured the incision and applied antibacterial ointment (Nitrofurazone, Phoenix Pharmaceutical, St. Joseph MO) to prevent infection. Stylets (34 gauge) were placed in cannulas to keep them free of debris until behavioral testing. Rats had at least 7 days to recover after surgery before behavioral testing.

Intracerebral Infusion

Drugs were delivered 5 minutes prior to testing. Stylets were removed and replaced with an injector needle connected to a Hamilton syringe on a Harvard Apparatus 22 syringe pump. Rats were injected with 0.5 μ l of either 8-OH-DPAT (Sigma; 2 μ g/ μ l in saline) or saline. The infusion speed was 0.5 μ l/1 minute. The syringe was left in the brain for 60 seconds after infusion to allow absorption of the vehicle. The drug solution was prepared freshly no more than 30 hours before use. The rats were manually restrained during injections by wrapping them in a cloth.

Experimental Design

A week after the last surgery, open field testing was conducted. Each rat went through two trials in the open field, the second 48 hours after the first. In the first trial, the rat was randomly selected to receive saline or drug, and on the second trial the other agent was administered. By the time of open field testing, five rats had lost their cannula. These were used to compare systemic administration of the drug to intracerebral administration; 0.02 ml of 2 mg/ml 8-OH-DPAT or saline was injected i.p. in these animals. Social interaction testing took place two weeks after open field testing. By this test, six animals had lost their cannula; these uncannulated animals were used as the partners for the cannulated rats. Experimental design for social interaction test was the same as open field testing, with each rat experiencing two trials. Again, drug or saline condition for the first trial was determined randomly. The forced swim test occurred about two months following the social interaction test, and the acoustic startle test was completed two weeks following the end of forced swim testing. For the forced swim and acoustic startle experiments, nine animals with intact cannula received intracerebral infusion of the drug. Seven rats received systemic injections in the forced swim test, and eight rats received systemic administration for the acoustic startle experiment. The two trials for the forced swim test were separated by a week, but otherwise followed the same design as the two previous tests. Acoustic startle testing occurred over three consecutive days.

Open Field

The open field apparatus consisted of a box with a base 60 cm x 60 cm, and walls about 28 cm in height. The base was a gray and marked with black lines to divide the area into 16 squares of equal size. Squares adjacent to the walls of the open field were classified as outer squares; there were 12 total. The four squares not adjacent to the walls were classified as inner squares. Each rat was placed in the center of the box, with the experimenter standing in a consistent place, and a video camera, also placed consistently, recording the activity of the rat. The room was dimly lit by a 40-watt lightbulb in a lamp

positioned such that seven outer squares were shadowed. The box was cleaned after each testing. Each rat was recorded for 8 minutes. Four measures were recorded for this experiment: the number of entries with all four paws into the inner squares, frequency of defecation or urination by the rat during the testing period, time spent in shadowed squares, and total number of squares crossed.

Social Interaction Test

The same apparatus used in the open field test was used to measure the level of social interaction of the rats. Partner rats of approximately the same weight (within 30 g) were placed in the box about 2 minutes before the target rat. At the beginning of the test, the target rat was placed on the opposite side of the box from the partner rat. The behavior of the target rat was video-taped for 8 minutes; duration of time that the target rat actively engaged in the following activities was measured: sniffing, following, crawling under or over, grooming, or fighting with the partner rat.

Forced Swim Test

A forced swim cylinder was constructed from two clear plastic snack food containers, measuring 40 cm in height, with a diameter of 16 cm. It was filled with room temperature water to a depth of 16 cm. Each rat was subjected to two 5 minute test periods, each preceded by a 15 minute pre-swim that occurred 20-24 hours before the test. Water was changed in between each test. Videos of the tests were analyzed. The rat's behavior every 5 seconds was classified as climbing, swimming, treading, or immobility. Climbing was defined as attempts to escape by climbing the sides of the chamber. The rats were judged to be swimming when they were actively paddling their limbs to move about the chamber. Treading was defined as slight movement of the limbs which did not result in movement around the chamber. Finally, rats were judged to be immobile when they were not moving their limbs, and making only those movements necessary to keep the head above water.

Acoustic Startle and Pre-Pulse Inhibition

In this test, the rat was placed in a restrictive metal cage (16.5 cm x 7 cm x 10 cm) mounted onto a platform that detected the amplitude of the rat's movement after a startle period; this platform was contained in a soundproof chamber (48 cm x 41 cm x 57 cm) in a darkened room (all equipment manufactured by Coulbourn Instruments, LeHigh Valley, PA). The experiment was programmed and the data was collected using Startle Reflex (version 4.2) software (Med Associates, Georgia VT). Testing consisted of three blocks of 14 trials each, with an interval of about 24 hours between blocks. For all three blocks, there was a one minute acclimation period, and a 30 second interval between trials. In the first block, all 14 trials consisted of 50 millisecond bursts of 105 dB white noise. Background noise consisted of 70 dB white noise. The startle stimulus in the second and third blocks was again a 50 ms 105 dB white noise. In the second and third blocks, the startle in 6 randomly selected trials were preceded by a 20 ms 74 dB white noise that occurred 100 ms before the startle. Background noise in the second and third blocks was 60 dB. The metal cage and platform were cleaned after testing of each animal.

Histology

After completion of behavioral tests, rats were deeply anesthetized with 1.0 ml Nembutal and were perfused first with 30 ml saline and then 30 ml of 10% paraformaldehyde in saline. Brains were excised and fixed in 10% paraformaldehyde. About three days before sectioning, brains were transferred to a solution of 10% paraformaldehyde and 30% sucrose. 42-micrometer slices of brain were prepared using a cryostat and fixed to microscope slides. Slices were stained in 0.1 % thionin solution and washed with distilled water. These slides were examined to determine proper placement of cannula.

Results

Histology

Because of complications during cryo-sectioning, cannula tracks could only be detected for 7 of 11 animals receiving intracerebral administration of drug. Of these

animals, one was found to have improper cannula placement (see Figure 1). For the other 6 animals, cannula placement ranged from +3.70 mm to +4.20 mm from bregma, in the OFC (see Figures 2 and 3). Data from the rat in which the cannula was misplaced was not excluded from statistical analyses, because this data did not contribute to significant trends. Thus, the reported statistical measures may be considered to be slightly conservative.

Open Field

Results of open field testing for the four variables examined are summarized in Table 1. Data for each dependent variable were analyzed using a mixed Analysis of Variance (ANOVA), with drug vs. saline as a within subjects variable and trial order (saline or drug injection in first trial) as a between subjects variable. No significant differences were found in number of crosses into inner squares after intracerebral (i.c.) infusion of 8-OH-DPAT ($M = 3.7$, $SD = 2.4$) or saline ($M = 2.2$, $SD = 2.6$), $F(1,9) = 1.40$, $p = 0.267$. Trial order did not have a significant effect, $F(1,9) = 0.011$, $p = 0.919$. There was no significant interaction of trial order with drug treatment, $F(1,9) = 0.49$, $p = 0.502$.

There was no significant difference in the frequency of urination or defecation by the animals in the open field after i.c. infusion of 8-OH-DPAT or saline, $F(1,9) = 1.75$, $p = 0.219$; nor was there a significant difference due to trial order, $F(1,9) = 0.048$, $p = 0.832$. However, there was a marginally significant interaction with trial order, $F(1,9) = 4.65$, $p = 0.059$ (see Figure 4). A post-hoc t-test revealed that animals that received saline on the first trial urinated or defecated more often ($M = 1.0$, $SD = 1.1$) than on the second trial, after receiving the drug ($M = 0.17$, $SD = 0.4$), $t(5) = 2.71$, $p < .05$.

Rats did not spend significantly different amounts of time in the shadowed squares of the open field box after i.c. infusion of 8-OH-DPAT or saline, $F(1,9) = 1.55$, $p = 0.245$. There was no significant effects of trial order for this measure, $F(1,9) = 0.003$, $p = 0.960$. However, there was a significant treatment by trial interaction for this measure,

$F(1,9) = 8.28, p < .05$ (see Figure 5). Rats spent significantly less time in shadowed squares during the second trial after infusion of 8-OH-DPAT ($M = 330, SD = 65.3$) than on the first trial after infusion of saline ($M = 384, SD = 32.3$), $t(10) = 2.60, p < .05$.

A significant drug effect was found in the measure of total movement; rats crossed significantly more squares after i.c. infusion of 8-OH-DPAT ($M = 158, SD = 23$) than after saline infusion ($M = 141, SD = 26$), $F(1,9) = 8.78, p < .05$. No significant difference due to trial order was found, $F(1,9) = 3.53, p = 0.093$. However, there was a marginally significant interaction between drug treatment and trial order, $F(1,9) = 4.66, p = 0.059$. This interaction is displayed graphically in Figure 6; a post-hoc t-test shows 8-OH-DPAT only increased motor activity in the first trial ($M = 177, SD = 7.8$), compared to saline treatment in the first trial ($M = 137, SD = 26.7$), $t(9) = 3.20, p = 0.011$.

Data were also analyzed to detect effects of 8-OH-DPAT that were hemisphere-specific. Paired t-tests were conducted to compare saline and drug infusions, with the sample limited to either animals receiving infusions to the right OFC or left OFC. Data from drug infusions into right OFC and into left OFC were also compared. There was no significant difference between drug and saline treatment for rats receiving infusions to the left OFC, $t(5) = 1.38, p > .05$. Number of crosses into inner squares after infusion of 8-OH-DPAT did not significantly differ depending on hemisphere of infusion, $t(9) = 0.33, p = 0.75$.

The data from animals receiving intraperitoneal injections were analyzed for the four open field measures, to allow comparison of systemic and localized effects of 8-OH-DPAT on anxiety and movement. No significant drug or trial effects were detected (see Table 2), though as can be seen in Table 1, trends for i.p. injections resembled those of i.c. infusions.

Social Interaction

Data from the social interaction test were examined with a mixed ANOVA, using drug vs. saline as a within subjects variable and trial order as a between-subjects variable.

Rats spent significantly less time engaged in social interaction after i.c. delivery of 8-OH-DPAT ($M = 120$, $SD = 50$) than after infusion of saline ($M = 145$, $SD = 42$), $F(1,9) = 7.81$, $p = 0.021$ (see Figure 7). There was not a significant difference in social interaction between the two trials, $F(1,9) = 0.269$, $p = 0.616$. The interaction between drug treatment and trial order was not significant, $F(1,9) = 2.52$, $p = 0.147$.

Forced Swim

Forced swim data was analyzed using mixed ANOVA, with drug vs. saline as a within subjects variable, and trial order as a between-subjects variable. Immobility was not affected by intracerebral infusion of 8-OH-DPAT ($M = 44.3$, $SD = 11.0$) compared to infusion of saline ($M = 46.4$, $SD = 7.5$), $F(1,7) = 0.35$, $p = 0.571$ (Figure 8). Trial order also did not have a significant effect on immobility after intracerebral infusion, $F(1,7) = 0.037$, $p = 0.853$. The interaction between trial order and treatment was not significant, $F(1,7) = 1.094$, $p = 0.330$.

Systemic administration of 8-OH-DPAT did significantly affect immobility. Rats were significantly less immobile after i.p. injection of 8-OH-DPAT ($M = 39.3$, $SD = 6.2$) than after i.p. injection of saline ($M = 49.1$, $SD = 6.1$), $F(1,5) = 9.68$, $p = 0.027$ (see Figure 9). Trial order did not have a significant difference, $F(1,5) = 0.688$, $p = 0.445$. The interaction between trial order and treatment was not significant, $F(1,5) = 0.049$, $p = 0.834$.

Pre-Pulse Inhibition

Results from the acoustic startle responses after intracerebral infusion of drug or saline are displayed in Figure 10, while responses following systemic injections are displayed in Figure 11. Average startle response to startle and pre-pulse stimuli were compared in a mixed 2x2x2 ANOVA, using 8-OH-DPAT or saline and startle or pre-pulse trials as within subject variables, and injection type (i.p. or i.c.) as a between subjects variable. A significant main effect was observed for stimulus-type; rats were startled less when the tone was preceded by a pre-pulse ($M = 65.8$, $SD = 28.3$) than when

the startle stimulus was presented alone ($M = 139.8$, $SD = 81.6$), $F(1,15) = 22.94$, $p < .001$. There was no significant difference observed due to treatment, $F(1,15) = 0.00$, $p = 0.993$. There were no significant effects observed for the interaction between stimulus type and type of injection, $F(1,15) = 0.01$, $p = 0.918$, nor between stimulus type and drug or vehicle, $F(1,15) = 0.03$, $p = 0.868$, nor in the three way interaction between stimulus type, drug administration, and route of administration, $F(1,15) = 0.27$, $p = 0.613$.

Discussion

The purpose of this investigation was to discover if infusions of 8-OH-DPAT, a 5-HT_{1A} agonist, into the orbitofrontal cortex had any effects on rats' behavior in paradigms related to symptoms of human psychopathology. Results of this study provide limited support to the role of orbitofrontal 5-HT_{1A} receptors in behaviors that are abnormal in some psychiatric disorders. Significant findings of this study include that 8-OH-DPAT increases locomotor activity in novel environments, and decreases social interaction. In combination with familiarity with the environment, infusion of 8-OH-DPAT decreased anxiety-like behavior. Furthermore, previous findings on the antidepressant effect of 8-OH-DPAT delivered systematically were replicated, but found not be mediated by 5-HT_{1A} receptors in the OFC.

Mice lacking the gene for the 5-HT_{1A} receptor were found to exhibit increased anxiety behavior and decreased exploratory behavior, as measured by total locomotor activity, in the open field test in two studies, though a third study failed to show this effect (Heisler et al., 1998; Parks et al., 1998; Ramboz et al., 1998). The treatment in this study, which increased rather than decreased activation of 5-HT_{1A} receptors, caused an increase in exploratory behavior. Thus, our results appear to corroborate the results of these genetic knockout studies, and suggest that the OFC may mediate exploratory behavior in novel environments. This effect may be caused by the increase in dopaminergic activity stimulated by activation of 5-HT_{1A} receptors, since the prefrontal dopaminergic system has a major role in regulating motivation and movement (Sakaue et

al., 2000; Shoblock et al., 2003). Also in this study, it was found that 8-OH-DPAT decreased the frequency of urinations or defecations by the rats, as well as decreased the time rats spent in shadowed squares; however, this decrease was only significant when the animals received the drug on the second trial. Thus, in familiar environments, 8-OH-DPAT may have anxiety reducing effects.

Infusion of 8-OH-DPAT into the OFC decreased social interaction of rats in this study. This finding mirrors the results obtained by File, Gonzalez and Andrews (1996), who found that infusion of 8-OH-DPAT into the hippocampus, another area where 5-HT_{1A} receptors are post-synaptic, decreased social interaction in rats. These results suggest that over-activity of 5-HT_{1A} receptors in the OFC may be involved in the deficits in social behavior observed in several disorders, especially social anxiety disorder, in which over-activity in the OFC may be pathological (Veit et al., 2002). This finding also serves to underscore the importance of the OFC in regulation of social behavior, as suggested by observations of patients with orbitofrontal damage. Although findings on increased concentration of orbitofrontal 5-HT_{1A} receptors have been mixed, the results of this study suggest that this neurochemical abnormality could be related to the social deficits observed in schizophrenia.

Previously it was found that systemic administration of 8-OH-DPAT has an anti-depressant effect in the forced swim test (Detka, Weiland & Lucki, 1995). Because drugs that selectively antagonized pre-synaptic 5-HT_{1A} receptors did not have an anti-depressant effect in the forced swim test, the authors of the study suggested that the anti-depressant effect of 8-OH-DPAT is mediated by post-synaptic receptors. In this study, we replicated the finding that systemic administration of 8-OH-DPAT reduces immobility in the forced swim test, but did not find a similar effect after infusion of the drug into the OFC. Thus, if post-synaptic 5-HT_{1A} receptors mediate the anti-depressant effect, the receptors are probably located in other prefrontal areas, the hippocampus or the amygdala. However, the possibility that higher doses of 8-OH-DPAT infused to the OFC

could have antidepressant-like effects cannot be ruled out. Further studies using higher drug doses are required to explore this possibility.

This study failed to find significant effects of 8-OH-DPAT administration, either systemic or intracerebral, on startle reactivity or pre-pulse inhibition. However, it has been reported in the literature that 8-OH-DPAT increases PPI in mice and decreases PPI in rats (Dulawa et al., 2000; Sipes & Geyer, 1995). The lack of effect of 8-OH-DPAT in this study may be due to the relatively low dose of drug used in this study. Sipes and Geyer (1995) found that 8-OH-DPAT disrupted PPI when delivered systemically at a dose of 0.2 mg/kg, though it did not have an effect at doses of 0.06 mg/kg or lower. In this study we used an intermediate dose, about 0.1 mg/kg, which may not have been sufficient for an effect to be observed. Sipes and Geyer also found that 8-OH-DPAT reduced PPI when infused into the raphe nuclei at a dose of 5 ug/0.5 ul, but not when delivered at a dose of 1 ug/ 0.5 ul. In this study we failed to observe an effect on PPI of infusing 8-OH-DPAT into the OFC at a dose of 1 ug/0.5 ul; thus we cannot determine if the lack of effect in this study was due to the area of the brain in which the drug was delivered, or whether the dose was insufficient.

One shortcoming of this study was the use of the same group of rats for all behavioral tests, and exposing each rat to two trials of each test. Although random counterbalancing of drug trials should have controlled for order effects that may have confounded results, we cannot rule out the possibility that previous experience with 8-OH-DPAT could have affected the rats' behavior in later tests. Verification of these results in an independent, and ideally larger sample is required. Replication of this study could also examine whether effects of 8-OH-DPAT in this study could be reversed by pre-treatment with WAY 100635, a selective 5-HT_{1A} antagonist, in order to demonstrate that the observed effects are specifically mediated by the 5-HT_{1A} receptor.

Despite these potential flaws of this study, the results provide some evidence suggesting that abnormal density or activity of 5-HT_{1A} receptors in the orbitofrontal

cortex could be involved in some psychopathological symptoms, especially social anxiety or withdrawal, which is characteristic of social anxiety disorder, schizophrenia, depression, and autism. The results of this study suggest topics for future research. For instance, the possibility that the effect of 8-OH-DPAT on exploratory behavior could be mediated by increased dopaminergic activity could be investigated through pre-treating rats with dopamine antagonists before 8-OH-DPAT administration. The role of the 5-HT_{1A} receptors in other prefrontal regions, especially the medial prefrontal and anterior cingulate cortices, would also likely contribute to our understanding of the role of cortical serotonergic activity in behavior. Infusion to the OFC of atypical anti-psychotic medications such as clozapine may also help to elucidate whether the affinity of these drugs for 5-HT_{1A} receptors is related to their clinical efficacy.

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Table 1: Summary of Open Field Results

	<i>n</i>	Crosses into inner squares	Urinations and defecations	Time spent in shadowed squares (sec)	Total squares crossed
<u>Intracerebral</u>					
8-OH-DPAT	11	<i>M</i> <i>SD</i> 3.7 (2.4)	<i>M</i> <i>SD</i> 0.5 (0.7)	<i>M</i> <i>SD</i> 347 (54)	<i>M</i> <i>SD</i> 158 (23)
Left	6	3.5 (2.6)	0.3 (0.5)	357 (63)	148 (23)
Right	5	4.0 (2.3)	0.6 (0.9)	335 (43)	170 (19)
Saline	11	2.2 (2.6)	0.8 (1.2)	367 (39)	141 (26)
Left	6	1.2 (2.4)	0.8 (1.2)	394 (16)	134 (26)
Right	5	3.4 (2.5)	0.8 (1.3)	334 (31)	150 (26)
Trial 1	11	2.5 (2.4)	0.9 (0.9)	376 (31)	155 (29)
Trial 2	11	3.5 (2.7)	0.4 (0.9)	337 (53)	144 (22)
<u>Systemic</u>					
8-OH-DPAT	5	1.4 (2.0)	1.0 (1.7)	357 (51)	157 (44)
Saline	5	2.4 (2.5)	0.4 (0.5)	392 (49)	126 (51)
Trial 1	5	1.8 (2.4)	0.2 (0.4)	376 (51)	121 (55)
Trial 2	5	2.0 (2.3)	1.2 (1.6)	373 (56)	161 (33)

Table 2. Summary of Statistical Analyses of Measures in Open Field After i.p. Injections (n=5)

Measure	<i>F</i> (treatment)	<i>p</i>	<i>F</i> (trial)	<i>p</i>	<i>F</i> (treatment x trial)	<i>p</i>
Crosses into inner squares	0.306	0.619	0.729	0.456	0.045	0.845
Defecations and Urinations	0.224	0.67	0.953	0.401	1.084	0.374
Time spent in shadowed squares	1.27	0.343	0.012	0.918	0.025	0.885
Total squares crossed	1.43	0.318	0.01	0.925	3.16	0.174

Figure Captions

Figure 1. Placement of cannula, showing cannula placed +4.70 mm from bregma (VO, VLO, and AI are OFC); based on rat brain atlas of Paxinos and Watson (1986)

Figure 2. Placement of cannula, showing cannula placed +4.20 mm from bregma (VO, VLO, and AI are OFC); based on rat brain atlas of Paxinos and Watson (1986)

Figure 3. Placement of cannula, showing cannula placed +3.70 mm from bregma (VO, VLO, and AI are OFC); based on rat brain atlas of Paxinos and Watson (1986)

Figure 4. Mean frequency of urinations or defecations (\pm SD) in the open field after infusion of saline or 8-OH-DPAT into OFC (n=11), by trial

Figure 5. Mean time spent in shadowed squares (\pm SD) in open field after infusion of saline or 8-OH-DPAT into OFC (n=11), by trial

Figure 6. Mean total squares crossed in open field (\pm SD) after infusion of saline or 8-OH-DPAT into OFC (n=11).

Figure 7. Mean time rats spent in social interaction (\pm SD) after infusion of 8-OH-DPAT or saline into the orbitofrontal cortex (n=11)

Figure 8. Mean percent immobility (\pm SD) in forced swim test after infusion of 8-OH-DPAT or saline into OFC (n=9).

Figure 9. Mean percent immobility (\pm SD) in forced swim test after i.p. injection of 8-OH-DPAT or saline (n=7).

Figure 10. Mean response (\pm SD) to startle-only or startle with prepulse after intracerebral infusion of saline or 8-OH-DPAT (n=9).

Figure 11. Mean response (\pm SD) to startle alone or startle with prepulse after intraperitoneal injection of saline or 8-OH-DPAT (n=8).

Figure 1

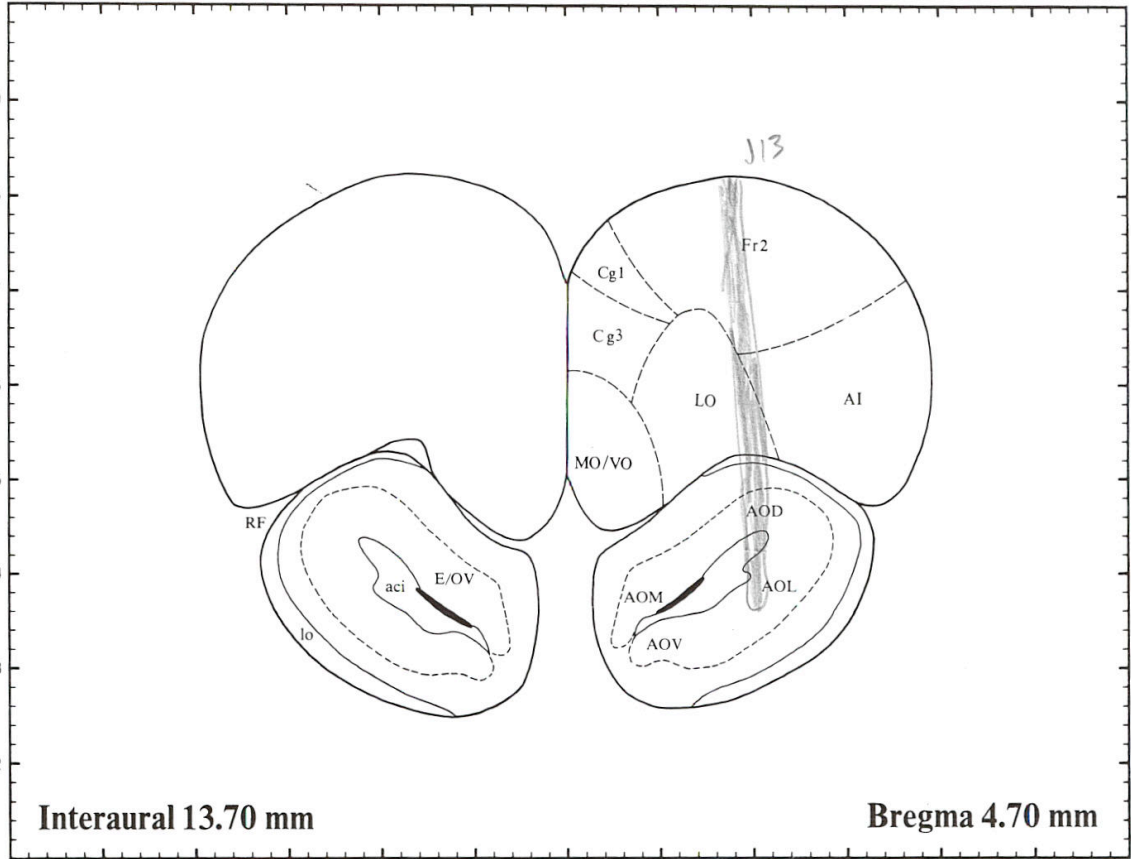


Figure 2

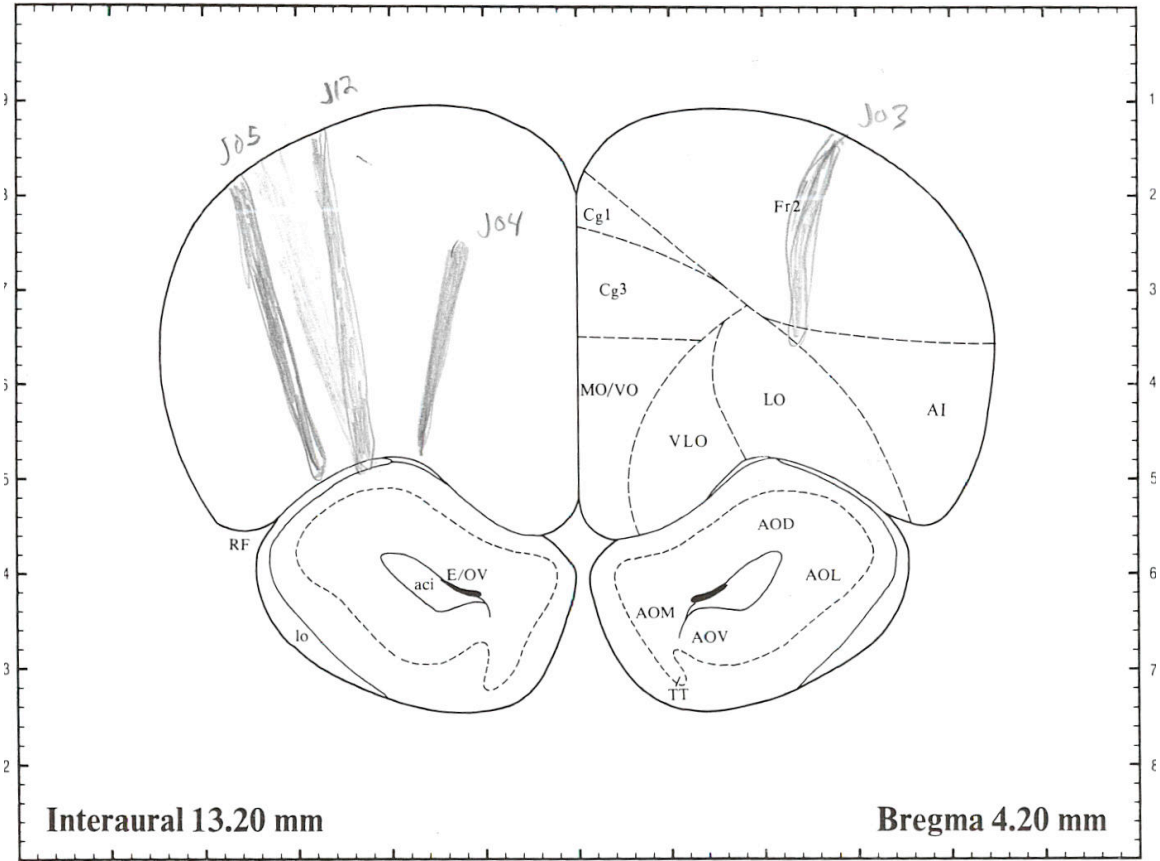


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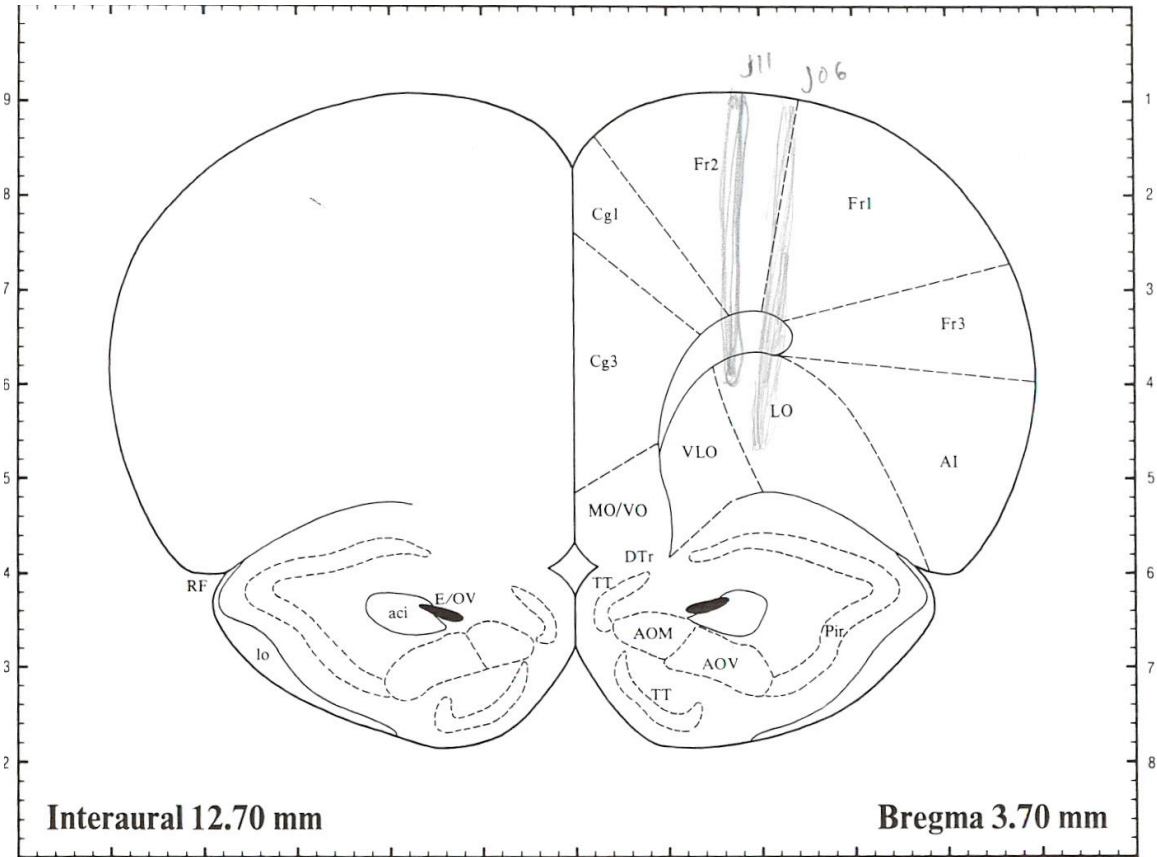


Figure 4

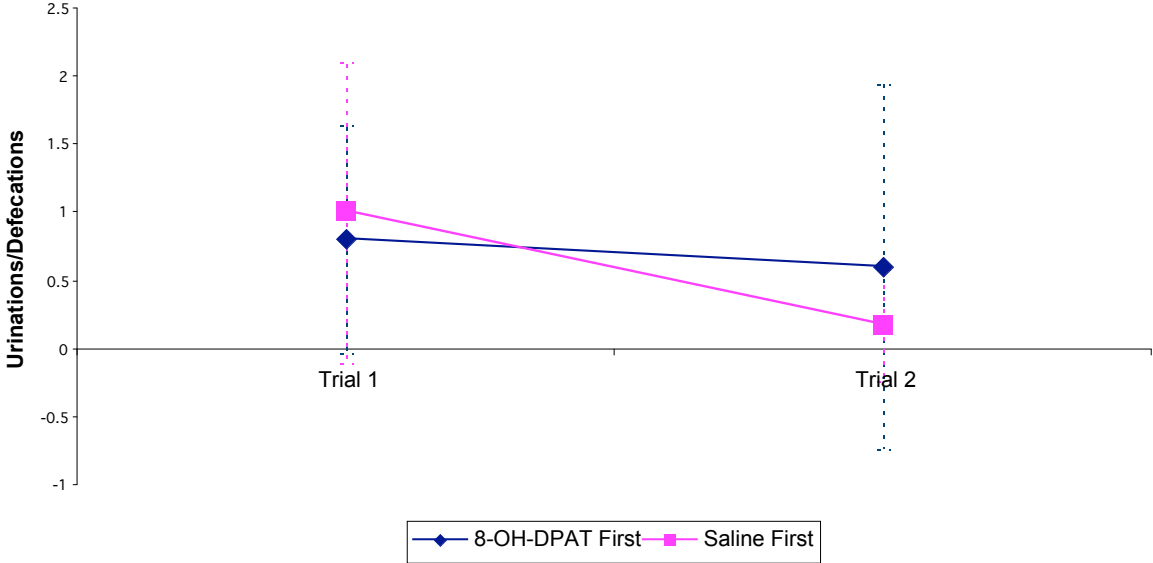


Figure 5

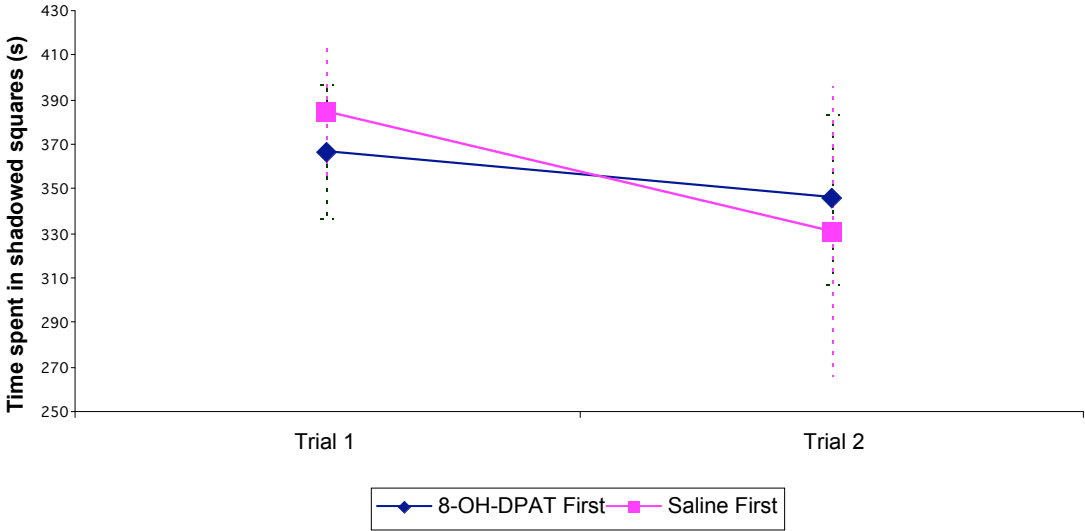


Figure 6

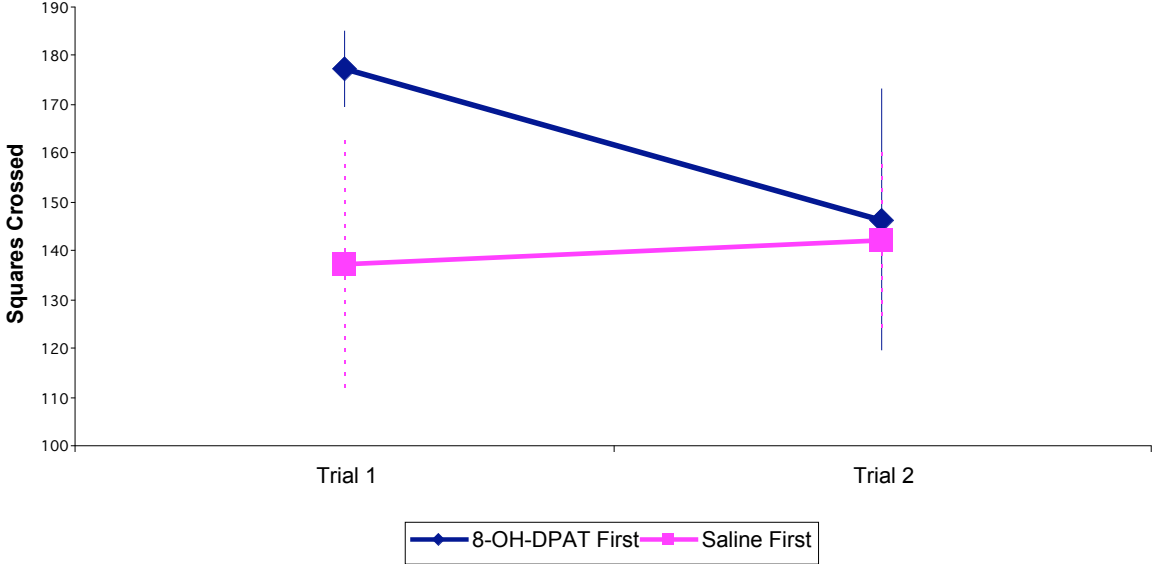


Figure 7

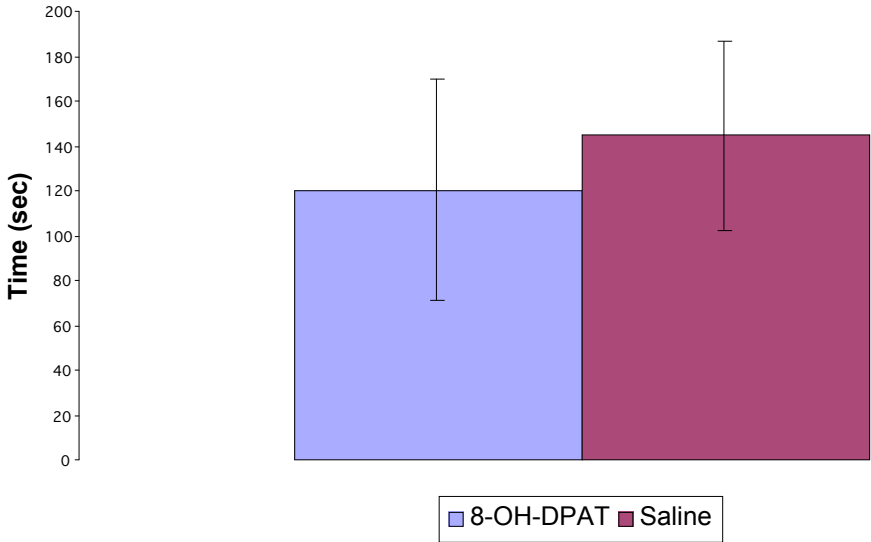


Figure 8

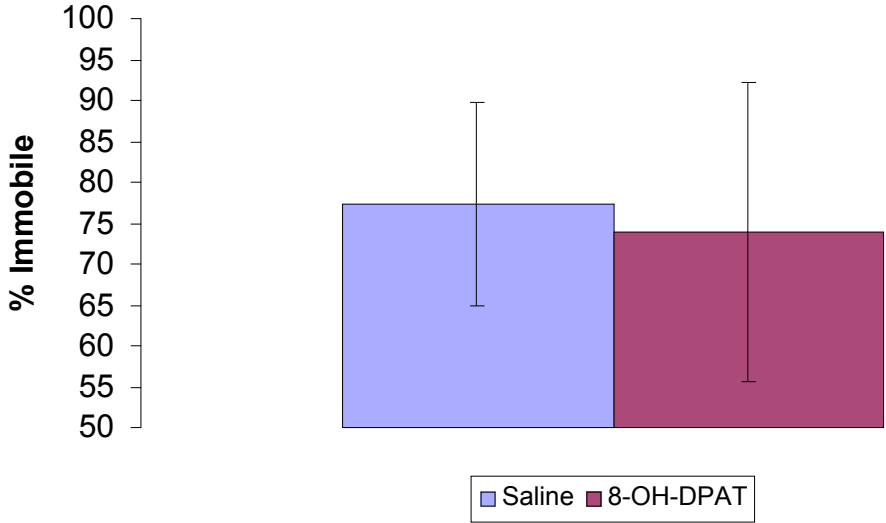


Figure 9

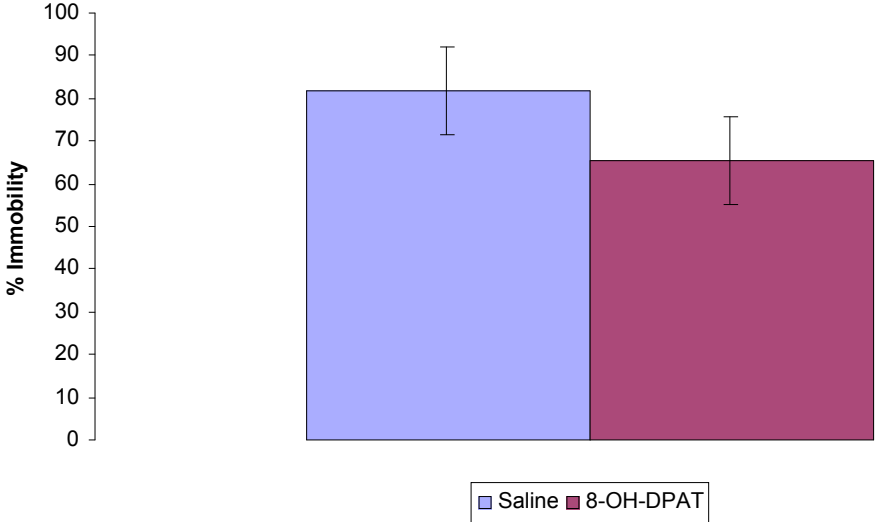


Figure 10

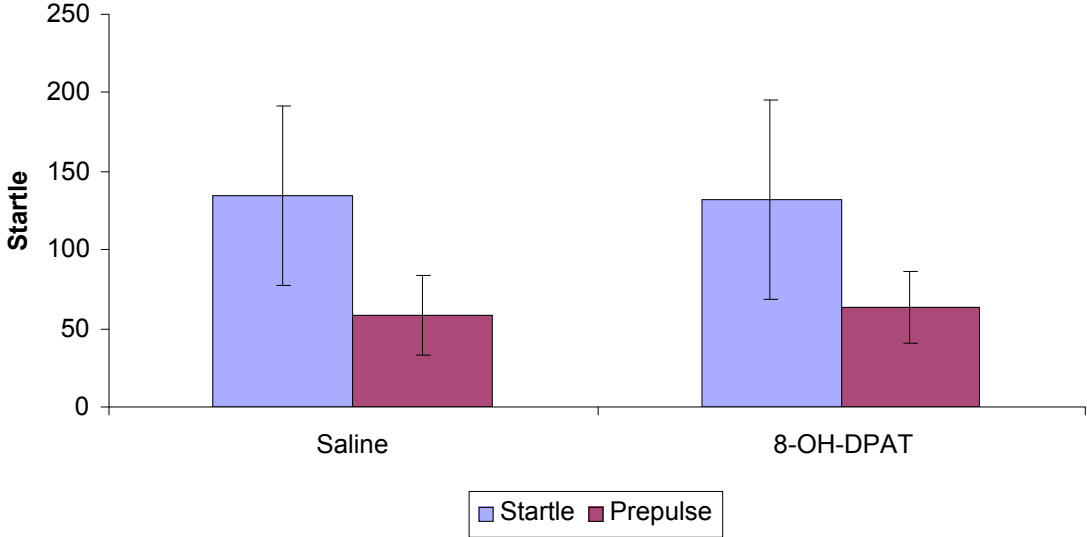
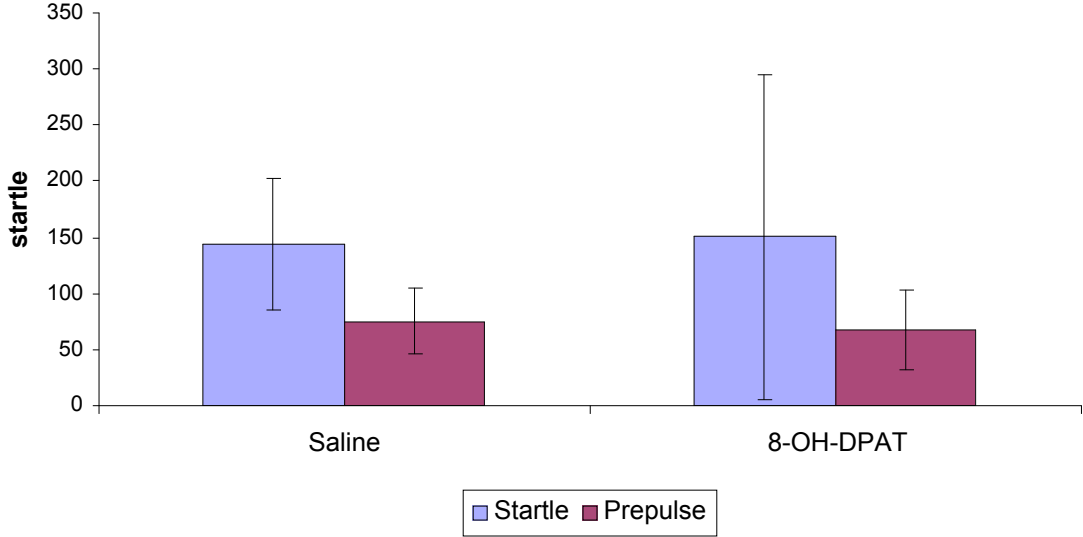


Figure 11



Appendix: The Pathophysiology of Psychiatric Disorders

Introduction

Diseases characterized by behavioral abnormalities have always been noted and considered to be problems in human societies. Although throughout history abnormal behavior was often defined as weakness of character, or the result of supernatural forces, in modern society the medical model has been applied to patterns of behavior that are clearly maladaptive for the individual. This medical model defines these abnormal patterns of behavior as diseases, seeks to understand their causes, and finally seeks to heal the suffering caused by these behavioral problems. In Western medicine, it was not until the 19th century that the brain was recognized to be the major organ controlling behavior, and therefore to be the center of emotional and cognitive changes noted in pathological states. Early attempts to describe the nature of psychiatric disorders and develop appropriate treatments, exemplified by Freud's work, were often hampered by the lack of appropriate scientific practices, the lack of general physiological knowledge about the nervous system, technological constraints on research, and predominant philosophies that biased and shrouded newer theories on such diseases.

Current models of psychiatric disorders are more sophisticated, and benefit from many developments in research techniques and technology. People suffering from psychiatric disorders or related neurological problems have been extensively studied, and collaborations of medical professionals has yielded such documents as the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV: American Psychiatric Association, 1994), which operationally define common behavioral and psychosomatic abnormalities as symptoms of various, discrete disorders. Another major change is that the

physiological origins of these disorders has been recognized and become a major area of scientific investigation, aided by advances in the fields of genetics, cell biology, and anatomy. Neuroscience has emerged as a major scientific discipline that seeks to determine the relationship between biological factors and psychological phenomenon, including behavior, cognition, and emotion, all of which are abnormal in psychiatric disorders.

Although the medical model of psychiatric disorders has gained wide acceptance, stigma related to mental illnesses persists, due in part to the failure of many to recognize that these illnesses are the result of myriad organic and environmental factors beyond the control of the mentally ill patients. Thus, continued investigation into the physiological basis of these disorders is critical for several reasons. Such research may act to reduce stigma attached to psychiatric disorders, as well as suggest new routes of treatment to relieve the suffering of the mentally ill.

This review attempts to give an introduction to some of the major theories on the physiological etiology and pathology associated with several common psychiatric disorders, including schizophrenia, autism, mood disorders and anxiety disorders. Recent findings on these disorders involve investigations into several related domains, including genetic predisposition, anatomical abnormalities (changes in activity or size of particular brain regions), abnormal neurotransmission, changes in intracellular signaling pathways, and abnormalities of the immune or endocrine systems.

Clinical Descriptions

Schizophrenia. Schizophrenia is perhaps the most crippling psychiatric disorder; affecting nearly 1% of the population worldwide, it is characterized by a rapid loss of

cognitive, emotional, and perceptual functioning. Kraepelin, who first described the disorder and gave it a name, insisted that it had an organic origin (Harrison, 1999).

One of the greatest difficulties in studying schizophrenia is the variety of symptom patterns and clinical courses that the disease can take. Such phenotypic variability has led to debate over whether schizophrenia should be considered a single disorder, or a spectrum of disorders. The DSM-IV lists five subtypes of schizophrenia (APA, 1994), and others have sought to conceive of schizophrenia as only two or three dimensional (Liddle, 2000). In general, the symptoms of schizophrenia are categorized as ‘positive’ or ‘negative’. The positive symptoms, which are sometimes termed ‘psychosis’, include bizarre hallucinations and delusions, and disorganized speech (Keefe & Harvey, 1994). The hallucinations can be of any sense, but are predominantly auditory; patients often hear voices. One theory accounting for hallucinations involving voices is that schizophrenic patients lose the ability to monitor their own thoughts, and perceive them as external in origin (Keefe & Harvey, 1994). Speech deficits in schizophrenic patients include frequent derailments and incoherence, which may reflect the delusions and hallucinations, or may reflect underlying cognitive impairments. The negative symptoms of schizophrenia include blunted or inappropriate affect, anhedonia, social withdrawal, loss of motivation, motor deficits, inability to concentrate, and poor insight, referring to the difficulty patients have in realizing that they have a disorder.

Most schizophrenic patients display both positive and negative symptoms, but certain types of symptoms cluster in the subtypes outline in the DSM-IV. Paranoid schizophrenia typically involves hallucinations and delusions, which usually involve persecution or feelings that one’s thoughts are being ‘transmitted’ to others (APA, 1994).

Disorganized schizophrenia is marked more by negative symptoms, especially abnormalities in affect and cognitive impairments (APA, 1994). Catatonic schizophrenia, which is rarely seen, is characterized by motor abnormalities, especially freezing in odd poses (APA, 1994). Undifferentiated schizophrenia involves a mix of symptoms that cannot be classified as one of the other types (APA, 1994). Finally, residual schizophrenia refers to patients who have passed a highly psychotic stage of the illness, meaning they do not suffer from hallucinations or delusions, but nevertheless exhibit some symptoms to a milder degree (APA, 1994).

The complex array of symptoms which can characterize schizophrenia makes diagnosis difficult, as the symptomology of schizophrenia overlaps partially with those of bipolar disorder, autism, delusional disorder, paranoid personality disorder, schizotypal personality disorder, dementia, substance abuse, and delirium due to brain damage or chemical toxins (Keefe & Harvey, 1994). Also, schizophrenic symptoms can afflict a person for only a brief period of time (less than 6 months), in which case the diagnosis will be brief psychotic episode or schizophreniform disorder (Carson, Butcher & Mineka, 1999).

It is the psychotic symptoms - hallucinations and delusions - which have been most successfully treated by psychiatric drugs thus far. But while anti-psychotic medications, also called neuroleptics, have reduced psychosis in some schizophrenic patients enough to allow them to be deinstitutionalized, they have not been as successful in reducing the negative symptoms. Lingering negative symptoms leave patients struggling with severe deficits in social and cognitive functioning; for this reason, many patients require constant supervision. Because cognitive disruptions are present even

when psychotic features are not, and because the social and cognitive deficits are just as problematic as delusions and hallucinations, some researchers now view psychosis as a secondary symptom of schizophrenia, and see the cognitive disruptions of short-term memory, attention and executive functions as the hallmark of the disorder (Holden, 2003).

Autism. In 1943, Kanner described for the first time in the modern era the condition now known as autism (Gillberg & Coleman, 2000). Since Kanner described the condition, there has been much debate about what constitutes the disorder, and whether or not autism can be differentiated from related developmental disorders. Etiological explanations for autism were heavily influenced by psychodynamic theories at first, but towards the end of the 20th century a consensus was reached that autism had a primarily physiological basis.

Classified as a pervasive developmental disorder (PDD), autism can be detected in children as young as 18 months, often by parents who may note rejection of physical contact, gaze avoidance, and other subtle signs of the disorder (Gillberg & Coleman, 2000). Symptoms are most evident in early childhood, and typically include communication difficulties, impairments in social abilities, sensorimotor problems, and stereotypies (Prater & Zylstra, 2002). Communication problems in autism listed in the DSM-IV include delay or total lack of language development, idiosyncratic use of language, or inability to sustain conversations (APA, 1994). Social impairments listed as symptoms in the DSM-IV include impaired use of facial expressions and nonverbal language, failure to develop relationships to a level appropriate to developmental level, lack of spontaneous sharing of experiences with others, and diminished social and

emotional reciprocity (APA, 1994). Other diagnostic criteria listed in the DSM-IV include inflexible adherence to specific or non-functional routines, and stereotyped or repetitive motor mannerisms (APA, 1994). Symptoms can also include abnormal responses to sensory stimuli, hyperactivity, abnormal eating habits, and aggression (Gillberg & Coleman, 2000). In addition to these symptoms, the majority (about 70 %) of autistic persons are mentally retarded, and many also suffer from seizure disorders (Gillberg & Coleman, 2000). Depression, anxiety, and obsessive-compulsive symptoms may also be co-morbid with autism (Prater & Zylstra, 2002). Autism has been characterized as ‘mindblindedness’, or marked by deficits in social cognitive abilities often called ‘theory of mind’ (Baron-Cohen, 1995). Theory of mind refers to the ability of humans to infer the goals, perspectives, and feelings of other humans. Autistic individuals consistently fail at simple tasks accomplished by non-autistic children that require an ability to understand the experiences and intentions of others (Baron-Cohen, 1995).

Part of the difficulty in studying autism has been its close resemblance to a number of other psychiatric conditions. Practitioners must differentiate autism from early-onset schizophrenia, schizoid personality disorder, epilepsy, tuberous sclerosis, and other developmental disorders like Asperger syndrome, Rett syndrome, and Heller syndrome (Berney, 2000; Gillberg & Coleman, 2000; Smalley, 1998). Asperger syndrome is diagnosed when a child exhibits the typical features of autism, but the symptoms are not extreme and the child is close to normal intelligence. The difference between Asperger syndrome and high functioning autism is thus very slight, and has

created debate about the validity of distinguishing between the two (Gillberg & Coleman, 2000).

Pervasive developmental disorders occur in the general population at a rate of about 63 cases per 10,000 people; rates for autism specifically are estimated to be between 6-20 cases per 10,000 (Prater & Zylstra, 2002). The disorder occurs more often in males than females, in about a 4:1 ratio for moderately handicapped cases, though the ratio is closer to 2:1 in severely handicapped cases (Prater & Zylstra, 2002). Autism tends to be a life-long disorder, though improvement in some symptoms is often seen in late childhood and adolescence (Gillberg & Coleman, 2000).

Affective disorders. The constellation of disorders involving changes in mood has one of the highest mortality rates of psychiatric illnesses (Nestler, Barrot, DiLeone, Eisch, Gold, & Monteggia, 2002). In addition to causing disturbances in patients' relationships with others, ability to work, and ability to enjoy life, affective disorders are the leading cause of suicide, a problem which has become prominent enough that the Surgeon General of the United States recently made its prevention a priority in public health (U.S. Public Health Service, 1999). As is the case for schizophrenia, research on depression is challenged by the variety of courses seen in mood disorders. The DSM-IV lists 10 different diagnoses related to depression (APA, 1994). Research on the physiopathology of depression is thus burdened with the necessity of determining whether these differential diagnoses are validated by different physiological characteristics. Although research is too limited on many of the diagnoses to allow conclusions on the validity of their differentiation to be made, evidence has been accumulating to suggest that the three major disorders studied - Major Depressive

Disorder (MDD), Dysthymic Disorder (DD), and Bipolar Disorder (BD) - differ in their neurobiology.

Duration and severity of illness differentiate MDD and DD from the clinical viewpoint. Both MDD and DD involve unipolar depression (manic episodes are not experienced), characterized by feelings of hopelessness, guilt and worthlessness, appetite changes (loss of appetite in typical depression, hyperphagia in atypical), anhedonia (inability to feel pleasure), social withdrawal, sleep disturbances (typically insomnia, atypically hypersomnia), fatigue, irritability and poor concentration (APA, 1994; Griffiths et al., 2000). The primary difference between these disorders is that MDD typically involves a more severe depression, but with a shorter course than dysthymia, in which symptoms may last for years. These disorders are often co-morbid, a condition called 'double depression' (Donaldson et al, 1997).

Major depression is a recurrent disorder, occurring more commonly among women than men, and is associated with a substantial risk of suicide (Davidson et al., 2002). This disorder may be present in 2-5% of the general population (Nestler et al., 2002). The illness is associated with a number of psychosocial and cognitive risk factors, including negative explanatory styles, poor coping skills, childhood maltreatment, and low social support (Davidson et al., 2002). Stressful life events are also an important factor in the onset of MDD, but the association between these events and onset of depressive episodes decreases as the number of previous depressive episodes increases, an effect called 'kindling' (Kendler, Thornton, & Gardner, 2001).

Dysthymia has a prevalence estimated at close to 3 % of the general population, affecting women more than men (Niculescu & Akiskal, 2001). Attempts have been made

to distinguish subtypes of dysthymia. One proposal differentiates between ‘anxious’ and ‘anergic’ dysthymia, the difference primarily being comorbidity of anxiety disorders in the former, although differences may also include neurobiological basis, responsiveness to medication, and gender distribution (Niculescu & Akiskal, 2001). Another proposal distinguishes between ‘subaffective’ dysthymia, which has primarily a biological basis, and ‘character spectrum’ dysthymia, which is based on personality (Griffiths et al., 2000). Social and interpersonal impairments are marked among DD patients, and the degree of impairment may correlate with the severity and chronicity of the disorder (Griffiths et al., 2000).

In BD, periods of depression resembling those in MDD alternate with periods of mania, which is characterized by an abnormally elevated or irritable mood, excessive energy, and sometimes psychosis (APA, 1994; Muller-Oerlinghausen, Berghofer & Bauer, 2002). Clinical observations have suggested that BD may be a constellation of related disorders, each manifested by a specific pattern of mood fluctuations. For instance, depressive and manic episodes may both be severe, or one type may be severe and the other less so; the cycling between depressive and manic episodes may occur slowly over a course of months, or happen over a course of days (Muller-Oerlinghausen et al., 2002). Bipolar disorder shares some clinical overlap with schizophrenia; as in schizophrenia, BD may involve cognitive impairments manifested both during the course of illness and in periods of remission (Bearden, Hoffman, & Cannon, 2001; El-Badri, Ashton, Moore, Marsh, & Ferrier, 2001). However, it has been found that the subjective experience of cognitive impairments, as well as disturbances in motility and perception, are more pronounced in schizophrenia than bipolar disorder (Arduini, Kalyvoka, Stratta,

Gianfelice, Rinaldi, & Rossi, 2002). The lifetime prevalence of BD is estimated to be about 1.5 %, with peak ages of onset between 15-24; 10-20 % of bipolar patients commit suicide (Muller-Oerlinghausen et al., 2002).

Anxiety disorders. Among the most prevalent of psychiatric disorders are the anxiety disorders. While not associated with the high mortality of affective illnesses or the debilitation of schizophrenia, the anxiety disorders can cause great discomfort among patients and are often comorbid with other disorders. The spectrum of anxiety disorders recognized by the psychiatric community includes such diverse diagnoses as specific phobia, obsessive-compulsive disorder, panic disorder, and post-traumatic stress disorder (APA, 1994). Each of these disorders is a focus for neurobiological investigation, but as most research has thus far focused on social anxiety disorder (SAD) and generalized anxiety disorder (GAD), these will be the focus of this review.

SAD, also called social phobia, is characterized by an intense, persistent, and irrational fear of being negatively judged by others in social situations (Bruce & Saeed, 1999). Individuals with this condition may experience the physical manifestations of anxiety - blushing, sweating, trembling - and will be preoccupied with the possibility of embarrassment during social interactions (Bruce & Saeed, 1999). Patients tend to respond to these symptoms by avoidance of social situations. This can have devastating effects on an individual's life, as evidenced by epidemiologic findings that large percentages of patients with SAD do not finish secondary school, have a low socioeconomic status, and receive welfare payments, suggesting that the disorder prevents people from working or attending school (den Boer, 2000). Two subtypes have been noted in SAD; in nongeneralized social phobia, the patient only experiences symptoms in specific social

situations, such as public speaking, while in generalized social phobia, the patient experiences symptoms in most social situations (den Boer, 2000). Onset of SAD typically occurs in early adolescence, and is typically untreated for years (Bruce & Saeed, 1999). Estimates for lifetime prevalence of SAD vary from 2-13 % (Stein & Gorman, 2001). More females than males suffer from SAD, in about a 2.5 to 1 ratio (den Boer, 2000). SAD is more often than not comorbid with other disorders, especially depression, substance abuse, and other anxiety disorders (den Boer, 2000).

The clinical features of social phobia overlap with several other disorders, including autism, schizoid and avoidant personality disorders, depression and panic disorder (den Boer, 2000; Mathew, Coplan, & Gorman, 2001). Avoidant personality disorder so closely resembles SAD that it has been proposed that the distinction between the two is only between degrees of severity of the same illness (den Boer, 2000). The clinical relationship between SAD and autism may be due to similar genetic risk factors for the two illnesses (Piven & Palmer, 1999).

GAD is characterized by constant worries about minor things that causes significant subjective suffering and impairs quality of life (Gale & Oakley-Browne, 2003). More common in women than men, GAD typically develops in adolescence, and is usually chronic in its course (Gale & Oakley-Browne, 2003). As is the case with SAD, patients with GAD typically have a comorbid psychiatric disorder, including affective illnesses, substance abuse, or other anxiety disorders (Gale & Oakley-Browne, 2003).

Genetic Influences

It has long been known that various phenotypes, physical as well as behavioral, run in families. Many studies have sought to determine if psychiatric disorders are

transmitted genetically, as various other medical conditions are. Results show that the genes an individual inherits do strongly influence whether or not that person will develop a mental illness, but that environmental factors remain important. Furthermore, recent studies have focused on explaining vulnerability to psychopathology as an interaction between genotype and environmental conditions.

Schizophrenia. Genetic predisposition for developing schizophrenia has been well established. Twin and adoption studies suggest that an individual who has a schizophrenic relative has a greater chance of developing the disorder than someone in the general population (Gottesman, 1991). Furthermore, the closer that relative is genetically, the greater the risk; an individual with a schizophrenic cousin, a third-degree relative, has about a 2% risk of developing schizophrenia, whereas an individual whose monozygotic twin is schizophrenic has about a 50% chance of developing the disorder (Gottesman, 1991). Two important qualifications on these findings are that schizophrenia is not due to a simple genetic effect and that the findings on monozygotic twins suggest that the environment plays a large role in risk for the disorder. The development of schizophrenia appears to be influenced by numerous genes, and though there have been many candidate genes examined, none have been linked to schizophrenia beyond doubt (Sawa & Snyder, 2002). It may be that there are diverse genetic polymorphisms related to schizophrenia, and that the disorder develops in individuals who carry enough of these genes to cross some threshold (Sawa & Snyder, 2002). A finding that supports this hypothesis is that relatives of schizophrenic individuals often exhibit mild symptoms of the disorder; for instance, Fanous et al. (2001) found that family members of schizophrenic patients exhibited many schizotypal features, including odd personality,

social isolation, poor relationships and odd speech habits. However, in these types of studies it is often difficult to tell whether genetics or shared environment causes the relationship in symptomology. Candidate genes suspected in contributing to the development of schizophrenia include those for neuregulin 1, dysbindin, COMT, and G72, proteins involved in synaptic plasticity and regulation of neurotransmission; however, the disease variants of these genes have not been identified (Kennedy et al., 2003).

Autism. Genetic predisposition also plays a large role in susceptibility to autism. Siblings are often concordant for the disorder, and monozygotic twins show greater concordance than dizygotic twins (Gillberg & Coleman, 2000). Rates of autism in siblings of an autistic person have been found to be 2-6%, far greater than in the general population, in which the prevalence is about 0.1% (Lamb, Moore, Bailey, & Monaco, 2000).

Further evidence of the genetic component of autism comes from studies that have found subclinical autistic symptoms - the 'broader autistic phenotype' - to be common among relatives of autistic persons. Social impairments, especially, appear to be common among relatives of autistic patients (Bailey, Palferman, Heavey, & Le Couteur, 1998). Reciprocal social behavior, referring to appropriate turn-taking in social interactions, has been shown to be highly heritable; Constantino and Todd (2000) found that monozygotic twins had much greater concordance for reciprocal social behavior than dizygotic twins. Piven and Palmer (1999) found increased rates of depression and social phobia among parents of autistic children that could not be explained by the stress associated with raising a child with a disability. However, such studies have generally

failed to find increased rates of schizophrenia, cognitive impairments, or epilepsy in relatives of autistic persons compared to controls (Bailey et al., 1998).

Findings on the genetic heritability of autism suggest that susceptibility to the disorder is multifactorial and likely involves several different genes (Lamb et al., 2000). Genome-wide linkage studies have uncovered a number of candidate genes involved in autism. Replicated findings have implicated regions on chromosomes 2q, 7q, 15q, 16p, and 19p (Philippe et al., 1999). A review of linkage studies suggests that the evidence is strongest for a susceptibility locus for autism on chromosome 7q (Lamb et al., 2000). Based on findings that autism is much more common in males than females, a link between the sex chromosomes and autism has also been hypothesized (Skuse, 2000). However, evidence for this hypothesis is lacking (Lamb et al., 2000). A modified hypothesis on the role of the sex chromosomes proposes that abnormal imprinting of genes on the X chromosome protective against autism may occur; these genes may be silenced if inherited from the mother, and activated when inherited from the father, which would contribute to the sex ratio seen in the disorder (Skuse, 2000). This hypothesis has not yet been tested experimentally, but differential social impairment based on inheritance of the X chromosome seen in people with Turner's syndrome suggests that the hypothesis is reasonable. In females with Turner's syndrome, one of the X chromosomes is missing; females with Turner's syndrome have higher social functioning if the remaining X chromosome is inherited from the father rather than the mother, implying that there may be important genes regulating social behavior imprinted on paternally inherited on the X chromosome (Scourfield, McGruffin, & Thapar, 1997).

Since males can only inherit the X chromosome from their mothers, they may thus be at higher risk for autism and other disorders characterized by impaired social functioning.

Affective disorders. There is a significant genetic component to affective disorders, with a heritability of 30-40% for MDD, as evidenced by studies on relatives of MDD patients, as well as adoption and twin studies (Sullivan, Neale, & Kendler, 2000). Genetic studies also reveal that MDD is a complex disorder, in which environmental influences are as important, if not more important, than genetic predisposition (Sullivan et al., 2000). An interesting finding on the interaction of genes and environment in MDD is that the association between stressful life events, such as losses of jobs or relationships, and onset of a first major depressive episode is weaker in individuals with a high genetic risk for MDD than patients with a low genetic risk (Kendler et al., 2001). In another dramatic example of gene-environment interactions in depression, it was found that what allele an individual has for the promoter region of the serotonin transporter gene determines how vulnerable that person is to developing a mood disorder after stressful life events (Caspi et al., 2003). While the high comorbidity between MDD and dysthymia may call into question the validity of the clinical differentiation of these disorders, Donaldson and colleagues (1997) found that DD was more commonly diagnosed in relatives of individuals diagnosed with DD or 'double depression' than in relatives of MDD or controls; they hypothesized that there may be two genetic predispositions for depression, one which cuts across affective diagnoses and predisposes individuals to develop MDD, and another that predisposes individuals to develop DD.

Anxiety disorders. Genetic heritability is a risk factor in SAD; studies have found that SAD has a greater prevalence in relatives of patients with SAD than in relatives of

controls (Li, Chokka & Tibbo, 2001). This is reinforced by findings described above that social impairments related to those seen in autism are highly heritable, and could predispose an individual to SAD as well as to autism.

Neuroanatomical Abnormalities

No obvious neuroanatomical features, such as the amyloid plaques of Alzheimer's disease, have been associated with psychiatric disorders, numerous studies have reported subtle anatomical changes in these disorders. Brain imaging techniques such as magnetic resonance imaging (MRI) or positron emission tomography (PET) allow the study of size and activity of brain regions *in vivo*, while post-mortem analyses reveal other anatomical changes, included abnormalities in cellular morphology, that could be related to disease processes. Because various behavioral functions are mediated by neurons in particular brain regions, gross anatomical changes could indicate that some psychiatric symptoms could be due to changes of activity of these regions.

Schizophrenia. In the brains of individuals with schizophrenia, the lateral and third ventricles appear to be enlarged (Harrison, 1999). This ventricular enlargement may correspond to a loss of brain tissue volume, which has been noted in the hippocampus and amygdala (Nelson et al., 1998), cerebral cortex - especially the temporal lobe - and thalamus (Harrison, 1999). A reduction in the volume of gray matter in the temporal and prefrontal cortex of schizophrenic patients was found in another MRI study (Sanfilippo et al., 2000). Although prefrontal white matter volume was not reduced in the patients compared to controls, reductions in prefrontal white matter were associated with greater expression of negative symptoms. White matter reductions among patients with high levels of negative symptoms were most severe in the orbitofrontal region (Sanfilippo et al.,

2000). These results have been replicated by another MRI study of schizophrenic patients that found cortical thickness to be reduced in certain areas of the temporal and prefrontal cortex, including the orbitofrontal region (Kuperburg et al., 2003). Reduction in the volume of various regions of the brain is apparently due to shrinkage of neurons, rather than loss of neurons (Zaidel, Esiri & Harrison, 1997).

Along with changes in the volume of specific parts of the brain, alterations in regional cerebral blood flow (CBF) have been associated with schizophrenia, (see Liddle, 2000). CBF is a general index of activity in the brain, with greater blood flow related to more activity. Neuroimaging studies examining CBF in schizophrenic brains have found psychomotor poverty to be related to low CBF in the left lateral frontal cortex and the left inferior parietal lobe, which is part of the association cortex. Symptoms related to disorganization (cognitive deficits) have been associated with low CBF in the prefrontal cortex, insular cortex, and lateral parietal lobe, and with high CBF in the anterior cingulate, medial frontal cortex, and thalamus. Reality distortion in schizophrenia has been associated with increased CBF in the left medial temporal lobe and ventral striatum, and decreased CBF in the right posterior cingulate and left superior temporal gyrus. Liddle (2000) postulates that since the role of some regions of the brain is to limit activity in other parts, that the findings of increased activity in some areas may be caused by underactivity in other parts. Other neuroimaging studies, reviewed by Grady and Keightley (2002) have focused on dysfunctional social cognition. In various disorders in which social functioning is altered, including schizophrenia, autism, post-traumatic stress disorder, and depression, abnormal functioning in the amygdala and dorsal cingulate gyrus have been found. Schizophrenic patients show deficits in face-processing and

detection of emotional expressions, which is associated with hypoactivity in the amygdala and ventral lateral prefrontal cortex.

The implications of these findings on the etiology of schizophrenia is unclear. Decreased cortical volume and increased ventricular size are present at the onset of symptoms; this has been taken as evidence that the etiology of schizophrenia is neurodevelopmental, as opposed to neurodegenerative (Harrison, 1999). However, the relationship between neuroanatomical changes in schizophrenia and the abnormalities in neurotransmission, which have been the focus of most recent research (see below), is ambiguous. It may be that alterations in neurotransmission can alter the functioning of neurons such that the morphology of the neurons is affected. However, it may be that dysfunction in the neurons, or alteration in the cellular composition of brain tissue, can account for the abnormal neurotransmission (Harrison, 1999). Deficits in prefrontal volume or activity may be associated with problems in emotional, social, and executive functioning in schizophrenic patients, while abnormalities in the temporal lobe have been speculated to underlie problems in language abilities of schizophrenic patients (Kuperburg et al., 2003).

Autism. A number of neuroimaging and post-mortem studies have searched for abnormalities in brain structures or activity in autism. Despite some conflicting results, these studies have uncovered possible dysfunctions in various neural systems in autism. Structures that may be abnormal in autism include the cerebellum, frontal lobe, amygdala, and temporal lobe.

Although the cerebellum is usually considered to be involved only in motor coordination, recent research has attributed non-motor functions, including selective

attentive ability, to the cerebellum (Allen & Courchesne, 2003). Brains of autistic individuals examined after death nearly always show abnormalities in the cerebellum, especially reduced levels of Purkinje neurons (Allen & Courchesne, 2003). Carper and Courchesne (2000) found the volume of the cerebellum to be reduced in autistic patients compared to healthy controls.

The lack of social intelligence, which is central to autism, is believed to be related to abnormalities of limbic system and frontal lobe functioning. When judging a person's thoughts and feelings from their facial expressions, healthy control subjects show activation of temporal regions, the amygdala, and areas of the prefrontal cortex (Baron-Cohen et al., 1999). Subjects with high-functioning autism or Asperger syndrome displayed less activation of the prefrontal regions and the amygdala in this study (Baron-Cohen et al., 1999). Another magnetic resonance imaging study on individuals with autism or Asperger syndrome found no differences in the volume or metabolism of the hippocampus or amygdala compared to controls, but found that metabolism in the cingulate gyrus was reduced in autistic and Asperger syndrome patients (Haznedar et al., 2000). Reduced activation of frontal regions during a social judgement task was evident in a small sample of Asperger syndrome patients in a study by Oktem et al (2001). Regional cerebral blood flow (rCBF) was found to be reduced in the left prefrontal cortex in autistic patients in a study by Ohnishi et al. (2000). The deficit in rCBF seen in these patients correlated with the severity of impairments in communication and social interaction (Ohnishi et al., 2000). Ohnishi et al. also found decreased rCBF in the hippocampus and amygdala, which correlated with the degree of severity in obsessive symptoms in the autistic subjects. While the volume of the frontal lobe does not appear to

differ from controls in autistic individuals, the volume of the frontal lobe does correlate inversely with the volume of the cerebellum (Carper & Courchesne, 2000). Taken together, these findings strongly suggest that functioning of frontal lobe regions is disturbed in people with autism and closely related disorders, and that this dysfunction is related to the social and communicative impairments central to the autistic spectrum.

Abnormalities in the posterior regions of the brain have also been noted, though the significance of these findings is not yet clear. Reduced rCBF has been noted in the temporal lobe of autistic individuals, possibly explaining sensory deficits often seen in people with the disorder since the temporal lobe functions in processing sensory information (Zilbovicius et al., 2000). The posterior region of the corpus callosum has been found to be significantly smaller in autistic brains compared to healthy controls (Piven, Bailey, Ranson & Arndt, 1997). This finding seems to contradict earlier findings by the same team that found posterior lobes of the cerebral cortex to be enlarged in autism; they hypothesize that more neurons in posterior regions of the brain may lead to more competition for axonal survival, which favors ipsilateral connections over contralateral connections (Piven et al., 1997).

Affective disorders. Evidence for hippocampal abnormalities in mood disorders is mixed. Some studies, but not all, using magnetic resonance imaging (MRI) have found hippocampal volume to be reduced in MDD and BD (Harrison, 2002). Another study found that hippocampal mRNA for complexins, synaptic proteins, was reduced in schizophrenia and BD but not MDD, compared to controls (Eastwood & Harrison, 2000). Inconsistencies in studies on hippocampal atrophy in depression may be due to methodological flaws that do not account for mediating factors such as age, severity of

illness, and duration of illness (Davidson et al., 2002). These studies also do not allow conclusions to be made on whether hippocampal abnormalities are causal in depression or whether they are symptoms; the latter may be more likely, in light of evidence that glucocorticoids, which are elevated in depression, can cause hippocampal damage (Davidson et al., 2002).

Cerebral blood flow and glucose metabolism have been found to be elevated in the amygdala in MDD; increases in these variables correlate directly with severity of the illness (Davidson et al., 2002). The amygdala is part of a network of brain structures crucial to social cognition and emotional memory, and the increased activity seen in depression may reflect abnormal acquisition of and rumination on emotional or arousing memories (Davidson et al., 2002; Grady & Keightley, 2002). The amygdala may be enlarged in BD, possibly indicating overactivity in that illness as well (Baumann & Bogerts, 2001).

Two regions in the frontal lobe, the anterior cingulate cortex and the prefrontal cortex, exhibit abnormalities in patients with MDD and BD (Harrison, 2002). Lesions in the white matter of the frontal lobe have been found to be associated with affective disorders, especially BD (Bearden, Hoffman & Cannon, 2001). Various studies, reviewed by Harrison (2002), have also found that neuronal size is reduced in both the anterior cingulate and prefrontal cortex. Cerebral blood flow and glucose metabolism are also reduced in these regions in depression (Davidson et al., 2002). Frontal lobe activity is essential in regulating drive, sensory processing, motor control, and cognition; thus the abnormalities seen in frontal lobe regions in affective disorders may reflect the cognitive, attentional, and motivational deficits of depression (Davidson, 2002; Harrison, 2002).

Nestler et al. (2002) have hypothesized that the mesolimbic dopamine system, comprising of the nucleus accumbens and ventral tegmental area, is dysfunctional in depression. The mesolimbic dopamine system has been noted for mediating the rewarding effects of natural reinforcers, as well as recreational drugs; disruption of this pathway could be responsible for the anhedonia seen in affective disorders (Nestler et al., 2002). No research has been conducted to examine altered activity or size of the nucleus accumbens or ventral tegmental area in depression, though neurochemical studies (see below) have lent some support to this hypothesis.

Reductions in glial density in the prefrontal cortex have been found in BD, a characteristic of that illness which differentiates it from schizophrenia (Rajkowska, Halaris & Selemon, 2001). Decreased glial cell density has also been found in MDD (Davidson et al., 2002). These deficits suggest that affective disorders are not neurodegenerative, since glial cells usually proliferate in response to degenerative processes, but beyond this the pathological significance of glial deficits in depression is not clear (Harrison, 2002).

Future studies on neuroanatomical features of mood disorders should compare neuroanatomy in DD as well as MDD and BD. Few differences between BD and MDD have been found in neuroanatomical studies, suggesting that the clinical differences in these disorders may stem more from differences in neurochemical or hormonal systems.

Anxiety disorders. Relatively few neuroimaging studies have been done on SAD or GAD, and those that have been done have generated conflicting results. One area of the brain that has been consistently been implicated in the disorder is the amygdala. This part of the brain receives highly processed sensory information, and projects to

hypothalamic and brainstem regions that mediate the physiologic signs of fear and anxiety (Davis & Whalen, 2001). Electrical stimulation of the amygdala can elicit feelings of fear and anxiety, and lesions of the amygdala blunt emotional expression (Davis & Whalen, 2001).

The prefrontal cortex may be another region exhibiting abnormalities in anxiety disorders. Patients with SAD and patients with conditioned fears exhibited greater activity in the anterior cingulate cortex and dorsolateral prefrontal cortex than control subjects in a positron emission tomography study (Li, Chokka & Tibbo, 2001). This may reflect abnormal anticipation and evaluation of rewards and threats (Li, Chokka & Tibbo, 2001). Increased activity of the prefrontal cortex may also occur in GAD, possibly reflecting excessive worrying and planning about the future (Stein, Westenberg & Liebowitz, 2002).

Abnormal Neurotransmission

Schizophrenia. Speculation that the symptoms of schizophrenia may be due to imbalances of the chemical messengers in the brain became the predominant etiological theory after it was discovered that the effective antipsychotic medications had their effects through antagonism of dopamine receptors. Since these original findings, many studies have found evidence of underactivity or overactivity of several different neurotransmitters.

Discovery of the mechanism of neuroleptic activity, combined with evidence that dopamine agonists such as amphetamine can cause psychotic symptoms, led to a theory that schizophrenia was caused by overactivity of dopamine in the brain (Sawa & Snyder, 2002). This theory has proved to be overly simplistic for several reasons: studies

measuring plasma levels of dopamine metabolites have not found evidence for increased dopaminergic activity in the brains of schizophrenic patients; the negative symptoms of the disorder are often alleviated by drugs that increase dopaminergic activity; and many patients do not respond to the typical (dopamine-antagonizing) antipsychotics (Keefe & Harvey, 1994). One study did find that D₂ receptors were expressed more in the striatum of brains of schizophrenic patients than controls (Al-Amin & Weinberger, 2000). D₂ receptors are autoreceptors, and stimulation of these receptors may inhibit tyrosine hydroxylase, an enzyme involved in converting tyrosine to dopamine. The finding of elevated D₂ receptors has not been replicated when treatment with neuroleptics has been controlled for; thus it is believed that treatment with antipsychotics may upregulate expression of the D₂ receptor (Al-Amin & Weinberger, 2000). Another weakness of the dopamine hypothesis is that although antipsychotics block D₂ receptors immediately after administration, clinical effects are not seen for another two weeks (Al-Amin & Weinberger, 2000); thus the mechanism of neuroleptic activity may involve regulation of gene expression (Undie, 2000), as will be discussed below.

Nevertheless, substantial evidence exists that suggests a role of dopamine in schizophrenia. Dopamine in the prefrontal cortex appears to be important in cognitive functions (Brozoski et al, 1979) and working memory (Sawaguchi & Goldman-Rakic, 1991), both of which are affected in schizophrenia. Genetic studies have found that polymorphisms of the gene encoding for catechol-O-methyltransferase (COMT), an enzyme which degrades dopamine, are associated with susceptibility to schizophrenia; this was a sex-specific effect which estrogen is suspected to mediate, since estrogen downregulates COMT (Shifman et al, 2002). The results of another study on COMT

genotype suggests that a high-functioning allele of the gene, which would deplete dopamine, especially in the prefrontal cortex, is associated with schizophrenia (Egan et al., 2001). It has also been found that mRNA for two dopamine receptors, D₃ and D₄, are decreased in the prefrontal cortex of schizophrenic patients compared to healthy controls, supporting the hypothesis that prefrontal hypodopaminergia is responsible for some of the symptoms of the disorder (Meador-Woodruff et al., 1997).

Jentsch and Roth (2000), clarified the contradiction between dopamine antagonists and agonists both having beneficial and detrimental effects on schizophrenic patients. The primary two dopaminergic pathways in the brain originate in the ventral mesencephalon. One pathway innervates the forebrain, and the other innervates subcortical structures, especially those structures in the limbic system. The mesocortical dopaminergic system utilizes D₁ receptors, while the mesolimbic dopaminergic system is based on D₂ receptors. Typical antipsychotics may antagonize the D₂ autoreceptors, leading to increased dopaminergic activity in the prefrontal cortex and thus clinical improvement. Atypical antipsychotics may agonize D₁ receptors, thus increasing dopaminergic activity in the prefrontal cortex. If these hypotheses are substantiated by further studies, it would suggest that schizophrenia involves decreased dopaminergic activity in cortical areas, especially the prefrontal cortex where executive cognitive functions are seated.

Evidence from various studies has been accumulating which suggests that abnormalities in the glutaminergic systems in the brain are associated with schizophrenia. Specifically, the ionotropic glutamate receptors - NMDA, AMPA and kainate - may be altered (Goff & Coyle, 2001). Decreased AMPA and kainate receptor binding has been

noted in the hippocampus of schizophrenic patients (Goff & Coyle, 2001). Others studies have found that the concentration of N-acetyl-aspartyl glutamate (NAAG), an NMDA receptor antagonist, is increased in the hippocampus of schizophrenic patients; correspondingly, the activity of glutamate carboxypeptidase II, an enzyme that cleaves NAAG into glutamate and another molecule, is decreased in the frontal cortex, temporal cortex, and hippocampus (Goff & Coyle, 2001). An enzyme which converts glutamate to (-aminobutyric acid (GABA), glutamic acid decarboxylase, has been found to be more active in the brains of schizophrenic patients (Gluck, Thomas, Davis, & Haroutunian, 2002). The NMDA receptors are activated by the amino acids glycine and D-serine, as well as by the artificial cycloserine; administration of these compounds to schizophrenic patients in preclinical trials has suggested that they may have some clinical benefit (Sawa & Snyder, 2002). However, the clinical benefits of glutamate agonizing drugs may only be for negative symptoms, and may actually aggravate positive symptoms (Deakin, 2000).

Additional evidence for the involvement of NMDA receptors comes from studies on the effects of phencyclidine (PCP) and ketamine, which are both NMDA antagonists. Both drugs can cause symptoms resembling features of schizophrenia, including social withdrawal, delusions, hallucinations, paranoia, affective blunting, and cognitive impairments (Anand et al., 2000; Jentsch, Redmond, Elsworth, Taylor, Yougren, & Roth, 1997). Jentsch et al (1997) administered PCP to monkeys repeatedly, over a course of 14 days. These monkeys displayed deficits in performance of a cognitive task that were present even four weeks after cessation of treatment, but which could be ameliorated by

treatment with clozapine, an atypical antipsychotic medication. This chronic treatment with PCP decreased dopamine utilization in the dorsolateral prefrontal cortex.

One shortcoming of the glutamate hypothesis is that NMDA receptor density does not appear to be aberrant in schizophrenia; other evidence, however, suggests that the subunit composition of NMDA receptors may be altered (Goff & Coyle, 2001). Mohn et al. (1999) studied this hypothesis. NMDA receptors are composed of two subunits, an NR1 subunit, and an NR2 subunit, of which there are four varieties. Mice with the gene for the NR1 subunit knocked out completely die perinatally, but Mohn et al. discovered that transgenic mice designed to express only 5 % of the normal levels of NR1 can survive into adulthood, despite reduced glutamatergic activity. These NR1 mutants show increased motor and stereotypic activity, which were reduced by administration of the antipsychotic drugs haloperidol and clozapine. The NR1 mutant mice also exhibited social withdrawal; they did not sleep with littermates and would not approach new mice introduced to their cages. Administration of the NMDA antagonists PCP and MK-801 did not have any effect on the transgenic mice.

Although these studies suggest hypoactivity of glutamate to be responsible for symptoms of schizophrenia, other evidence suggests that a hypoglutamatergic hypothesis may be overly simplistic. NMDA receptors occur on GABAergic neurons as well as glutamatergic neurons, providing a mechanism by which hyperglutamatergic activity could increase inhibition of various brain functions (Deakin, 2000). The same study that found increased activity of glutamic acid decarboxylase in the brains of schizophrenic patients also found that the activity of phosphate-activated glutaminase, which converts glutamine to glutamate, is increased in the dorsolateral prefrontal cortex, suggesting high

glutamate metabolism in general as pathological in schizophrenia (Gluck et al., 2002). Although ketamine antagonizes NMDA receptors, it has been found that its effects can be reversed by administration of Lamotrigine, which blocks the sodium channels associated with NMDA receptors and decreases glutamate release (Anand, Charney, Oren, Berman, Hu, Cappiello, & Krystal, 2000). It has been found that infusion of NMDA into the ventral, but not dorsal, hippocampus disrupts pre-pulse inhibition (PPI, a behavioral marker of schizophrenia) and increases locomotor activity (Zhang, Bast, & Feldon, 2002). Since evidence for abnormal concentration of glutamate in schizophrenic brains is questionable, it has been suggested that the effect on schizophrenic symptoms by aberrant glutamatergic functioning may be mediated by disturbed cortical wiring rather than neurochemical imbalances (Deakin, 2000). For instance, the increased locomotor results of the Zhang et al study (2002) may have been due to increased mesolimbic dopaminergic activity caused by excitation of glutamatergic projections from the ventral hippocampus to the nucleus accumbens.

The role of GABA, which usually functions as an inhibitory agent in the central nervous system, has also been investigated in schizophrenia research. Complementing previous findings on the effects of NMDA infusion in the ventral hippocampus (Zhang, Bast & Feldon, 2002), Bast et al. (2001) found that administration of the GABA_A receptor antagonist picrotoxin in the ventral hippocampus caused hyperactivity and PPI disruption in mice. GABA receptors also influence dopaminergic activity; GABAergic drugs can have either an excitatory or inhibitory effect, depending on the ratio of GABA_A and GABA_B receptors present (Wassef, 2000). Muscimol, a GABA agonist, has

hallucinogenic effects and may cause clinical deterioration in schizophrenic patients (Wassef, 2000).

Another neurotransmitter system which may be affected in schizophrenia is serotonin (5-HT). Interest in this neurotransmitter was stimulated first by research on lysergic acid diethylamide (LSD), which agonizes 5-HT_{1A} receptors in the Raphe nuclei and causes hallucinations, perceptual distortions, and a dissociated sense of self (Abi-Dargham & Krystal, 2000). However, interest waned when it was found that LSD-induced psychosis did not closely resemble schizophrenia. More recent interest in the role of serotonin in the disease has stemmed from the finding that atypical antipsychotics, which are much more effective in treating the negative symptoms than typical antipsychotics, tend to have high affinity for serotonin receptors (Sawa & Snyder, 2002). Direct evidence that serotonin may have a role in schizophrenia comes from findings that 5-HT_{1A} receptors are increased, and 5-HT_{2A} receptors are decreased, in the dorsolateral prefrontal cortex of brains of schizophrenic patients (Burnet et al, 1996). Since 5-HT_{1A} receptors are inhibitory in the neocortex, and 5-HT_{2A} receptors when expressed on pyramidal cells are excitatory, it has been speculated that the imbalance in these receptors in the prefrontal cortex may impair integration of frontal cortex activity with activity elsewhere in the brain (Burnet et al, 1996). The 5-HT_{2C} receptor has also been examined in schizophrenia. The mRNA transcribed for this receptor is edited by adenosine deaminases, producing heterogeneity in the structure of these receptors; this RNA editing has been found to be deficient in schizophrenia (Sodhi et al., 2001).

The final two neurotransmitter systems which may be afflicted in schizophrenia are the sigma (Φ) receptors and adrenergic system. The case for the former is built

largely on the fact that Φ -receptor agonists - including cocaine - often have effects partially resembling psychosis, and that most neuroleptics have a high antagonistic affinity for these receptors (Frieboes, 2000). Sigma receptors are found in some of the brain structures which show abnormalities in the disease, including the hippocampus, amygdala and nucleus accumbens (Frieboes, 2000). These receptors also appear to interact with other neurotransmitter systems, including the dopaminergic and glutamatergic systems (Frieboes, 2000). Since the endogenous ligand for Φ receptors has yet to be found, research is currently limited on the role this system plays in schizophrenia.

Evidence supporting a role of adrenergic receptors in schizophrenia is also based on drug activities. Many atypical antipsychotic drugs have antagonistic activity at \forall -1 adrenoceptors, and stimulation of these receptors can impair cognitive functions of the prefrontal cortex (Arnsten, 2000). The \forall -1 adrenergic antagonist prazosin has been reported to block the effects of PCP on PPI (Goff & Coyle, 2001). Interestingly, \forall -1 adrenoceptors are engaged by norepinephrine, which is released at high levels during stress (Arnsten, 2000), which may be a mechanism by which stressful situations can increase the chance of psychotic relapse in schizophrenic patients (Keefe & Harvey, 1994). There is some debate about the role of \forall -2 adrenoceptors in schizophrenia. Although it has been found the \forall -2 adrenergic antagonist idazoxan enhanced antipsychotic effects and increased cortical dopamine release when administered as a supplement to the antipsychotic raclopride (Hertel et al, 1999), it has been suggested elsewhere that \forall -2 adrenergic agonists may improve prefrontal cortical functions (Arnsten, 2000).

Autism. Studies on how neurotransmitter systems are impacted in autism have not been as fruitful in determining the etiology of the disorder as for other disorders, but there have been some important findings. Evidence has been found suggesting roles of serotonin (5-HT) and (-aminobutyric acid (GABA) in autism. Several other systems have also been examined.

Serotonin is involved in the regulation of affiliation, aggression, mood, and obsessive behaviors, all of which tend to be abnormal in autism (Klauck et al., 1997). Levels of plasma 5-HT have been found to be elevated in some autistic patients, and abnormally low in others, depending on co-morbid conditions such as tuberous sclerosis or hypothyroidism (Gillberg & Coleman, 2000). Other evidence for a role of 5-HT in autism comes from clinical trials of drugs that block 5-HT reuptake, such as clomipramine or fluoxetine, which have been shown to reduce obsessive-compulsive symptoms, stereotypies and hyperactivity in autistic patients (Tsai, 1999). The relationship between serotonergic related genotypes and autism has been investigated, and it has been found that autism is associated with higher frequency of an allele in the transcriptional control region for the serotonin transporter protein than healthy controls (Klauck et al., 1997). However, these results were in complete contrast to earlier studies on the same alleles, suggesting either heterogeneity in the disorder or methodological difficulties (Klauck et al., 1997). Another study failed to find differences between autistic individuals and healthy controls in binding site densities for 5-HT_{1A} and 5-HT₂ receptors in the hippocampus (Blatt et al., 2001). These results suggest that abnormalities of serotonergic activity in autism, if they exist, may be related to only a subset of symptoms or be evident only in a subset of patients.

GABA is considered to be the most important inhibitory neurotransmitter in the central nervous system, and gene knockout studies suggest that seizure disorders may be related to decreased GABA receptor functioning (Simeone, Donevan & Rho, 2003). The common comorbidity of epilepsy in autistic individuals thus suggests that GABA dysfunction may occur in autism. Reduced density of GABA_A binding sites have been found in the hippocampus of autistic individuals, which may decrease the threshold for seizures in the disorder (Blatt et al., 2001). Another study found that enhancing GABAergic functioning by supplementation with the neuropeptide carnosine (which modulates diffusion of metal ions crucial for functioning of GABA receptors) improved speech and social behavior in autistic children (Chez et al., 2002). Genetic linkage studies have found an association between a cluster of genes coding for GABA_A receptor subunits on chromosome 15 and autism, though this finding has not always been replicated (Lamb et al., 2000). Though more research is needed on the subject, it appears that hypoactivity of GABA may underlie some symptoms of autism, seizures in particular.

A hypothesis that dopaminergic hyperactivity may be involved in autism has been proposed based on evidence from drug treatment trials (Tsai, 1999). Dopamine agonists tend to aggravate some autistic symptoms, such as stereotypies and aggression, while anti-psychotic medications used to treat schizophrenia, which are generally dopamine antagonists, have been found to alleviate various symptoms, such as social withdrawal and stereotypies, of autistic individuals (Tsai, 1999). Abnormalities in the activity of acetylcholine in the brain has also been tested in autistic patients, based on evidence that disruption of cholinergic innervation of cortical areas during early development can cause

profound cognitive impairments (Perry et al., 2001). Binding to muscarinic cholinergic receptors in the parietal cortex was found to be significantly reduced in autistic patients compared to healthy controls, and binding to nicotinic receptors was significantly reduced in both the parietal and frontal cortices of the same individuals (Perry et al., 2001). The authors of the study hypothesized that the abnormalities they found in the cholinergic system may be related to epilepsy and reduced pain sensitivity seen in many autistic individuals (Perry et al., 2001). Further research is necessary to clarify if and how the cholinergic and dopaminergic systems are abnormal in autism.

Affective disorders. Evidence has been accumulating suggesting there are dysfunctions in several neurotransmitter systems in mood disorders, particularly serotonin (5-HT) and norepinephrine (NE). Early studies focused on deficits in serotonin in depression; Asberg et al. (1976), for example, found that the concentration of 5-hydroxyindoleacetic acid, a 5-HT metabolite, correlated with severity of depression in a subset of depressed patients. Decreased concentration of 5-HT metabolites has consistently been found to be a biological marker for suicide (Maris, 2002). Gene knockout studies have substantiated the role of serotonin abnormalities in depression. Mice lacking the 5-HT_{1A} receptor gene seem to be protected against depression-like behavior in a hopelessness test (Heisler et al., 1998). Since this receptor is an autoreceptor for 5-HT in the cerebral cortex, amygdala and hippocampus, suppression of the 5-HT_{1A}-R gene increases serotonergic activity (Heisler et al, 1998). Likewise, the most frequently prescribed medications for MDD and DD are the serotonin specific re-uptake inhibitors (SSRI's), which increase serotonergic activity by preventing the re-uptake of 5-HT from the synaptic cleft; these drugs have been shown to be effective in

improving mood in depressed individuals (Ables & Baughman, 2003). SSRI's are not usually the primary medication used to treat BD, but they have been effective in improving mood during depressed phases of patients with that disorder (Muller-Oerlinghausen et al., 2002). Despite findings such as these, attempts to link polymorphisms in genes for 5-HT receptors to affective disorders have usually not found any significant relationships (Oliveira et al., 2000; Vincent et al., 1999).

While serotonergic drugs tend to effectively improve mood, noradrenergic drugs have been more successful in countering the amotivational symptoms of affective disorders (Schramm, McDonald, & Limbird, 2001). Norepinephrine is released in response to stress, causing general physiological arousal; because depression has been hypothesized to be a state of chronic hyperarousal, hypernoradrenergic activity has been implicated in affective disorders (Wong et al., 2000). The hypernoradrenergic hypothesis has been supported by findings that levels of NE in the cerebrospinal fluid are significantly higher in depressed patients than controls, even during sleep (Wong et al., 2000). Even a single exposure to inescapable shock can result in elevated levels of NE metabolites in rats in reaction to exposure to a neutral stimulus that was paired with the shock; this effect can be seen several days after the exposure (Cassens et al., 1980). Furthermore, it has been found that rats exposed to chronic stressors exhibited greater increases in NE in response to a novel stressor compared to controls (Nisenbaum et al., 1991). These studies suggest that the noradrenergic system may mediate the effect of stress on precipitating depression. Mice with the gene for α_{2A} -adrenergic receptors knocked out displayed less mobility in the swim test, which is considered an animal model of depression (Schramm, McDonald, & Limbird, 2001). Since this gene expresses

an autoreceptor that inhibits NE release and mediates sedative and analgesic effects (Kable, Murrin, & Bylund, 2000), these findings further support the hypernoradrenergic hypothesis for depression.

An older hypothesis, advanced in the 1960's, proposed that depression was associated with decreased levels of norepinephrine (Nemeroff, 1998). One study purporting to support this alternative hypothesis found lower levels of binding to NE transporter (NET), a membrane protein that functions in terminating synaptic activity of NE, in MDD patients (Klimek et al., 1997). The authors suggested that since reduced levels of NE down-regulate NET, that their findings support the hyponoradrenergic hypothesis; however, if the lower levels of NET binding observed were due to the pathology of depression instead of reduced NE, the results would further support the hypernoradrenergic theory. Another study found that mice with the NET gene knocked out did not differ from wild-type mice in behavior after chronic stress, but showed less depressive behavior after a novel stressor (Haller et al., 2002). These results parallel those of Nisembaum et al., summarized above. It has been hypothesized that down-regulation of noradrenergic receptors occurs as an adaptation to chronic stress, and that appropriate responses to novel stressors would thus require excessive NE release (Nisembaum et al., 1991). Since NET-knock-out mice have elevated levels of NE regardless of stress, this may have desensitized post-synaptic NE receptors, and led to a blunting of the response to a novel stressor in Haller and colleagues' study.

Decreased dopaminergic transmission has also been hypothesized to have a role in depression, possibly via the mesolimbic reward system (Nestler et al., 2002). The dopaminergic and serotonergic systems interact closely with each other, especially in

cortical and limbic areas; thus disturbances in the dopaminergic system may complement the abnormalities in serotonergic activity described above (Renard et al., 2001). It has been found that augmenting antidepressant treatments with antagonists of dopamine autoreceptors increases the antidepressant effect of treatment (Renard et al., 2001).

Several lines of evidence suggest that abnormal levels of norepinephrine, serotonin, dopamine, and receptors for these neurotransmitters are not central to the pathophysiology of affective disorders. As mentioned above, attempts to link genes related to serotonin to depression have generally failed. Also, whereas antidepressant drugs have nearly immediate pharmacological effects, clinical improvement typically does not occur for at least a week after treatment has begun, suggesting that slower processes, such as altered gene expression (see below), mediate improvement (Gould & Manji, 2002). Also, antidepressants do not improve symptoms in many patients, suggesting that correcting neurotransmitter imbalances does not necessarily lead to clinical improvement.

Anxiety disorders. Research on neurotransmitter abnormalities in patients with anxiety disorders has generated some conflicting results, but has also uncovered some promising leads. Evidence is accumulating that demonstrates roles of serotonin (5-HT) and dopamine (DA) in the pathophysiology of anxiety disorders. Less substantiated theories have proposed that there may be abnormalities in noradrenergic and (-aminobutyric acid (GABA) neurotransmission.

The serotonin specific reuptake inhibitors (SSRIs), which have become the most common treatment for depression, have also been shown to be effective in treating both SAD (Stein et al., 2001) and GAD (Sramek, Zarotsky & Cutler, 2002). Treatment with

SSRIs may alleviate one the major characteristics of SAD, avoidance of social situations; one study found that subjects exhibited more social affiliative behavior after several weeks of SSRI treatment (Knutson et al., 1998). These findings have led to the hypothesis that abnormal serotonergic activity may characterize anxiety disorders. One replicated finding is that the 5-HT_{1A} autoreceptor, which modulates serotonergic activity, regulates behaviors related to anxiety (Parks et al., 1998). Mice deficient in the 5-HT_{1A} receptor show decreased exploratory behavior and increased avoidance of novel or stressful situations, behaviors that model anxiety in humans (Parks et al., 1998; Heisler et al., 1998; Ramboz et al., 1998). Polymorphisms in a regulatory region of the gene for the serotonin transporter have been found to account for some of the heritability of anxiety-related personality traits (Lesch et al., 1996). These polymorphisms have also been found to be associated with variation in activation of the amygdala in response to fearful stimuli (Hariri et al., 2002). 5-HT may also mediate the effect of substance P on mood and anxiety; mice deficient in the receptor for substance P, neurokinin receptor-1, displayed less anxiety-like behavior which was coupled to enhance serotonergic firing (Santarelli et al., 2001).

Another hypothesis on the neurobiology of SAD holds that the neural substrates which link social recognition with reward systems in the brain are abnormal (Mathew, Coplan & Gorman, 2001). Since the mesolimbic projections of the ventral tegmental area have been found to act as the reward system in the brain, and since this system utilizes dopaminergic transmission, altered dopaminergic activity has been suspected as having a role in anxiety disorders (Mathew, Coplan & Gorman, 2001). Tiihonen and colleagues (1997) examined this hypothesis and found that the density of striatal dopaminergic

reuptake sites was lower in patients with social phobia. They hypothesized that this was due to reduced dopaminergic synapses in patients with SAD (Tiihonen et al., 1997). Another study on patients with SAD found that there was less D₂ receptor binding in the striatum compared to controls (Schneier et al., 2000). A more general role of D₄ receptors in mediating anxiety responses to unconditioned stimuli was found by Falzone et al. (2002); mice with the gene for the D₄ receptor knocked out showed greater anxiety responses to unconditioned stimuli - the open arms of the elevated plus maze - than wild-type mice. The greater anxiety response was reversed by treatment with the anxiolytic agents benzodiazepines and ethanol. Evidence against a role of abnormal dopaminergic activity in anxiety includes the difficulty replicating the above findings and the general failure of dopaminergic medications to have an effect on SAD (Li, Chokka & Tibbo, 2001).

Since the symptoms of anxiety often resemble autonomic hyperarousal, abnormalities in noradrenergic functioning have been investigated as a possible etiological factor in anxiety, due to the role of NE in regulating the hypothalamic-pituitary-adrenal (HPA) axis (Mathew, Coplan & Gorman, 2001). Although some studies have found evidence of NE hyperactivity in anxiety, other studies have generated conflicting results, making the exact role of NE in anxiety unclear (Li, Chokka & Tibbo, 2001). Drugs that block β -adrenergic receptors have some benefit in treating symptoms of performance anxiety, including tremors, dizziness and sweating, these drugs do not appear to have any long term benefit for patients with anxiety disorders (Li, Chokka & Tibbo, 2001).

Observations that patients with GAD and SAD respond favorably to ethanol and benzodiazepines has led to a hypothesis that GABA dysfunction may be involved in anxiety (Li, Chokka & Tibbo, 2001). It has been suggested that genetic differences in GABAergic tone in the amygdala may predispose individuals towards dysfunctional responses to stress or anxiety (Davis & Whalen, 2001). However, little research has been carried out to fully investigate the role of GABA in the pathology of anxiety disorders.

Abnormalities in Intracellular Signaling Pathways

Communication between cells is not achieved by neurotransmitters and receptors alone. Activation of receptors has many downstream effects inside the cell, such as the activation of second messengers and phosphorylation cascades; these intracellular signaling pathways, in turn, affect neurotransmitter release, and can alter gene transcription. Because abnormalities in these cellular events are likely to result in abnormal communication between neurons and thus alter behavior, intracellular signaling has been another focus of investigation in the neurobiology of psychiatric disorders. As a relatively new area of investigation, abnormal signaling has been examined primarily in schizophrenia and depression.

Schizophrenia. Undie (2000) reviewed some of the findings on abnormal cellular signaling in schizophrenia, which include: altered phospholipase C and intracellular calcium release; altered responsiveness of adenylate cyclase - especially in patients with negative symptoms; and higher levels of cyclic-AMP dependant protein kinase A. Additionally, it has been found that administration of adenylate cyclase activators elevated mood in some patients, that administration of amphetamines in rats produced

prolonged activation of protein kinase C in cortical regions, and that antipsychotics modulate activity of several protein kinases (Undie, 2000).

One signaling molecule which has received much attention is retinoic acid (Vitamin A). Retinoids are essential nutrients which play a large role in regulating gene expression, especially in embryonic brain development (Goodman, 1998). Mice with the gene for retinoic acid receptors deleted can survive to adulthood, but exhibit locomotive impairment, and reduced striatal expression of D1 and D2 dopamine receptors (Krezel et al, 1998). Abnormal levels of retinoids - either toxicity or deficits - can result in symptoms resembling those of schizophrenia, including thought disorder, mental deficit and enlarged ventricles (Goodman, 1998). Also, several genetic loci linked to schizophrenia involve genes that play roles in retinoid signaling or metabolism (Goodman, 1998).

The effectiveness of some antipsychotic medications may be, in part, due to their effects on gene expression, which is mediated by intracellular signaling pathways. For instance, the antipsychotic haloperidol is known to increase the expression of certain genes such as neurotensin; this effect is not seen when the drug is administered to mice deficient in protein kinase A (Adams, Brandon, Chartoff, Idzerda, Dorsa, & McKnight, 1997). There is also some evidence that typical and atypical antipsychotics may differ in their patterns of gene expression modulation, perhaps explaining the discrepancies in clinical benefit between those groups (Undie, 2000). The expression of dozens of different genes appears to be altered in schizophrenia (Hakak et al, 2001), providing further evidence that the mechanisms which regulate gene expression may be altered in schizophrenia.

Affective disorders. The delay between start of drug treatment of depression and clinical improvement suggests that antidepressants do not improve symptoms via their direct effects on neurotransmitter systems, but rather through indirect effects on slower processes in the brain. Intracellular signaling pathways may mediate such indirect effects, since these pathways regulate gene transcription and mediate the slower adaptations of neurons to their environment. Research on the activity of these signaling networks in depressed patients has revealed another dimension to the pathophysiology of mood disorders.

GTP-binding proteins (G proteins) are receptor coupled proteins that are responsible for transducing over 80% of extracellular signals to intracellular signaling pathways (Gould & Manji, 2002). There is a great diversity in these proteins, both in the type of receptors they are coupled with and the subunit composition of the proteins (Gould & Manji, 2002). Postmortem studies on BD patients have found that the concentration of one G protein that activates adenylate cyclase, $G_{\alpha s}$, is increased compared to healthy controls (Gould & Manji, 2002). Further evidence that abnormalities in G proteins are involved in BD comes from findings that lithium and antidepressants can affect the subunit composition of such proteins (Gould & Manji, 2002). Such abnormalities may be specific to BD, since similar studies in MDD patients have generated conflicting results. Gene linkage and mRNA studies have generally not found any mutations in G protein genes or abnormal levels of G protein mRNA associated with BD, so observed alterations in G protein activity may be due to downstream effects of other signaling abnormalities (Bezchlibnyk & Young, 2002).

One of the most important intracellular signaling pathways, which may be abnormal in mood disorders, is the adenylate cyclase pathway. In this pathway, activated receptors cause G proteins to activate or inhibit adenylate cyclase, which converts adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP); cAMP activates protein kinase A and cAMP response element binding protein (CREB), which regulate transcription factors, cytoskeletal proteins, enzymes, and other cellular proteins (Gould & Manji, 2002). Adenylate cyclase activity appears to be decreased in unipolar depression (Gould & Manji, 2002). In BD, responsiveness of adenylate cyclase to stimulation of β -adrenergic receptors is blunted (Bezchlibnyk & Young, 2002). Decreased activity of adenylate cyclase may be a trait marker in BD (Gould & Manji, 2002). Lithium treatment appears to increase baseline adenylate cyclase activity, but attenuates receptor-mediated activation of the enzyme (Gould & Manji, 2002). Long-term treatment with antidepressants increases CREB mRNA and protein, increases levels of brain-derived neurotrophic factor (BDNF), and increases activity of protein kinase A (Gould & Manji, 2002).

A second major signaling pathway affected in mood disorders is the phosphatidylinositol (PI) pathway. In this system, G protein-linked signal transduction causes a cell membrane component, phosphoinositide 4,5-biphosphate (PIP₂), to be broken down to diacylglycerol (DAG) and inositol-1,4,5-triphosphate (IP₃), both of which act as second messengers (Gould & Manji, 2002). DAG activates protein kinase C, which is active in a number of cellular processes, including cell growth, cell proliferation, gene expression, and neuronal plasticity (Gould & Manji, 2002). IP₃ regulates calcium release; calcium-activated proteins play a role in activating ion channels, signaling

molecules, transcription factors, and other important proteins (Gould & Manji, 2002). Hyperactivity of protein kinase C has been noted in BD; furthermore, it appears that this increased activity is linked to the manic state, since hyperactivity of the enzyme is not noted during depressive phases of the illness or after successful treatment with lithium (Hahn & Friedman, 1999). Increased activity of protein kinase C has been found to desensitize the α -_{2A} adrenergic autoreceptors, linking findings of abnormal cell signaling to the hypernoradrenergic hypothesis (Laing et al., 1998). General PI pathway hyperactivity has been implicated in BD, since it has been found that levels of PIP2 are elevated in BD patients (Bezchlibnyk & Young, 2002). Baseline concentrations of calcium ions have also been noted in BD patients, both in the manic and depressive phases (Bezchlibnyk & Young, 2002).

Endocrine and Immunological Abnormalities

The central nervous system influences the functioning of all organ systems in the body, and receives feedback from these systems to optimize the functioning of the organism. An essential component of this control is communication between the brain and other parts of the body, accomplished in part by the peripheral nervous system, but also dependent on hormones, signaling molecules which travel long distances in the body and act more slowly. Communication between the nervous system and the immune system is another crucial component of the brain's influence over other body systems. The prominence of psychosomatic symptoms such as changes in eating or sleeping behavior in psychiatric disorders suggests that disturbances in the communication between the nervous, endocrine and immune systems may be a central part of the physiology of these disorders. Since many hormones are synthesized from lipids,

abnormal lipid metabolism has also been examined in mental illness. Abnormal hormonal responses to stress are suggested to underlie the symptoms of depression and anxiety, while immunological abnormalities may influence the neurological abnormalities in autism.

Affective disorders. In accordance with the hypernoradrenergic hypothesis, which postulates that depression is a state of chronic hyperarousal, recent research suggests that depression may be associated with abnormal activity of the hypothalamus-pituitary-adrenal (HPA) axis, which mediates the body's physiological response to stress (Dinan, 1994). Disturbances in HPA activity may mediate the changes in the immune system which also occur in depression (Anisman, Ravindran, Griffiths & Merali, 1999). Abnormalities in thyroid hormones may also be involved in depression (Bauer, Heinz & Whybrow, 2002).

Activation of the HPA axis is the body's primary endocrine response to stress. This activation begins with the release of corticotropin-releasing hormone (CRH) from the paraventricular nucleus of the hypothalamus; CRH then causes adrenocorticotropin (ACTH) to be released from the pituitary gland. ACTH then stimulates the adrenal glands to release glucocorticoids, of which cortisol is the most important (Dinan, 1994). The influence of these hormones on mood is demonstrated in Cushing's syndrome, which is characterized by excessive levels of cortisol; patients with this disorder often show behavioral and emotional symptoms resembling depression, such as insomnia, fatigue, and lack of concentration (Dinan, 1994). CRH administered to monkeys intracerebroventricularly caused an increase in glucose metabolism in the hippocampus and amygdala and increased depressive behavior; however, this effect was seen only in

socially housed animals, and not in individually housed monkeys (Strome et al., 2002). In depressed patients, the release of ACTH in response to CRH infusion is blunted, possibly because CRH levels are elevated and CRH receptors on the anterior pituitary are accordingly down-regulated (Dinan, 1994). However, the relative balance of these hormones may be different between MDD and DD, and between patients who exhibit typical and atypical symptoms. Anisman and colleagues (1999) found that ACTH was elevated only in patients with atypical MDD, and that cortisol levels were not elevated in DD or atypical MDD.

Abnormal activity of CRH in affective disorders may be linked to abnormalities in the serotonergic and noradrenergic systems, since these neurotransmitters mediate the release of CRH in the hypothalamus (Dinan, 1994). Additionally, glucocorticoids can mediate the excitatory effect of NE and 5-HT on the paraventricular nucleus, enhancing release of CRH (de Kloet, Vreugdenhil, Oitzl & Joels, 1998). Thus it is unclear whether hormonal or neurotransmitter abnormalities are primary to the pathophysiology of depression, since the systems are linked in a feedback loop.

Lipid metabolism has been examined as a biological marker of depression, since metabolic pathways may be affected by neural, hormonal, or immunological signaling, and products of lipid metabolism may be involved in various forms of cellular signaling. In depression, lipid levels may be decreased. For instance, in a study that compared suicidal and non-suicidal psychiatric patients with health controls matched for body mass index, suicidal patients with MDD had significantly reduced serum cholesterol, triglyceride, and lipoprotein levels (Lee & Kim, 2003). The link between lipid metabolism and depression may be that serotonergic activity influences release of the

hormone leptin, which increases serum levels of triglycerides, cholesterol, and other lipids, and may regulate eating, sex and locomotor behavior. Levels of cholesterol and leptin are decreased in the serum of patients with BD, whether in a manic phase or in remission (Atmaca et al., 2002).

In MDD, certain elements of the immune system are suppressed, including proliferation of lymphatic cells and activity of natural killer cells (Maes, 1995). But there are also signs of increased immune system activity in MDD, especially among immunological molecules mediating inflammatory responses. Maes and colleagues (1995) monitored plasma levels of interleukins, which act as signaling molecules in the immune system, in MDD patients. They found that concentrations of interleukin-6, soluble interleukin-6 receptor, and soluble interleukin-2 receptor were elevated in MDD compared to controls. These elevated concentrations were present during acute phases of the illness and during remission, and were not mitigated by antidepressant treatment, suggesting that these abnormal concentrations are trait markers for depression.

Concentrations of interleukins may differentiate MDD and DD. Anisman et al. (1999) found that production of interleukin-2 was reduced in DD patients and atypical MDD patients, but not typical MDD patients; also, production of interleukin-2 was found to be correlated with levels of NE in depressed patients, but not controls. Furthermore, they found that levels of interleukin-1 β , a pro-inflammatory cytokine, were elevated in DD patients but not MDD. Administration of interleukin-1 β has been found to increase plasma ACTH concentration and NE utilization in mice (Lacosta, Merali, & Anisman, 1998), again linking NE overactivity to hormonal change, since NE activation of the paraventricular nucleus enhances CRH release. In a similar study using rats, chronic

administration of interleukin-1 β increased latency of escape in response to foot shock, an animal model of depression; thus chronic inflammatory states may be associated with depression (Bonaccorso, Maier, Meltzer, & Maes, 2003).

A role of thyroid hormones in regulating mood is suggested by observations that disorders of the thyroid gland often are associated with mental disturbances (Bauer, Heinz, & Whybrow, 2002). Thyroid hormones probably have a role in regulating serotonergic and noradrenergic neurotransmission. Hypothyroid rats have been found to have increased activation of 5-HT_{1A} autoreceptors in the brainstem, which decreases overall serotonergic transmission to cortical areas (Bauer et al., 2002). This deficiency in serotonergic transmission can be corrected by administration of the thyroid hormone T3 (Bauer et al., 2002). T3 thyroid hormone receptors are found in high concentrations in the nuclei and projection sites of the noradrenergic system, suggesting another mechanism by which the thyroid hormones may regulate mood (Bauer et al., 2002).

Anxiety disorders. Gene knockout studies have shown that corticotropin releasing hormone (CRH), which instigates HPA activation, may mediate anxiety behavior. The CRH receptor-1 is highly expressed in the pituitary gland, hippocampus, neocortex, and amygdala; mice deficient in this receptor demonstrated no morphological differences from wild-type mice in these areas (Timpl et al., 1998). However, the adrenal medulla was reduced in size in these mutants, and they showed less anxiety behavior in the open field and light-dark tests (Timpl et al., 1998). These mice had similar basal levels of adrenocorticotrophic hormone (ACTH) compared to wild-type mice, but the increase in ACTH after a forced swim test was blunted in the mutants (Timpl et al., 1998). CRH binding protein is another molecule that regulates HPA activation, by degrading CRH

and blocking ACTH secretion (Karolyi et al., 1999). Mice deficient in the gene for CRH binding protein showed more anxiety-like behavior in the elevated plus maze (Karolyi et al., 1999). Taken together, these findings suggest that hyperactivity of the HPA axis could cause increased anxiety. However, they do not necessarily show that the HPA axis is overactive in human anxiety disorders.

Various other molecules involved in the endocrine system have been shown either to be abnormal in anxiety disorders or mediate anxiety responses. Neuroactive steroids have been found to interact with GABA receptors and the HPA axis, and may play a role in anxiety disorders (Le Melleo & Baker, 2002). Although Le Melleo and Baker (2002) did not find significant differences in plasma levels of neuroactive steroids between patients with GAD and controls, they have proposed that the effect of SSRI's on anxiety may be mediated by up-regulation of allopregnanolone, which dampens HPA activity and has anxiolytic effects.

Some studies have investigated lipid metabolism in anxiety. In one such study, mice deficient in the gene for 5-lipoxygenase displayed less anxiety-like behavior in the elevated plus maze (Uz, Dimitrijevic, Tueting & Manev, 2002). The enzyme 5-lipoxygenase functions in the synthesis of eicosanoids, but its role in the central nervous system is still largely unknown (Uz et al., 2002). 5-lipoxygenase is up-regulated by glucocorticoids, which are produced as the endpoint of HPA activation (Uz et al., 2001). The significance of these findings is not yet clear.

Kusnecov, Liang and Shurin (1999) found that stimulation of T-lymphocytes with a bacterial agent caused an up-regulation of CRH mRNA in the amygdala, and caused mice to display more anxiety-like behavior in a stressful situation. They hypothesized

that immunological challenges may start a cascade of events that affect emotionality (Kusnecov, Liang & Shurin, 1999).

Autism. Immunological abnormalities in autism include observations of autoimmunity. In autistic individuals, autoantibodies have been found against neuron-axon filament proteins, cerebellar neurofilaments, myelin basic protein, and 5-HT receptor (Krause, He, Gershwin & Shoenfeld, 2002). Presence of these antibodies suggests that the immune system of autistic individuals may target cytoarchitectural elements in the brain as foreign invaders, and attack these proteins (Krause et al., 2002). Such an autoimmune response may be induced by viral or bacterial infections. Further evidence that autoimmunity may have a role in the pathology of autism comes from an epidemiological study, which found rates of autoimmune disorders, especially type I diabetes, rheumatoid arthritis, systematic lupus erythematosus, and hypothyroidism, to be significantly higher in relatives of autistic individuals than in relatives of healthy controls (Comi et al., 1999). Other abnormalities in the immune system of autistic individuals that have been found include weakened antibody response to vaccinations, reduced number of T cells and CD4+ cells, and decreased activity of natural killer cells (Krause et al., 2002). Taken together, these findings suggest that genetic influences on the immune system coupled with environmental insults such as infections in early development may interact to alter neural development in a pathological manner. However, this theory has been criticized due to the fact that signs of autoimmune activity, such as anti-brain antibodies, are not uncommon, and that autism does not share many features with other autoimmune disorders like lupus or multiple sclerosis (Korvatska et al., 2002). Thus, immune abnormalities in autism could be secondary to a neurological defect.

Neurodevelopmental and Plasticity Abnormalities

Although the development of the brain from embryonic ectodermal tissue is not fully understood, it is likely that abnormalities in this process could result in abnormalities in the functioning of the mature nervous system. Even after the brain is fully formed, there remains throughout the life-span continual developmental processes occurring in the brain, such as neurogenesis, the creation or modification of synapses, and maintenance of the survival and protection of neurons. Adaptive behavior results from the complex interaction of neurons in various parts of the brain, and abnormal synaptic plasticity, apoptosis, and myelination could thus be a factor in psychopathology.

Schizophrenia. Emerging global concepts on the etiology of schizophrenia are converging on the developmental features and disturbed neural connections characteristic of the disorder. According to this model, neonatal complications and genetic factors subtly affect the processes governing growth and maturation of the brain, resulting in abnormalities which only manifest themselves as clinical symptoms later in life. Evidence supporting this model comes from several sources, including studies on schizophrenia genetics, epidemiological literature on the prevalence of neonatal and birth difficulties in people who later develop schizophrenia, findings on behavioral abnormalities in children who later develop schizophrenia, and studies on neonatal insults which can create abnormalities that lie dormant throughout an organism's maturation.

Large cohort studies have uncovered some epidemiological predictors of schizophrenia; these findings typically relate to neonatal and birth difficulties. People born during winter and spring months, when their mothers would have been at a greater risk for infection, have a slightly greater risk for schizophrenia (Hultman, Sparen, Takei,

Murray, & Cnattingius, 1999; Jones, 1997). Similarly, people born during epidemics of influenza have a greater risk for schizophrenia (Jones, 1997). Obstetric complications, especially hypoxic damage, postnatal brain injury and maternal bleeding, have likewise been associated with schizophrenia (Fearon, Cotter & Murray, 2000; Jones, 1997; Hultman et al., 1999). Other epidemiological studies have found that children who later develop schizophrenia exhibit some behavioral, cognitive and social deficits, including lower IQ, delayed developmental milestones in speech and motor abilities, and more social awkwardness and isolation (Jones, 1997).

Mechanisms via which neonatal complications may increase risk of schizophrenia are still largely unknown, but there have been some important findings on the issue. Fatemi et al. (2002) have demonstrated that maternal exposure to influenza virus in mice can lead to increased pyramidal cell density and decreased pyramidal nuclear size in newborns. Prenatal viral infection may also cause defective neuronal migration by reducing levels of Reelin, an extracellular protein (Fatemi 2002). Reelin deficits and pyramidal cell atrophy have been noted in schizophrenic patients (Sawa & Snyder, 2002; Zaidel, Esiri, & Harrison, 1997). As noted earlier, retinoic acid plays a large role in regulating embryonic gene transcription; it is known that some viruses contain DNA fragments which can activate retinoid-responsive transcription (Goodman, 1998). Prenatal lesions of the dorsolateral prefrontal cortex in monkeys may not affect the monkeys' performance on neuropsychological tests until they reach sexual maturity (Jones, 1997).

In accordance with the neurodevelopmental model of schizophrenia is mounting evidence that the development and maintenance of neural connections may be impaired.

A rare genetic disorder, metachromatic leukodystrophy, has garnered attention from schizophrenia researchers because it causes psychosis and cognitive deficits closely resembling schizophrenia in adolescents and adults (Holden, 2003). In metachromatic leukodystrophy, arylsulfatase A, an enzyme involved in the metabolism of lipids composing the myelin sheath, is inactive; this leads to demyelination, especially of connections between the frontal lobe and other cortical or subcortical areas (Hyde, Ziegler & Weinberger, 1992). Low levels of arylsulfatase A activity have also been noted in schizophrenic patients, raising the possibility that abnormal metabolism of myelin lipids could predispose individuals to psychiatric disorders (Mihaljevic-Peles, Jakovljevic, Milicevic & Kacun, 2001). Likely myelin and axonal abnormalities have also been reported in the temporal lobes of people with schizophrenia (Foong, Maier, Barker, Brocklehurst, Miller, & Ron, 2000). Hakak et al. (2001) found that a group of genes related to myelination showed reduced expression in schizophrenic patients. Disturbances in synaptic organization may also occur in schizophrenia, as indicated by findings that levels of GAP-43 and synaptophysin, two proteins important in the establishment of synaptic connections, are abnormal in schizophrenic brains (Perrone-Bizzozero et al., 1996). An interesting link to findings on abnormal glutamatergic activity in schizophrenia is findings that glutamate plays a major role in brain development; neurotrophic activity, which promotes outgrowth of neurites, may depend upon activity of NMDA receptors (Fearon, Cotter & Murray, 2000). Neonatal injury, such as hypoxia, may overstimulate glutamate receptors and cause some enduring neurological damage (Fearon, Cotter & Murray, 2000). In addition to abnormal neurotrophic activity, abnormal apoptotic activity may also impair proper development in schizophrenia. One

post-mortem analysis of tissue from brains of schizophrenic, bipolar, and healthy subjects revealed significantly less cells in brains of schizophrenia exhibiting signs of apoptosis, which could indicate an adaptive response to damage caused in schizophrenia, or abnormal response to typical pro-apoptotic signals (Benes et al., 2003). Myelin abnormalities, glutamate overactivity in neonatal development, and abnormal neuronal migration (due perhaps to reduced levels of Reelin) may result in intracortical disconnectivity from which symptoms of schizophrenia could be explained (Al-Amin & Weinberger, 2000).

Autism. Since the symptoms of autism are evident even in the first few years of life, it has been hypothesized that complications during embryonic development or birth may have a causal role in the disorder. Abnormalities in the immune system noted in autism may be related to prenatal and perinatal events.

A study comparing prenatal and perinatal complications in the births of autistic children to national statistics found that uterine bleeding during gestation was significantly more common in the autism group (Juul-Dam, Townsend & Courchesne, 2001). Rhesus incompatibility between mother and child was also more common in the autistic group than the general population, though this trend did not reach statistical significance (Juul-Dam et al., 2001). The association between prenatal uterine bleeding and autism was also found in a study by Wilkerson, Volpe, Dean and Titus (2002). In this study, low birth weight, viral infections in the mother, and use of medications during pregnancy by the mother were also associated with autism (Wilkerson et al., 2002). It is unclear at this point how some of these factors relate to the pathology of autism.

However, other studies show that viral infections during prenatal and neonatal periods may affect neural development.

Rats infected neonatally with the Borna disease virus (BDV) show loss of Purkinje cells in the hippocampus and cerebellum, and also exhibit abnormalities in growth, play behavior, and learning, all effects resembling features of autism (Hornig et al., 1999). The loss of Purkinje cells may have been due to a down-regulation of the anti-apoptotic protein Bcl-2 that was observed in the study, as well as up-regulation of pro-apoptotic proteins Fas and caspase-1 (Hornig et al., 1999). Neonatal insults, such as infection, have also been shown to down-regulate Reelin and increase pyramidal cell density in mice (Fatemi et al., 2002). Reduced levels of the proteins Reelin and Bcl-2 have also been found in the cerebellum of autistic individuals (Fatemi, Stary, Halt & Realmuto, 2001). Reelin functions in brain development, and Bcl-2 inhibits apoptosis; deficits of these proteins may help explain the atrophy of Purkinje neurons seen in the autistic brain (Fatemi et al., 2001).

Biological markers of early development in the cerebellum have been shown to be abnormal in autism. The high comorbidity between autism and tuberous sclerosis, which has a similar behavioral phenotype, may be due to mutations in the gene for the protein tuberin (Smalley, 1998). Tuberin is expressed at high levels in the Purkinje cells of the cerebellum during embryonic and neonatal periods, and has a role in neural growth and differentiation (Smalley, 1998). Mutations in other proteins critical in neural development have been examined for involvement in autism, including methyl-CpG-binding protein 2 (MeCP2), FOXP2, and neuroligins. Mutations in MeCP2 cause Rett syndrome, a developmental disorder related to autism, characterized by abnormal social development

(Zoghbi, 2003). MeCP2 is believed to have a role in the development or maintenance of synapses. Neuroligins (NLGNs) may also function in the development of synapses; mutations of NLGN-3 and -4 are suspected in causing autism or Asperger's syndrome (Zoghbi, 2003). FOXP2 is a transcription factor; mutations in this gene can cause speech and language impairments, and is thus considered a possible candidate for development of autism (Korvatska et al., 2002).

Affective disorders. An important topic of recent research on mood disorders has focused on the role of neural plasticity, neurogenesis, and neurotrophins in depression. The assumption that the adult brain no longer produces new neurons was discredited by findings of neurogenesis in the hippocampus and olfactory bulbs (Kempermann & Gage, 1999). Common antidepressants, including fluoxetine and imipramine, stimulate neurogenesis in the hippocampus, and this effect appears to be critical for the efficacy of these drugs (Santarelli et al., 2003). A recent study found that glucocorticoids and pro-inflammatory molecules of the immune system, such as IL-6, which may be elevated in depression, inhibit hippocampal neurogenesis (Monje, Toda & Palmer, 2003). This study also found that indomethacin, a non-steroidal anti-inflammatory drug (NSAID), restored neurogenesis after cytokine-induced neuroinflammation had reduced neurogenesis. These findings raise an interesting hypothesis that NSAIDs could have antidepressant activity in diseases that cause inflammation. Some somatic diseases can induce depression-like 'sickness behavior' in humans and rodents, which is characterized by fatigue, loss of appetite, and malaise. In rodents, the NSAID zaltoprofen was able to reduce the loss of body weight in a 'sickness behavior' model (Okamoto, 2002).

Neurogenesis is likely dependent on the activity of neurotrophins, including bone-derived neurotrophic factor (BDNF), and transcription factors, such as cyclic-AMP response element binding protein (CREB); these proteins mediate neural plasticity phenomenon such as formation of new dendritic spines or synaptic connections (Duman, 2002). Evidence for altered synaptic plasticity in mood disorders revolves around studies on CREB and BDNF in depressed patients. As mentioned above, chronic antidepressant treatment up-regulates CREB; it has also been found that experimental over-expression of CREB produces antidepressant effects (Duman, 2002). However, mice deficient in the CREB gene displayed lower levels of immobility in the forced swim test; furthermore, the antidepressants desipramine and fluoxetine further reduced immobility in these mice, indicating that CREB does not mediate the effects of these drugs (Conti et al., 2002). These seemingly contradictory results, that over-expression and under-expression of CREB can have anti-depressant effects, may be due to the multiple downstream effects of CREB activation, which can differ between various areas of the brain. BDNF has been found to have neurotrophic effects on serotonergic neurons (Duman, 2002). Furthermore, infusion of BDNF or neurotrophin-3 into the hippocampus had antidepressant effects in the forced swim test (Shirayama et al., 2002). BDNF is down-regulated by stress, and this down-regulation may be involved in the neuronal and glial atrophy noted in depressed patients (Duman, 2002). BDNF may protect against depression both by repairing damage to neurons done by stress and by protecting neurons from further damage (Nestler et al., 2002). Alternatively, since BDNF affects learning and memory, it has been suggested that abnormal levels of BDNF could lead to abnormal and maladaptive learning and memory of stressful events (Shirayama et al., 2002).

Conclusions: Emerging Neurobiological Models for Psychiatric Disorders

It is clear from the literature that schizophrenia, autism, depression and anxiety are complex disorders that emerge from interactions between environmental conditions and genetic predispositions, and affect not only aspects of the nervous system, but also immunological and endocrine systems. Findings on the co-morbidity between some disorders, physiological abnormalities common to several different disorders, and overlap of symptoms indicates that a view of psychopathology incorporating spectrums of non-pathological to pathological extremes may be more proper than the established practice of identifying mental illnesses as discrete phenomenon. Indeed, a radical revision of the DSM has been proposed, which would replace the current axes (clinical syndromes, personality disorders, medical conditions, psychosocial problems, global assessment) with genotype, neurobiological phenotype, behavioral phenotype, environmental factors, and therapeutic targets (Helmuth, 2003). Such a revision may have to wait until the neurobiological pathology and etiology of mental illness is more completely known and empirically validated. Currently, competing neurobiological models exist for each of the disorders, and too many uncertainties remain to confirm any as definitive.

Schizophrenia. Schizophrenia, probably the most complex mental illness in terms of symptoms, may also be the most complex in pathophysiology. Early theories that focused on abnormal dopaminergic neurotransmission proved fruitful in the development of effective anti-psychotic drugs, but have not completely explained schizophrenia. Recently, the most intriguing model for the neurobiology of schizophrenia has been the neurodevelopmental hypothesis, which predicts that early environmental factors interact with certain alleles of developmental genes to cause abnormalities in the development

and connectivity of the nervous system that eventually are manifested as mental illness. This theory cannot yet fully explain all of the various symptoms and courses of schizophrenia, and does not suggest immediate therapeutic targets. But it is perhaps the best explanation of how so many different neurotransmitter and signaling pathways could be affected, since abnormal neuro-development would presumably alter many different neurochemical systems.

Autism. The physiological basis of autism remains largely a mystery. It is clear that autism is not merely a neurochemical imbalance, nor due to damage of any particular area of the brain. Evidence for autism as an autoimmune disorder is intriguing, but far from definitive. The most compelling model is the neurodevelopmental hypothesis, similar to schizophrenia, in which environmental factors (especially in prenatal and perinatal stages) interact with developmental genes to cause abnormal neural connectivity and functioning.

Affective disorders. A complete model of the physiology of mood disorders would have to corroborate some of the cognitive and developmental psychological findings on the etiology of depression. Multiple anatomical systems display abnormal functioning in depression, but the link between them appears to be stress. Stressors, especially those that are chronic and/or inescapable, produce predictable neurochemical, immunological and hormonal responses that are observed in depression. Social stress in particular may have a crucial role in depressive etiology. Social stressors, including defeat and isolation, decrease serotonergic and increase noradrenergic activity, and also activate the HPA axis (Blanchard, McKittrick, & Blanchard, 2001). The effects of these social stressors in animal models may help explain why low social status, significant life events such as loss

or failure, and lack of intimate life partners or other sources of support are associated with depression in humans (Blanchard et al., 2001). The emerging physiological picture of depression is thus one of maladaptive response to stress, in which abnormalities in the feedback loops between neurotransmitter release, immune signaling compounds, and hormonal levels leads to amplification of typical stress responses. However, this model is complicated by the findings on the importance of neural plasticity, especially hippocampal neurogenesis, in mediating mood and response to anti-depressant medication. Neurochemical and hormonal abnormalities could be responsible for depressive symptoms, while abnormal plasticity could underlie the duration of symptoms.

Anxiety disorders. Research on the neural substrates of anxiety disorders has been hampered by difficulty in replicating promising findings. The high comorbidity of GAD and SAD, especially with affective illnesses, and the similarities between the physiopathology of these disorders raise the possibility that these disorders are not wholly differentiable. The onset of these anxiety disorders typically occurs at an early age and usually precedes the comorbid condition, suggesting that SAD and GAD may be prodromal syndromes for affective illnesses. Like depression, anxiety disorders may represent maladaptive stress responses of neurochemical and hormonal systems, though thus far it is not obvious how these maladaptive responses can become enduring in the brain.

As neuroscience research expands its techniques, topics of study, and interactions with other scientific disciplines, new models of psychiatric illnesses (and possibly non-psychiatric disorders) will likely emerge, and new therapeutic interventions will be discovered. Continued research on the pathophysiology of mental disorders, employing

imaging, neuropsychological, and postmortem studies on humans as well as animal models, will contribute to our understanding not only of illnesses but also the physiological components of normal behavior, since it will be necessary to distinguish between typical and atypical neurobiological functioning.

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