Susan L. Andersen
Nathalie L. Dumont
Martin H. Teicher
Department of Psychiatry
Harvard Medical School
Laboratory of Developmental Psychopharmacology
McLean Hospital
Belmont, MA 02478

Differences in Behavior and Monoamine Laterality Following Neonatal Clomipramine Treatment

Received 31 May 2001; Accepted 15 July 2001

ABSTRACT: *Postnatal treatment between 8 to 21 days of age with clomipramine (15 mg/kg, twice daily) produces an animal model that has many of the behavioral hallmarks of depression. In this study, we investigated the enduring behavioral and neurochemical effects of this early treatment in adult animals. Locomotor activity was increased in clomipramine-treated males, but not females, relative to vehicle-treated subjects. Increases in anxiety-like behavior in the elevated plus maze also were observed in clomipramine-exposed adults, but no sex differences were detected. Clomipramine-treated animals had shifts in the laterality of monoamines in limbic regions with lower serotonin levels on the right side while vehicle-treated animals had lower serotonin on the left side. The lateralization of dopamine content demonstrated the same pattern. This decline in monoaminergic content is consistent with clinical studies demonstrating decrements in serotonin as well as alterations in the lateralization of function in individuals with major depressive order.*
 Dev Psychobiol 41: 50–57, 2002. Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/dev.10055

Keywords: *accumbens; activity; amygdala; anxiety; clomipramine; depression; gender; laterality; serotonin; sex*

Theories on the underlying neurochemical basis of depression suggest that diminished serotonin in limbic regions underlie affective symptoms (Deakin, 1998). Furthermore, the role that differential contributions of the right and left hemisphere play in mood is becoming more established. Briefly, the right side of the human brain is believed to contribute to our more emotional states while the left hemisphere functions in a more analytical and rational fashion (Joseph, 1988). The two hemispheres work in tandem to produce our overall moods, often with the left hemisphere modulating the right hemisphere (Harmon-Jones & Allen, 1997) in the normal case, and either a decline in left-hemisphere function or an increase in right-hemisphere activity contributes to affective disorders (Bench, Friston, Brown, Frackowiak, & Dolan, 1993; Bruder et al., 1989; Burton & Labar, 1999; Klemm et al., 1996). Given the relationship between serotonin and depression, higher imipramine binding in right cortical areas that is higher in normal females than males (Arato, Frecska, Tekes, & MacCrimmon, 1991) is important for understanding the pathophysiology of affective disorders. This asymmetry may lead to the higher predilection of females to develop depression, which is one of the few major psychiatric disorders that is two- to threefold more prevalent in females than males (Kessler, McGonagle, Swartz, Blazer, & Nelson, 1993).

Attempts to model depression have been numerous and modestly successful through the years and have been primarily based on alterations in activity levels

Correspondence to: S. L. Andersen
Contract grant sponsor: NIH R01
Contract grant number: MH 43474 to MHT

(Teicher, Barber, Lawrence, & Baldessarini, 1989). Some models, such as the amphetamine withdrawal, capture aspects of the anhedonia and retarded locomotor effects of depression. Others, such as isolation-induced hyperactivity, capture the characteristics of agitated depression. To date, no perfect experimental procedures in animals are available for characterizing antidepressant drugs.

In striving to achieve as many of the clinical symptoms of depression as possible, postnatal treatment with clomipramine demonstrates many features of agitated depression in adulthood. This animal model of depression is produced paradoxically by chronic treatment of developing rats (between postnatal Days 8–20) with the tricyclic antidepressant clomipramine. Stemming from initial studies by Mirmiran and colleagues (Mirmiran, van de Poll, Corner, van Oyen, & Bour, 1981), which demonstrated increased REM sleep in adult rats, additional depressive-like behavioral symptoms including diminished intracranial self-stimulation (Vogel, Neill, Hagler, & Kors, 1990), decreased aggressiveness (Vogel, Hartley, Neill, Hagler, & Kors, 1988), impaired sexual activity (Mirmiran et al., 1981; Neill, Vogel, Hagler, Kors, & Hennessey, 1990), and increased immobility in a forced swim paradigm (Velazquez-Moctezuma & Diaz Ruiz, 1992; Hansen, Sanchez, & Meier, 1997) have since been documented. Clomipramine-exposed subjects also display enhanced sensitivity to stress (Prathiba, Kumar, & Karanth, 1998) and have attenuated exploratory behavior (as an index of anxietylike behavior) in the elevated plus maze (Yannielli, Kargieman, Gregoretti, & Cardinali, 1999). With the exception of Dwyer and Rosenwasser (1998), who found that clomipramine-treated female rats have an increased circadian amplitude relative to salinetreated male and female rats, sex differences in animals exposed postnatally to clomipramine have hardly been investigated.

Preclinical evidence suggests that anatomical laterality exists in nonhuman species (Denenberg, 1983; Rodriguez, Martin, & Santana, 1994; Ross, Glick, & Meibach, 1981), but may be not be entirely hard-wired. Testosterone increases cortical thickness in the right hemisphere of male rats while its absence shifts the laterality to a more left-sided bias (Diamond, 1991). Pioneering studies by Denenberg and colleagues (Denenberg et al., 1982; Garbanati et al., 1983) demonstrated how early experience alters laterality. Stress also may influence laterality of cortical structures (Diamond, 1991). Thus, the lateralization of function in the mammalian brain is susceptible to manipulation early in life.

To determine the relationship between sex and laterality and the behavioral and neurochemical manifestations of early clomipramine treatment, we tested subjects in an activity monitor, the elevated plus maze, and assayed key limbic and motor areas in the right and left hemispheres for lateralized changes in the monoamine systems. Specifically, we wanted to determine the brain regions and neurotransmitter systems that are intricately changed as a result of clomipramine treatment to aid in the dissection of their role in previously observed behavioral changes.

MATERIALS AND METHODS

Subjects

Lactating female Sprague-Dawley rats were housed with their litters on a 12:12 hr light:dark cycle with lights on at 07:00 hr; food and water provided ad libitum. Litters were culled to 8 pups of equal numbers of males and females on postnatal Day 1 (P1), weaned at P25, and group housed with littermates. Two male and 2 female subjects in each litter were assigned to either clomipramine treatmemt (15 mg/ml, sc) or saline vehicle, and toe-clipped for identification. Treatments were administered twice daily at 9:00 a.m. and again at 3 p.m. between P8 to P21, according to the method of Mirmiran et al. (1981). To avoid the potential artifactual effects that sometime emerge when multiple pups are studied from a given litter, we utilized no more than a single male and female pup from each litter in each experimental procedure. Thus, we studied single subjects from each gender from a given litter in studies of locomotion, elevated plus maze behavior, and neurochemical analyses of monoamine content. Twelve litters were used for these studies.

Locomotor Activity

Activity was monitored using a computer-interfaced, infrared motion analysis system (MacReflex, Qualysis) that is capable of tracing the $X–Y$ position of 12 infrared reflective markers at 10 Hz, with a resolution of ~40 μm (Teicher, Andersen, Wallace, Klein, & Hostetter, 1996). Animals were placed in 38×76 cm test chambers for a 1-hr test period at P60. Activity was then analyzed for changes in displacement, amount of movement, immobility duration, spatial and temporal scaling exponents, and total area covered.

Activity data were analyzed based on a powerful schema developed by Geyer and Paulus (1992) for the study of $X–Y$ time series data. The fundamental unit of analysis is the microevent, which is defined in three dimensions by its position and duration. A new

microevent begins when the centerpoint of the marker moves more than a predefined distance (nominally 4 mm) from the last microevent. Duration is the amount of time spent at this location before the subject moves to the next microevent position. The complete sequence of microevent positions is graphed and analyzed to determine total displacement (in pixels and mm), number of position changes, and the average amount of time between position changes.

The major feature of this approach is the derivation of temporal and spatial scaling exponents, which have been used to provide insight into the behavior of complex systems. The spatial scaling exponent *d*, is a measure of the complexity of the movement path and is calculated by ascertaining the rate of information decay at progressively lower levels of temporal resolution (Geyer & Paulus, 1992). It corresponds to the concept of fractal dimensions and ranges from 1.0 (*straight line movement*) to 2.0 (*hypercomplex, convoluted movement patterns*). The temporal scaling exponent α is calculated from the stochastic log–log reciprocal relationship between the frequency of occurrence of microevents of different durations. This parameter varies between 0 (*inactivity*) and 1 (*incessant activity*), and indicates the degree to which a subject is moving in its environment (Geyer & Paulus, 1992).

Elevated Plus Maze

A separate set of subjects was tested in the elevated plus maze (two open arms of 50×10 cm and two closed arms of 50×10 cm with 40 cm high sides) at P70 (Andersen & Teicher, 1999). Each subject was placed into the elevated plus maze facing the closed arm, and duration spent in each arm (considered when all four paws are located within the arm) was recorded for a 5-min period. The maze was washed with a mild disinfectant before each subject to minimize residual scents from the preceding subject.

Regional Monoamine Assays

For neurochemical analyses, subjects were removed from the home cage and sacrificed on P80 for males while females were sacrificed ± 2 days of this age at diestrous. The brains were rapidly removed, chilled, and dissected on ice within 3 min of decapitation. Left and right prefrontal cortex, striatum, nucleus accumbens, hippocampus, and amygdala were dissected on ice, with left/right hemispheres being dissected within 10 s of the other, and stored at $-70°$C until analysis (Andersen & Teicher, 1999). Dopamine and its major metabolites 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA), and serotonin and its metabolite, 5-hydroxy indole acetic acid (5-HIAA), and norepinephrine were assayed by high-performance liquid chromatography with electrochemical detection (HPLC-EC). Tissue samples were homogenized in 0.1 N perchloric acid containing 0.1 m*M* EDTA, 0.4 m*M* sodium metabisulfite, and 10 ng of dihydroxybenylamine (DHBA) as an external standard. The homogenate was centrifuged for 5 min at $9{,}000 \times g$, and 100 µl of the supernate was injected into a Waters HPLC system (Milford, MA) with a 250×4.6 mm, C18 particle size column (Bioanalytical Systems, Lafayette, IN). Mobile phase consisted of 50 m*M* sodium acetate, 1.3 m*M* heptanesulfonic acid, 3% acetonitrile, and 2 m*M* EDTA (pH 3.5), perfused at 1 ml/min over a glassy carbon electrode set at 700 mV.

Statistics

Data were analyzed with two-way ANOVAs, with drug and hemisphere as main factors and sex as a covariate (Systat, Evanston, IL). Findings were considered significant at the $p < 0.05$ level.

RESULTS

Weight Gain

Significant differences were observed between clomipramine-treated pups and the vehicles at the termination of treatment at P21, $F(1, 44) = 21.93$, $p < 0.05$. Weight was reduced 13.8% for males and 17.8% in females.

Locomotor Activity

Differences in locomotor activity levels were readily observed during the 1-hr test period. Treatment × Sex interactions were observed for the number of displacements, $F(1, 9 = 5.28)$, $p < 0.05$, immobility duration, $F(1, 9) = 7.16$, $p < 0.05$, area covered, $F(1, 9) = 10.38$, $p < 0.01$, and microevents, $F(1, 9) = 7.32$, $p < 0.01$. Males that were treated with clomipramine between P8 to P20 were significantly more active than any other group (Figure 1). This was reflected most strikingly in decreased immobility and marginally captured with the temporal scaling exponent ($p = 0.09$), which was elevated in clomipramine-treated subjects. Qualitatively, however, the movements between the vehicle and clomipramine subjects did not differ. Spatial scaling was not significantly altered ($p = 0.29$) as a result of treatment nor was the forward-to-reverse ratio. These data further suggest

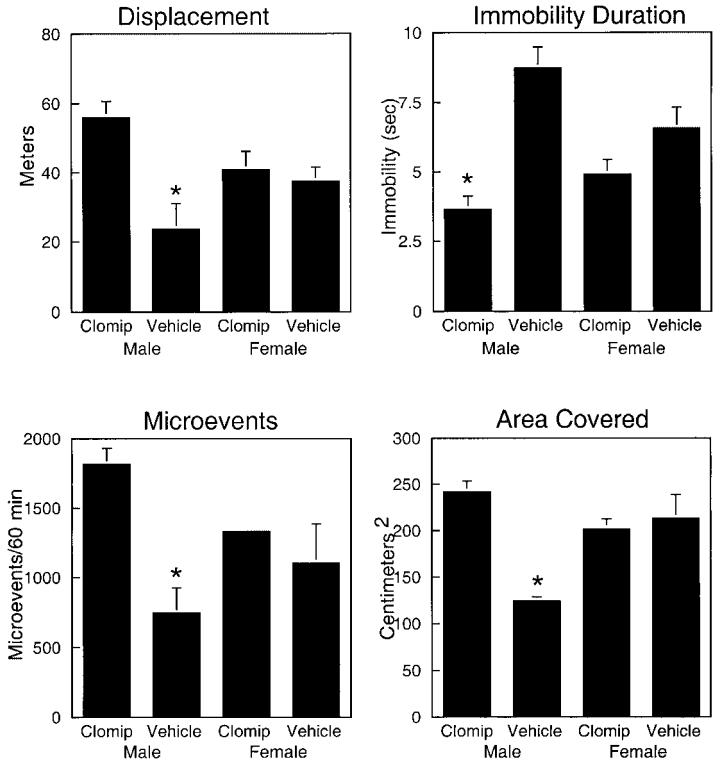

FIGURE 1 Effects of clomipramine exposure on overall levels of activity in males and females. Means $\pm$ *SE* are presented for $n = 8$ subjects for each condition for displacement, immobility duration, microevents, and area covered. Clomipramine-treated males demonstrated the highest levels of activity when compared with treated females or vehicles of either sex. Following a significant Treatment $\times$ Sex interaction for each measure, *significant differences between male treatment groups at the $p < 0.05$ level.

no increased predilection to stereotypy or akathisia, where the animals are active but not ambulating.

Elevated Plus Maze

Clomipramine-treated subjects spent a mere $14.72 \pm 3.5\%$ of their time in the open arms while vehicle-treated subjects spent $45.32 \pm 5.5\%$ of their time in the open arms, reflecting a 3.06-fold difference, $F(1, 7) = 20.6$, $p < 0.01$. No gender differences were observed in the percent time spent in the closed arm ($p = 0.55$).

Neurochemistry

Nucleus Accumbens. Overall, drug-induced alterations occurred in both serotonin and dopamine of the nucleus accumbens. Serotonin reversed its laterality, $F(1, 17) = 4.64$, $p < 0.05$ (Figure 2). Serotonin content was greater on the right than left of vehicle controls, but greater on the left than right of clomipramine-treated subjects. Pooled (right plus left) serotonin content, however, was entirely unaltered by clomipramine ($p > 0.9$).

Clomipramine also exerted the same pattern of effect on dopamine laterality, $F(1, 16) = 4.77$, $p < 0.05$. Vehicle controls had a right > left pattern whereas clomipramine-treated subjects had the opposite. When collapsed across hemispheres, dopamine content remained significantly attenuated in treated relative to control subjects, $F(1, 16) = 7.08$, $p < .05$. Estimated dopamine turnover (HVA/DA) was significantly altered as a result of treatment, $F(1, 14) = 5.55$, $p < 0.05$. Turnover was greater on the right than left in vehicle controls, but opposite in direction in clomipramine-treated subjects. Norepinephrine was not significantly effected.

Prefrontal Cortex. Serotonin content was not significantly effected by clomipramine treatment in the prefrontal cortex (Figure 2). However, serotonin utilization (5-HIAA/5-HT) was elevated in the prefrontal cortex, $F(1, 16) = 4.37$, $p < 0.05$, in treated

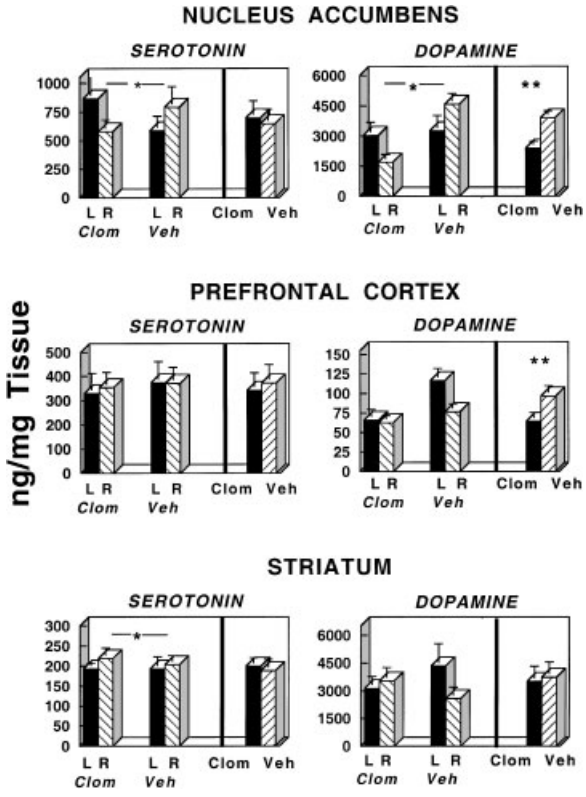

FIGURE 2 Serotonin and dopamine content (ng/mg tissue) in the nucleus accumbens, prefrontal cortex, and striatum. Means $\pm$ *SE* are presented for $n = 8$ to 10 subjects for each condition for each hemisphere (left side) and the average of the right and left hemisphere (right side). Both serotonin and dopamine significantly shifted laterality from a right-sided dominance to a left-sided dominance following clomipramine treatment. Alterations in serotonin and dopamine content also were observed in the prefrontal cortex and striatum. *significant interaction between treatment groups and hemisphere; **significant main effect of treatment independent of hemisphere at the $p < 0.05$ level.

subjects, with no significant effects on laterality. Pooled dopamine levels were reduced in the prefrontal cortex of clomipramine-treated subjects, $F(1, 18) = 5.40$, $p < 0.05$ (Figure 2). Clomipramine treatment was associated with a significant reduction in lefthemisphere dopamine content, $F(1, 18) = 5.74$, $p < 0.05$, but little change in right. Lateralized differences in dopamine utilization also failed to manifest a significant drug-induced effect ($ps > 0.5$).

Striatum. There was relatively little effect of clomipramine on serotonin content of the striatum. It appeared that clomipramine induced or augmented a right > left laterality of serotonin relative to controls, $F(1, 18) = 4.63$, $p < 0.05$, where vehicle controls had nearly equivalent levels on each side but clomipramine-treated subjects had a modest right-sided dominance. No significant alterations were observed in pooled content or in pooled or hemispheric metabolite levels. There also were no significant alterations in pooled dopamine measures or in its laterality.

Amygdala and Hippocampus. There was a substantial shift in the laterality of serotonin turnover in the amygdala following clomipramine treatment. Vehicle controls showed minimal laterality, but clomipramine-treated subjects had a robust left > right asymmetry ($p < 0.05$). Clomipramine-treated subjects also had a marginal decrease in pooled dopamine content, with no significant shift in laterality. The neurochemistry of the hippocampus was not significantly altered following clomipramine treatment.

Clomipramine-Induced Sex Differences in the Laterality of Monoamines

Contrary to our predictions, it appeared that the effects of clomipramine on monoamine laterality occurred to a similar extent in male and female subjects (Gender $\times$ Treatment: $ps > 0.2$). In short, gender did not significantly modify the effects of clomipramine-treatment on monoamine laterality.

DISCUSSION

The results of this study clearly demonstrate that early clomipramine treatment produces enduring sex-dependent changes in activity, and significantly alters measures of anxiety and the lateralization of the monoamine systems of adult rats. Early clomipramine treatment appears to more selectively target the limbic regions of the nucleus accumbens, has modest effects in amygdala, prefrontal cortex, and the striatum, but spares the hippocampus in our hands. Overall, the effects of clomipramine treatment are subtle, as they produce shifts in the laterality of serotonin and dopamine, and do little to the overall content and turnover in the region with the exception of reduced dopamine in accumbens and prefrontal cortex in adulthood. This lack of overall changes in neurochemistry is consistent with other results (Feenstra, van Galen, Te Riele, Botterblom, & Mirmiran, 1996; but see Vijayakumar & Meti, 1999). Whether the overall transmitter declines found by Vijayakumar and Meti (1999) are due to the 50% decline in food intake in their subjects is not clear. In our hands as well, however, we observed significant weight differences between treatment groups at P21 following cessation of treatment. The more modest effect (less

than 20%) on weight gain in our pups may mediate the different neurotransmitter differences observed between the laboratories.

The observed increase in locomotor activity and anxiety in clomipramine-treated subjects may be related to shifts in the laterality of dopamine and serotonin. Lateralization of both of these neurotransmitters plays an important role in human activity (Braun, Larocque, Daigneault, & Montour-Proulx, 1999) and possibly anxiety as suggested by studies in rats (Andersen & Teicher, 1999). Greater right activation in frontal cortex is associated with increased panic disorder (Wiedemann et al., 1999) while hypoperfusion (Klemm et al., 1996) or serotonin binding (Mayberg et al., 1988) in left hemisphere is associated with depression.

Sex-dependent effects in activity that were observed in this study are reminiscent of sex differences observed in attention deficit hyperactivity disorder (ADHD), where males outnumber females 3 to 1 (Biederman, Faraone, & Spencer, 1994). A significant reduction in dopamine content following neonatal 6-hydroxydopamine lesions results in hyperactivity in young animals in a putative animal model of ADHD (Shaywitz, Gordon, Klopper, & Zelterman, 1977). Dopamine parameters were altered by clomipramine in the nucleus accumbens and may have contributed to the hyperactivity. However, since the clomipramine affected dopamine content similarly in males and females, there are presumably other factors responsible for the gender difference in hyperactivity. We have previously observed robust gender differences in the overproduction and pruning of dopamine receptors in the stratium, and have theorized that this is associated with the enhanced risk for hyperactivity in males (Andersen, Rutstein, Benzo, Hostetter, & Teicher, 1997; Andersen & Teicher, 2000). Future studies on the effects of clomipramine on the ontogeny of dopamine and serotonin receptors may help to explain resulting gender differences in activity. A second possibility may arise from sex-dependent differences in mother–pup interactions, where clomipramine treatment differentially altered the dam's treatment (Moore & Morelli, 1979). While these interactions were not assessed in this study, they represent an important factor worthy of study, as it could lead to a different cascade of changes than those predicted by drug treatment alone.

Shifts in the laterality of serotonin and dopamine indeed may play a role in the emergence of depression. Little preclinical data is available on the development of the laterality of neurotransmitter systems, although anatomical data suggests greater right-sided cortical thickness than left-sided that decreases with maturation (Diamond, Johnson, Young, & Singh, 1983). It is plausible that different critical periods exist for the ontogeny of the monoamine systems in the right and left hemisphere. Decreases in the lateralization of brain dopamine levels occur with maturation (Rodriguez et al., 1994), although not much is known about serotonin lateralization. Given that neurotransmitters, especially serotonin, act as trophic factors in brain development (Liu & Lauder, 1992; Todd, 1992; Towle et al., 1989) and that dopamine and serotonin develop in complimentary ways (Jackson, Bruno, Stachowiak, & Zigmond, 1988; Towle et al., 1989), exogenous perturbations of either system with clomipramine or any other psychotropic medication may act to inhibit normal development, and this possibility should be appraised before prescribing these medications to very young children.

REFERENCES

Andersen, S. L., Rutstein, M., Benzo, J., Hostetter, J. C., & Teicher, M. H. (1997). Sex differences in dopamine receptor overproduction and elimination. NeuroReport, 8, 1495–1498.

Andersen, S. L., & Teicher, M. H. (1999). Serotonin laterality in amygdala predicts performance in the elevated plus maze in rats. NeuroReport, 10, 3497–3500.

Andersen, S. L., & Teicher, M. H. (2000). Sex differences in dopamine receptors and their relevance to ADHD. Neuroscience and Biobehavioral Reviews, 24, 137–144.

Arato, M., Frecska, E., Tekes, K., & MacCrimmon, D. J. (1991). Serotonergic interhemispheric asymmetry: Gender difference in the orbital cortex. Acta Psychiatry Scandanavia, 84, 110–111.

Bench, C. J., Friston, K. J., Brown, R. G., Frackowiak, R. S., & Dolan, R. J. (1993). Regional cerebral blood flow in depression measured by positron emission tomography: The relationship with clinical dimensions. Psychological Medicine, 23, 579–590.

Biederman, J., Faraone, S. V., & Spencer, J. (1994). Gender differences in a sample of adults with attention deficit hyperactivity disorder. Psychiatry Research, 53, 13–29.

Braun, C. M., Larocque, C., Daigneault, S., & Montour-Proulx, I. (1999). Mania, pseudomania, depression, and pseudodepression resulting from focal unilateral cortical lesions. Neuropsychiatry, Neuropsychology, Behavior Neurology, 12, 35–51.

Bruder, G. E., Quitkin, F. M., Stewart, J. W., Martin, C., Voglmaier, M. M., & Harrison, W. M. (1989). Cerebral laterality and depression: Differences in perceptual asymmetry among diagnostic subtypes. Journal of Abnormal Psychology, 98, 177–186.

Burton, L. A., & Labar, D. (1999). Emotional status after right versus left temporal lobectomy. Seizure, 8, 116–119.

Deakin, J. F. (1998). The role of serotonin in panic, anxiety, and depression. International Clinical Psychopharmacology, 13(Suppl. 4), S1–S5.

Denenberg, V. H. (1983). Lateralization of function in rats. American Journal of Physiology, 245, R505–R509.

Denenberg, V. H., Rosen, G. D., Hofmann, M., Gall, J., Stockler, J., & Yutzey, D. A. (1982). Neonatal postural asymmetry and sex differences in the rat. Developmental Brain Research, 2, 417–419.

Diamond, M. C. (1991). Hormonal effects on the development of cerebral lateralization. Psychoneuroendocrinology, 16, 121–129.

Diamond, M. C., Johnson, R. E., Young, D., & Singh, S. S. (1983). Age-related morphologic differences in the rat cerebral cortex and hippocampus: Male–female; right–left. Experimental Neurology, 81, 1–13.

Dwyer, S. M., & Rosenwasser, A. M. (1998). Neonatal clomipramine treatment, alcohol intake, and circadian rhythms in rats. Psychopharmacology (Berlin), 138, 176–183.

Feenstra, M. G., van Galen, H., Te Riele, P. J., Botterblom, M. H., & Mirmiran, M. (1996). Decreased hypothalamic serotonin levels in adult rats treated neonatally with clomipramine. Pharmacology Biochemistry & Behavior, 55, 647–652.

Garbanati, J. A., Sherman, G. F., Rosen, G. D., Hofmann, M., Yutzey, D. A., & Denenberg, V. H. (1983). Handling in infancy, brain laterality, and muricide in rats. Behavioral Brain Research, 7, 351–359.

Geyer, M. A., & Paulus, M. P. (1992). Multivariate and nonlinear approaches to characterizing drug effects on the locomotor and investigatory behavior of rats. NIDA Research Monographs, 124, 203–235.

Hansen, H. H., Sanchez, C., & Meier, E. (1997). Neonatal administration of the selective serotonin reuptake inhibitor Lu 10-134-C increases forced swimming-induced immobility in adult rats: A putative animal model of depression? Journal of Pharmacology and Experimental Therapeutics, 283, 1333–1341.

Harmon-Jones, E., & Allen, J. J. (1997). Behavioral activation sensitivity and resting frontal EEG asymmetry: Covariation of putative indicators related to risk for mood disorders. Journal of Abnormal Psychology, 106, 159–163.

Jackson, D., Bruno, J. P., Stachowiak, M. K., & Zigmond, M. J. (1988). Inhibition of striatal acetylcholine release by serotonin and dopamine after the intracerebral administration of 6-hydroxydopamine to neonatal rats. Brain Research, 457, 267–273.

Joseph, R. (1988). The right cerebral hemisphere: emotion, music, visual–spatial skills, body image, dreams, and awareness. Journal of Clinical Psychology, 44, 630–673.

Kessler, R. C., McGonagle, K. A., Swartz, M., Blazer, D. G., & Nelson, C. B. (1993). Sex and depression in the National Comorbidity Survey: I. Lifetime prevalence, chronicity, and recurrence. Journal of Affective Disorders, 29, 85–96.

Klemm, E., Danos, P., Grunwald, F., Kasper, S., Moller, H. J., & Biersack, H. J. (1996). Temporal lobe dysfunction and correlation of regional cerebral blood flow abnormalities with psychopathology in schizophrenia and major depression—A study with single photon emission computed tomography. Psychiatry Research, 68, 1–10.

Liu, J., & Lauder, J. M. (1992). Serotonin promotes region-specific glial influences on cultured serotonin and dopamine neurons. Glia, 5, 306–317.

Mayberg, H. S., Robinson, R. G., Wong, D. F., Parikh, R., Bolduc, P., Starkstein, S. E., Price, T., Dannals, R. F., Links, J. M., Wilson A. A., Ravert, H. T., & Wagner, Jr., H. N. (1988). PET imaging of cortical S2 serotonin receptors after stroke: Lateralized changes and relationship to depression. American Journal of Psychiatry, 145, 937–943.

Mirmiran, M., van de Poll, N. E., Corner, M. A., van Oyen, H. G., & Bour, H. L. (1981). Suppression of active sleep by chronic treatment with chlorimipramine during early postnatal development: Effects upon adult sleep and behavior in the rat. Brain Research, 204, 129–146.

Moore, C. L., & Morelli, G. A. (1979). Mother rats interact differently with male and female offspring. Journal of Comparative and Physiological Psychology, 93, 677–684.

Neill, D., Vogel, G., Hagler, M., Kors, D., & Hennessey, A. (1990). Diminished sexual activity in a new animal model of endogenous depression. Neuroscience and Biobehavioral Reviews, 14, 73–76.

Prathiba, J., Kumar, K. B., & Karanth, K. S. (1998). Hyperactivity of hypothalamic pituitary axis in neonatal clomipramine model of depression. Journal of Neural Transmission, 105, 1335–1339.

Rodriguez, M., Martin, L., & Santana, C. (1994). Ontogenic development of brain asymmetry in dopaminergic neurons. Brain Research Bulletin, 33, 163–171.

Ross, D. A., Glick, S. D., & Meibach, R. C. (1981). Sexually dimorphic brain and behavioral asymmetries in the neonatal rat. Proceedings of the National Academy of Sciences, USA, 78, 1958–1961.

Shaywitz, B. A., Gordon, J. W., Klopper, J. H., & Zelterman, D. A. (1977). The effect of 6-hydroxydopamine on habituation of activity in the developing rat pup. Pharmacology Biochemistry & Behavior, 6, 391–396.

Systats, Systant Inc. Evanston, IL. (1990–1992).

Teicher, M., Barber, N., Lawrence, J., & Baldessarini, R. (1989). Motor activity and antidepressant drugs: A proposed approach to categorizing depression syndromes and their animal models. In G. Koob, C. Ehlers, & D. Kupfer (Eds.), Animal models of depression (pp. 135–161). Boston: Birkhauser.

Teicher, M. H., Andersen, S. L., Wallace, P., Klein, D. A., & Hostetter, J. (1996). Development of an affordable high-resolution activity monitor system for laboratory animals. Pharmacology Biochemistry & Behavior, 54, 479–483.

Todd, R. D. (1992). Neural development is regulated by classical neurotransmitters: Dopamine D2 receptor

stimulation enhances neurite outgrowth. Biological Psychiatry, 31, 794–807.

Towle, A. C., Criswell, H. E., Maynard, E. H., Lauder, J. M., Joh, T. H., Mueller, R. A., & Breese, G. R. (1989). Serotonergic innervation of the rat caudate following a neonatal 6- hydroxydopamine lesion: An anatomical, biochemical, and pharmacological study. Pharmacology Biochemistry & Behavior, 34, 367–374.

Velazquez-Moctezuma, J., & Diaz Ruiz, O. (1992). Neonatal treatment with clomipramine increased immobility in the forced swim test: An attribute of animal models of depression. Pharmacology Biochemistry & Behavior, 42, 737–739.

Vijayakumar, M., & Meti, B. L. (1999). Alterations in the levels of monoamines in discrete brain regions of clomipramine-induced animal model of endogenous depression. Neurochemical Research, 24, 345–349.

Vogel, G., Hartley, P., Neill, D., Hagler, M., & Kors, D. (1988). Animal depression model by neonatal clomipramine: Reduction of shock induced aggression. Pharmacology Biochemistry & Behavior, 31, 103–106.

Vogel, G., Neill, D., Hagler, M., & Kors, D. (1990). A new animal model of endogenous depression: A summary of present findings. Neuroscience and Biobehavioral Reviews, 14, 85–91.

Wiedemann, G., Pauli, P., Dengler, W., Lutzenberger, W., Birbaumer, N., & Buchkremer, G. (1999). Frontal brain asymmetry as a biological substrate of emotions in patients with panic disorders. Archives of General Psychiatry, 56, 78–84.

Yannielli, P. C., Kargieman, L., Gregoretti, L., & Cardinali, D. P. (1999). Effects of neonatal clomipramine treatment on locomotor activity, anxiety-related behavior, and serotonin turnover in syrian hamsters. Neuropsychobiology, 39, 200–206.