Published in final edited form as:

Neuroscience. 2013 September 17; 0: 213–224. doi:10.1016/j.neuroscience.2013.06.006.

Motor Stereotypies and Cognitive Perseveration in Non-human Primates Exposed to Early Gestational Irradiation

Lynn D. Selemon and Harriet R. Friedman

Department of Neurobiology, Yale University School of Medicine, New Haven, CT

Harriet R. Friedman: hrfriedman@gmail.com

Abstract

A number of psychiatric illnesses have been associated with prenatal disturbance of brain development, including autism, attention deficit hyperactivity disorder, and schizophrenia. Individuals afflicted with these disorders exhibit both repetitive motor and cognitive behavior. The potential role that environmental insult to the developing brain may play in generating these aberrant behaviors is unclear. Here we examine the behavioral consequences of an early gestational insult in the non-human primate. Rhesus macaques were exposed to x-irradiation during the first trimester of development to disrupt neurogenesis. The behavior of five fetally irradiated monkeys (FIMs) and five control monkeys (CONs) was observed as they matured from juvenile (1.5 years) to adult ages (4–5 years). Home-cage behavior was indistinguishable in the two groups. In the testing cage, circling was prevalent in both groups at juvenile ages, persisting to adulthood in three of the five FIMs. One FIM executed a ritualized motor sequence marked by semi-circling and undulating head movements. Seven macaques (4 FIMs, 3 CONs) were tested on a spatial Delayed Alternation (DA) task as adults. Perseverative errors and non-perseverative errors were recorded in early stages of the testing, at the 0 delay interval. While performing DA, FIMs made more errors of perseveration than CONs yet the number of total errors committed did not differ between groups. The presence of motor stereotypies and cognitive perseveration in fetally irradiated non-human primates suggests that environmental insult to the embryonic brain may contribute to repetitive motor and cognitive behaviors in neuropsychiatric diseases.

Keywords

Behavior; Neurodevelopment; Cortico-striatal; Dopamine; Autism; Schizophrenia

Complex motor stereotypies are a core feature of many pervasive developmental disorders (American Psychiatric Association, 1994). Repetitive behavior is most often associated with

Corresponding Author: Lynn D. Selemon, Ph.D., Department of Neurobiology, Yale University School of Medicine, PO Box 208001, New Haven, CT 06520-8001, Phone: 508-540-5306, FAX: 203-785-5263, ldselemon@aol.com.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Disclosure/Conflict of Interest

Drs. Selemon and Friedman have no conflicts of interest with this manuscript.

autism but in addition has been described in patients with attention deficit hyperactivity disorder (ADHD), Tourette's syndrome, Rett's disorder, and Fragile X syndrome (Wing and Gould, 1979; Hagberg et al., 1983; Frith and Done, 1990; Tsiouris and Brown, 2004). Motor stereotypies are also symptomatic of schizophrenia, especially the catatonic subtype (Manschreck, et al., 1982; Frith and Done, 1983; Ridley, 1994; Ungvari et al., 2010). Interestingly, normal young children exhibit motor stereotypies that are indistinguishable from the pathologic state; however, these diminish by about age five (Thelen et al., 1981; Evans et al., 1997; Leekam et al., 2007). The presence of motor stereotypies has also been documented in both humans and non-human primates following early sensory, environmental or social deprivation (Spitz, 1945; Bachara and Phelan, 1980; Ridley, 1994; Fazzi et al., 1999; Bos et al., 2010).

Pathologic repetition manifests at different functional levels: repetitive behavior ranges from the predominantly motor, such as tics, tremors, more complex motor stereotypies, motor programs, and rituals, to those that involve the cognitive domain, as for example preoccupation of thought (rumination), excessive focusing of attention (fixation), and inflexibility in planning and strategic execution (Ridley et al., 1994). In autism, the most commonly described repetitive motor behaviors are complex stereotypies of the orofacial region (grimacing) and of the arms and hands (hand flapping) (Campbell et al., 1990). In contrast, repetitive mobility in catatonic schizophrenia may include pacing or turning in circles, in addition to grimacing (DSM-IV, American Psychiatric Association, 1994; Mayo Clinic website).

Repetitive cognitive behavior is prevalent in adult neuropsychiatric disorders, including autism, schizophrenia and Obsessive Compulsive Disorder (OCD). In autistic individuals these behaviors include: preoccupations, circumscribed interests, and insistence on sameness (Carcani-Rathwell et al., 2006; Richter et al., 2007). Children with autism also exhibit more stereotyped responding in random choice tasks than non-autistic children with comparable levels of mental deficiency: that is autistic children tend to alternate between the two available choices (Frith, 1970; 1972). Subjects with schizophrenia have difficulty set shifting as evidenced by poor performance on the Wisconsin Card Sort Task (Weinberger et al., 1986). Schizophrenic subjects also exhibit stereotyped responses on a random button press test (Morrens et al., 2006), utilize both stereotyped responding and perseveration, i.e., repeating the same choice, on a random choice test (Frith and Done, 1983), and exhibit repetitive patterns of speech (Manschreck et al., 1985). Finally, cognitive repetitive behavior is also central to (OCD) in which overpowering urges to repeat rituals related to grooming and hygiene are most commonly observed (Rapoport, 1988). We will use the term "cognitive perseveration" to refer to the specific instance of cognitive repetitive behavior that involves repetitive choice of one item on a two- item choice task in which random choice or alternating choice of the two items is the most optimal strategy.

Motor stereotypies and cognitive perseveration may share an underlying neurobiologic substrate. For example, avian studies have shown that motor stereotypies correlate with cognitive perseveration on extinction or random choice tasks, suggesting a link between disinhibition of motor programs and failure to inhibit inappropriate cognitive responses (Garner and Mason, 2002; Garner et al., 2003). Notably, this same association between

increased cognitive perseveration and the presence of motor stereotypies has been described in schizophrenic subjects (Frith and Done, 1983). Moreover, both are thought to arise from disinhibition of striatal loop circuitry either via cortical disinhibition or dysregulation of dopamine transmission in the striatum (Evenden and Robbins, 1983; Castagne et al., 2009; Porsolt et al., 2010).

Schizophrenia and autism, disorders in which repetitive behaviors manifest, are thought to arise from disturbances in neurodevelopment. For example, epidemiologic studies over the past few decades have established that there is an association between environmental insult in the first half of gestation and increased risk for later development of schizophrenia with a wide spectrum of non-specific prenatal insults, e.g., maternal malnutrition, maternal folic acid deficiency, maternal infection, maternal stress and Rh incompatibility, conferring this increased risk (Brown, 2011). Similar links between prenatal insult and autism are beginning to emerge (Martin et al., 2008; Atladottir et al., 2010; Brown, 2012). While it is not known what developmental mechanisms are compromised by these many different factors, neurogenesis could be impacted since it is a prominent and critical developmental process associated with early brain development.

We have used fetal exposure to radiation to model prenatal environmental insult to the developing brain in schizophrenia. Radiation is lethal to dividing cells and has been shown to decrease cell number selectively in regions that are in the process of neurogenesis, i.e. final mitosis to produce prospective neurons (Algan and Rakic, 1997). Our previous studies have uncovered a remarkable degree of similarity between the neuropathology following early gestational exposure to radiation in the macaque and the neuropathology of schizophrenia. Widespread, but non-uniform, volume deficits have been observed most prominently in the thalamus, cortical gray matter and putamen (Schindler et al., 2002; Selemon et al., 2005; 2009; Aldridge et al., 2012). A similar global neuropathologic profile has been described in schizophrenia (Harrison, 1998; Selemon, 2001; Shenton et al., 2001; 2010). Thalamic neuron number overall and in the mediodorsal nucleus is reduced in fetally irradiated monkeys (FIMs) (Selemon et al., 2009); reduction of neuron number in the mediodorsal nucleus has also been described in brains from schizophrenic subjects (Pakkenberg, 1990; Young et al., 2000; Popken et al., 2000). The dorsolateral prefrontal cortex in FIMs is characterized by diminished cortical surface area but not thickness (Selemon et al., 2013), as has been reported in schizophrenic subjects (Guttlerez-Galve et al., 2010). We have also found abnormally high cortical neuronal density in the dorsolateral prefrontal cortex of FIMs (Selemon et al., 2013), a finding analogous to that in postmortem studies of schizophrenic brains (Selemon et al., 1995; 1998; 2003). Moreover, cognitive evaluation of eight of the ten monkeys that are subjects in the present study has established that FIMs exhibit a profound deficit on a manual spatial Delayed Response (DR) task at adult ages despite demonstrating proficiency as juveniles (Friedman and Selemon, 2010). Impairment of executive function is a cardinal feature of schizophrenia (Barch, 2005), a disease with onset in late adolescence/early adulthood. Certainly, fetal irradiation cannot reproduce the full scope of symptomatology and pathology associated with schizophrenia, but the fetally irradiated monkey model does replicate many key features of the disease.

In the present study, we examine the behavioral outcomes associated with disruption of neurogenesis during the early gestational period. The overall question we are addressing is whether environmental interference with neurogenesis, an essential developmental process, can produce repetitive behavior similar to that observed in neuropsychiatric illnesses. We chose early gestation as the time frame for radiation exposure because environmental insult in the first trimester has been shown to increase the risk for later development of schizophrenia and autism (Susser and Lin, 1992; Brown et al., 2004 Atladottir et al., 2010). Specifically, we examined whether (1) monkeys exposed to early gestational irradiation exhibit aberrant motor behaviors as juveniles; (2) abnormal motor behaviors persist until or emerge during adulthood; and, (3) fetally irradiated monkeys exhibit evidence of cognitive perseveration.

2. Experimental Procedures

2.1 Subjects

Ten Rhesus macaques were studied behaviorally from juvenile ages (18–31 months) to adulthood (4–5 years). Five were FIMs, i.e., monkeys exposed to doses of ionizing x-irradiation in early gestation as described in detail below. Five were control monkeys (CONs); four of these had been sham-irradiated at comparable times in early gestation, and the fifth was a non-irradiated control (Table 1). Animal designations include group (FIM or CON) followed by the first letter of the monkey's name in capitals and monkey's sex in small script, e.g., CON-Mm is a control male monkey. All experimental procedures, housing, care, and behavioral testing involving non-human primate subjects were performed in accordance with guidelines established by the Yale Institutional Animal Care and Use Committee.

2.2 Fetal irradiation exposure

The irradiation protocol has been described in detail previously (Algan and Rakic, 1997). Pregnant monkeys were sedated with ketamine (5–10 mg/kg), administered in conjunction with atropine (0.02 mg/kg). Ultrasound was used to locate the head of the fetus and to estimate the depth of the head from the abdominal surface. A 250 kV, 15 mA Stabilipan x-ray tube delivered a beam of irradiation (area 5×5 cm) to the head of the fetus. Head depth was factored into the determination of the duration of the exposure necessary to achieve the target dose of irradiation (Table 1). Fetal irradiation occurred at gestational days E30 - E41 with 3–4 exposures of 50 cGy given usually every other day for a total exposure dose of 150–200 cGy. Four of the five CONs were subjected to sham irradiation, i.e., the pregnant mothers were sedated, and ultrasound was used to localize the fetus but radiation was not administered (Table 1). Following irradiation or sham irradiation, the status of the pregnant monkeys was carefully monitored and viability of the fetus was confirmed by ultrasound throughout the remainder of the gestational period.

2.3 Birth and housing

Eight of the monkeys (4 FIM, 4 CON) were born naturally at term (E165) and stayed with their mothers until weaning at 6 months of age. Six were then pair housed, and two (CON-Vf and FIM-Sf) were singly housed in the adult non-human primate colony at Yale

University School of Medicine after attempts to pair house them together failed. Control and irradiated monkeys were not paired systematically as gender and age had to be taken into consideration. Some of the subjects in this study were pair-housed with other monkeys in the colony. CON-Lf was delivered by Caesarian section when the pregnancy went beyond the expected date of delivery; attempts to reunite her with her mother were unsuccessful. FIM-Am was delivered naturally but rejected by his mother. These two monkeys were raised in the primate nursery for six months and then pair-housed in the adult colony. Note that in both instances in which housing differed, i.e., nursery housing versus housing with the mother and single housing versus pair housing, the irradiated monkey exhibited repetitive behaviors while the control monkey did not. The health and well-being of all ten animals was carefully monitored throughout life. All ten were physically healthy; body weights did not differ between groups at any age (see Aldridge et al., 2012).

2.4 Behavioral observations

Five sets of data were collected (Table 2), but not all monkeys were included in all datasets for the following reasons. Behavioral observations in the home cage and in the Wisconsin General Testing Apparatus (WGTA) were not performed for the youngest two monkeys (CON-Lf and FIM-Am) because they were born approximately one year later than the others (Table 1) and technician resources were not available when they were of appropriate age (Table 2). CON-Lf, FIM-Am and CON-Jf were not introduced to the Delayed Alternation (DA) task and therefore error data for testing on DA are not available for these animals (Table 2).

2.4.1. Home cage behavioral observations—Behavioral observation sessions began when the monkeys were juveniles and continued for 5 months (Table 2). Monkeys were observed in their home cages for 20 sessions lasting ½ hour each. Pair-housed individuals were observed with the cohabitant present. Observations of a standard set of behaviors (Table 3) were noted using Monkey Watcher software, developed by Jonathon Traupman. This software allows the observer to tap a computer key that is coded for each behavior. Data are represented as per cent time spent in each behavior per session and averaged across 20 sessions for each monkey.

2.4.2 Behavioral observations in the WGTA—In order to observe the monkeys in a more controlled environment, additional behavioral observations were conducted while animals were in the WGTA but not engaged in any behavioral task. The monkeys were 38–50.5 months old at the time of these observations (Table 2). Food treats were available to the animals on the testing board in front of the WGTA. Fifteen sessions of ½-hour duration were observed for each animal. The Monkey Watcher program again was used to quantify observed behaviors. An additional 11–13 sessions were used to further study a set of specific behaviors that had been most commonly recorded; these behaviors are indicated (with asterisks) in Table 3.

2.4.3. Comparison of behavior at juvenile and adult ages while performing DR—One session of DR was videotaped for each monkey at juvenile and adult ages (Table 2) A two-minute segment encompassing the midpoint of the taped session was randomly

selected for study as this interval best represented the “steady state” behavior of each monkey. These two-minute segments were viewed by two individuals who were naive to the identity of the monkeys and to the purpose of the study. The incidence of three events was recorded: (1) sitting for longer than 5 seconds, (2) vocalizations, and (3) circling.

2.4.4. Counts of circling from videotapes of adults during cognitive testing—A more in depth study of circling behavior was undertaken by viewing all available videotapes from adult cognitive testing sessions. Adult monkeys (Table 2) were videotaped during cognitive testing on DA, DR, Visual Pattern Discrimination (VPD) or while performing a reaching task. The tapes also included one session for each monkey in the WGTA in which no task was given, except for FIM-Am in which two no-task sessions were videotaped. Food treats were provided as during visual observation in the WGTA. It should be emphasized that here we are reporting behavior of the monkeys while engaged in these tasks, not testing data. Cognitive data for DR and VPD have been reported, along with a detailed description of these two tests (Friedman and Selemon, 2010). Testing on DA had advanced beyond the 0 delay for only four of the seven monkeys that were tested, and training on the reaching task was in only preliminary stages for all ten monkeys. DA requires the monkey to retrieve a food reward from one of two covered wells in front of the WGTA. The reward is placed alternately in right and left wells. A screen is lowered for the prescribed delay period between trials. Thirty trials per day were administered on this task. The reaching task (described in detail in Diamond, 1990) requires the monkey to retrieve a food reward from a translucent box that has an opening in one side. The open side of the box is randomly rotated so that the opening faced the monkey (front) or was on the right or left side. The number of trials per session on the reaching task was variable and dependent on performance of the individual monkey.

Videotapes were viewed by one observer (LDS) to record all instances of circling behavior: full circles as well as semi-circles. The initial direction of the movement was documented. Paired semicircles, a semicircle in one direction followed immediately by a semicircle in the reverse direction, were scored as one circling event with its direction given by the initial semicircle. Individual videotaped sessions generally lasted 5–15 minutes. More than one hour of videotaped sessions was available for each of the ten monkeys. The average length of videotaped material available for viewing for each animal was comparable for CONs (93.1 ± 7.1 min) and FIMs (97.5 ± 9.2 min; $p = .602$). The mean number of circling events (circles and paired semicircles) per minute of videotape was calculated for each monkey.

2.4.5. Perseveration on the DA task—Seven adult monkeys (Table 2) completed DR testing and were trained on the initial stage of DA, i.e. at the 0-sec delay. As noted above, three of the seven advanced to longer delays. However, perseveration data were collected based on the 0-sec delay when all monkeys were at the same stage of testing. Correct performance on DA requires alternating between left and right food wells to uncover the reward. Picking the same well on two consecutive trials was scored as a non-perseverative error; picking the same well on more than two consecutive trials was scored as a perseverative error. The total number of non-perseverative errors and total (perseverative + non-perseverative) errors were counted and expressed as number of errors per 100 trials.

2.5. Statistics

Statistics were performed using IBM SPSS Statistics (ver.19). The non-parametric Mann-Whitney U test was used to compare means between groups because of the small number of subjects. Data are expressed as mean $\pm$ standard error of the mean.

3. Results

3.1. Home cage behavior

No group differences in behaviors were found when the monkeys were observed in their home cages (Fig. 1). Stress behaviors represented < 1% of behavior in five of the eight monkeys. FIM-Bm (6.0%), CON-Om (5.1%), and CON-Vf (1.7%) exhibited somewhat higher incidences of stress behaviors. Motor stereotypies were most frequent in CON-Jf (23.5%) and FIM-Sf (26.5%) but did not deviate substantially from group means (Fig. 1). Fine stereotypies were observed most frequently (10.0%) for FIM-Bm (Fig. 1). All monkeys spent about half of their time in stimulus driven responses and much less time in behaviors independent of stimuli (Fig. 1). Grooming behavior (0.3–5.0%), static posturing (0.1–1.0%), and submissive behaviors (0.0–1.3%) represented a small proportion of all behaviors. Monkeys spent between 3.1 and 12.2% of their time eating.

3.2 Behavior in the WGTA

Behavioral observation in the WGTA revealed that CONs (12.6%) spent more time doing fine motor stereotypies than FIMs (4.8%, $p = 0.043$) (Fig. 1). Two FIMs (FIM-Lf and FIM-Bm) exhibited very large numbers of motor stereotypies although there was not a significant difference between groups. As in the home cage, stress behaviors were infrequently observed for all animals although somewhat more common for CON-Om (3.1%) and FIM-Bm (6.3%). All monkeys spent a large proportion of time in stimulus driven behaviors and virtually no time in behaviors independent of stimuli (Fig. 1). Grooming (0.0–0.2%), static posturing (0.0–2.0%) and submissive behaviors (0.0–2.6%) were not prevalent. Most monkeys spent 2.5–7.6% of the time in the WGTA eating with the exception being FIM-Bm (0.8%).

No significant group differences were found based on additional observation of specific behaviors (see Table 3); however, the two FIMs who exhibited elevated numbers of motor stereotypies (see above) were now observed circling (FIM-Lf, 44.3%) and pacing (FIM-Bm, 40.1%) (Fig. 2). Note that semi-circling behavior was tabulated as “pacing” and not “circling” during these observational sessions. FIM-Bm also saluted with some frequency (6.1 %) as did CON-Om (1.7%) though less often. CON-Vf and FIM-Lf vocalized during these sessions; all others did not. Jumping side-to-side was observed infrequently for CON-Vf (4.3%) and FIM-Tm (2.3%). In addition CON-Vf paced side-to-side (8.0%).

3.3. Behavior while performing DR at juvenile and adult ages as observed in 2-min videotape clips

Two-tailed Pearson's inter-rater correlations ($N = 20$) were all significant for observational tallies (sits: 0.926, $p < 0.001$; vocalizations: 0.989, $p < 0.001$; circles: 0.960, $p < 0.001$). No significant group differences were observed for the three recorded behaviors at juvenile or

adult ages. However, when incidences of these behaviors in juveniles versus adults were compared for each group, significant differences were observed (Fig. 2). Notably the majority of CONs and FIMs circled as juveniles but circling persisted into adulthood only in the FIM group for FIM-Lf and FIM-Bm. Circling behavior was significantly reduced in adult CONs (0.4 ± 0.3 circles) compared to juvenile CONs (14.4 ± 6.0 circles; $p = 0.015$) whereas circling did not significantly diminish in the FIM group in adults (13.1 ± 7.8 circles) compared to juveniles (19.4 ± 8.0 circles; $p = 0.249$). Vocalization was decreased in adult FIMs (2.6 ± 1.7 vocalizations) in comparison to juvenile FIMs (23.3 ± 3.3 vocalizations; $p = 0.009$) and tended to be reduced in adult CONs (1.1 ± 0.9 vocalizations) versus juvenile CONs (11.2 ± 4.3 vocalizations; $p = 0.085$) as well. Although there were no age-related differences in sitting for either group, sitting did increase for the majority of animals in adulthood. Only one control monkey (FIM-Lf) sat often during the DR session as an infant whereas 6 monkeys (3 CONs and 3 FIMs) sat for long periods as adults.

3.4 Circling as observed during videotaped sessions of adult cognitive testing

Eight of the ten monkeys were full adults at the time of videotaping (~5 years old). CON-Lf and FIM-Am were approximately one year younger (~4 years old) (Table 2); however mean ages of the groups did not differ (CONs: 58.9 ± 2.86 months; FIMs: 60.3 ± 3.37 months; $p = .462$). FIMs exhibited more circling behavior (2.27 ± 1.06 circles/min of video) than CONs (0.10 ± 0.08 circles/min of video; $p = 0.047$) (Fig. 3). In particular, FIM-Lf (5.51 circles/min) and FIM-Bm (3.92 circles/min) exhibited pronounced circling (or paired semi-circling in the case of FIM-Bm). In one session, FIM-Lf circled 43 times in a span of 3 minutes. Circling was also elevated in FIM-Sf (1.59 circles/min) compared to any of the CONs (highest was CON-Mm at 0.32 circles/min). Two CONs never circled; FIM-Tm circled only once.

For the seven monkeys who circled more than once, the direction of circling was invariant for six. FIM-Lf (545 circling events) and FIM-Sf (177 circling events) always circled in the clockwise direction whereas FIM-Bm (353 circling events) began all paired semicircles and full circles in the counterclockwise direction. CON-Mm (30 circling events) and CON-Vf (9 circling events) circled clockwise while CON-Lf (6 circling events) circled counterclockwise. FIM-Am preferred the counterclockwise direction; 39 of 41 circling events were in the counterclockwise direction for this monkey.

Circling behavior was notable not only because of its prominence in the behavioral repertoire of FIM-Bm but also because of the invariant nature of the movements accompanying the circling. In particular, FIM-Bm executed a rigid sequence of movements that always began with a counterclockwise semicircle immediately followed by a clockwise semicircle (Fig 4). At the beginning of an event, the head was lifted and the neck tilted upward and toward the back of the cage. As the circling commenced the head was whipped around in a tilting movement (Fig. 4). These paired semi-circling events were often repeated many times in succession and sometimes ended with a complete counterclockwise circle.

3.5 Perseverative errors on DA

FIMs (9.4 ± 1.3 per 100 trials) made more perseverative errors on DA than CONs did (1.5 ± 0.6 per 100 trials; $p = 0.034$) (Fig. 5). The total number of errors (perseverative + non-perseverative) did not differ between groups (CONs: 27.8 ± 4.5 per 100 trials; FIMs: 37.8 ± 2.2 per 100 trials; $p = 0.157$). All four FIMs made more perseverative errors than the three CONs (Fig. 5).

4. Discussion

Non-human primates exposed to x-irradiation in early gestation exhibited both repetitive motor (circling) and cognitive (perseveration) behavior. FIMs circled excessively as adults while observed during cognitive testing and made more errors of perseveration on DA than CONs. Although circling behavior was present in both groups as juveniles, it persisted into adulthood only in FIMs. Notably, FIMs did not exhibit behavioral abnormalities during observation in their home cages, and the only significant difference between FIMs and CONs when observed in the testing cage setting but not engaged in a task was that FIMs exhibited less time than CONs in fine motor behaviors.

The presence of both repetitive motor and cognitive behavior in these animals suggests that environmental injury to the developing brain during early gestation may be associated with dysfunction of control mechanisms governing the selection of motor programs and cognitive responding. These findings are relevant to understanding the etiology of motor stereotypies and cognitive perseveration in neurodevelopmental diseases like autism, ADHD, and schizophrenia.

4.1 Home cage behavior versus testing cage behavior

Behavioral abnormalities were detected only when the FIMs were observed in the testing cage, not in the home cage. The home cage represents a less controlled environment than the WGTA as day to day activity of the other animals in the primate colony varies and results in changing auditory and visual ambient stimuli. In addition, most of the monkeys were pair housed so that interaction with the cohabitating monkeys also contributed to the changing dynamics of the home cage environ. Thus, detection of behavioral differences in the WGTA could be attributed to the more consistent background state in the testing cage allowing for more meaningful comparison across monkeys. Another possibility is that the WGTA constituted a mildly stressful environment for the monkeys that may have elicited behavioral abnormalities in the FIMs. While we cannot entirely discount this possibility, there are some compelling arguments to refute this explanation. For instance, all ten animals were familiar with the WGTA and had experienced positive reinforcement, i.e., getting food treats, with this environment. At the time of behavioral observation in the WGTA, eight of the monkeys had been tested extensively on DR, and the two youngest had been acclimated to the testing environment and had undergone preliminary testing on DR. In addition, stress behaviors were not observed more frequently in the WGTA than in the home cage. Alternatively, the WGTA may simply restrict the available repertoire of possible behaviors and enhance those behaviors that are self-generated. If this is the case, it is interesting that the type of motor

behavior accentuated in the two groups of monkeys differed: fine motor stereotypies predominated in the CONs whereas gross motor stereotypies emerged in two of the FIMs.

There is a large body of literature demonstrating that stereotypies may develop in caged animals particularly if those animals are reared in isolation (for review, see Ridley, 1994). However, it seems very unlikely that housing or rearing conditions accounted for the presence of stereotypies in FIMs in this study since the animals were raised in social conditions with appropriate stimulation and enrichment. Moreover housing and rearing conditions were comparable in the two groups. Eight of the ten monkeys were raised with their mothers until 6 months of age and then pair-housed in the adult colony; one FIM and one CON were nursery raised, and one FIM and one CON were singly housed in the adult colony. Of the nursery-raised and singly-housed monkeys, in each instance only the FIM exhibited repetitive behaviors.

4.2 Persistent circling behavior in adult irradiated monkeys

Comparison of the monkeys at juvenile and adult ages showed that circling behavior was prevalent in both groups of animals as juveniles but persisted only in 3 of the FIMs as adults. The observation of circling in adult FIMs therefore probably represents failure to suppress a youthful behavior with maturation to adulthood rather than emergence of an abnormal behavior that did not previously exist.

We observed that FIMs circled exclusively, or for one FIM preferentially, in one direction though not the same direction for all animals. It is well established that unidirectional circling in rodents can be induced by causing an imbalance in the dopamine innervation of the striatum (Ungerstedt and Arbuthnott, 1970). Predominant leftward circling has also been described in never medicated or chronically unmedicated schizophrenic patients, indicating more pronounced over-activity of dopamine stimulation on the right side (Bracha, 1987). It is unclear why fetal irradiation might lead to asymmetry of the dopamine innervation of the striatum, and unfortunately, we do not know whether there are hemispheric differences in the neuropathology in these animals. Postmortem studies of these animals have been limited to the left hemisphere (Selemon et al., 2009; 2013) and magnetic resonance imaging studies have been performed bilaterally (Aldridge et al., 2012). It is worth noting that CONs also showed selective directionality of circling although the number of circling events was much smaller.

The motor stereotypies observed in the FIMs may be characterized as whole body stereotypies because they involved coordinated movements of the whole body in circling. These whole body stereotypies are distinct from the complex stereotypies limited to the upper limbs that have been most commonly described in autistic children (Campbell et al., 1990). OCD patients perform complex rituals that involve whole body motor programs, but these usually involve hand washing or other grooming activities that represent excessive expression of what is normally a functional behavior (Rapoport, 1988). Interestingly, “turning in circles” is a symptom of the catatonic subtype of schizophrenia (Mayo Clinic website), and even those schizophrenic subjects who do not circle excessively often show a pronounced preference for left-ward turning (Bracha, 1987).

4.3 Motor stereotypies and cognitive perseveration: a common neurobiologic substrate?

All four FIMs that were tested on DA committed more perseverative errors than CONs. Studies of schizophrenia subjects have established an association between repetitive motor behavior and cognitive perseveration tendencies in speech (Manschreck et al., 1981). In addition, animal studies have shown that the presence of motor stereotypies correlates with cognitive perseveration on random choice tasks (Garner and Mason, 2002; Garner et al., 2003). In this study, the three FIMs who circled also committed perseverative errors. However, on an individual basis we found a disassociation between the two behavioral abnormalities as FIM-Tm who did not exhibit gross motor stereotypies committed perseveration errors as well. Motor stereotypies in rodents and primates can be induced by an asymmetric imbalance in the dopamine innervation of the neostriatum or by chronic sensitizing doses of amphetamine or cocaine (Ungerstedt and Arbuthnott, 1970; Ridley, 1994; Castner and Goldman-Rakic, 1999). These studies strongly implicate the nigrostriatal dopaminergic pathway as an underlying substrate for repetitive motor behavior. Neonatal lesions of the hippocampus and amygdala in non-human primates are also associated with delayed onset of motor stereotypies but these have been attributed to altered development of the prefrontal cortex and subcortical dopamine pathways secondary to the original temporal lobe lesion (Bauman et al., 2008). Graybiel (2008) makes a strong case for cortico-striatal circuitry as the underlying substrate for both motor and cognitive repetitive behavior. Furthermore, in studies in the non-human primate the striosomal compartment of the neostriatum has been pinpointed in mediating motor stereotypies associated with drug sensitization (Saka et al., 2004). These findings suggest a role for “limbic” frontal cortices, i.e., orbitofrontal, medial frontal and anterior cingulate cortices, in the generation of motor stereotypies as these cortices project to the striosome compartment (Graybiel et al., 2000). Cognitive perseveration is also mediated by cortico-striatal projections but may more specifically involve the dorsolateral prefrontal cortex and its projection to the caudate nucleus (Bilder and Goldberg, 1987; Robbins, 1990). Thus, the neurobiologic substrates for stereotypies and cognitive perseveration, although parallel and overlapping, may not be identical.

4.4 Neuropathology in irradiated monkeys

For nine of ten of the animals (not CON-Vf) included in the present study, volumetric data based on magnetic resonance imaging were available at four ages: 6 months, 12 months, 3 years, and 5 years of age. The FIMs exhibited reduced cortical gray matter and putamen volumes across all ages compared to CONs (Aldridge et al., 2012). These volumetric reductions are consistent with a deficit in the cortico-striato-thalamo-cortical loops that mediate selection of motor programs. Somewhat surprisingly, FIM-Bm had the largest brain of any monkey in the study. In contrast, cortical and putamen volumes for FIM-Bm were near the mean for the CON group at the adult age, perhaps representing a relative deficit. Although speculative, this relative deficit could account for the stereotyped semi-circling with a pronounced head lilt, which was a signature feature of FIM-Bm's behavioral repertoire. However, individual differences in neuropathology do not fully explain the behavioral differences between animals. For example, FIM-Tm did not exhibit motor stereotypies yet his profile of volumetric reduction was similar to those of FIM-Lf and FIM-Sf who did circle excessively (Aldridge et al., 2012). Note that all four FIMs tested on DA

committed perseverative errors despite the observation that FIM-Bm had a larger caudate volume than any of the other monkeys in the study (Aldridge et al., 2012). Nonetheless, four of the five FIMs had smaller volumes relative to CONs in all four structures examined (cortex, caudate, putamen, thalamus), underscoring the fact that cortico-striato-thalamo-cortical loops may be compromised by early gestational irradiation exposure (Aldridge et al., 2012).

Postmortem studies in FIMs have further documented the cellular pathology underlying deficits in thalamic and cortical volume. Cell counts in a cohort of FIMs, not including the monkeys in this study, uncovered reduced neuron number in the thalamus as a whole and in the mediodorsal nucleus (Selemon et al., 2009). These findings mirror the reduction of neuron number in the mediodorsal nucleus of the thalamus observed in brains from schizophrenic subjects (Pakkenberg, 1990; Young et al., 2000; Popken et al., 2000). In a recent study of morphologic changes in Walker's area 46 of the dorsolateral prefrontal cortex, which included the ten monkeys in this study, cortical neuron number was unchanged and neuronal density was increased (Selemon et al., 2013). Comparable elevated neuronal density has been observed in postmortem brains from schizophrenic subjects and has been interpreted as a correlate of reduced cortical connectivity (Selemon et al., 1995; 1998; 2003). Together these findings point to a number of parallels in the pathology of FIMs and schizophrenic brains and lend further support to the idea that abnormalities in cortico-striato-thalamo-cortical circuitry might play a role in the generation of repetitive behaviors.

4.5 Relevance to neurodevelopmental disease

Motor and cognitive repetitive behaviors are core features of several neuropsychiatric diseases such as autism, ADHD, OCD, and schizophrenia (Frith and Done, 1980; 1983; Wing and Gould, 1979). These neuropsychiatric conditions are thought to arise from a combination of genetic and environmental factors (Trottier et al., 1999; Faraone and Khan, 2006; Tandon et al., 2008; Taylor, 2011; Latimer et al., 2012). It is therefore difficult to determine whether neuropsychotic symptoms are the product of malfunctioning genetic programs or the consequence of prenatal disruption of normal brain development by environmental factors. The present study illustrates that experimental interference with early gestational brain development can lead to the motor stereotypies and cognitive perseveration in the adult non-human primate. Previously, Martin et al (2008) showed that prenatal exposure of Rhesus macaques to serum antibodies collected from mothers of autistic children produced whole body stereotypies in these animals. Together with the Martin et al. (2008) findings, the present study highlights the potential for early brain insult to lead to adverse psychomotor consequences that persist into adulthood.

Acknowledgments

We thank Heidi Voegeli for behavioral observation and videography of the monkeys at juvenile ages. This work was supported by National Institutes of Health grant MH59329 (LDS) and the Washington University Silvio Conte Center grant MH071616 (John G. Csernansky, M.D., Program Director).

Abbreviations

ADHD	Attention Deficit Hyperactivity Disorder
CON	control monkey
DA	Delayed Alternation
DR	Delayed Response
FIM	fetally irradiated monkey
OCD	Obsessive Compulsive Disorder
RS	Random Sampling
VPD	Visual Pattern Discrimination
WGTA	Wisconsin General Testing Apparatus

References

- Aldridge K, Wang L, Harms MP, Moffitt AJ, Cole KK, Csernansky JG, Selemon LD. Early prenatal environmental insult results in localized brain volume deficits: A longitudinal analysis of the fetally irradiated macaque. *PLoS One*. 2012; 7:e43109. [PubMed: 22905212]
- Algan O, Rakic P. Radiation-induced, lamina-specific deletion of neurons in the primate visual cortex. *J Comp Neurol*. 1997; 12:335–352. [PubMed: 9133572]
- American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed.. Washington, DC: American Psychiatric Association; 2000.
- Atladdottir HO, Thorsen P, Ostergaard L, Schendel DE, Lemcke S, Abdallah M, Parner ET. Maternal infection requiring hospitalization during pregnancy and autism spectrum disorder. *J Autism Dev Disord*. 2010; 40:1423–1430. [PubMed: 20414802]
- Bachara GH, Phelan WJ. Rhythmic movement in deaf children. *Percept Mot Skills*. 1980; 50:933–934. [PubMed: 7402876]
- Barch DM. The cognitive neuroscience of schizophrenia. *Ann Rev Clin Psychol*. 2005; 1:321–353. [PubMed: 17716091]
- Bauman MD, Toscano JE, Babineau BA, Mason WA, Amaral DG. Emergence of stereotypies in juvenile monkeys (*Macaca mulatta*) with neonatal amygdala or hippocampus lesions. *Behav Neurosci*. 2008; 122:1005–1015. [PubMed: 18823158]
- Bilder RM, Goldberg E. Motor perseverations in schizophrenia. *Arch Clin Neuropsychol*. 1987; 2:195–214. [PubMed: 14589613]
- Bos KJ, Zeanah CH Jr, Smyke At, Fox NA, Nelson CA 3rd. Stereotypies in children with a history of early institutional care. *Arch Pediatr Adolesc Med*. 2010; 164:406–411. [PubMed: 20439790]
- Bracha HS. Asymmetric rotational (circling) behavior, a dopamine-related asymmetry: Preliminary findings in unmedicated and never-medicated schizophrenic patients. *Biol Psychiatry*. 1987; 33:995–1003. [PubMed: 3607140]
- Brown AS. The environment and susceptibility to schizophrenia. *Prog Neurobiol*. 2011; 93:23–58. [PubMed: 20955757]
- Brown AS. Epidemiologic studies of exposure to prenatal infection and risk of schizophrenia and autism. *Dev Neurobiol*. 2012; 72:1272–1276. [PubMed: 22488761]
- Brown AS, Begg MD, Gravenstein S, Schaefer CA, Wyatt RJ, Bresnahan M, Babulas VP, Susser ES. Serologic evidence of prenatal influenza in the etiology of schizophrenia. *Arch Gen Psychiatry*. 2004; 61:774–780. [PubMed: 15289276]
- Campbell M, Locascio JJ, Choroco MC, Spencer EK, Malone RP, Kafantaris V, Overall JE. Stereotypies and tardive dyskinesia: Abnormal movements in autistic children. *Psychopharmacol Bull*. 1990; 26:260–266.

- Carcani-Rathwell I, Rabe-Hasketh S, Santosh PJ. Repetitive and stereotyped behaviors in pervasive developmental disorders. *J Child Psychol Psychiatry*. 2006; 47:573–581. [PubMed: 16712634]
- Castagne V, Moser PC, Porsolt RD. Preclinical behavioral models for predicting antipsychotic activity. *Adv Pharmacol*. 2009; 57:381–418. [PubMed: 20230767]
- Castner SA, Goldman-Rakic PS. Long-lasting psychotomimetic consequences of repeated low-dose amphetamine exposure in rhesus monkeys. *Neuropsychopharmacol*. 1999; 20:10–28.
- Diamond A. Developmental time course in human infants and infant monkeys, and the neural bases of inhibitory control in reaching. *Ann N Y Acad Sci*. 1990; 608:637–69. [PubMed: 2075965]
- Evans DW, Leekman JF, Carter A, Reznick JS, Henshaw D, King RA, Pauls D. Ritual, habit and perfectionism: The prevalence and development of compulsive-like behaviour in normal young children. *Child Develop*. 1997; 68:58–68. [PubMed: 9084125]
- Evenden JL, Robbins TW. Increased response switching, perseveration and perseverative switching following *d*-amphetamine in the rat. *Psychopharmacol*. 1983; 80:67–73.
- Faraone SV, Khan SA. Candidate gene studies of attention deficit/hyperactivity disorder. *J Clin Psychiatry*. 2006; 67(Suppl 8):13–20. [PubMed: 16961425]
- Fazzi E, Lanners J, Danova S, Ferrarri-Ginevra O, Gheza C, Luparia A, Balottin U, Lanzi G. Stereotyped behaviours in blind children. *Brain Dev*. 1999; 21:522–528. [PubMed: 10598052]
- Friedman HR, Selemon LD. Fetal irradiation interferes with adult cognition in the non-human primate. *Biol Psychiatry*. 2010; 68:108–111. [PubMed: 20399419]
- Frith CD, Done DJ. Stereotyped responding by schizophrenic patients on a two-choice guessing task. *Psychol Med*. 1983; 13:779–786. [PubMed: 6665094]
- Frith, CD.; Done, DJ. Stereotyped behavior in madness and in health. In: Cooper, SJ.; Dourish, CT., editors. *Neurobiology of Stereotyped behavior*. Oxford: Clarendon Press; 1990. p. 232-259.
- Frith U. Studies in pattern detection in normal and autistic children. II. Reproduction and production of color sequences. *J Exp Child Psychol*. 1970; 10:120–135. [PubMed: 5459646]
- Frith U. Cognitive mechanisms in autism: Experiments with color and tone sequence production. *J Autism Child Schizophr*. 1972; 2:160–173. [PubMed: 5068668]
- Garner JP, Mason GJ. Relationship between cage stereotypies and behavioural disinhibition in laboratory rodents. *Beh Brain Res*. 2002; 136:83–92.
- Garner JP, Meehan CL, Mench JA. Stereotypies in caged parrots, schizophrenia and autism: Evidence for a common mechanism. *Beh Brain Res*. 2003; 145:125–134.
- Graybiel AM. Habits, rituals, and the evaluative brain. *Ann Rev Neurosci*. 2008; 31:359–387. [PubMed: 18558860]
- Graybiel AM, Canales JJ, Capper-Loup C. Levodopa-induced dyskinesias and dopamine-dependent stereotypies: A new hypothesis. *Trends Neurosci*. 2000; 23(Suppl.):S71–S77. [PubMed: 11052223]
- Guttlerez-Galve L, Wheeler-Kingshott CAM, Altmann DR, Price G, Chu EM, Leeson VC, Lobo A, Barker GJ, Barnes TRE, Joyce EM, Ron MA. Changes in the frontotemporal cortex and cognitive correlates in first episode psychosis. *Biol Psychiatry*. 2010; 68:51–60. [PubMed: 20452574]
- Hagberg B, Aicardi J, Dias K, Ramos O. A progressive syndrome of autism, dementia, ataxia and loss of purposeful hand use in girls: Rett's syndrome: Report of 35 cases. *Ann Neurol*. 1983; 14:471–479. [PubMed: 6638958]
- Harrison PJ. The neuropathology of schizophrenia: A critical review of the data and their interpretation. *Brain*. 1999; 122:593–624. [PubMed: 10219775]
- Latimer K, Wilson P, Kemp J, Thompson L, Sim F, Gillberg C, Puckering C, Minnis H. Disruptive behaviour disorders: A systematic review of environmental antenatal and early years risk factors. *Child Care Health Dev*. 2012; 38:611–628. [PubMed: 22372737]
- Leekam S, Tandos J, McConachie H, Meins E, Parkinson K, Wright C, Turner M, Arnott B, Vittorini L, Le Couteur A. Repetitive behaviors in typically developing 2-year-olds. *J Child Psychol Psychiatry*. 2007; 48:1131–1138. [PubMed: 17995489]
- Manschreck TC, Maher BA, Ader DN. Formal thought disorder, the type-token ratio, and disturbed voluntary motor movement in schizophrenia. *Biol Psychiatry*. 1981; 13:7–15.

- Manschreck TC, Maher BA, Rucklos ME, Vereen DR. Disturbed voluntary motor activity in schizophrenia disorder. *Psychol Med.* 1982; 12:73–84. [PubMed: 6123128]
- Manschreck TC, Maher BA, Hoover TM, Ames D. Repetition in schizophrenic speech. *Lang Speech.* 1985; 28:255–268. [PubMed: 3836315]
- Martin LA, Ashwood P, Braunschweig D, Cabanlit M, Van de Water J, Amaral DG. Stereotypies and hyperactivity in rhesus monkeys exposed to IgG from mothers of children with autism. *Brain Beh Immunity.* 2008; 22:806–816.
- [last accessed May 18, 2013] Mayo Clinic website. <http://www.mayoclinic.com/health/catatonicschizophrenia/DS00863/DSECTION=symptoms>
- Morrens M, Hulstijn W, Lewi PJ, De Hert M, Sabbe BG. Stereotypy in schizophrenia. *Schizophr Res.* 2006; 84:397–404. [PubMed: 16549339]
- Pakkenberg B. Pronounced reduction of total neuron number in the mediodorsal thalamic nucleus and nucleus accumbens in schizophrenics. *Arch Gen Psychiatry.* 1990; 47:1023–1028. [PubMed: 2241504]
- Popken, GJ; Bunney, WE., Jr; Potkin, SG.; Jones, EG. Subnucleus-specific loss of neurons in medial thalamus of schizophrenics. *Proc Natl Acad Sci USA.* 2000; 97:9276–9280. [PubMed: 10908653]
- Porsolt RD, Moser PC, Castagne V. Behavioral indices in antipsychotic drug discovery. *JPharmacol Exper Therapeut.* 2010; 333:632–638.
- Rapoport JL. The neurobiology of obsessive-compulsive disorder. *J Am Med Assoc.* 1988; 260:2888–2890.
- Richter J, Bishop SL, Kleinke JR, Lord C. Restricted and repetitive behaviors in young children with autism spectrum disorders. *J Autism Dev Disord.* 2007; 37:73–85. [PubMed: 17195920]
- Ridley RM. The psychology of perseverative and stereotyped behavior. *Progr Neurobiol.* 1994; 44:221–231.
- Robbins TW. The case for frontostriatal dysfunction in schizophrenia. *Schizophr Bull.* 1990; 16:391–402. [PubMed: 2287930]
- Saka E, Goodrich C, Harlan P, Madras BK, Graybiel AM. Repetitive behaviors in monkeys are linked to specific striatal activation patterns. *J Neurosci.* 2004; 24:7557–7565. [PubMed: 15329403]
- Schindler MK, Wang L, Selemon LD, Goldman-Rakic PS, Csernansky JG. Abnormalities of thalamic volume and shape detected in fetally irradiated rhesus monkeys with high dimensional brain mapping. *Biol Psychiatry.* 2002; 51:827–837. [PubMed: 12007457]
- Selemon LD. Regionally diverse cortical pathology in schizophrenia: Clues to the etiology of the disease. *Schizophr Bull.* 2001; 27:349–377. [PubMed: 11596841]
- Selemon LD, Rajkowska G, Goldman-Rakic PS. Abnormally high neuronal density in the schizophrenic cortex: A morphometric analysis of prefrontal area 9 and occipital area 17. *Arch Gen Psychiatry.* 1995; 52:805–818. [PubMed: 7575100]
- Selemon LD, Rajkowska G, Goldman-Rakic PS. Elevated neuronal density in prefrontal area 46 in brains from schizophrenic patients: Application of a 3-dimensional, stereologic counting method. *J Comp Neurol.* 1998; 392:402–412. [PubMed: 9511926]
- Selemon LD, Mrzljak J, Kleinman JE, Herman MM, Goldman-Rakic PS. Regionalspecificity in the neuropathologic substrates of schizophrenia: A morphometric analysis of Broca's area 44 and area 9. *Arch Gen Psychiatry.* 2003; 60:69–77. [PubMed: 12511174]
- Selemon LD, Wang L, Nebel MB, Csernansky JG, Goldman-Rakic PS, Rakic P. Direct and indirect effects of fetal irradiation on cortical gray and white matter volume in the macaque. *Biol Psychiatry.* 2005; 57:83–90. [PubMed: 15607304]
- Selemon LD, Begovic A, Rakic P. Selective reduction of neuronal number and volume of the mediodorsal nucleus of the thalamus in macaques following irradiation at early gestational ages. *J Comp Neurol.* 2009; 515:454–464. [PubMed: 19459221]
- Selemon LD, Ceritoglu C, Ratnanather JT, Wang L, Harms MP, Aldridge K, Begovic A, Csernansky JG, Millier MI, Rakic P. Abnormalities of the primate prefrontal cortex caused by radiation in early or midgestation. *J Comp Neurol.* 2013; 521:1040–1053. [PubMed: 22911497]
- Shenton ME, Dickey CC, Frumin M, McCarley RW. A review of MRI findings in schizophrenia. *Schizophr Res.* 2001; 49:1–52.

- Shenton ME, Whitford TJ, Kubicki M. Structural neuroimaging in schizophrenia: From methods to insights to treatments. *Dialog Clin Neurosci*. 2010; 12:317–332.
- Spitz RA. Hospitalism – An inquiry into the genesis of psychiatric conditions in early childhood. *Psychoan Study Child*. 1945; 1:53–74.
- Susser ES, Lin ST. Schizophrenia after prenatal exposure to the Dutch Hunger Winter of 1944–1945. *Arch Gen Psychiatry*. 1992; 49:983–988. [PubMed: 1449385]
- Tandon R, Keshavan MS, Nasrallah HA. Schizophrenia, “just the facts” what we know in 2008. 2. Epidemiology and etiology. *Schizophr Res*. 2008; 102:1–18.
- Taylor S. Etiology of obsessions and compulsions: A meta-analysis and narrative review of twin studies. *Clin Psychol Rev*. 2011; 31:1361–1372. [PubMed: 22024245]
- Thelen E. Kicking, rocking, and waving: contextual analysis of rhythmical stereotypies in normal human infants. *Animal Behav*. 1981; 29:3–11.
- Trottier G, Srivastava L, Walker CD. Etiology of infantile autism: a review of recent advances in genetic and neurobiological research. *J Psychiatry Neurosci*. 1999; 24:103–115. [PubMed: 10212552]
- Tsiouris JA, Brown WT. Neuropsychiatric symptoms of fragile X syndrome: Pathophysiology and pharmacotherapy. *CNS Drugs*. 2004; 18:687–703. [PubMed: 15330685]
- Ungerstedt U, Arbuthnott GW. Quantitative recording of rotational behavior in rats after 6-hydroxy-dopamine lesions of the nigrostriatal dopamine system. *Brain Res*. 1970; 24:485–493. [PubMed: 5494536]
- Ungvari GS, Caroff SN, Gerevich J. The catatonia conundrum: Evidence of psychomotor phenomena as a symptom dimension in psychotic disorders. *Schizophr Bull*. 2010; 36:231–238. [PubMed: 19776208]
- Weinberger DR, Berman KF, Zec RF. Physiologic dysfunction of dorsolateral prefrontal cortex in schizophrenia. III. Role of neuroleptic treatment, attention, and mental effort. *Arch Gen Psychiatry*. 1986; 43:114–124. [PubMed: 3947207]
- Wing L, Gould J. Severe impairments of social interaction and associated abnormalities in children: Epidemiology and classification. *J Autism Dev Disord*. 1979; 9:11–29. [PubMed: 155684]
- Young KA, Manaye KF, Liang C-L, Hicks PB, German DC. Reduced number of mediodorsal and anterior thalamic neurons in schizophrenia. *Biol Psychiatry*. 2000; 47:900–953.

HIGHLIGHTS

- Fetal irradiation in macaques results in repetitive motor and cognitive behavior.
- Excessive circling was observed in three of the five fetally irradiated monkeys.
- Irradiated monkeys committed more perseverative errors on Delayed Alternation.
- Environmental insult may contribute to repetitive behaviors in psychiatric illness.

Figure 1.

Individual plots of percent time spent in four behavioral categories in the animal's home cage (above) and in the Wisconsin General Testing Apparatus (WGTA) (below). No differences were observed in home cage behavior. Fine motor stereotypies were reduced in FIMs (filled triangles) compared to CONs (open triangles). Two of the four FIMs exhibited elevated motor stereotypies. $\triangle$ = CON-Mm, $\triangleright$ = CON-Om, $\triangleleft$ = CON-Vf, ∇ = CON-Jf, $\blacktriangle$ = FIM-Tm, $\blacktriangleright$ = FIM-Lf, $\blacktriangleleft$ = FIM-Sf, $\blacktriangledown$ = FIM-Bm. Asterick indicates $p < 0.05$.

Figure 2.

Plots of percent time spent in three specific behaviors in the WGTA. Group differences between CONs (open triangles) and FIMs (filled triangles) were not observed; however, one FIM exhibited prevalent circling and another showed prominent pacing (semicircling) behavior. Threatening behavior, a sign of stress, was low in both groups. $\triangle$ = CON-Mm, $\triangleright$ = CON-Om, $\triangleleft$ = CON-Vf, ∇ = CON-Jf, $\blacktriangle$ = FIM-Tm, $\blacktriangleright$ = FIM-Lf, $\blacktriangleleft$ = FIM-Sf, $\blacktriangledown$ = FIM-Bm.

Figure 3.

Comparison of juvenile and adult behavior while performing the manual spatial Delayed Response (DR) task. Sitting was more prevalent in both CONs (open triangles and circle) and FIMs (filled triangles and circle) as adults than as juveniles though significant age-related differences were not found. Vocalization decreased in adult FIMs compared to juvenile FIMs and tended to be lower in adult CONs compared to juvenile CONs. Circling decreased in CONs with age, but remained high in two of the three adult FIMs. Note that only FIM-Tm as an adult (▲filled with star) was proficient on DR (Friedman and Selemon, 2010) and that he sat more than any other FIM and did not vocalize or circle. Δ = CON-Mm, $\triangleright$ = CON-Om, $\triangleleft$ = CON-Vf, ∇ = CON-Jf, O= CON-Lf, $\blacktriangle$ = FIM-Tm, $\blacktriangleright$ = FIM-Lf, $\blacktriangleleft$ = FIM-Sf, $\blacktriangledown$ = FIM-Bm, $\bullet$ = FIM-Am.

Figure 4.

Circling frequency as observed in videotaped cognitive testing sessions of adult monkeys. Circling behavior was elevated in FIMs (filled triangles and circle) compared to CONs (open triangles and circle) with three FIMs showed higher circling behavior than any CON. $\triangle$ = CON-Mm, $\triangleright$ = CON-Om, $\triangleleft$ = CON-Vf, ∇ = CON-Jf, $\circ$ = CON-Lf, $\blacktriangle$ = FIM-Tm, $\blacktriangleright$ = FIM-Lf, $\blacktriangleleft$ = FIM-Sf, $\blacktriangledown$ = FIM-Bm, $\bullet$ = FIM-Am. Asterick indicates $p < 0.05$.

Figure 5.

Sequential photographs of FIM-Bm illustrating one circling event. FIM-Bm was videotaped while in the WGTA for testing on the reaching task. He is shown initiating a semicircle in the counterclockwise direction coupled with a semicircle in the clockwise direction. His head and neck stretches upward and over his left shoulder to lead the motion in the counterclockwise direction and then dips downward and up again over his right shoulder to lead the motion in the clockwise direction. This sequence often was repeated multiple times and sometimes ended with a full counterclockwise circle.

Figure 6.

Errors made while performing the Delayed Alternation (DA) task. FIMs (filled triangles) made more perseverative than CONs (open triangles) despite making the same number of total (perseverative + non-perseverative) errors. Errors were tallied as animals performed the task at the 0 delay interval. $\triangle$ = CON-Mm, $\triangleright$ = CON-Om, $\triangleleft$ = CON-Vf, $\blacktriangle$ = FIM-Tm, $\blacktriangleright$ = FIM-Lf, $\blacktriangleleft$ = FIM-Sf, $\blacktriangledown$ = FIM-Bm. Asterick indicates $p < 0.05$.

Table 1

Dose and Exposure to Ionizing Radiation

Animal	Sex	DOB	Time in Embryonic Day (E) and Irradiation Dose (in cGy)	Total Dose	Graph Symbol
CON-Mm	M	032301	4 doses ketamine - E29,E32,E34,E36	0	△
CON-Or	M	042501	2 doses ketamine - E34,E36	0	△
CON-Vf	F	073101	3 doses ketamine - E39,E41, E43	0	▽
CON-Jf	F	081401		0	▽
CON-Lf	F	072902	4 doses ketamine - E32,E34,E37,E39	0	○
FIM-Tm	M	021901	E34(50), E36(50), E38(50), E41(50)	200	▲
FIM-Lf	F	032301	E30(50), E33(50), E35(50), E37(50)	200	▲
FIM-Sf	F	042701	E32(50), E34(50), E36(50)	150	▼
FIM-Bm	M	052601	E35(50), E37(50), E38(50)	150	▼
FIM-Am	M	082902	E33(50), E35(50), E37(50)	150	●

Table 2

Age (in months) at Time of Behavioral Observation

Animal	Home Cage	WGTA	RS Videotape		Videotape	Errors on DA
			Juvenile	Adult		
CON-Mm	34-43	44-49.5	22	66	64-65	58-58.5
CON-Om	32-42	43-48.5	24.5	58	63-64	60-62
CON-Vf	30-39	38-43.5	18	56	60-61	60.5-61.5
CON-Jf	29.5-38.5	39-44.5	24.5	55.5	59.5-60.5	
CON-Lf			30.5	49	48-49	
FIM-Tm	35.5-44	45-50.5	26	68	65.5-66.5	59-59.5
FIM-Lf	34-43	44-49.5	30	59.5	64-65	64-65
FIM-Sf	33-42	39-44.5	31	59.5	63-64	63-64
FIM-Bm	32-41	42-47.5	30	58	62-63	60-62.5
FIM-Am			29.5	48	47-48	

DA = Delayed Alternation; RS = Random Sampling; WGTA = Wisconsin General Testing Apparatus

Table 3

Categories of Behavior Recorded with Monkey Watcher

Stimulus Driven Responses	
Stress	Watch/stare
Self-biting	Responses to stimuli
Self-grasping	Tracking observable stimuli
*Threaten	Responses Independent of Stimuli
*Vocalize	Grasp at air
Motor Stereotypies	Stare off into space
*Pace	Inspect arms or hands
*Circle	Grooming
*Side-to-side pace	Static posturing
*Jump side-to-side	Two arm stretch
*Salute	Clinging to bars
Somersault	Holding bars, staring into space without moving
One arm twirl	
Fine Motor Stereotypies	
Fiddle with bars	Submissive behavior
Rotate toy	*Lip smack
Repetitive grasping of face	*Present
Repetitive movements of hands or feet	Eating

* specific behaviors that were recorded in additional sessions of WGTA observation