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MOTOR STEREOTYPIES AND COGNITIVE PERSEVERATION IN NON-HUMAN PRIMATES EXPOSED TO EARLY GESTATIONAL IRRADIATION

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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. Published by Elsevier Ltd. on behalf of IBRO.

Key words: behavior, neurodevelopment, cortico-striatal, dopamine, autism, schizophrenia.

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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.

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INTRODUCTION

Complex motor stereotypies are a core feature of many pervasive developmental disorders (American Psychiatric Association, 2000). Repetitive behavior is most often associated with 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, 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, 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, 2000; 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, a disease in which overpowering urges to repeat rituals related to grooming and hygiene are 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, 1999; 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 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 10 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 FIM 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) FIMs exhibit evidence of cognitive perseveration.

EXPERIMENTAL PROCEDURES

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