Sensory Processing Disorders in a Nonhuman Primate Model: Evidence for Occupational Therapy Practice

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Evaluation of sensory processing function serves as a critical component of treatment planning and implementation of intervention in pediatric occupational therapy practice. We developed a Sensory Processing Scale for Monkeys (SPS–M), based on human tests, that measures behavioral responses to a series of tactile stimuli. This assessment has been used to assess sensory processing in adult rhesus monkeys exposed to prenatal alcohol, stress, or postnatal lead. Control monkeys from undisturbed pregnancies showed a habituation pattern, prenatally stressed monkeys showed sensitization, and prenatal alcohol–exposed monkeys showed relatively high responsiveness without habituation across trials. Lead-exposed monkeys showed sensitization compared to nonlead-exposed controls, and chelation reduced the sensitization in lead-exposed animals. Aver- sive responsiveness was associated with up-regulated striatal dopamine receptor binding measured with positron emission tomography.


Occupational therapists often play a crucial role in addressing sensory processing disorders (SPD) in children with autism, Asperger’s syndrome, attention deficit hyperactivity disorder (ADHD), or fragile X syndrome and children who were previously institutionalized or who have other developmental disabilities (Ayres & Tickle, 1980; Baranek & Berkson, 1994; Cermak & Daunhauer, 1997; Mangeot et al., 2001; Miller et al., 1999). Because the goal of occupational therapy is to enhance children’s participation in the occupations of social interaction, self-care, learning, and play activities, many occupational therapists use a sensory-based frame of reference in practice, posited on the hypothesis that remediation of SPD will improve occupational participation.

This article puts forth the basic idea that modeling SPD in a nonhuman primate model holds promise for the advancement of the knowledge and evidence base of the occupational therapy profession. We propose that shedding light on the possible etiological factors and neurobiological correlates of SPD will lead to better treatment and prevention of SPD and have a positive impact on occupational therapy theory and practice.

Background

Human Studies of Disrupted Sensory Processing

Throughout her career, A. Jean Ayres (1972) argued that “disordered sensory integration accounts for some aspects of learning disorders and that enhancing sensory integration will make academic learning easier for those children whose problem lies in that domain” (p. 1). Ayres (1964) coined the term tactile defensiveness to describe key behaviors as “feelings of discomfort and a desire to escape the situation when certain types of tactile stimuli are experienced” (p. 8). She conducted
factor analytic studies, and results were remarkably consistent in relating tactile defensiveness to hyperactive and distractible behavior in children (Ayres, 1965, 1969).

Despite the historical prominence of Ayres's tradition and the dramatic increase in interest over the past decade in the clinical symptoms associated with SPD, there is a striking lack of empirical evidence to establish the etiological and neurobiological correlates. Studies that exist, however, report a replicable phenomenon. Overresponsiveness and underresponsiveness to environmental stimuli and paradoxical responses to sensory stimuli were reported in people with autism (Kientz & Dunn, 1997; Miller, Reisman, McIntosh, & Simon, 2001), Fragile X syndrome (Miller et al., 2001), and ADHD (Mangeot et al., 2001) and in previously institutionalized Romanian children adopted by American families (Cermak & Daunhauer, 1997). Also, teacher ratings and a laboratory measure were used to assess tactile defensiveness in 34 school-age children with developmental disabilities (Baranek & Berkson, 1994). The assessment involved lightly stroking the child's left cheek with a cotton swab 10 times while the child was engaged in a computer game. The tactile defensiveness score, based on ratings of facial grimace, withdrawal from the stimulus, scratching or pressing on the cheek after stimulation, or negative vocalizations, showed an inverse relationship to the developmental ages of the children, as assessed by the Vinyland Adaptive Behavior Scales (Sparrow, Balla, Cicchetti, & Doll, 1984).

**Prenatal Alcohol, Prenatal Stress, and Early Life Lead Exposure**

Ayres (1979) hypothesized that “genetic factors in certain children may make one part of the brain more vulnerable than usual. In this highly vulnerable state, environmental toxins may interfere with sensory integrative development” (p. 54). We explored this notion by examining whether the offspring of monkeys exposed to a moderate level of alcohol in utero, prenatal stress, or postnatal stress might be more susceptible to SPD. In humans, lead exposure is associated with lower IQ test scores as well as other behavioral effects, including restlessness and inattention, and aggression in elementary school boys (Burns, Baghurst, Sawyer, McMichael, & Tong, 1999). Similarly, prenatal alcohol exposure is associated with parent reports of problems in attention, social, and aggression domains and impaired performance on executive function tasks (Mattson, Goodman, Caine, Delis, & Riley, 1999). Prenatal stress also has been linked to parent reports and direct observations of poor attention and reduced behavioral regulation (Huizink, de Medina, Mulder, Visser, & Buitelaar, 2002). Because postnatal lead, prenatal alcohol exposure, and prenatal stress are associated with inattention, aggression, and poor behavioral regulation, these prenatal or early postnatal experiences may possibly induce alterations in sensory processing.

**Physiological Mechanisms Underlying Disrupted Sensory Processing**

The nature of the biopsychological processes associated with SPD has not been clearly established in human studies. At one level, the concept of sensory processing refers to alterations in physiological responses that reflect activation in the central and autonomic nervous system. Miller and colleagues (2001) compared the electrodermal responses of 19 children clinically identified by parent reports and parent interviews as having SPD, with 19 age- and gender-matched controls. Children with SPD had higher magnitude electrodermal responses and less evidence of habituation over repeated exposure to sensory stimulation compared to control children (McIntosh, Miller, Shyu, & Hagerman, 1999).

Some of the same investigators (McIntosh et al., 1999) compared electrodermal activity of 26 children clinically diagnosed with ADHD with 30 children who were typically developing, matched for age and gender. Children with ADHD scored worse on the Short Sensory Profile (McIntosh et al., 1999). A significant Group by Trial interaction for electrodermal reactivity to sensory stimuli indicated that the ADHD group demonstrated a larger initial reaction to sensory stimuli with subsequent habituation to levels similar to those of children who were typically developing (Mangeot et al., 2001).

**Development of an Animal Model: Purposes and Limitations**

Correlational evidence from human research reveals a link between SPD and reduced occupational participation and performance. Methodological issues, however, limit conclusions from human studies. Therefore, we believe it is important to examine this phenomenon in experimental animal studies. In other words, before conclusions can be drawn with certainty about early events that might cause SPD, effects similar to those found in human studies need to be demonstrated in laboratory studies in which the experimenter systematically controls the environment and subjects are assigned randomly to treatment and control groups. We also believe that it is important to conduct studies with nonhuman primates, subjects that are closely related to humans. When a similar pattern of findings associated with SPD emerges across mammalian species, including nonhuman primates, extending the conclusions to humans becomes more convincing.

Several benefits of the animal model are that it can provide information on how brain–behavior relations, prenatal...
and postnatal factors, and context and experience contribute to behavioral function. Animal models have been used extensively in medical research, and their utility has been well established. In psychiatry and psychology, animal models have been used to study a number of disorders, including depression, schizophrenia, and anxiety. Harlow’s (1958) seminal work reported the adverse effects of maternal deprivation in monkeys at a time when physical contact between parents and children was thought to be unimportant. This work has proven useful in understanding depression and has particular relevance today to the study of children subjected to early maternal deprivation within institutions in Eastern Europe (Cermak & Daunhauer, 1997).

Harlow’s (1958) work served as the springboard for numerous animal studies on the role of early caregiving at that time and up to the present. Contact with and proximity to caregivers has been found important for modulating stress reactivity to potentially noxious stimulation in human infants and children (Gunnar, 2000). This hypothesis is based on evidence that early “handling” of rat pups, involving brief separation from the mother and handling by human experimenters, originally thought to be stressful, was in fact advantageous to the animals in that handled rats had better coping skills later in life than nonhandled rats. Furthermore, positive effects were derived from licking and grooming that the pups received on return to their mothers (Liu et al., 1997). Increased stress reactivity was found in the offspring of strains of rats in which mothers performed less grooming and licking. When such pups were cross-fostered to strains in which mothers performed increased grooming and licking, the offspring were less stress reactive. These rodent studies demonstrate how an early environment with low tactile stimulation could contribute to the development of a less well-organized stress system (Gunnar, 2000). However, the leap from rodents to humans is a long one.

**Wisconsin Sensory Processing Primate Studies**

We have developed a Sensory Processing Scale for Monkeys (SPS–M). Our methods are adapted from human studies (Baranek & Berkson, 1994; Miller et al., 1999). We report sensory processing findings from two experiments: (a) moderate-level prenatal alcohol or prenatal stress exposure and (b) early postnatal lead treatment. Because both experiments are longitudinal studies, the monkeys have been tested on a wide variety of tasks, including measures of neonatal behavior (Schneider, Roughton, & Lubach, 1997; Schneider & Suomi, 1992); a variety of learning tasks (Schneider, Moore, & Kraemer, 2001); and, most recently, positron emission tomography (PET) (Schneider et al., 2005). We are interested in the striatum, which consists of the caudate nucleus and putamen, because striatal circuits regulate frontal cortex circuits and are involved in shifting attention sets, inhibitory control, and executive function. We are interested in dopamine because it is a critical regulator of frontal–striatal function, which is identified as a region involved in the modulation of complex cognitive functions, including attention and executive function.

**Method**

**Subjects**

Rhesus monkeys (*Macaca mulatta*) born to healthy adult female rhesus monkeys were randomly assigned to treatments. The Institutional Animal Care Committee approved all studies in advance. In the prenatal stress condition, mothers were removed from home cages (Monday through Friday during days 90–145 postconception in a 165-day gestation period) and exposed to a noise stressor consisting of three random noise blasts during a 10-min period. This procedure was designed to mimic recurrent daily episodic stress. In the alcohol condition, females consumed 0.6 g/kg daily throughout gestation. Another group of females that consumed alcohol (as above) and underwent noise stress treatment (as above) were referred to as the alcohol/stress group (see Schneider et al., 1997, for details).

In the lead experiment, only female offspring were used and infants were randomly assigned to 1 of 6 conditions: no lead, 1 year of daily lead intake, or 2 years of daily lead intake, in combination with either chelation therapy or nonchelation treatment beginning at the end of the first year of life. The lead-chelating agent succimer was administered in an attempt to rapidly lower the blood lead levels of the monkeys randomly assigned to the 3 chelation therapy groups. Monkeys in the nonchelation groups received a sucrose solution in place of succimer. All infants were housed with their mothers in individual cages during the first 6 months of life. At the time of the studies they were housed in same sex pairs. When they were 5–7 years of age, they were tested with the SPS–M described below. The prenatal alcohol and prenatal stress animals also were assessed for striatal dopamine system function, using the PET methodology described below.

**Sensory Processing Scale for Monkeys.** Sensory processing testing was conducted in a testing cage located in a dimly lit and sound-shielded room. A human experimenter stood beside the cage and administered the tactile stimulation items through the bars of the cage. A second experimenter videotaped the session for later scoring. Both experimenters were blind to the experimental conditions of the animals. The first tactile stimulus consisted of a feather, the
second stimulus was a cotton ball, and the third stimulus was a stiff craft brush. Six trials of each stimulus were administered as a swipe to the cheek and neck area to assess the pattern of responsiveness across trials.

Raters blind to the treatment condition of the animals scored the videotapes for degree of withdrawal from tactile stimuli on a 0 to 3 rating scale. Two raters coded 13 different animals to assess interrater reliability. Interrater reliability as percentage agreement within .25 on the rating scale exceeded 99%. Each animal's overall magnitude of response to a stimulus texture was calculated as the average score across trials. A linear trend score was calculated by multiplying linear trend coefficients (5, 3, 1, −1, −3, −5) by the sensory scores for trials of each stimulus. Positive values of the linear trend scores represented habituation across trials (higher scores represented a steeper decline across trials), whereas negative linear trend scores represented an increase over trials, or sensitization. To determine whether performance on the SPS–M was related to dopamine (DA) system function, DA measures (see below) were correlated with the SPS–M scores using Pearson product-moment correlations.

Positron emission tomography. All PET procedures followed an overnight fast. On the morning of the PET scan, animals were anesthetized with ketamine (15 mg/kg), intubated, and transported to the PET facility. On arrival, isoflurane anesthesia was initiated at 3% to 5% and maintained at 1.25% to 1.5% throughout the duration of the procedure. A fixed laser line reference aligned each animal in the PET scanner for horizontal slice imaging parallel to the orbital–meatus line at the center of the 7 slice, 5.5 cm field of view in the ECAT 933 (Siemens CTI, Knoxville, Tennessee) scanner.

DA synthesis was assessed using 6-[18F]-fluoro-tyrosine as a PET tracer (see DeJesus, Endres, Shelton, Nickles, & Holden, 1997, for details). The tracer used to assess D2 receptors (D2R) was [18F]-fallypride, an F-18 labeled raclopride analog developed by Mukherjee and colleagues (1997). Tracer injection of 5 mCi (millicuries) in 1–5 ml normal saline was followed by a dynamic sequence of images over 90 min, including a total of 13 frames with duration increasing from 2 min to 10 min. At the end of scanning, animals were extubated, allowed to awaken, returned to their transport cages, and transported to the animal care facility.

PET images were reconstructed from the raw data, and standard regions of interest (ROI) were placed on the occipital cortex (an area known to contain little significant D2 DAergic innervation) to produce reference region time-activity curves for use as input functions in graphical analysis. Other ROI were placed to cover both left and right caudate and putamen in the basal ganglia. Time activity data for these ROI were analyzed with the graphical method of Logan and colleagues. (1996). Our method assumes that the unbound components of the tracers are the same in the target regions (e.g., striatum) as in the reference region (e.g., occipital cortex).

Results and Discussion

In the prenatal alcohol or prenatal stress experiment, control monkeys showed the typical habituation pattern of gradually decreasing amplitude of withdrawal response over repeated trials. Monkeys that were prenatally stressed showed a pattern of sensitization in which the amplitude of response increased over trials. Monkeys that were exposed prenatally to alcohol showed relatively high amplitude responsiveness without either habituation or sensitization across trials. Also, response on the SPS–M was positively correlated with DA receptor density in the striatum as measured with PET (Schneider et al., 2006).

In the lead experiment, the nonlead-exposed groups showed a low and relatively stable response magnitude over trials, whereas the lead-exposed groups showed a stronger withdrawal response that increased in magnitude after the first few trials. Chelation therapy modified the lead effect in lead-exposed monkeys such that they did not sensitize to the repeated stimulation over trials. The nonchelated lead-exposed animals showed sensitization (stronger withdrawal) over trials. In 2-year lead-exposed animals that were not chelated, the magnitude of response increased dramatically over the first few trials and remained high, whereas the response of the 2-year lead-exposed and chelated monkeys was relatively stable over time. Chelation altered the response of nonlead-exposed monkeys, resulting in an attenuated withdrawal response on initial trials relative to nonchelated, nonlead-exposed monkeys (Gajewski, Moore, Laughlin, & Schneider, 2006).

The finding that prenatal conditions of stress, prenatal alcohol exposure, and early postnatal lead exposure influenced the pattern of responses to sensory stimuli shows the utility of the SPS–M scale for assessing sensory processing. These results concur with other studies showing that prenatal stress and prenatal alcohol exposure can have enduring effects on learning and behavioral regulation (Mattson et al., 1999; Van den Bergh & Marcoen, 2004).

Although the mechanisms underlying prenatal stress effects have not yet been determined, rodent studies suggest that the effects are mediated at several areas of the brain, including the hippocampus, septum, amygdala, and frontal cortex (Coe, Lubach, & Schneider, 2002; Weinstock, 2001). Evidence shows that maternal glucocorticoids during stressful events cross the placental barrier (Zarrow,
Philpott, & Denenberg, 1970), influencing the developing prenatal brain (Uno et al., 1990). The findings by Gitau, Cameron, Fisk, and Glover (1998), showing a positive linear relationship between maternal and prenatal concentrations of cortisol in humans, support the notion that maternal stress hormones can affect prenatal levels of stress hormones. Accumulating evidence from rodent studies also indicates that prenatal stress alters neurotransmitter concentrations in offspring, including DA, norepinephrine, and serotonin (5-HT) (Peters, 1990; Weinstock, 2001). Effects on major modulatory neurotransmitter systems could alter synaptic function or the wiring of the brain during early development, potentially contributing to later abnormalities in modulation of sensory input from the environment.

Although prenatally stressed monkeys showed sensitization to repeated stimuli compared to controls who showed habituation, prenatal alcohol-exposed monkeys in the present study showed an initial high magnitude response, which remained high. Interestingly, these data concur with human studies showing that alcohol-exposed neonates demonstrated reduced habituation to auditory and visual stimuli 24 to 27 hr after birth (Streissguth, Barr, & Martin, 1983). Similarly, in rodent studies, alcohol-exposed neonates showed a trend for requiring more trials to habituate to olfactory stimuli than controls (Barron & Riley, 1992), as well as reduced habituation of the cardiac orienting reflex to a novel olfactory stimulus (Hunt & Phillips, 2004). A large body of literature links prenatal alcohol exposure to central nervous system deficits (Livy, Miller, Maier, & West, 2003). Neurotransmitter levels were affected as well, including decreased DA uptake, deficits in serotonin reuptake sites, and altered DA neurotransmitter function (Schneider et al., 2005; Sutherland, McDonald, & Savage, 1997). The developing brain is susceptible to alcohol-induced apoptotic neurodegeneration (Ikonomidou et al., 2000), and it is possible that prenatal alcohol exposure could compromise cortical plasticity and acquisition of adaptive behavioral responses to environmental stimuli. Neuromodulators or neurotransmitters serve important roles in amplifying or attenuating signals from neurons and producing signaling patterns between various neuronal networks, which might have adverse effects on habituation to repeated sensory stimuli.

The pattern of response to sensory stimuli was related to striatal DA receptor binding, as measured by PET. The striatum, or the caudate and the putamen, is part of the basal ganglia. The striatum and the frontal cortex, jointly referred to as frontostriatal circuitry, are thought to modulate inhibitory control (Casey, 2001). High D2R binding was positively correlated with high behavioral withdrawal responses to tactile stimuli. High D2R binding could yield an exaggerated response to sensory stimuli (Volkow, Fowler, Wang, & Swanson, 2004). Interestingly, several developmental disorders characterized by poor inhibitory control involve disruptions of the basal ganglia and frontal cortex (frontostriatal circuitry). ADHD, involving reduced inhibition of attention to irrelevant stimuli, involves abnormalities in the basal ganglia and prefrontal cortex (Castellanos et al., 1994). PET studies have shown disruptions in the caudate nucleus associated with Tourette’s syndrome, a disorder of poor inhibitory control of complex movements (Wolf et al., 1996). The caudate nucleus has been found to be altered in people with obsessive–compulsive disorder, which involves poor inhibitory control of thoughts and behaviors (Rosenberg et al., 1997). Thus, a common theme is that disruptions of circuits involving the basal ganglia and frontal cortex, or frontostriatal circuitry, might underlie an array of developmental disorders and possibly play a role in SPD.

In this article, we have argued that occupational therapists would benefit from understanding information from animal models that advance knowledge and evidence base for the profession. The basis for this view is that animal models provide opportunities to systematically manipulate variables of choice and examine causality. Also, studies not possible in human children, such as PET studies, can be done with animal subjects. Moreover, the brains of monkeys and humans are phylogenetically similar. Development of occupational therapy theories and practices that are supported by animal studies may lead to occupational therapy practices that are better appreciated in the scientific community. We have highlighted that rhesus monkeys show behavioral variability of the phenotype defined as SPD. We also have described evidence that a subtype of SPD, termed sensory overresponsivity, characterized by excessive withdrawal to nonnoxious tactile stimuli, is associated with increased D2-type receptor binding, which may reflect hypersensitivity of receptors. We are further planning to assess other DA receptors (D1-type), DA transporters, serotonin receptors, and transporters, as well as dynamic imaging studies investigating DA release in these monkeys.

Although the animal work has contributed to our understanding of human development, a number of limitations need to be noted. First, animals are kept in a controlled environment, with reduced physical and social variation, in which intervening variables occurring in a natural environment are reduced. Although this controlled environment can reduce potential confounds, intervening variables would likely increase or decrease the relationship among prenatal stress, alcohol exposure, or postnatal lead exposure and later sensory processing in a natural environment. Second, there are many routes to a disorder, and outcomes of children are based on numerous factors, including...
genetic factors. Research is currently under way in which we are examining how candidate causal mechanisms interact with genetic vulnerabilities to enhance or diminish the likelihood that SPD is expressed. ▲

References


Sutherland, R. J., McDonald, R. J., & Savage, D. D. (1997). Prenatal exposure to moderate levels of ethanol can have long-lasting effects on hippocampal synaptic plasticity in adult offspring. Hippocampus, 7, 232–238.


