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Sensory Processing in Rhesus Monkeys: Developmental Continuity, Prenatal Treatment, and Genetic Influences

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Neonatal sensory processing (tactile and vestibular function) was tested in 78 rhesus macaques from two experiments. At ages 4–5 years, striatal dopamine D_2 receptor binding was examined using positron emission tomography. At ages 5–7 years, adult sensory processing was assessed. Findings were: (a) prenatal stress exposure yielded less optimal neonatal sensory processing; (b) animals carrying the short rh5-HTTLPR allele had less optimal neonatal sensory scores than monkeys homozygous for the long allele; (c) neonatal sensory processing was significantly related to striatal D_2 receptor binding for carriers of the short allele, but not for animals homozygous for the long allele; and (d) there was moderate developmental continuity in sensory processing from the neonatal period to adulthood.

Sensory processing disorder (SPD) is a developmental regulatory dysfunction characterized by marked under- or overresponsiveness to non-noxious sensory stimulation (Ayres & Robbins, 1979). SPD is related to impairments in daily activities, including learning, self-care, and social behavior (Dunn & Westman, 1997). This condition is a particular challenge for people with developmental disabilities, including autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), fragile X syndrome, anxiety disorders, and other developmental disabilities (Baranek, David, Poe, Stone, & Watson, 2006; Ben-Sasson, Carter, & Briggs-Gowan, 2009; Miller et al., 1999; Parush, Sohmer, Steinberg, & Kaitz, 2007). Although approximately 21% of typically developing children showed symptoms of sensory processing dysfunction, only 25% of these children also met criteria for another *Diagnostic and Statistical Manual of Mental Disorders* (3rd ed.) diagnosis. Importantly, increased sensory sensitivity is related to impairments in family life even in those SPD children without other psychiatric conditions (Carter, Ben-Sasson, & Briggs-Gowan, 2011). There is a need for early identification of children affected by SPD in order to provide them with effective interventions to improve their developmental outcomes.

In this article, we examine developmental continuity of sensory processing function from early infancy to adulthood in a nonhuman primate

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model. This article reports results from a new neonatal subscale of sensory processing function from a rhesus neonatal assessment based on recent principal components analysis of over 400 monkeys reared in seven different pregnancy conditions (Coe, Lubach, Crispen, Shirtcliff, & Schneider, 2010). The neonatal primate assessment was originally adapted from the Brazelton Neonatal Behavioral Assessment Scale (1984) and established previously with rhesus monkeys (Schneider, Moore, Suomi, & Champoux, 1991).

Here, we present the new neonatal sensory processing subscale results for two experiments: (a) monkeys prenatally exposed to moderate dose alcohol, mild daily stress, both, or neither; and (b) monkeys exposed to moderate dose alcohol during early gestation, middle to late gestation, or both (continuous through gestation) or control. Although these monkeys were included in the Coe et al. (2010) secondary analysis, we examine the following questions in the context of our longitudinal studies of the animals in these two experiments. First, do the prenatal treatments in our two experiments influence neonatal sensory processing? In Coe et al.'s (2010) article, pregnancy conditions were combined across experiments. In this article, we examine treatment effects for our two original factorial designs: (a) Prenatal Alcohol × Prenatal Stress and (b) Early Gestation Prenatal Alcohol × Late Gestation Prenatal Alcohol. Second, is there developmental continuity from neonatal sensory processing to adult sensory processing? Third, are there effects or interactions with serotonin transporter gene, a gene closely related to both stress responsivity and other neurobiological functions? Fourth, how is neonatal sensory processing related to dopamine (DA) function in the striatum, an area that is part of the regulatory corticostriatal loop? Next, we expand the rationale for each research question.

Effects of Prenatal Stress and Prenatal Alcohol Exposure

In humans a variety of negative effects of prenatal stress and prenatal alcohol exposure have been found, but studies have not focused specifically on sensory processing. For prenatal stress, longitudinal studies have found long-term effects on behavioral regulation. For example, Lin, Crnic, Luecken, and Gonzales (2014) found that prenatal stress predicted infant negativity, which in turn was related to impaired self-regulatory capacity. Regulatory behaviors were defined as self-comforting behaviors and gazing away from distressing objects, behaviors that are likely to be related to sensory processing functioning. Prenatal stress has also been found to be related to dysregulated infant states, infant temperament, socioemotional development, and behavior problems (Huizink, de Medina, Mulder, Visser, & Buitelaar, 2002; O'Connor et al., 2007). Prenatal alcohol is more widely known as a developmental neurotoxicant, with correlational evidence showing associations with neurobehavioral problems including reduced inhibitory control, impulsivity, attention deficits, and problems in regulation of arousal (see Mattson, Crocker, & Nguyen, 2011, for a review). One study that specifically addressed fetal alcohol spectrum disorder and sensory processing reported that "children with FASD were three times more likely to be classified in a clinically significant category on the Short Sensory Profile than peers with typical development" (Jirikowic, Olson, & Kartin, 2008).

What is unique to our study is the use of the nonhuman primate model to tease apart the effects of combined prenatal conditions that are often confounded in human correlational research. In humans, prenatal perturbations such as prenatal alcohol, prenatal stress, or the combination often covary with each other and with other lifestyle factors, including poor nutrition, use of other substances, and exposure to environmental stressors. In our first experiment, we used a factorial design of prenatal stress alone, moderate level prenatal alcohol alone, their combination, and control. In our second experiment, we factorially manipulated the timing of moderate level prenatal alcohol exposure: exposure during early gestation, middle–late gestation, continuous gestational alcohol, and control. Animals in all conditions within the two studies were exposed to identical research protocols since birth. They were assessed with sensitive instruments translated from those used to assess neurobehavior and brain function in humans, such as the Newborn Behavioral Assessment Scale (Brazelton, 1984) and the Habituation to Tactile Stimuli Applied to the Face (FACE-HAB), which involved light touch stimulus applied to the subjects face (cheek) repeated for 10 trials (Baranek & Berkson, 1994).

It was previously found that when the monkeys were assessed as adults, prenatal stress increased withdrawal responses and reduced habituation to repeated tactile stimulation (Schneider et al., 2008). In the second experiment, examining the gestational timing of prenatal alcohol exposure (early gestation, mid to late gestation, continuous, or control), an interaction occurred such that monkeys exposed to

early gestation alcohol carrying the short (*s*) rh-5HTTLPR allele showed less reactivity to tactile stimulation as adults (Schneider et al., 2009).

Developmental Continuity of Sensory Processing

Developmental continuity of sensory processing is important because psychological functions that show continuity have greater potential to induce maladaptations later in life. In addition, when there is developmental continuity, it raises the importance of early intervention for prevention of later problems. Developmental continuity of functions closely related to sensory processing has been examined in a few human studies. In a study of over 1,300 children from a representative sample in Israel, children were assessed three times between 11 and 48 months of age with the "sensory sensitivities" subscale of the Infant Toddler Social and Emotional Assessment (ITSEA; Ben-Sasson, Carter, & Briggs-Gowan, 2010), and then at school age, 7–10 years old. At school age, the research team used the Sensory Over-Responsivity scale (Schoen, Miller, & Green, 2008). Sensitivity scores on the ITSEA were significantly associated with school-age sensory overresponsivity scores. Children with sensory overresponsivity at school age were 3–7 times more likely to have had high-ITSEA sensory sensitivity scores compared with children without sensory overresponsivity at school age. Moreover, one-third of those children with ITSEA scores above the clinical cutoff in Years 1 and 2 had persistent sensory overresponsivity at school age and over half of children with high overresponsivity at 3 years of age had elevated overresponsivity at school age. Thus, overresponsivity during infancy and toddlerhood predicted clinically significant sensory overresponsivity at school age (Ben-Sasson et al., 2010).

Continuity was also examined by DeGangi, Breinbauer, Doussard-Roosevelt, Porges, and Greenspan (2000) with a sample of 88 U.S. infants selected in four categories: normal, mild or moderate "regulatory disorders," and pervasive developmental disorders. The children were first assessed for regulatory disorders when they were between 7 and 30 months of age. Regulatory disorders were measured in five areas, one of which was "distress to sensory challenges" defined as follows: resists cuddling, distress when face or hair is washed, hates car seat, avoids certain textures, avoids clothing, fear when being swung in the air or rough play, and startle or distress to loud sounds. Children were classified into normal and moderate to severe regulatory disorder groups, and responding to sensory challenges was only one aspect of the regulatory disorder classification. At 36 months of age, the children were given a full clinical assessment, including the Sensorimotor History Questionnaire for Preschoolers (SHQP), a 51-item questionnaire measuring self-regulation, sensory processing of touch and movement, motor planning, emotional maturation, and behavioral control. The results showed that children with either mild or moderate regulatory disorder between the ages of 7 and 30 months scored significantly higher (less optimal regulation) than normal children on the SHQP at 36 months of age (Cohen's $d = 3.4$). In addition, children with moderate regulatory disorder were highly likely to have a clinical diagnosis, with 55% showing sensory integration problems, or hypersensitivities to touch and movement.

These studies of children raise the importance of examining continuity of sensory processing in an animal model. In human studies, correlated and confounding variables may be responsible for developmental continuity, whereas in animal research, there is more control. In both animals and humans, however, developmental continuity can be the result of the important cascading effects of early developmental processes on later functioning through a variety of neurological and behavioral mechanisms.

Genetic Contributions to SPD

Our third research question is whether the serotonin transporter gene affects sensory processing in monkeys, as well as whether it is a modulator of either treatment effects or developmental continuity. Recent evidence of genetic contributions to SPD in humans comes from the Wisconsin Twin Research Program, suggesting moderate heritability of sensory overresponsivity (Keuler, Schmidt, Van Hulle, Lemery-Chalfant, & Goldsmith, 2011). Sensory overresponsivity was assessed in 2,052 individual twins at age 2 with 13 items from the ITSEA and the Toddler Behavior Assessment Questionnaire (Goldsmith, 1996) that measures tactile and auditory overresponsivity. Genetic influences accounted for 52% of the variance in tactile overresponsivity and 38% for auditory overresponsivity (Goldsmith, Van Hulle, Arneson, Schreiber, & Gernsbacher, 2006). Both tactile and auditory overresponsivity were moderately related to negative affect (rs = .26 and .21, respectively) and fear (rs = .28 and .20, respectively) but not to effortful control (Keuler et al., 2011).

A growing number of studies examining the effect of genes on vulnerability to depression and other stress-related disorders report increased risk for these psychiatric disorders in those carrying the short allele of the serotonin transporter-linked polymorphic region (5-HTTLPR), especially under enhanced stressful life conditions (Caspi et al., 2003). A common functional length polymorphism in the promoter sequence of the serotonin transporter gene (5-HTTLPR) has been found to impact the transcription rate of the gene, with the short (*s*) allele less efficient than the long (*l*) allele. Caspi et al. (2003) found a significant interaction between 5-HTTLPR and stressful life events and childhood maltreatment in the development of depression. This study has been widely cited, and numerous follow-up studies have been conducted. Two meta-analyses of a subset of these studies failed to find evidence supporting this gene–environment interaction (Munafò, Durrant, Lewis, & Flint, 2009; Risch et al., 2009). However, a more recent larger meta-analysis, including all relevant studies (54 studies), found strong evidence that 5-HTTLPR moderates the relationship between stress and depression (Karg, Burmeister, Shedden, & Sen, 2011).

The serotonin system is important to consider when assessing molecular pathways involved in early life vulnerability for mental health-related phenotypes. Serotonin regulates a number of developmental functions involved in neural circuit formation and plays an important role in modulating developmental plasticity during critical periods of neural development. For example, exposure to selective serotonin reuptake inhibitors during brain development impacts fetal physiology and is associated with poor neonatal adaptation and increased risk for ASDs (Gentile & Galbally, 2011).

In rhesus macaques (*Macaca mulatta*), a serotonin transporter polymorphism (rh5-HTTLPR) is present that is functionally similar to the human 5-HTTLPR variant (Bennett et al., 2002). Researchers have found an interaction between postnatal stress (peer rearing) and the serotonin transporter gene such that carrying the rh5-HTTLPR short allele and stress exposure yielded higher ACTH levels during social separation (Barr et al., 2004; Bennett et al., 2002). Similarly, in our first experiment that manipulated prenatal alcohol and prenatal stress, an interaction was found such that prenatal alcohol-exposed monkeys carrying the short (*s*) rh5-HTTLPR allele (*l*/*s* and *s*/*s*) were more irritable during the neonatal period and showed higher ACTH and cortisol levels when separated from their mothers for weaning at 6 months of age than prenatal alcohol-exposed monkeys homozygous for the long allele (*l*/*l*) or than controls regardless of genotype (Kraemer, Moore, Newman, Barr, & Schneider, 2008). In the second experiment that manipulated gestational timing of alcohol, an interaction was found when they were adults such that early gestation alcohol-exposed monkeys carrying the *s* allele showed lower tactile reactivity compared with *l*/*l* alcohol-exposed monkeys as well as mid to late alcohol-exposed monkeys and controls regardless of genotype (Schneider et al., 2009).

The DA System and Early Life Vulnerability

Our fourth research question is whether neonatal sensory processing is related to DA function, particularly in the striatum, a brain area with important regulatory functions. The DA system has also been linked to early life vulnerability and plays an important role in regulating mood, affect, motivation, and reward responses and motor behavior. The striatum, which consists of the caudate nucleus and putamen, receives inputs from all cortical areas and the thalamus, and projects to frontal lobe areas (prefrontal, premotor, and supplementary motor areas). Those circuits regulate the cortex, play a role in predicting future events, and are involved in shifting attention sets, movement, and spatial working memory (Herrero, Barcia, & Navarro, 2002). Therefore, alterations in striatal DA function may have widespread effects on behaviors such as self-regulation, motor hyperactivity, and arousal.

Several findings have been reported with respect to DA function assessed by in vivo positron emission tomography (PET) scan and adult sensory processing function in monkeys. In the Prenatal Alcohol × Prenatal Stress experiment, it was found that upregulation of dopaminergic function in the striatum (specifically, increased DA D_2R binding potential) was related to reduced habituation to repeated tactile stimuli (Schneider et al., 2008). Moreover, in the gestational alcohol-timing experiment, the relationship between D_2 binding in striatum and adult tactile sensitivity differed across treatment groups; specifically, early alcohol-exposed monkeys showed a positive correlation between D_2R binding and tactile responsivity, whereas the other groups and controls showed either a negative correlation or no correlation (Schneider et al., 2009). Therefore, in the present report we examined whether D_2 binding in the striatum during adulthood was associated with neonatal sensory processing.

Method

Experiment 1: Prenatal Alcohol × Prenatal Stress Experiment

Details are available elsewhere (Schneider, Roughton, & Lubach, 1997). Briefly, the pregnant monkeys were randomly assigned to one of four prenatal treatment conditions: (a) prenatal alcohol, voluntary daily consumption of 0.6 g/kg of a 6% volume/volume (*v*/*v*) alcohol solution sweetened with Nutrasweet (300 mg/100 ml; Equal Sweetener; Merisant US Inc., Chicago, IL) on gestational days 0–165; (b) control, voluntary daily consumption of a solution equivolemic and equicaloric to the alcohol (8 g/100 ml; days 0–165); (c) mild prenatal stress, exposure to three noise bursts five times weekly on gestational days 90 through 145; (d) prenatal alcohol + prenatal stress treatment as described earlier (#1 plus #3).

Experiment 2: Gestational Timing of Prenatal Alcohol Experiment

Details are available elsewhere (Schneider, Moore, & Becker, 2001). Briefly, the pregnant monkeys were randomly assigned to one of the four prenatal treatments: three of which involved voluntary daily consumption of 0.6 g/kg (as in the Prenatal Alcohol × Prenatal Stress experiment) during the following gestational periods: (a) early gestation, days 0–50; (b) middle–late gestation, days 50–135; (c) continuous throughout gestation, days 0–135; or (d) control (equicaloric and equivolemic sucrose solution).

General Procedures

All monkeys in both experiments were fed a standard ration for pregnant and nursing mothers of Purina Monkey Chow (Purina Mills, St. Louis, MO) supplemented 3 times weekly with fresh fruit. Tap water was available ad libitum. All females were housed under identical conditions, undisturbed except for necessary routine animal husbandry, with the exception of the treatments as described earlier. Lighting and temperature housing conditions were controlled with 16 hr light (6 a.m. lights on), 8 hr dark, and temperature 21°C + 5°C.

Subjects

Experiment 1: Subjects were 39 rhesus monkeys (*M. mulatta*), 23 females and 16 males, derived from the mothers in the four treatment groups described earlier: control (10 females and 3 males), prenatal stress-only (2 females, 6 males), prenatal alcohol-only (7 females, 2 males) and prenatal stress + prenatal alcohol (4 females, 5 males).

Experiment 2: Subjects were 39 rhesus monkeys, 22 females and 17 males, derived from the mothers described earlier: control (8 females, 2 males), early gestation alcohol exposure (4 females, 6 males), mid to late gestation alcohol exposure (6 females, 4 males) and early + late gestation exposure (4 females, 5 males).

Infant monkeys in both experiments were housed with their mothers in individual cages during the first 6 months of life. During the 1st month of life they were separated briefly from their mothers once a week and tested for neonatal neurobehavior (Schneider et al., 1997, 2001). At 6 months, they were separated from their mothers for weaning and then reared in mixed-sex peer groups consisting of 5–6 monkeys from similar prenatal conditions. From 32 months of age on, the animals were pair housed with same-sex peers.

Primate Neonatal Sensory Assessment

A 20-min battery of developmental tests has been described in detail previously (Schneider & Suomi, 1992; Schneider et al., 1991). The assessment was administered weekly on days 4, 9, 15, and 22 (± 1) at approximately 10 a.m. The battery was modeled after the Brazelton Neonatal Behavioral Assessment Scale (Brazelton, 1984). For this study, sensory processing was scored based on a recent principal component analysis conducted with a large sample of rhesus monkeys (Coe et al., 2010). The sensory processing score consisted of tactile items (avoidant response to tactile stimulation of extremities and Galant's bias to flex laterally toward dorsal tactile stimulation), vestibular items (response to rotation test, maintaining body extension while suspended in prone position, parachute response or limb extension during "parachute" descent), and vocalizations per minute. All items were scored on a 3-point scale (0, 1, and 2), with "2" being optimal. All monkeys were tested as described above on 4–22 days of age. The neonatal test data for Experiment 1 were collected between May 1993 and April 1996, and between February 1997 and April 1999 for Experiment 2.

Adult Sensory Processing Scale for Monkeys (SPS-M)

The adult SPS-M has been described in detail previously (Schneider et al., 2008). It was adapted

from laboratory observational measures of sensory processing for children (Baranek & Berkson, 1994; Miller et al., 1999). Adult sensory processing testing was conducted in a 53 × 44-cm testing cage situated in a dimly lit and sound-shielded room (62 dB) with a masking white noise of 65–70 dB. Each monkey was tested individually by a human experimenter who stood beside the cage and administered a series of 18 tactile stimulation items through the bars of the cage such as a swipe to the cheek and neck area to assess the pattern of responsiveness across trials. Prior to the first presentation of each stimulus, the stimulus was placed in full view and touching range of the monkey and remained there for approximately 3 s. Once the animal looked at the object, the examiner slowly moved the stimulus into the cage and began the series of trials. Raters blind to the condition and history of the animals scored the subjects' responses for degree of withdrawal from tactile stimuli in 0.25 increments on a 0–3 rating scale with the integers labeled as follows: 0 = *no withdrawal*; 1 = *slight withdrawal*, such as turning head away from the stimulation; 2 = *moderate withdrawal*, such as turning full body away from stimulation; 3 = *extreme withdrawal*, such as moving body away from stimulation.

As described previously, six scores were calculated for each subject: the average response over the six trials of the three stimulus texture and a linear habituation score for each texture (Schneider et al., 2008). Higher values of the linear trend scores represent higher habituation across trials. Negative linear trend scores represent an increase over trials or sensitization. In the article we report the results for Sensory Factor 1 as given in Schneider et al. (2008). This factor represents the magnitude of sensory response across three tactile stimuli (feather, cotton ball, and brush) and failure to habituate to the first two textures, feather and cotton ball (Schneider et al., 2008). The animals of Experiment 1 were tested in August of 2000, and the animals of Experiment 2 were tested in August of 2002.

PET Procedure

Details of the PET studies can be found in Roberts et al. (2004). Monkeys were fasted overnight and anesthetized with ketamine (15 mg/kg). Anesthesia during PET scans was maintained with 1.25%–2.0% isoflurane. The tracer used to assess DA D_2 receptors was [^{18}F]Fallypride ([^{18}F]FAL), an F-18-labeled raclopride analog. About 5 mCi in 1–5 ml normal saline of [^{18}F]FAL were administered as an intravenous bolus and a dynamic sequence of images over 90 min, including a total of 13 frames with duration increasing from 2 to 10 min was collected. PET images were reconstructed from the raw data using the Ordered Subset Estimation Method. Standard regions of interest (ROIs) were placed on the occipital cortex (an area known to contain little significant dopaminergic innervation) in order to produce reference region time–activity curves for use as input functions in graphical analysis. Other ROIs were placed to cover both left and right caudate and putamen (jointly referred to as the striatum) in the basal ganglia. Time–activity data for the ROIs were analyzed with the graphical method of Logan et al. (1996). The outcome measure obtained from the Logan plot is the distribution volume ratio (DVR), the ratio of the FAL distribution volume in the target region (striatum) to that in the reference region (occipital cortex). DVR is related to D_2R availability by the following relationship: $DVR = [(Bmax/Kd) + 1]$, where Bmax is the mass-specific concentration of available receptors not occupied by endogenous DA, and Kd is the receptor–ligand dissociation rate constant. These PET scans were conducted between April 1998 and September 2002 for the animals of Experiment 1, and between November 2000 and May 2003 for the animals of Experiment 2.

DNA Extraction and Genotyping

Blood samples for genotyping were collected when the animals were approximately 6–9 years old in May of 2002 for Experiments 1 and 2. DNA was isolated from whole blood using standard extraction methods. Using a protocol modified from that of Lesch and colleagues (Lesch et al., 1997), rh-5HTTLPR was amplified from 25 ng of genomic DNA with oligonucleotide primers (stpr5, 5′-GGCGTTGCCGCTCTGAATGC-3′; intl, 5′-CAGGGGAGATCCTGGGAGGG-3′) in 15 μl reactions using Platinum Taq and the PCRX Enhancer System kit, according to the manufacturer's protocol (Invitrogen, Carlsbad, CA). Amplifications were performed on a Perkin-Elmer (Fremont, CA) thermocycler (9,700), with one cycle at 96°C/5 min followed by 30 cycles of 94°C/15 s, 60°C/15 s, 72°C/30 s, and a final 3-min extension at 72°C. Amplicons were separated by electrophoresis on 10% polyacrylamide gels, and the short (*s*, 398 bp) and long (*l*, 419 bp) alleles of the rh5-HTTLPR

were identified by direct visualization following ethidium bromide staining.

Analyses for Treatment Effects

The following steps were carried out on the neonatal sensory scores for the Prenatal Alcohol × Prenatal Stress experiment in order to arrive at a model. First, the neonatal sensory scores were analyzed in a 2 (prenatal alcohol) × 2 (prenatal stress) × 2 (sex of animal) analysis of variance (ANOVA). There were no interactions with sex of animal (all ps > .45); the interactions of sex with other factors were eliminated from the model, but the main effect of sex was retained as a main effect. Second, a 2 (prenatal alcohol) × 2 (prenatal stress) × 2 (rh5-HTTLPR gene) ANOVA was conducted to test for interactions with gene. There were no interactions with rh5-HTTLPR gene, so the gene interactions were removed from the model, but gene was retained as a main effect. Third, a 2 (prenatal alcohol) × 2 (prenatal stress) ANOVA with added main effects of sex and gene and the interaction of Sex × Gene was run to test the Sex × Gene interaction. The Sex × Gene interaction was nonsignificant (p > .50) and was removed from the model. Hence, the model reported here is a 2 (prenatal alcohol) × 2 (prenatal stress) factorial with the main effects of sex of animal and rh5-HTTLPR gene included.

The same steps were carried out on the Early Gestation Alcohol × Late Gestation Alcohol experiment. There were no interactions with sex of animal (smallest p > .14), so the sex interactions were removed from the model. There was one marginal interaction with gene (Early × Late × Gene), $F(1, 27) = 3.65$, $p < .07$, so gene interactions were removed. The Sex × Gene interaction was also nonsignificant (p > .30). The final model reported here is a 2 (early gestation alcohol) × 2 (late gestation alcohol) factorial with the main effects of sex of animal and rh5-HTTLPR gene included.

Relationships Among Variables

Relationships among neonatal sensory scores, adult sensory scores, and D_2R binding were analyzed by Pearson correlations separately by experiment, as well as combined over the two experiments. Scatter plots were examined for outliers. The equality of regression lines for the rh5-HTTLPR gene groups and for the experimental cohort were tested for the regression of both adult sensory scores and D_2R binding on neonatal sensory scores.

Results

Effects of Prenatal Treatment and Serotonin Genotype on Neonatal Sensory Scores

In the Prenatal Stress × Prenatal Alcohol experiment, the ANOVA of Prenatal Stress (2) × Prenatal Alcohol (2) plus main effects of gene (2) and sex (2) on the neonatal sensory scores showed a significant main effect of gene, $F(1, 33) = 6.13$, $p = .019$, and a significant main effect of prenatal stress, $F(1, 33) = 4.66$, $p = .038$, that was qualified by a Prenatal Alcohol × Prenatal Stress interaction, $F(1, 33) = 4.24$, $p = .047$. Prenatal stress reduced sensory processing optimality (i.e., increased tactile overresponsivity and reduced vestibular function) compared with no prenatal stress. The interaction of prenatal stress and prenatal alcohol exposure on neonatal sensory processing indicated that the control group differed from the three treatment groups. The means of the four treatment groups for this experiment are shown in the left-hand panel of Figure 1. The main effect of gene is shown in the two left bars of Figure 2, showing that the short allele carriers had lower (less optimal) sensory scores compared with (l/l) monkeys.

In the gestational timing of alcohol experiment, there were no significant treatment effects or interactions on neonatal sensory scores, and the effect of serotonin transporter gene was also nonsignificant (ps > .22). There was a trend toward an effect of sex of animal, $F(1, 29) = 3.92$, $p = .057$, indicating that female animals had slightly more optimal scores than males (Ms = 1.32, 1.17; SEs = .047, .052, respectively). The right-hand panel of Figure 1 shows the means of the four treatment groups for this experiment, and the right-hand panel of Figure 2 shows the means for this experiment as a function of serotonin transporter genotype.

Neonatal Sensory Scores and Adult SPS-M Continuity

Figure 3 demonstrates the significant relationship between neonatal sensory score (x-axis) and adult tactile sensory score (y-axis) for the two experiments combined, $r = -.304$, $p < .01$. In the left-hand panel, there are separate symbols for the two serotonin gene groups, and in the right-hand panel, there are separate symbols for the two experimental cohorts. The regression lines do not differ significantly by serotonin transporter gene grouping, p > .45. Also, the regression lines for the two experiments did not differ significantly, but there was a trend toward a stronger relationship in the Prenatal Alcohol × Prenatal Stress experiment, $F(2, 65)$ =

Figure 1. Mean neonatal sensory scores for the four treatment groups of the Prenatal Alcohol × Prenatal Stress experiment (left-hand panel) and for the four treatment groups of the gestational timing of alcohol experiment (right-hand panel). Bars are ± 1 *SE*. Higher scores are more optimal functioning.

Figure 2. Mean neonatal sensory scores for carriers of the *l/l* and *l/s, s/s* variants of the serotonin transporter gene in the Prenatal Alcohol × Prenatal Stress experiment (left-hand bars) and in the gestational timing of alcohol experiment (right-hand bars). Error bars are ± 1 *SE*.

2.83, $p = .066$. These results show moderate developmental continuity in sensory function across a wide age range (1 month to 5–7 years) in both experiments and regardless of serotonin transporter genotype.

Neonatal Sensory and D_2R Binding in Striatum

Figure 4 displays the relationship between neonatal sensory score (*x*-axis) and D_2R binding in the striatum measured in vivo with PET (*y*-axis). In the left-hand panel, there are separate symbols for the two serotonin transporter gene groups, and in the right-hand panel, there are separate symbols for the two experimental cohorts. The overall correlation between neonatal sensory score and D_2R binding is nonsignificant, but the relationship is strikingly different for the two serotonin gene groups in the left-hand panel. The regression lines differ significantly by serotonin transporter gene grouping, $F(2, 68) = 7.01$, $p < .01$. The relationship between striatal DA D_2R density and neonatal sensory function was significant for carriers of the short allele, $r = -.50$, $p < .01$, but was not significant for *l/l* animals, $r = -.01$, $p > .90$. In the right-hand panel, the regression lines do not differ significantly by experimental cohort, $F(2, 68) = 1.17$, $p > .31$. Hence, D_2R binding in the striatum is related to sensory functioning only for animals carrying the *s* serotonin transporter genotype.

Discussion

The analyses reported here for neonatal sensory processing in rhesus monkeys yielded four principal findings. First, in the Prenatal Alcohol × Prenatal Stress experiment we found (a) there was an interaction such that animals exposed to either mild prenatal stress or moderate dose prenatal alcohol showed less optimal neonatal sensory processing function compared to control animals, and a main effect of prenatal stress and (b) *s* allele carriers of the rh5-HTTLPR gene had less optimal sensory

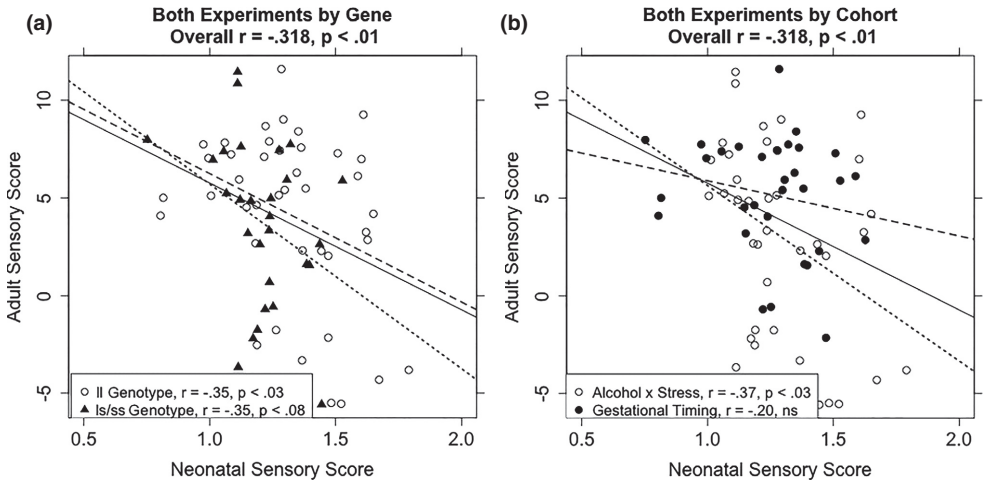

Figure 3. Relation between neonatal sensory score (*x*-axis) and adult SPS-M score (*y*-axis) plotted with separate symbols for each serotonin gene (left-hand panel) and separate symbols for experimental cohort (right-hand panel). Regression lines do not differ significantly by either serotonin gene or experimental cohort. In the left-hand panel, the dashed line is the regression for the *l*/*l* gene group, the dotted line is the regression for the *l*/*s*, *s*/*s* serotonin gene group, and the solid line in the regression for all animals combined. In the right-hand panel, the dotted line is the regression for the Prenatal Alcohol × Prenatal Stress animals, the dashed line is the regression for the gestational alcohol-timing animals, and the solid line is the regression for all animals combined.

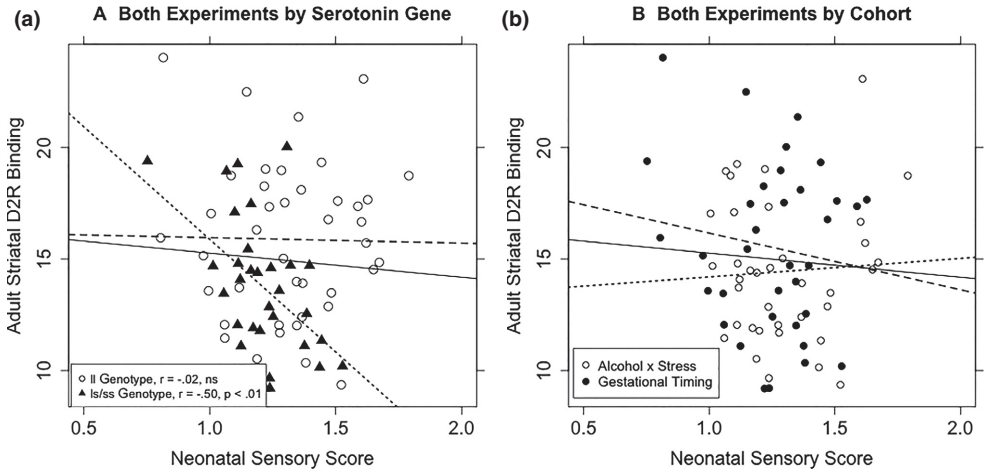

Figure 4. Relation between neonatal sensory score (*x*-axis) and D_2R binding in striatum with separate symbols for serotonin transporter gene (left-hand panel) and for experimental cohort (right-hand panel). Regression lines for serotonin transporter gene groups differ significantly, $p < .01$. In the left-hand panel, the dashed line is the regression for the homozygous long gene animals ($r = -.02$, *ns*), the dotted line is the regression for the short allele carriers ($r = -.50$, $p < .01$), and the solid line is the regression for all animals combined ($r = -.07$, *ns*). In the right-hand panel, the dotted line is the regression for the Prenatal Alcohol × Prenatal Stress cohort ($r = .06$, *ns*), the dashed line is the regression for the gestational timing cohort ($r = -.14$, *ns*), and the solid line is the regression for all animals combined. Regression lines do not differ significantly by experimental cohort, $p > .31$. The overall correlation across all animals, $r = .07$, *ns*; Prenatal Alcohol × Prenatal Stress experiment, $r = .06$, *ns*; gestational timing of alcohol experiment, $r = -.14$, *ns*.

processing scores compared with *l*/*l* monkeys. In the gestational timing of alcohol experiment, neither the alcohol nor the serotonin transporter main effects attained significance. Second, across both experiments we found that (a) neonatal sensory processing function correlated with adult tactile sensory function, indicating moderate continuity of sensory processing function across a wide age range, and (b) neonatal sensory processing function correlated with adult upregulation of striatal D_2R function in monkeys carrying the *s* rh5-HTTLPR, providing evidence of a link between DA, serotonin genotype, and sensory processing function. We discuss each of these findings below.

Prenatal Stress, Neonatal Sensory Function, and Later Outcomes

Our first finding, that prenatal stress yielded animals with less optimal neonatal sensory processing function in the Prenatal Alcohol × Prenatal Stress experiment, is consistent with correlational evidence from humans indicating that prenatal stress has long-lasting effects on behavioral regulation (O'Connor et al., 2007). Although the mechanisms underlying prenatal stress-induced developmental effects have yet to be fully explicated, prenatal stress acts through a combination of neuroendocrine, immune/inflammatory and vascular trajectories to alter the maternal placental–fetal system to influence a range of birth outcomes (Wadhwa & Federenko, 2006). A positive linear relationship between maternal and prenatal fetal concentration of cortisol has been shown in humans (Gitau, Cameron, Fisk, & Glover, 1998). In both humans and nonhuman primates, prenatal stress induces maternal release of catecholamines, which can constrict placental blood vessels and cause fetal hypoxia, which in turn can alter brain development (Teixeira, Fisk, & Glover, 1999). Prenatal stress can also impact the activity of the placental barrier enzyme 11B-hydroxysteroid dehydrogenase-2, which converts cortisol to the inactive cortisone, potentially altering the neurodevelopmental outcomes of offspring (Welberg, Thrivikraman, & Plotsky, 2005). Moreover, prenatal stress alters the intestinal microflora in rhesus monkey newborn infants, which can increase vulnerability to infection (Bailey, Lubach, & Coe, 2004).

Animal studies have also shown that prenatal stress induces changes in the hippocampus, septum, amygdala, and frontal cortex (Weinstock, 2001) and can alter neurotransmitter concentrations (e.g., DA, serotonin, and norepinephrine) as well as transporter and receptor binding (Converse et al., 2013; Roberts, et. al, 2004; Weinstock, 2001). Altered neurotransmitter concentrations can perturb normal neuronal migration and differentiation, which then can result in "miswiring" and altered synaptic function (Oberlander, 2012). Prenatal stress has been shown to reduce expression of brain-derived neurotrophic factor in prefrontal cortex and striatum (Fumagalli, Bedogni, Perez, Racagni, & Riva, 2004), which plays an important role in synaptic plasticity and cellular homeostasis. In addition, Staples, Porch, and Savage (2014) showed that prenatal stress, prenatal alcohol exposure, and the combination altered the activity of proteins involved in hippocampal synaptic plasticity. Thus, prenatal stress could alter neonatal sensory processing function via multiple interacting changes in neuroendocrine and neurodevelopmental processes.

A second finding reported here is that monkeys carrying the *s* allele rh5-HTTLPR variant displayed less optimal neonatal sensory processing function (i.e., tactile overresponsivity and poorer vestibular function) compared with *l*/*l* monkeys. This finding occurred in the Prenatal Alcohol × Prenatal Stress experiment, and it supports the view that the *s* allele genotype may be linked to increased sensitivity and vigilance to external stimuli (Ellis & Boyce, 2011). Serotonin transporter function is intimately related to stress responsivity. Our finding of less optimal neonatal sensory processing function in *s* allele carriers is consistent with human findings that serotonin transporter gene variants modulate Hypothalmic pituitary Adrenal Axis (HPA) responsiveness at birth. Specifically, human newborn infants carrying the *s* allele display increased stress-induced cortisol secretion when compared with *l*/*l* allele carriers (Mueller, Brocke, Fries, Lesch, & Kirschbaum, 2009). Glucocorticoids regulate serotonin transporter expression and are decreased in *s* allele carriers (Glatz, Mossner, Heils, & Lesch, 2003). Our findings are also consistent with others studies in rhesus monkeys showing that peer-reared monkeys carrying the short allele exhibit more aggressive and fearful behavior, higher levels of HPA stress reactivity, and increased alcohol consumption compared with long allele *l*/*l* carriers (Barr et al., 2004; Bennett et al., 2002). Along similar lines, in our Prenatal Alcohol × Prenatal Stress experiment, we previously reported that prenatal alcohol-exposed *s* carriers showed increased neonatal irritability and enhanced stress responsivity when separated from their mothers for weaning at 6 months of age (Kraemer et al., 2008). Moreover, in the gestational timing of alcohol experiment an interaction was found such that monkeys exposed to alcohol during early and middle to late gestation, and carrying the *s* allele showed lower cerebrospinal fluid levels of the serotonin metabolite 5-HIAA during adolescence (Schneider, Moore, Barr, Larson, & Kraemer, 2011).

Early life serotonin regulates a variety of cellular processes involved in cortical circuit formation. Serotonin regulates thalamocortical pathways and wiring during embryonic and early postnatal life and the migration speed of cortical interneurons (Riccio et al., 2011). Moreover, dendritic growth of cortical neurons has been shown to be regulated by serotonin fibers (Chameau et al., 2009). In addition, the finding that excess serotonin can disrupt the

normal wiring of the rodent somatosensory cortex is intriguing in the context of our sensory processing findings (Persico et al., 2001).

Developmental Continuity in Sensory Processing Function

Our third finding is that there is moderate developmental continuity across a wide age range from neonatal sensory processing to adult sensory function. This relationship was slightly stronger in the Prenatal Alcohol × Prenatal Stress Experiment, and it was virtually identical across gene groups. Our findings support the correlational results in the few existing longitudinal studies with children (Ben-Sasson et al., 2010; Goldsmith, Lemery-Chalfant, Schmidt, Arneson, & Schmidt, 2007). Studies with human toddlers have shown that *lower* sensory risk, as measured on the sensory–regulatory domain of Baranek et al. (2006) standardized questionnaire for autism spectrum screening, was associated with increased receptive language at 30 months of age (Ben-Sasson & Gill, 2014). This raises the possibility that modulating responses to sensory stimuli may contribute to receptive language development. For example, it is possible that sensory gating, that is, sorting relevant from irrelevant stimuli, may be an important aspect of separating speech from background.

Our finding of moderate developmental continuity suggests that poor early-life sensory processing could have cascading effects on other aspects of development. As children develop, they experience a wider range and increased intensity of sensory inputs and enhanced demands for adaptive responses. Future studies are needed to explore whether interventions for sensory processing dysfunction early in life may enhance children's potential for adaptive outcomes. Our finding of moderate continuity suggests more research is needed to examine why some individuals develop childhood and adult sensory processing dysfunction while others are resilient. Identifying factors that potentiate adaptive neurodevelopmental outcomes over time is important.

Our fourth finding is that neonatal sensory processing scores are correlated with adult striatal DA D_2R binding, evaluated using in vivo PET neuroimaging, and that this relationship depends on serotonin transporter genotype. For monkeys carrying the *s* allele, the correlation between neonatal sensory processing function and D_2R binding was significant, while the correlation between sensory processing and D_2R binding for *l*/*l* genotype monkeys was not. Thus, less optimal neonatal sensory processing function (tactile overresponsivity and poor vestibular function) was associated with upregulation of D_2R binding. This upregulation can occur as a compensatory response to lower levels of synaptic DA. These findings suggest that the underlying etiological mechanisms of sensory processing dysfunction across the life span may involve neurobiologically rooted vulnerabilities and complex interactions of the serotonin and DA systems.

It is interesting that serotonin, one of the phylogenetically and ontogenetically oldest neurotransmitters, has multiple receptor subtypes that can modulate the release of many other major neurotransmitters, including DA, as well as glutamate, GABA, acetylcholine, and norepinephrine (Barnes & Sharp, 1999). Moreover, comodulation of serotonin and DA in the prefrontal cortex can impact complex neuronal circuits, affecting neuronal plasticity, excitability, synaptic transmission, and other biochemical functions, hence affecting various brain functions and behaviors (Di Pietro & Seamans, 2011; Wang & Wong-Lin, 2013). Dysregulation of serotonin and DA in the prefrontal cortex has been implicated in a number of psychiatric disorders, including schizophrenia, ADHD, depression, and addiction (Robbins & Arnsten, 2009). Thus, interacting risk factors (such as carrying the [*s*] 5-HTTLPR genotype) may lead to maladaptive behavior over time perhaps related to continuity in sensory processing. How high-risk situations, such as prenatal perturbations, can amplify neurobiologically rooted vulnerabilities over time, yielding continuity across time, needs to be examined further.

It has been previously reported that increased DA D_2R binding in the striatum was related to adult sensory processing in monkeys (Schneider et al., 2008). Also, in the Prenatal Alcohol × Prenatal Stress Experiment, higher striatal DA transporter binding was associated with less optimal sensory processing when the animals were adults (Converse et al., 2013). These findings suggest that sensory processing dysfunction, as a result of prenatal stress, might represent a fundamental neuroadaptation in the DA system. Our findings support a body of literature suggesting that frontostriatal DA dysfunction might contribute to the behavioral impairments reported in children from prenatally stressed pregnancies. In rats, prenatal stress has been reported to alter dopaminergic indices including DA cell number, DA turnover, and D_2R density. Our studies suggest that altered functioning of the dopaminergic neuromodulatory circuits might play a role in the phenotypic expression of sensory processing dysfunction.

Limitations

There are several limitations of this study. One is that the candidate gene was limited to one functional 5-HTT marker (vs. haplotype). Candidate loci that affect functioning of other neurotransmitter systems are likely important and relevant to sensory processing function. A worthwhile approach for future research will be to determine how multiple vulnerability genes interact with one another and environmental factors in predicting sensory processing behaviors over time. A second limitation is that the Prenatal Alcohol × Prenatal Stress experiment showed less optimal neonatal sensory processing for both the continuous prenatal alcohol and prenatal stress exposed animals, but in the gestational timing of alcohol experiment, the prenatal continuous alcohol-exposed animals did not show this deficit. A possible reason for this difference in the continuous alcohol groups across experiments is that the gestational timing of alcohol animals received fewer days of alcohol exposure (135 days compared with 165 days in the Prenatal Alcohol × Prenatal Stress experiment). Finally, caution is necessary in generalizing from monkeys to humans, and thus it is critical to extend these findings in humans. If similar results are found in humans, early intervention studies will then be needed. One promising approach is sensory integration occupational therapy remediation employed early in life (Miller, Coll, & Schoen, 2007).

Conclusion

A central finding of this study is that prenatal stress yielded less optimal neonatal sensory processing and that there was moderate developmental continuity across a wide age range to adulthood. Our findings of the early emergence of sensory processing function with moderate developmental continuity suggest that some individuals are born vulnerable to sensory processing dysfunction. Our experiments suggest that this vulnerability can be due to several genetic and environmental factors. If vulnerable neonates can be identified, intervention is possible early in life during a time of high brain plasticity. Our results also suggest that reducing prenatal stress could play a role in decreasing the incidence of sensory processing problems. Thus it is important that healthcare professionals take findings like these into account when advising pregnant women about lifestyle factors, such as prenatal stress and alcohol use during pregnancy.

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