Prenatal exposure to antidepressants and depressed maternal mood alter trajectory of infant speech perception

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Language acquisition reflects a complex interplay between biology and early experience. Psychotropic medication exposure has been shown to alter neural plasticity and shift sensitive periods in perceptual development. Notably, serotonin reuptake inhibitors (SRIs) are antidepressant agents increasingly prescribed to manage antenatal mood disorders, and depressed maternal mood per se during pregnancy impacts infant behavior, also raising concerns about long-term consequences following such developmental exposure. We studied whether infants' language development is altered by prenatal exposure to SRIs and whether such effects differ from exposure to maternal mood disturbances. Infants from non–SRI-treated mothers with little or no depression (control), depressed but non–SRI-treated (depressed-only), and depressed and treated with an SRI (SRI-exposed) were studied at 36 wk gestation (while still in utero) on a consonant and vowel discrimination task and at 6 and 10 mo of age on a nonnative speech and visual language discrimination task. Whereas the control infants responded as expected (success at 6 mo and failure at 10 mo) the SRI-exposed infants failed to discriminate the language differences at either age and the depressed-only infants succeeded at 10 mo instead of 6 mo. Fetuses at 36 wk gestation in the control condition performed as expected, with a response on vowel but not consonant discrimination, whereas the SRI-exposed fetuses showed accelerated perceptual development by discriminating both vowels and consonants. Thus, prenatal depressed maternal mood and SRI exposure were found to shift developmental milestones bidirectionally on infant speech perception tasks.

infancy | maternal depression | critical periods

Language, our most quintessential human characteristic, involves a complex interplay between biology and experience. At birth, infants possess an initial preparedness for language and a developmental readiness that supports learning any of the world's languages (1–3), yet also already show privileged processing to the native language from prenatal listening experience (4–6). During the following weeks and months of life, infants become progressively attuned to the properties of their native language, including its rhythmical and segmental (e.g., consonant) information (reviewed in refs. 7 and 8). The high degree of regularity in the timing of sequential tuning to properties of the native language suggests a series of critical or sensitive periods, i.e., points in development when the system is maximally influenced by input.

The timing of onset of these sensitive periods seems to be maturationally constrained. Infants born 3 mo preterm attune to the phonetic properties (9) of their native language at the same gestational age as full-term infants, not according to the number of months of postnatal listening experience. Such maturational constraints can protect development: ensuring the optimal consecutive stabilization of the perceptual components that contribute in a step-wise fashion to language acquisition (10). However, it is known from research in other systems that highly aberrant input, and/or exposure to drugs or disease can change the timing of critical periods. For example, research with nonhuman animals shows that the timing of brain plasticity in the visual system can be shifted forward or reopened after closure by pharmacological manipulations, and that total sensory deprivation from birth (i.e., dark rearing) can delay the onset and closure of relevant critical periods (11). There are situations in which human infants are exposed to pharmacological agents and/or biological disparities that alter experience even in utero. Could such exposure shift the timing of sensitive periods in language development that typically appear to be maturationally controlled?

Prenatal exposure to maternal mood disturbances and antidepressants used to manage these disorders are exemplars of two increasingly common early life experiences that have long-term effects on behavior and development in childhood (12). During pregnancy, 15% to 20% of women experience mood disorders (e.g., depression) and between 5% and 13% of pregnant women are treated with an antidepressant drug (13, 14). Serotonin reuptake inhibitor (SRI) antidepressants are among the most commonly used drugs during pregnancy (14). Animal models have reported that perinatal antidepressant exposure impairs early 5-hydroxytryptamine (5-HT) homeostasis, influences mature cortical network function [eg, development of the auditory (15) and somatosensory cortex (16)], and affects long-term neurobehavior (17, 18). Our understanding of similar neuroanatomical and functional consequences in humans is limited. Because SRIs readily cross the placenta and the blood–brain barrier (19), concerns have been raised about the developmental consequences of altered fetal 5-HT signaling (12, 20) or other downstream consequences (21) following prenatal SRI exposure. Importantly, antenatal maternal mood disturbances also have adverse consequences on later cognitive and language development (22–24) and affect early 5-HT levels (25), leading to confusion about how to distinguish the developmental impact of SRIs from antenatal maternal mood disturbances.

Given the neurobehavioral consequences of SRI exposure and depressed maternal mood, we asked whether exposure to SRIs or to gestational maternal depression (not treated with an SRI) has an impact on the timing and precision of speech perception milestones. To provide a sensitive assay in humans, we tested infants on two perceptual tasks that have been extensively studied: (*i*) auditory discrimination of a nonnative consonant speech sound

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contrast (26) and (*ii*) visual discrimination of the change from one language to another while watching silent talking faces (27).

For the auditory task, we tested discrimination of the Hindi phonetic contrast between dental /da/ vs. retroflex /Da/ alveolar stops, a distinction both English- and Hindi-learning infants have been shown to discriminate as young infants. Listening experience maintains discrimination of this distinction in Hindi-learning infants, but English-learning infants who do not hear this distinction regularly show a dramatic decline in discrimination performance by 10 mo of age (26, 28). Speech perception was tested by using a modified version of the alternating/nonalternating procedure (*Materials and Methods*). Infants were habituated to the dental /da/ sound and then played instances of the same /da/ sound (i.e., nonalternating trial) or a new trial with alternating dental /da/ and retroflex /Da/ sounds. Discrimination in this procedure is indicated by longer looks during the alternating test trials that include the new /Da/ sound.

The visual language discrimination task tested a similar age-related decline in perceptual discrimination. Young infants visually tell apart English and French at 4 and 6 mo of age, but fail at 8 mo unless they are raised bilingual (27, 29). As in the earlier work of Weikum et al. (ref. 27 and *Materials and Methods*), infants were habituated to silent video clips of three bilingual speakers reciting sentences in English and then immediately shown test trials of the same three speakers silently reciting sentences in French. Discrimination in this task is indicated by a recovery in looking time during the test trials.

We tested infants at 6 mo of age, before they typically experience a decline in sensitivity to nonnative language information, and again at 10 mo, by which time typically developing infants show a decline in performance on each task. We compared three groups of infants at each age: SRI-exposed infants whose depressed mothers had been prescribed SRI medications during pregnancy, depressed-only infants whose mothers had depressive symptoms but chose not to take medication, and control infants whose mothers did not meet our criteria for depression or take psychotropic medications during pregnancy. Maternal depression at the time of testing was included as a covariate.

We predicted that infants exposed to neither depressive maternal symptoms nor SRIs would show discrimination on both tasks at 6 mo, but fail at 10 mo as their sensitive period for nonnative visual and auditory information begins to close. If SRI exposure and/or maternal mood impact the timing of sensitive period closure, the discrimination profile would be different. Acceleration would be shown by a failure to discriminate in the auditory and/or visual task already at 6 mo, whereas a delay in sensitive period closure could be shown by continued success even at 10 mo of age.

To complement our test of the timing of sensitive period closure, we also tested the participants at a time when their speech sound categories would be developing or "opening." At 36 wk gestation, typically developing fetuses are capable of discriminating vowel sounds (e.g., /a/ and /i/) (30, 31), but no evidence exists for consonants. We tested 36 wk-gestation fetuses on discrimination of a consonant (/da/ as in "dot" vs. /ta/ as in "tot") and a vowel (/a/ as in "ah" vs. /i/ as in "ee") contrast. Fetal heart rate was recorded in response to stimuli presented via a speaker pointed at the mother's abdomen. The sounds were modified and amplified to ensure transmission across the uterine wall (*Materials and Methods*). The previous work would predict success in the vowel but not the consonant condition. Developmental acceleration would be indicated by successful discrimination of both the vowel and consonant distinction, whereas disruption would be indicated by failure on both.

Results

Infant Age: 6 and 10 Mo. In the first experiment comparing performance at 6 and 10 mo, 32 control infants, 21 infants of non–SRI-treated prenatally depressed mothers, and 32 infants of SRI-treated depressed mothers were analyzed. Maternal and infant characteristics are listed for all participants (Table 1). There were no significant differences across groups in the mothers' demographics, but mothers in the SRI-exposed and depressed-only groups reported significantly higher levels of depression [i.e., Hamilton Rating Scale for depression (HAM-D) scores] prenatally and at time of testing (Table 1). There were no significant differences in the number of trials required to reach habituation criterion, number of male and female sex, or birth characteristics across the three groups of infants.

Repeated-measures analyses of covariance (ANCOVAs) were used to compare trial (alternating vs. nonalternating for the auditory Hindi discrimination task, habituation vs. switch for the visual language task), and prenatal exposure group (control, depressed-only, or SRI-exposed). Concurrent postnatal maternal mood was controlled by adding the mother's score on the HAM-D on the day of testing as a covariate. SRI exposure included all medications listed in Table 1 because our small sample sizes for each type of SRI did not permit further analysis of differential drug outcomes. Effect sizes (η^2) estimating the magnitude of the difference between the variables are reported.

Hindi sound discrimination at 6 mo. Controlling for maternal mood at 6 mo, a repeated-measures ANCOVA examining trial (alternating or nonalternating) and exposure group (control, depressed-only, SRI-exposed) revealed a significant within-subjects interaction for trial by exposure group [$F(2,67) = 4.376$, $P = 0.016$, $\eta^2 = 0.116$]. When split according to exposure group at 6 mo, there was a significant main effect for trial in the control group: the infants looked significantly longer during the alternating trials [$F(1,24) = 9.271$, $P = 0.006$, $\eta^2 = 0.279$]. A nonsignificant trend, but favoring the nonalternating or familiar trial, was found in the depressed-only group [$F(1,18) = 2.490$, $P = 0.12$, $\eta^2 = 0.122$]. There were no significant effects in the SRI-exposed group [$F(1,26) = 0.306$, $P = 0.585$, $\eta^2 = 0.012$; Fig. 1*A*].

Hindi sound discrimination at 10 mo. When split according to exposure group at 10 mo, there were no significant interactions or differences for infants in the control [$F(1,27) = 0.058$, $P = 0.812$, $\eta^2 = 0.002$] or SRI-exposed groups [$F(1,29) = 0.144$, $P = 0.708$, $\eta^2 = 0.005$], but there was a significant main effect for trial in the depressed-only group [$F(1,15) = 5.886$, $P = 0.028$, $\eta^2 = 0.282$; Fig. 1*B*]. At this age (10 mo), infants in the depressed-only group looked longer during the alternating trials (similar to the 6-mo controls). An exploratory follow-up multivariate ANOVA of the depressed-only group at both ages revealed a significant interaction between 6 and 10 mo [$F(2,33) = 8.382$, $P = 0.007$, $\eta^2 = 0.203$], confirming the change from a familiarity (i.e., nonalternating) to a novelty (i.e., alternating) preference.

Visual language discrimination at 6 mo. Controlling for maternal mood at 6 mo, a repeated-measures ANCOVA examining trial (final habituation vs. test), and exposure group (control, depressed-only, SRI-exposed) revealed a significant within-subjects main effect for trial [$F(1,58) = 5.337$, $P = 0.024$, $\eta^2 = 0.084$] and trial-by-maternal mood interaction [$F(1,58) = 5.192$, $P = 0.026$, $\eta^2 = 0.082$]. There was also a significant between-subjects main effect for exposure group [$F(2,58) = 3.160$, $P = 0.05$, $\eta^2 = 0.098$]. Because there was a significant interaction for mood in the overall ANCOVA, the follow-up analyses at 6 mo split the data according to exposure group and controlled for maternal mood at 6 mo.

In the control group there was a significant difference between the final habituation and test trials [$F(1,24) = 13.954$, $P = 0.001$, $\eta^2 = 0.368$] and a significant interaction between trial and maternal mood at time of study [$F(1,24) = 7.434$, $P = 0.012$, $\eta^2 = 0.237$]. A follow-up linear regression analysis revealed a negative correlation between looking time to the switch and maternal depression [$B(1,24) = -0.486$, $P = 0.012$, $r^2 = 0.237$]. No significant differences were found for the depressed-only [$F(1,11) =$

Table 1. Participant characteristics at 6 and 10 mo

Characteristic	Control		Depressed only		SRI-exposed		
	Mean ± SD	*n*	Mean ± SD	*n*	Mean ± SD	*n*	*P* value
Maternal details							
Prenatal HAM-D (56)	3.61 ± 2.01	32	12.95 ± 4.93	21	10.67 ± 4.97	32	0.01*
6 mo HAM-D (56)	4.11 ± 3.99	28	11.42 ± 5.85	19	10.93 ± 6.58	28	0.01*
10 mo HAM-D (56)	3.57 ± 3.60	30	11.05 ± 7.58	19	10.07 ± 7.52	30	0.01*
Education (y)	18.91 ± 3.65	32	17.71 ± 3.02	21	17.38 ± 3.84	32	0.21
Prenatal SRI medications (median mg/d)							
Paroxetine	—	—	—	—	27.5 ± 9.57	4	—
Fluoxetine	—	—	—	—	46.67 ± 23.09	3	—
Sertraline	—	—	—	—	90 ± 80.23	5	—
Citalopram	—	—	—	—	33.33 ± 19.66	6	—
Escitalopram	—	—	—	—	50 ± 0	1	—
Venlafaxine	—	—	—	—	154.42 ± 55.39	13	—
Alcohol (no. of drinks during pregnancy)	4.39 ± 8.60	32	4.67 ± 6.00	21	4.69 ± 8.45	32	0.99
Smoking (yes/no)	0 ± 0	32	0.05 ± 0.22	21	0.03 ± 0.18	32	0.51
Age at delivery (y)	33.47 ± 3.88	32	36.3 ± 5.95	21	33.56 ± 5.90	32	0.11
Infant details							
Sex (M/F)	14/18	32	12/9	21	(14/18	32	—
Birth gestational age (wk)	39.79 ± 1.45	32	39.78 ± 1.81	21	38.96 ± 1.48	32	0.07
Birth weight (g)	3448 ± 503	32	3530 ± 441	21	3267 ± 440	32	0.11
Duration of prenatal SRI exposure (d)	—	—	—	—	255.41 ± 51.84	32	—
Age at 6 m study (d)	183.96 ± 5.61	28	186 ± 6.15	19	184.57 ± 5.67	28	0.45
Age at 10 m study (d)	307.03 ± 7.16	30	308.89 ± 7.47	19	306.43 ± 4.33	30	0.41

*Significant at $P < 0.05$.

0.09, $P = 0.926$, $\eta^2 = 0.001$] or SRI-exposed groups [$F(1,21) = 0.613$, $P = 0.442$, $\eta^2 = 0.028$; Fig. 2*A*].

Visual language discrimination at 10 mo. When split into exposure groups and analyzed at 10 mo (controlling for maternal mood at 10 mo), there were no significant differences for the control [$F(1,18) = 1.626$, $P = 0.218$, $\eta^2 = 0.083$] or SRI-exposed groups [$F(1,21) = 0.031$, $P = 0.861$, $\eta^2 = 0.001$], but the depressed-only group showed a significant main effect for trial [$F(1,14) = 6.023$, $P = 0.028$, $\eta^2 = 0.301$; Fig. 2*B*]. Like the 6-mo-old infants in the control group, the 10-mo-old infants in the depressed-only group increased their looking to the language switch.

Fetal consonant and vowel discrimination. In the second experiment, 14 fetuses of mothers taking SRI medications during their pregnancy and 20 nonexposed fetuses were tested. With the exception of higher depressive symptoms in the SRI-treated group (based on HAM-D score), maternal demographic and health characteristics did not differ between the groups (Table 2). Independent-samples Mann–Whitney *U* comparisons were used to examine infant state (asleep/awake) at the time of the study and showed no significant difference between the state of the infants in the control group versus the SRI-exposed group for the consonant study ($P = 0.191$) or vowel study ($P = 0.503$).

As the sample size was not adequate for three groups, the effect of prenatal maternal mood was controlled by including it as a covariate. Heart rate deceleration during a 10-s window was used as the dependent variable following a switch in speech sound delivered from a speaker to the mother's abdomen (*Materials and Methods*). It was predicted that nonexposed fetuses would discriminate the vowel contrast but not the consonant contrast.

The vowel discrimination data were analyzed by using two-by-two-by-10 [group (exposed vs. nonexposed) by trial type (preswitch vs. postswitch) by test trial] repeated-measures ANCOVAs, with maternal mood score (per HAM-D) at 36 wk gestation included as a covariate. There were no significant main effects, but there was a significant interaction between trial type (preswitch vs. postswitch) and test trial [$F(1,31) = 3.91$, $P = 0.031$, $\eta^2 = 0.11$] and a significant trial type-by-test trial-by-maternal mood (per HAM-D) interaction [$F(1,31) = 4.18$, $P = 0.025$, $\eta^2 = 0.12$].

To probe these significant interactions, a repeated-measures ANOVA using prenatal maternal mood (per HAM-D) as a

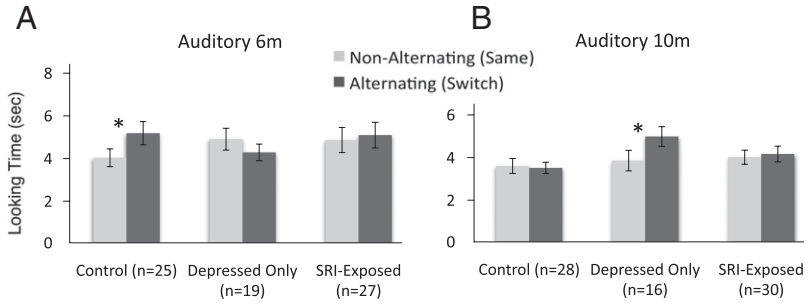

Fig. 1. Comparison of alternating (Hindi dental and retroflex) trials to nonalternating (Hindi dental) trials after being habituated to Hindi dental syllable (*$P < 0.05$). Error bars represent SEM. (*A*) Data from control ($n = 25$), depressed-only ($n = 19$), and SRI-exposed infants at 6 mo ($n = 27$). (*B*) Data from control ($n = 28$), depressed-only ($n = 16$) and SRI-exposed ($n = 30$) infants at 10 mo.

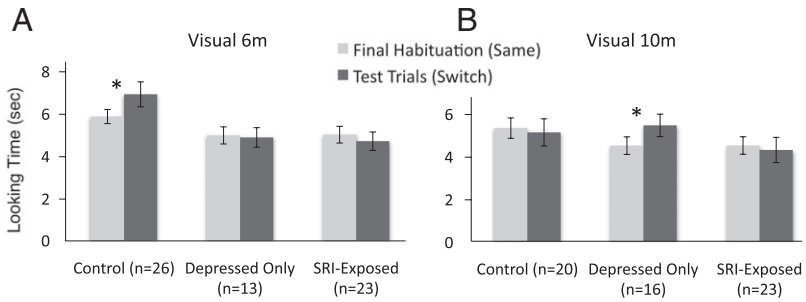

Fig. 2. Comparison of final three English habituation trials to two sets of three test trials following the visual language switch to French (*$P < 0.05$). Error bars represent SEM. (*A*) Data from control ($n = 26$), depressed-only ($n = 13$), and SRI-exposed ($n = 23$) infants at 6 mo. (*B*) Data from control ($n = 20$), depressed-only ($n = 16$) and SRI-exposed ($n = 23$) infants at 10 mo.

covariate was conducted across the preswitch condition test trials and postswitch condition test trials. There was no significant difference in the preswitch condition, but a change in heart rate in the postswitch condition [$F(1,31) = 3.08$, $P = 0.05$, $\eta^2 = 0.09$]. Pair-wise comparisons revealed a significant decline in heart rate between trials 2 and 4 ($P < 0.05$), with no main effect or interaction for exposure group or maternal mood (Fig. 3*A*).

The consonant data were analyzed by using the same two-by-two-by-10 [group (exposed vs. nonexposed) by trial type (preswitch vs. postswitch) by test trial] mixed ANCOVA, and again controlled for maternal mood by including the HAM-D score as a covariate. There was a significant group (exposure)-by-trial type (preswitch vs. postswitch)-by-trial interaction [$F(1,31) = 3.56$, $P = 0.04$, $\eta^2 = 0.10$], with no interaction for maternal mood. Follow-up analyses controlling for maternal mood revealed no significant differences in the nonexposed group, but the exposed group showed a significant decline in heart rate between the preswitch and postswitch trials [$F(1,12) = 6.66$, $P = 0.024$, $\eta^2 = 0.36$; Fig. 3*B*].

Discussion

This research was designed to examine whether early altered neurochemistry or maternal mental health can change the timing of critical periods in human language development. The results support an accelerated timing of perceptual attunement in SRI-exposed infants; however, postnatal maternal mood also had an impact. Whereas nonexposed infants of control mothers exhibited the typical pattern of discrimination at 6 mo and perceptual narrowing by 10 mo of age, the SRI-exposed infants already showed a more mature pattern, with failure to discriminate nonnative vowel and visual language changes at 6 mo that persisted to 10 mo. Their equivalent behavior to nonexposed fetuses on the vowel discrimination task at 36 wk in utero, coupled with their advanced perceptual capacity on the native consonant discrimination task, further supports an interpretation that failure to discriminate at 6 and 10 mo reflects a generally accelerated development of the speech perception system upon early SRI exposure.

Interestingly, maternal depression had the opposite effect. Infants in this group showed unreliable discrimination at 6 mo, with a tendency toward a familiarity rather than a novelty preference. However, at 10 mo, they reliably discriminated the nonnative speech sound difference and the change between visual English and visual French. Exposure to maternal depressed mood seems to delay stable discrimination, which ultimately extends the period of sensitivity to nonnative distinctions. Thus, exposure to maternal depression and prenatal SRI exposure appear to exhibit opposite effects on the development of infant speech perception. However, whether this reflects the impact of pre- or postnatal maternal mood remains to be determined.

A mechanistic explication of the biology by which SRIs and maternal depression disrupt critical period timing is essential. One possible explanation is that altered 5-HT levels that result from prolonged gestational antidepressant exposure could change the precision of language representation in the brain. Although direct

Table 2. Fetal participant characteristics

	Nonexposed		SRI-exposed		
Characteristic	Mean ± SD	*n*	Mean ± SD	*n*	*P* value
Maternal details					
Education (y)	17.4 ± 2.58	20	16.57 ± 4.31	14	0.528
HAM-D score (56) at 36 wk gestation	6.4 ± 5.11	20	10.79 ± 3.77	14	0.007*
Smoking (yes/no)	0	20	0.07 ± 0.27	14	0.336
Alcohol (no. of drinks for entire pregnancy)	5.1 ± 8.34	20	4.79 ± 7.63	14	0.912
Prenatal SRI medications (median mg/d)					
Paroxetine	—	—	20 ± 0	2	—
Fluoxetine	—	—	20 ± 0	1	—
Sertraline	—	—	25 ± 0	1	—
Citalopram	—	—	30 ± 17.32	3	—
Venlafaxine	—	—	144.71 ± 69.79	7	—
Fetal details					
Sex (M/F)	9/11	20	5/9	14	—
Fetal study gestational age (wk)	36.38 ± 0.76	20	36.26 ± 0.37	14	0.521
Birth gestational age (wk)	40.28 ± 0.98	20	38.78 ± 1.64	14	0.002*
Duration of prenatal SRI exposure (d)	—	—	256.07 ± 47.93	14	—

*Significant at $P < 0.05$.

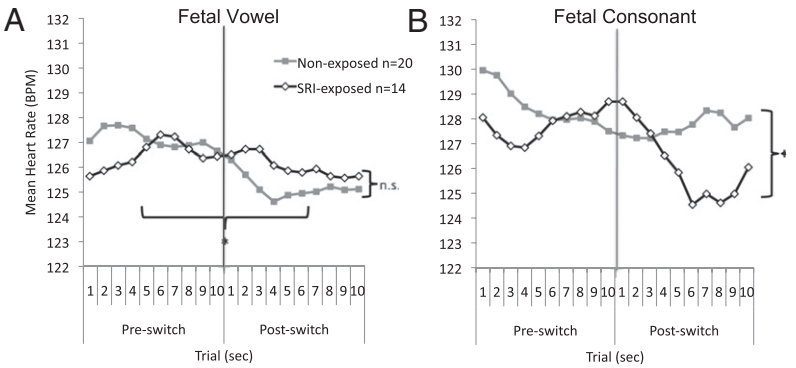

Fig. 3. Mean fetal heart rate during a speech discrimination task. The *y* axis represents fetal heart rate in beats per minute (BPM); the *x*-axis represents the 10 preswitch and 10 postswitch trials. Preswitch comprises repeated presentations of the same sound, and postswitch comprises repeated presentations of the changed speech sound (*$P < 0.05$). (*A*) SRI-exposed ($n = 14$) and nonexposed ($n = 20$) fetuses at 36 wk gestation in response to a change in vowel sounds (/a/ vs. /i/). (*B*) SRI-exposed ($n = 14$) and nonexposed ($n = 20$) fetuses at 36 wk gestation in response to a change in consonant sounds (/da/ vs. /ta/).

human evidence has not been reported, exposure to SRIs early in life has been shown to alter tonotopic organization and receptive field properties in the primary auditory cortex (A1) of rats (15), suggesting that a disruption in auditory coding per se could explain a failure to discriminate speech at 6 and 10 mo by SRI-exposed infants. However, this cannot account for the finding of precocious consonant discrimination in utero by SRI-exposed fetuses. Thus, when all the findings are taken into account, the effect of early SRI exposure appears to be one of accelerated attunement to the properties of the native language.

Emerging reports from animal models suggest that early SRI exposure has a positive influence, reversing or "correcting" the adverse effects of prenatal maternal stress exposure (32–34). Although they are of interest, our results are not entirely consistent with that pattern, as, in our case, SRI exposure appears to lead to an "over-correction." Below, we discuss how SRI exposure could influence age-related changes in speech perception.

Modulating 5-HT levels increase cortical plasticity in the adult visual system (35, 36). SRIs in particular can reopen cortical plasticity (37), but the means by which they do so has been largely undescribed. Recent insight into the cellular and molecular mechanisms underlying critical period onset and closure in the neocortex of mice now offers a more detailed mechanistic explanation. The maturation of excitatory–inhibitory local circuit balance appears pivotal (11). Any manipulation that ultimately accelerates/delays GABA circuit function will accelerate/delay critical period timing. By analogy, maturational milestones in the auditory system may also reflect a shifted excitatory–inhibitory balance. Apart from the popular action of SRIs on 5-HT transport, these drugs are notorious for their off-target effects (21). Notably, in response to submaximal GABA concentrations, fluoxetine can potentiate current flux through $GABA_A$ receptors containing the α1 subunit (38). Benzodiazepine use early in life is already known to accelerate critical period onset by this mechanism (39).

Turning to the infants of non–SRI-treated but depressed mothers, the compelling finding is their robust discrimination at 10 mo of the nonnative speech sound contrast and the visual language change. This result provides evidence for a delay of the critical period for attunement to the properties of the native language rather than a gross perceptual impairment. An organic difficulty in learning and/or performance on the habituation tasks is one explanation for unreliable discrimination performance at 6 mo. Newborns of depressed mothers show inferior performance on the Brazelton assessment (40, 41), with lower orientation scores, abnormal reflexes, inferior excitability, and withdrawal scores (42). However, the successful discrimination at 10 mo by infants born to depressed mothers not treated with an SRI may be better explained by a delayed critical period trajectory caused by early stimulus deprivation.

By analogy to dark-rearing in the visual system (11), infants of depressed mothers may not hear sufficient speech, or sufficiently engaging speech, to initiate the neurological changes that trigger critical period onset. Depressed mothers do not modify their speaking style (43, 44) to produce the exaggerated "motherese" that infants prefer (45–48), and which can highlight speech sound differences (49). Newborns of depressed mothers fail to show face/voice preference (22) whereas older infants do not learn as well from their mothers' infant-directed speech (50). Thus, maternal depression may have resulted in subthreshold levels of appropriately engaging speech input. Further support for this possibility is provided by the significant correlation we observed between depression scores at 6 mo and performance in the visual language discrimination task even in control infants.

In summary, we have found that exposure to SRIs accelerates speech perception development, whereas exposure to maternal depression initially disrupts performance and ultimately delays perceptual narrowing by prolonging the period of sensitivity to nonnative distinctions. These findings are particularly compelling when we consider that the timing of speech perception development is typically considered to be maturationally delimited. What is unknown at this time, and of key clinical importance, is whether these small perturbations in critical period timing of core perceptual components of language acquisition have a lasting impact. To date, there are no published reports of language delay in infants or young children with SRI exposure. However, sequential timing and ordered emergence of developing systems is an essential characteristic of optimal development, as it allows more complex processes to build on first established, more foundational representations (51).

We know that, in typical language development, infants use the representations established in native speech sound discrimination to direct later word learning (10) and in rhythmical discrimination to direct later parsing of syntactic units (52). Thus, disruptions in the perceptual foundations of language could have a cascading impact on optimal language development (53). A recent population-level finding reports an intriguing association between prenatal SRI exposure and an increased risk for autism in early childhood (54), raising critical questions (55) about the long-term developmental implications of early mistiming in language development. By providing a deeper mechanistic understanding of how and when developmental trajectories are altered by early exposure to maternal mood disturbances and/or SRI exposure, more optimal outcomes can be realized for infants and their mothers.

Materials and Methods

Participants. Informed consent was obtained from mothers recruited during their second trimester, and their infants were tested at 36 wk gestation and at 6 mo and 10 mo of age. Mothers were interviewed by trained research assistants by using the HAM-D (56) during the second and third trimesters of pregnancy and when their infants were 6 and 10 mo of age. Averages of the prenatal scores were used to classify the 6- and 10-mo-old infants into three groups: no SRIs and HAM-D scores <8 (control group), no SRIs and HAM-D scores ≥8 (depressed-only group) and SRI-exposed. The HAM-D cutoff score chosen was 8 because scores of 8 to 13 signify mild depression (57).

Auditory Task. A total of 78 infants were tested at 6 mo, and 82 were tested at 10 mo. At 6 mo, participants were excluded for experimenter error (n = 1) and fussiness (n = 6). At 10 mo, participants were excluded for experimenter error (n = 0), fussiness (n = 4), and parental interference (n = 4).

Visual Task. A total of 78 infants were tested at 6 mo, and 80 were tested at 10 mo. At 6 mo, participants were excluded for experimenter error (n = 0), fussiness (n = 11), parental interference (n = 2), failure to habituate (n = 1), and failure to watch the screen (n = 2). At 10 mo, participants were excluded for experimenter error (n = 1), fussiness (n = 16), parental interference (n = 1), failure to habituate (n = 2) and bilingual exposure to French (n = 1).

Fetal Task. Fetuses of 23 mothers treated with an SRI antidepressant agent and 46 non–SRI-treated mothers were tested. Participants were excluded as a result of experimenter error (n = 1 exposed; n = 2 nonexposed), incomplete heart rate signal (n = 4 exposed; n = 7 nonexposed), and fetal movement during our window of interest (n = 4 exposed; n = 17 nonexposed). As we could not distinguish fetal heart rate responses to the speech stimuli from changes associated with fetal movement, any recorded movement that occurred (according to maternal button press) during the 10-s preswitch or 10-s postswitch period rendered the recording ineligible for inclusion in the study. There were no differences between the number of movements that occurred before or after the sound switch and no significant group differences in movements between the fetuses included for analysis and those excluded for movement or missing data.

Stimuli. ***Hindi sound discrimination.*** The Hindi dental /da/ and retroflex /Da/ syllables were the same as those used by Werker and Lalonde (28). They were taken from an eight-step continuum of /da/ sounds created by using the Mattingly synthesizer at Haskins Laboratories. Each syllable was 275 ms in length. As the stimuli were synthesized, the duration, pitch, and loudness were constant across all stimuli.

Visual language discrimination. The visual speech stimuli were the same as those used by Weikum et al. (27). The faces of three bilingual (French/English) speakers were filmed while they recited sentences in both French and English. The audio was removed from the clips.

Fetal sound discrimination. The consonant stimuli were from a database prepared by the laboratory of Colin Phillips at the University of Maryland. Alveolar /da/ and /ta/ sounds were generated by using the cascade vocal tract of the Klatt speech synthesizer for Macintosh (SenSyn; Sensimetrics). These speech sounds are identical except for the timing of voice onset between the initial consonant burst and subsequent vowel sound. Both are stop consonants produced by obstructing the airflow by placing the tongue at the alveolar ridge. However, /da/, which is "voiced," has simultaneous onset of voicing with the release of the consonant, whereas there is a lag between the release and the onset of voicing in /ta/, making it "voiceless." Our stimuli were 275 ms in length, the vowel followed the consonant burst immediately in the /da/ sound, and there was a 40-ms lag between the initial consonant burst and subsequent vowel in the /ta/ stimuli. Detection of the burst by the fetus is essential for the critical timing cue between voiced /da/ and voiceless /ta/ to be perceived. Because the initial burst at the release of the consonant comprises primarily high frequency information, and because high frequency information is more likely to be attenuated by the uterine wall (58), we amplified the low frequency portion of the burst (below 1,000 Hz using Adobe Audition software). The vowel stimuli /a/ and /i/ were 200 ms in length, prepared by using Mbrola software, and matched in intensity by using Adobe Audition software.

Procedure. ***Hindi sound discrimination.*** Infants sat on their parents' lap facing a 32-inch flat screen television that was positioned on a table 24 inches off the floor and 36 inches from the infant. Small toys or pacifiers were permitted for infants who were fussy before the start of the study. Infants were tested with a version of the alternating/nonalternating paradigm (59). Stimuli was presented at ∼68 db using Bose Companion II speakers, and the experiment was run by using Habit X software (60) installed on a dual core Intel Xeon Mac Pro computer (Macintosh). The infants were presented with the dental /da/ sound until they habituated. Habituation was reached when their looking time to a black-and-white checkerboard on three consecutive trials decreased to 50% of their looking time during the longest habituation trial. There were two types of test trials. In "new" trials, the retroflex /Da/ sound alternated with the dental /da/ sound to which they had been habituated (i.e., /da/Da/da/Da/da/). In "old" trials, they heard only the same /da/ sound heard during habituation (i.e., /da/da/da/da/da). The interstimulus interval (ISI) was 500 ms. Each trial continued for 16 s or until the infant ended the trial by not watching the checkerboard for more than 2 s. Infants heard six test trials—three alternating and three nonalternating—and infants were randomly assigned to one of two different orders. To prevent inadvertently influencing their infant, parents wore Peltor Workstyle noise-cancelling headphones (3M) and listened to masking music played at ∼75 db.

Visual language discrimination. Stimuli were presented by using the Habit X software and computer equipment used in the previous study. Infants were shown the faces of the three speakers silently reciting different sentences in English. The stimuli were presented seamlessly as blocks of three in which the speaker order was always the same for each infant. Infants were randomly assigned to one of four different speaker orders. When looking time in a block of three habituation trials decreased to 60% of the looking time in the longest block of three habituation trials, the program automatically started playing test trials in French. The test trials contained the same speakers in the same order so that the infants would not notice a difference as a result of speaker order and were seamlessly presented following the test trials. The test trials contained new sentences in French from each speaker. As in previous work, the test trials were repeated to ensure that the infants had adequate viewing time to detect the stimulus change. The discrimination score was average looking time during the two blocks of three trials.

Fetal sound discrimination. A Bose Companion II speaker was positioned ∼10 cm from the mother's abdomen on a thick pillow or large foam wedge on the mother's lap (n = 2 exposed; n = 3 nonexposed) or, when space permitted, beside the mother (n = 12 exposed; n = 17 nonexposed). All fetuses were tested following a 50-min rest session. In an attempt to reduce experimenter bias and use a more ecologically valid method, we did not wait for each fetus to achieve a certain heart rate pattern, but instead played the stream of sounds continuously following the 50 min of rest by the mothers. The sounds were played from an iPod nano (Macintosh) at 95 ± 3 db as measured from an Extech 407735 sound meter. To provide partial masking to avoid maternal influence on fetal behavior, the mothers listened to the children's story, "The Golden Fish" (http://storynory.com/2006/08/27/the-golden-fish/), through Peltor Workstyle noise-cancelling headphones (3M) at ∼75 db. Every fetus was exposed to 15 min of language sounds. The first 2 min contained a consonant switch and the last 2 min contained a vowel switch. Subjects were randomly assigned to one of four conditions. One consonant sound was repeated every second (ISI of 725 ms) for 1 min to familiarize the fetus to the sound and then immediately switched to repetitions of the other consonant sound for 30 s. The same protocol was followed for the vowel sounds (they were played every second; ISI of 800 ms).

Fetal heart rate was continuously monitored using a Toitu MT-325 Fetal Actocardiograph. The heart rate variability and movement patterns were used to determine the state of the fetuses at the time of testing. This would help to ensure that any effects were a result of stimuli presented and not masked by the state of the fetus. Four states were classified according to the procedure outlined by DiPietro et al. (61). Infants were classified as in quiet sleep (little or no heart rate variability and little or no movements), active sleep (moderate heart rate variability with episodic accelerations and some movements), quiet awake (a rhythmic oscillatory heart rate pattern within a wider bandwidth than quiet sleep and little or no movements), or active awake (high heart rate variability during which accelerations may be fused into tachycardia and movements). The 15 min for the language study was broken into five 3-min blocks. Each 3-min block was analyzed to determine the infant state during that portion.

The Toitu heart rate tracings were also imported into the computer program DigitizeIt (http://www.digitizeit.de/), allowing a 1-Hz recording of the fetus's heart rate. Following the procedure of Kisilevsky et al. (62), the 10 s before (i.e., preswitch) and 10 s after the switch (i.e., postswitch) were analyzed. The data were analyzed for heart rate decelerations that occurred in response to the sound switch, indicating that the fetuses noticed the change in sound (63).

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