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Fine Motor Differences and Prenatal Serotonin Reuptake Inhibitors Exposure

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Abstract

Objective—To examine fine motor differences between preschoolers with prenatal serotonin reuptake inhibitor (SRI) exposure and children of mothers with major depression disorder.

Study design—A subset of children (N=40), from a larger study on the effects of prenatal SRI and untreated major depression disorder participated in a kinematic task of visual motor and fine motor functions at ages 4–5 years: SRI exposure (n=15), untreated major depression disorder exposure (n=10), and the control group (n=15). The task was to reach and secure a peg then drop it in a small hole near the start position in the light condition with full visibility or in the glow condition in which a phosphorescent peg glows in the dark. Movement tracking software measured the positioning of the moving hand and fingers.

Results—In the Glow condition, the SRI group had a higher proportion of maximum aperture than the group with major depression disorder and the SRI group was slower than the major depression disorder group to drop the peg into the hole. In the Glow condition, the trajectory of the SRI group was less straight than the major depression disorder group, and the major depression disorder group had a straighter trajectory than the control group.

Conclusion—This study provides evidence that preschool aged children with prenatal SRI exposure have poorer fine motor and visual-motor control compared with prenatal untreated major depression disorder.

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Keywords

Efference copy; visual-motor development; kinematics; grasp; reach

Newborns exposed to SRIs demonstrate significantly poorer motor quality compared with nonexposed infants.¹⁻⁶ At 18 months of age, SRI exposed children showed worse performances in motor quality on the Bayley Behavioral Rating Scale⁷ and delayed motor milestones up to 40 months.⁸ Few studies, however, have examined motor development and motor control skills in SRI exposed children beyond 4 years of age. Moreover, the measurement tools used may not be precise enough to detect more nuanced effects of SRIs that could suggest delay in neural processes involved in motor control that may be of clinical importance.

A highly precise methodology to evaluate variation in fine motor movements is kinematics analysis, in which the trajectory of the reaching hand and the finger aperture were monitored by an optoelectronic motor analysis system. Acquisition and execution of fine motor skills requires the coordinated participation of multiple structures in the motor cortex, basal ganglia, cerebellum and spinal cord.⁹ Fine motor development involves modifications of the cortical representations of the body caused by sensory input including sensorimotor input affecting somatotopin maps, efference copy development, and visual-motor coordination.¹⁰ Somatotopin maps refer to adjacent neurons in neural tissue that respond selectively to stimuli presented to adjacent locations on the body. Efference copy is a series of copies of efferent signals from the motor cortex into the sensory cortex and the periphery. Together with internal models, efference copies can enable the brain to predict the effects of an action system.

Although kinematic analysis has been applied to normative preschool age children,^{11, 12} this study takes advantage of kinematic analysis to evaluate the impact of prenatal exposure to SRI on motor function at later preschool ages (4-5 years). Our hypotheses are that prenatal SRI exposure will result in less efficient reaching (eg, increased movement units [MUs], shorter proportion of time to the end of the first MU, slower peak velocity; longer phase duration; and less straightness). Further, we hypothesize that the Glow condition when the peg is seen but not the moving hand will be less efficient due to efference copy.

Methods

The subsample consisted of 40 children with a mean age of 4.75 years (range= 4.33 to 5.25 years) who participated in a larger study¹³ on the effects of prenatal SRI exposure on fetal, infant, and child outcomes: 15 exposed to SRI, 10 exposed to untreated mothers with major depression disorder, and 15 controls. The study was approved by the Institutional Review Board at Women & Infants Hospital of Rhode Island, and written informed consent was obtained from the parents.

Women aged 18 to 40 were recruited in the community and through mental health professionals, and were enrolled between 22 and 34 weeks of pregnancy. Women were included in the SRI exposure group if they were on a SRI for a minimum of four weeks

during the pregnancy. Inclusion in the major depression disorder exposure group required a minimum of four consecutive weeks of symptomatic major depression disorder, as defined by the Structural Clinical Interview for DSM-IV Psychiatric Diagnoses.¹⁴ The non-exposure control group included women with no psychiatric diagnoses during pregnancy and at least one year prior, no use of psychotropic or other medication during the pregnancy, and mild or no depressive symptoms. The majority of the women taking SRIs were using sertraline (64%); the remainder used citalopram (24%) or escitalopram (4%). Exclusion criteria for the mothers were: use of anticonvulsants or antipsychotics,^{15, 16} alcohol consumption (>1 drink/week), cigarette and/or illegal drug use during pregnancy, diagnoses of psychotic or bipolar disorders, thyroid conditions, hypertension, and diabetes. Anxiety disorders were allowed in the SRI and major depression disorder groups as well as medications such as zolpidem, diphenhydramine, and other types of antidepressants/anxiolytics. Premature births (<36 weeks of gestation) or infants with known genetic, medical, or physical anomalies were excluded.

Children were instructed to reach and grasp a series of identical cylindrical pegs (5 cm in height × 2.5 cm in diameter) roughly an arm's length away on a table and then return with the peg toward the start position, dropping the peg in a small opening (Figure; available at www.jpeds.com). The task was performed in two experimental conditions. In the Light condition, both hand and peg were visible. In the Glow condition, the lights were turned off and only the peg, coated with phosphorescent paint, was visible. The small opening for the drop was also coated with phosphorescent paint and visible in both conditions. The children grasped and dropped a total of 15 pegs in each lighting condition. The pegs were separated into sets with 5 pegs each. The Light and Glow conditions alternated every 5 pegs. If trials were unsuccessful or likely to be unscorable, an additional set of 5 pegs of the same condition were conducted.

Two cameras with infrared illuminator rings recorded the procedure from different angles. The children wore a glove on their dominant hand that had reflective markers on the distal aspect of the thumb and index finger, and on the proximal region between these two fingers that we called the “web”. Reflective markers were also placed on the pegs. The reflective markers appear as bright spots on the camera footage, allowing for later digitizing and tracking of movements of each marker using the Vicon Motus® software (Vicon Motus, Boston, Massachusetts) at 100 frames per second. This provided coordinates for each marker in each frame.

The task had two phases of primary interest: reach and drop. The reach phase began with the web marker's first movement towards the peg and ended when the child grasped the peg. The drop phase began when the mid-pinch (defined as the center between the index and thumb markers) was exactly at 4 cm from where the child drops the peg. The reach involved control of the hand and entire upper extremity, and was evaluated using the coordinates of the centrally located web marker. The drop involved fine motor control of the fingers and the variables in this phase used the coordinates of the distally located mid-pinch.

The dependent measures derived from the kinematic record of each trial are shown in Table I (available at www.jpeds.com). Definitions are included. The reach measures were chosen to

allow comparison with other kinematic studies and to provide a detailed assessment of the development of reaching. The drop measures are unique to this study and provide additional challenge for a young child not only to release the peg into a small opening, but also to recalibrate speed during the approach to the target area. Final analyses tested kinematic parameters by study groups.

Statistical Analyses

Demographic characteristics were assessed using one-way analysis of variance (ANOVA) for continuous measures or chi-square for categorical measures. Prior to statistical analysis, the frame-by-frame coordinates were incorporated into trials then into outcome variables within study groups. Generalized estimating equations (GEE) were used to compare the three groups (SRI, major depression disorder, and control) in each of the Light and Glow conditions independently. This extension of the general linear model allows more flexibility in the distributions of the dependent variable and accounts for the correlated nature of the observations within each subject. The general form of the GEE model used for these analyses incorporated a categorical variable for depression group (SRI, major depression disorder, and control) as well as the specification for the repeated nature of the data based upon the subject. Light and Glow conditions were examined in separate GEE models. Furthermore, three covariates that were related to one or more reaching condition were included in the models: mothers' level of depression at the study visit, child's mean age (months) at the study visit and gestational age (Table II). In addition, children varied in the number of sets (5 trials each) that were completed in the session. The greater the number of sets, the greater the likelihood of practice effects. Thus, number of sets was included as a covariate as well. Pairwise comparisons of the parameter estimates for any significant group main effects were examined with the Fisher least significant difference. Peak velocity models were adjusted for arm length.

Child sex and Index of social position at study visit (socioeconomic status) were not associated with any reaching measures and were not included as covariates. All statistical analyses were performed using SPSS 17.0.

Results

Demographic information of the children and their mothers is detailed in Table II. Depression over pregnancy did not differ between the SRI and the major depression disorder groups. ($P=.550$). Similarly, depression severity at the study visit did not differ between the SRI and major depression disorder groups ($P=.324$). With the control group included, the depression severity across groups was significant ($P=.035$). There were no other significant maternal or child differences among the three groups.

Adjusted means (SE) are shown in Table III. Significant pairwise effects were indicated by ^a (SRI or major depression disorder vs. control group) and ^b (SRI vs. major depression disorder).

In the Glow condition, the efficiency of the reach and grasp is indicated by a lower proportion of maximum aperture. In this case, the SRI group had a higher maximum

aperture than the major depression disorder group ($P=.002$). There were no significant differences between groups in the number of MU, proportion of time to the end of the first MU, or peak velocity in the Light or Glow conditions.

A shorter phase duration from the onset of the drop phase (4 cm from the hole) to the release of the peg indicates greater efficiency. In the Glow condition, the SRI group had a longer phase duration than the major depression disorder group ($P<.001$) indicating less efficiency. Further, the major depression disorder group had a shorter phase duration than the control group ($P=.021$), indicating less efficiency in the control group in this case.

Decreased straightness values in the drop phase indicate a straighter trajectory. In the Glow condition, the SRI group showed increased straightness values indicating a longer trajectory than the major depression disorder group ($P=0.007$). Further the major depression disorder group showed decreased straightness values than the control group ($P=.011$) indicating less efficiency in the control group. There were no significant differences between groups in the number of minor MU in the Light or Glow conditions.

Group differences were found in the Glow condition but not the Light condition. The SRI group showed less efficient reaching and grasping of a glowing peg without sight of the arm and hand than the major depression disorder group. Further the SRI group took longer to return the peg to the hole near to the start position in part due to greater curvature in the returning reach.

Discussion

Subtle deficits in fine motor control may not be observable from a standard motor exam. Kinematic testing is particularly well-suited for measurement of sensory and motor functions in reaching and discrimination tasks. Motor planning and execution of a directed reach includes processing information (e.g., attention, discrimination), localization of the target, and implementation of the reach by muscles and joints. Kinematic analysis measures how the reach was executed including straightness (distance the hand traveled compared with the shortest distance to the target), smoothness (number of movement units; a movement unit is defined as an acceleration followed by deceleration), velocity, and percentage of the total reach made up by the first movement unit.^{17, 18} Kinematic measures demonstrate developmental changes across infancy and early childhood toward greater efficiency with age.¹⁹ Recent evidence with 15-month-olds when infants could see the object (glowing) but not their hand showed poorer quality of movement than in the light condition.²⁰ Successful reaching depends on how well the child processes sensory information such as sight to know where the object is. Kinematic tests are particularly sensitive to deficits in sensory-motor integration.

We established a kinematic task that included reaching, grasping, and dropping a peg into a small opening near the start position. Based on earlier findings of poorer motor function with younger children exposed to SRI, we anticipated that SRI exposure will compromise visual-motor coordination (reaching in the Light condition) and efference copy signals (reaching in the Glow condition) relative to children not exposed (control). We had

anticipated deficits in spatial-visual motor coordination in the Light, which we assessed by comparing measures of smoothness (MU) in a specific motor task between exposure groups. However, we found no differences in reaching parameters in the Light.

We then compared the kinematic measures by group in a condition in which the child's hand was not visible, requiring them to rely solely on efference copy for the task. We found that children with prenatal SRI exposure have poorer fine motor control at 4.33 to 5.50 years of age compared with children who were not exposed to SRIs. Our results are consistent with our hypothesis suggesting poorer input-mediated fine-tuning of motor control related to SRI exposure. Although previous studies have reported a connection between SRI exposure and motor deficits, negative motor findings tend to be resolved prior to the ages in the current kinematics sample.^{21, 22}

The SRI group in our study did not show poorer efficiency and decreased straightness in the Light condition relative to the major depression disorder group. This finding suggests that children with prenatal SRI exposure do not have deficits in visual-motor coordination at this age. The limited motor coordination observed in the Glow condition could hinder normal development of efference copy, as efference copy is calibrated and perfected by visual and somatic input. Prenatal SRI exposure could also be responsible for altered connectivity within the efference copy signaling pathway. We suggest that fine motor deficits could affect the formation of neural pathways, as proprioception and efference copy were all significantly affected in the SRI group.

These fine motor deficits were particularly evident in the Drop condition when the SRI group performance was consistently poor on most variables in the Glow condition. Given the gradual development of fine motor control throughout the first decade of life, we might expect that SRI exposure effects may persist rather than resolve due to increased difficulty in fine motor tasks confronting the children.

Most of our findings were between the SRI group and the major depression disorder group. This could suggest that prenatal major depression disorder exposure does not affect visual-motor coordination of movement. A more plausible explanation is based on the known association of prenatal exposure to major depression disorder and attention deficits,²³ whereby poor attention could cause the major depression disorder group to have poorer performances. We did not find evidence for attentional deficits on our kinematic task in these young children. In fact, the children of mothers with major depression disorder performed better than either the SRI group or the control group, though these finding was not statistically significant.

Based on our previous work with clinical and non-clinical populations of infants,^{24, 25} we developed a kinematics paradigm to measure fine motor control, including visual-motor coordination, and efference copy development of young children. Visual-motor coordination is best observed in the Light condition. In the Glow condition, the moving hand was not seen during the reach but efferent copies could provide guidance toward the target.

These findings support a connection between prenatal SRI use and fine motor deficits, possibly due to poor sensorimotor learning and efference copy development. Although our

results show that there are deficits associated with prenatal SRI exposure, prenatal major depression disorder exposure might present risks to the developing fetus. Depression results in chronic elevation of norepinephrine and cortisol levels, which can result among other things in suppressed neurogenesis and hypothalamic–pituitary–adrenal axis dysregulation.²⁶

More research is necessary before we can properly compare prenatal SRI versus major depression disorder exposure. In addition, some of the mothers of the SRI and major depression disorder groups also had other psychiatric diagnoses (mostly anxiety disorder) for which some were taking psychotropic medication. We did have strict exclusion criteria regarding other diagnoses and medications, but the ones we chose to allow were so common among depressed women that a population without any other psychiatric diagnosis would have been both difficult to find but also not representative of the depressed population.

The principal limitation of this study is its small sample size. Digitizing or processing multiple trials from a single individual is time intensive. There were many reasons for adding additional sets of trials due to unintended parent interventions, child obstructing the top of the peg needed for digitizing, or child playing with the task such as not using a pincer grasp or reaching with a curvilinear trajectory. These behaviors were not related to SRIs, major depression disorder or control, but could invalidate several trials, resulting in missing data and exclusion of the case if extensive. Studies of the effects of prenatal exposure to SRIs can be problematic if only comparing the exposed children to control children or only to major depression disorder-exposed. Our inclusion of both SRI and major depression disorder groups is a strength of our study but the small sample size may limit our ability to detect additional group differences (type 1 error). We were unable to determine if the effects of SRI exposure were related to the timing of the exposure. It is well known that the first trimester is critical for nervous system and organ development and when exposure to psychotropic drugs can have the most detrimental effects. It would also be important to study and compare subclasses of SRIs (selective SRIs and Serotonin/Norepinephrine Reuptake Inhibitors) as some SRIs are already known to have more deleterious effects than others.²⁷

Limitations notwithstanding, we have studied a highly sophisticated, precise measure of motor control and related that to prenatal SRI exposure. The fact that these kinematic effects were observed at 4 to 5 years of age suggests that there may be long-term effects of prenatal SRI exposure as the demands on the motor system increase in complexity. This study also invites the use of kinematics for the study of other clinical populations in which motor involvement is suspected. Finally, study of the motor pathways offered through kinematics may enable us to understand the neural basis of these motor deficits.

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Abbreviations

SRI	Serotonin Reuptake Inhibitors
MU	Movement Units

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Figure.

Experimental setup for kinematics procedure: (A) Room setup during procedure. The subject sits at a table with 5 pegs and attempts to drop them into the nearby hole one at a time. Two infrared (IR) cameras placed at different angles record the procedure. The subject's mother holds the child's other hand to avoid use of both hands. The experimenter hides behind a curtain to avoid unnecessary play. (B) Representation of the glove worn by subjects during the procedure. The IR reflective markers (gray) reflect the light to the cameras and enable the tracking software to compute coordinates of all markers at 100 HZ. (C) Representation of the pegs used in the procedure. The body is either painted black (Light condition) or with phosphorescent paint (Glow condition). The top of the pegs has IR markers to enable similar tracking as the markers on the hands.

Table I

List of dependent measures.

Dependent measure	Definition
Reach Phase	
Number of movement units (MU)	A count of the number of speed peaks in a reach. A speed peak was defined as maximum speed between two minima where the difference between a minimum and the peak must be at least 10 mm/s (<i>Clifton, RK, Rochat P, Robin DJ, Berthier NE. Multimodal perception in the control of infant reaching. 1994. J Exp Psychol Hum Percept Perform 29(4):876-886</i>) The peak speed must also be greater than 20% of the maximum hand speed (<i>Konczak J, Dichgans J. The development toward stereotypic arm kinematics during reaching in the first 3 years of life. 1997. Exp Brain Res 117(2):346-354</i>)
Proportion of time the first movement unit (MU)	During the reach, the time from movement onset until the end of the first MU. A lower proportion indicates a jerky trajectory at the onset of the reach.
Peak velocity (cm/s)	The highest velocity of the hand over the course of a reach (<i>Babinsky E; Braddick O, Atkinson J. The effect of removing visual information on reach control in young children. 2012. Exp. Brain Res 222:291-302</i>)
Proportion of maximum aperture	During the reach, the child opens his thumb and pointer fingers to prepare for the grasp. Higher proportion indicates a wider aperture than is necessary to grasp the object.
Drop Phase	
Phase duration (ms)	The time of the reach from entering the drop phase (4 cm from the hole) to releasing the object
Number of minor MU	A count of minor speed peaks in the drop phase. A speed peak was defined as a maximum speed between two minima. The criterion of reaching greater than 20% of the maximum phase speed was not applied.
Straightness	Determined by dividing the distance the hand traveled (hand Path) by the straight-line distance between entering the drop zone and the hand's position at object release. A ratio of 1.0 would represent a perfectly straight trajectory. Increasing values reflect greater deviation from the straight line (<i>von Hofsten. Development of visually guided reaching: the approach phase. 1979. J Hum Mov Stud 5:160-178</i>)

Table II

Maternal and child characteristics.

Characteristics	SRI N=15	major depression disorder N=10	control N=15	Group
Mother	<i>N (%)</i>	<i>N (%)</i>	<i>N (%)</i>	<i>P value</i>
Marital status (% married)	7 (46.7)	7 (70.0)	10 (66.7)	.405
High school graduate	13 (100.0)	9 (90.0)	14 (93.3)	.540
	<i>Mean (SE)</i>	<i>Mean (SE)</i>	<i>Mean (SE)</i>	
Maternal age at delivery (years)	30.1 (1.2)	26.60 (1.4)	27.7 (1.3)	.148
Depression over pregnancy ^b	21.7 (3.0)	24.4 (3.0)		.550
Depression severity at study visit	16.3 (3.6) ^c	11.2 (3.2) ^c	6.2 (1.2)	.035
Index of social position at study visit	39.9 (3.9)	32.8 (3.3)	44.2 (4.1)	.169
SRI use in pregnancy (day)	133.9 ^a			
Child	<i>N (%)</i>	<i>N (%)</i>	<i>N (%)</i>	<i>P value</i>
Sex (% females)	8 (53.3)	6 (60.0)	7 (46.7)	.805
Infant race (% nonwhite)	6 (40.0)	6 (60.0)	3 (21.4)	.158
Infant ethnicity (% Hispanic)	4 (26.7)	5 (50.0)	3 (20.0)	.259
Preterm delivery	2 (13.3)	1 (10.0)	0	.360
	<i>Mean (SE)</i>	<i>Mean (SE)</i>	<i>Mean (SE)</i>	
Gestational age at birth	39.3 (0.4)	38.9 (0.5)	40.0 (0.3)	.134
Mean age (months) at study visit	57.1 (0.8)	59.0 (1.0)	55.9 (0.7)	.050

^aNumber of days of SRI use in pregnancy: minimum=14; maximum=273.

^bSRI and major depression disorder were compared for depression over pregnancy. No differences found.

^cSRI and major depression disorder were compared for depression severity at the study visit. No differences found (P=.324)

SE = standard error

Table III

Results in 4- to 5-year-olds in the Light and Glow conditions.

Reach Phase	Adjusted Means (SE)		Adjusted P value		
	SRI n=15	major depression disorder N=10	control N=15		
Number of movement units (MU)	Light	2.63 (0.17)	2.54 (0.22)	2.40 (0.16)	.664
	Glow	3.16 (0.21)	2.90 (0.17)	2.91 (0.17)	.585
Proportion of time to the end of first MU	Light	0.22 (0.02)	0.23 (0.01)	0.25 (0.01)	.131
	Glow	0.19 (0.01)	0.17 (0.01)	0.18 (0.01)	.669
Peak velocity (cm/s)	Light	64.2 (1.9)	61.0 (2.6)	66.3 (3.0)	.384
	Glow	56.9 (2.0)	58.2 (3.2)	61.8 (2.8)	.392
Proportion of maximum aperture	Light	0.65 (0.02)	0.60 (0.02)	0.63 (0.03)	.201
	Glow	0.66 ^b (0.02)	0.58 ^b (0.02)	0.64 (0.03)	.003 ^{**}
Drop Phase					
Phase duration (ms)	Light	449 (28.5)	382 (31.5)	428 (43.0)	.287
	Glow	655 ^b (31.8)	441 ^{ba} (34.1)	581 (38.1)	<.001 ^{**}
Number of minor MU	Light	2.71 (0.26)	2.72 (0.41)	2.75 (0.49)	.996
	Glow	3.85 (0.35)	2.98 (0.38)	3.75 (0.32)	.192
Straightness	Light	1.57 (0.04)	1.47 (0.06)	1.48 (0.06)	.244
	Glow	1.68 ^b (0.05)	1.53 ^{ab} (0.03)	1.66 (0.04)	.004 ^{**}

Group P-value -

* P<0.05,

** P<.01

Adjusted Post hoc comparisons:

SRI or major depression disorder to control group, $P < .05$.

SRI to major depression disorder group, $P < .05$.

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