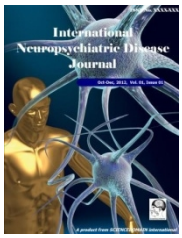

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Prenatal Exposure to Maternal Anxiety is Associated with Less Developed Smooth Pursuit Eye Movements in Six-Month-Old Infants: An Initial Study

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Authors' contributions

All authors participated in and take responsibility for all aspects of the study. *This work was supported by USPHS Grants MH056539, MH080859, MH086383 and HD058033. The funding institutions played no ongoing role in study design, data analysis, or manuscript preparation.* *All authors read and approved the final manuscript.*

Research Article

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ABSTRACT

Aims: There are an increasing number of reports suggesting an association between maternal anxiety experienced during pregnancy and adverse outcomes of the offspring. However, exploration of the biological changes in the brain that mediate that relationship has been hampered by the lack of appropriate biomarkers. This report represents an initial step exploring whether a potential infant biomarker, smooth pursuit eye movements, may be associated with prenatal exposure to maternal anxiety.
Study Design: Blinded cross-sectional study.
Place and Duration of Study: Department of Psychiatry, University of Colorado School of Medicine. Data collected from July 2011 to May 2012.
Methodology: Forty-three infants including 34 whose prenatal maternal anxiety status were identified (12 with a known maternal prenatal anxiety diagnosis and 22 without) had eye movements recorded during a smooth pursuit eye movement task at four and/or six months of age.
Results: At 6 months of age, infants with prenatal exposure to maternal anxiety,

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compared to infants without such exposure, spent a higher percentage of time utilizing smooth pursuit (t=2.7, df=24, *P*=.013), had longer duration of smooth pursuit uninterrupted by saccades (t=2.5, df=24, *P*=.019), and had decreased frequency of forward saccades (t=3.8, df=24, *P*=.001). No differences between groups were identified at 4 months of age.
Conclusion: Smooth pursuit abnormalities may, at six months of age, be a potential biomarker for prenatal maternal anxiety exposure.

Keywords: Smooth pursuit; infants; anxiety; pregnancy.

1. INTRODUCTION

A growing body of evidence suggests that prenatal exposure to maternal anxiety has long-term implications for development of the child. Offspring of a mother with anxiety demonstrate altered fetal heart rate [1] and motor activity *in utero* [2]; and, after birth, heightened response to novel stimuli at four months of age [3,4]; lower developmental assessment scores at eight months of age [5]; more behavioral and emotional problems at four years of age [6]; and increased risk for later development of a range of mental illnesses—including ADHD and anxiety symptoms [7], autism [8], depressive symptoms [9], and schizophrenia [10]. While there is an established relationship between maternal anxiety and child development, there has been less work, in the human, focused on developing physiologic infant biomarkers of the developmental brain changes mediating these effects. Biomarkers can be of critical value in identifying relevant brain regions and determining the time course of their development [11]. In addition, biomarkers can provide proximal evidence concerning whether interventions successfully modify risk. This paper examines whether an adaptation of one known adult and older child biomarker of risk for mental illness—deficits in smooth pursuit eye movement (SPEM)—is associated with maternal anxiety in infants.

In SPEM tasks, the subject's eyes follow a moving stimulus. While the initiation of SPEM is largely driven by information received in the visual cortex, maintaining the image on the fovea involves higher levels of cortical function, especially those functions involved in attention and prediction [12]. During SPEM tasks, saccades (high-velocity eye movements used to redirect the line of sight) may serve to compensate for poor performance or to anticipate object motion [13]. Generally, higher saccadic frequencies indicate poorer performance. SPEM deficits have been found in adults with a variety of disorders, including schizophrenia [14], affective disorders [15], Parkinson's disease [16,17], and obsessive compulsive disorder [18]. In children and adolescents, decreased SPEM performance has been linked with ADHD, autism, reading disorder, and childhood-onset schizophrenia [19]. These same SPEM deficits have also been found in unaffected, adult first-degree relatives of patients with schizophrenia [20,21] and children who have a parent with psychosis [22]; both of these findings suggest that SPEM deficits are a marker of increased vulnerability to mental illness. To date, no one has identified whether this biomarker of vulnerability can be identified in infancy.

Recent advances in technology have facilitated the task of studying smooth pursuit tasks in infants [23]. It has been suggested that smooth pursuit performance in typically developing infants is relatively mature by six months of age in normally developing infants [24]. However, the work to date has focused on normative development. This project reflects an initial effort to expand on this work by examining the relationship between infant smooth pursuit task performance and prenatal exposure to maternal anxiety.

2. MATERIALS AND METHODS

2.1 Participants

Forty-three mother-infant dyads successfully participated in infant eye-tracking when the infant was either four or six months of age; only 17 subjects (40%) participated at both time points, including only 11 who completed the more difficult 12.5 degrees target velocity task. As such, with limited exceptions (described below), analyses are cross-sectional. Eighteen dyads were recruited from an ongoing longitudinal study at a county hospital and thirty-one were recruited by postcards sent out to new mothers through a state birth registry. We excluded mothers with an alcohol abuse disorder during pregnancy, infants born at a gestational age of less than 36 weeks, and infants with major neurological disorders such as seizures. Age at time of testing was adjusted for gestational age at birth. Demographics are summarized in Table 1.

2.2 Maternal Diagnoses

Anxiety diagnoses were best estimate diagnoses made after an experienced psychiatric clinician (MD, DO, or MSW) completed a Structured Clinical Interview for DSM-IV (SCID-I) with the subject's mother. A supplement for ADHD was also utilized. All interviews were completed within six months of giving birth, and translation services were provided when necessary. Mothers were considered to have a prenatal anxiety disorder if they described symptoms during pregnancy meeting criteria for Generalized Anxiety Disorder (GAD), Post Traumatic Stress Disorder (PTSD), Obsessive Compulsive Disorder (OCD), Panic Disorder, or Agoraphobia. Mothers who met diagnostic criteria for an anxiety disorder prior to pregnancy and continued to have subsyndromal symptoms during pregnancy were considered as having a prenatal anxiety disorder.

2.3 Eye-Tracking Procedure

Eye tracking data collection and analyses were completed blind to maternal diagnostic status.

Direction of the babies' gaze was measured using a remote Applied Science Laboratories (ASL) Eye Trac 6000 infrared camera. This system calculates gaze position using the relationship between the infrared reflections from the cornea and the pupil. Sampling frequency was 60 Hz. The right eye was always measured.

The stimulus was a white dot with a diameter of one degree of visual angle presented on a black, 40-inch TV screen. Black cardboard surrounded the set-up on all sides in order to limit distractions, and all lights were turned off for the duration of the experiment to optimize the camera's detection of the eye.

Two experimenters conducted the study: The first monitored the camera system and controlling computer, while the second assisted with the baby. Mothers were permitted to remain in the testing room if they desired and were seated in a corner where they could not be seen by their infants.

Table 1. Characteristics of mothers and infants in the study

	Total (n=43)[a]		Anxiety-disordered (n=12)		Non-anxiety-disordered (n=22)		Statistical Analysis[b]	
Infant characteristics								
	n	**%**	**n**	**%**	**n**	**%**	***P***	
Gender:								
Male	22	51	8	67	10	45	.30	
Female	21	49	4	33	12	55		
Race/ethnicity:								
Caucasian/Non-Hispanic	13	30	1	8	7	32	λ^2=2.46	
Caucasian/Hispanic	18	42	6	50	9	41	*P*=.29	
Other/Mixed/Unknown	12	28	5	42	6	27		
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**t**	***P***
Gestational age at birth (weeks)	39.5	1.6	38.7	2.0	40.0	1.1	2.11	.052
Weight at birth (grams)	3241	489	3130	618	3305	402	0.99	.31
Adjusted age at 4-month recording (days)[c]	126[d]	8	125[f]	8	130[h]	6	1.52	.15
Adjusted age at 6-month recording (days)[c]	193[e]	9	187[g]	5	195[i]	8	3.37	.002
Maternal characteristics								
Age at delivery (years)	26	6	25	6	27	6	0.84	.41
Education (years)	12	3	11	2	13	4	1.91	.065
Socioeconomic Index of Occupations[j]	33	22	27	12	37	26	1.56	.13
	n	**%**	**n**	**%**	**n**	**%**	***P***	
Anxiety diagnoses during pregnancy:[k]								
Generalized Anxiety			8	67				
Post-Traumatic Stress			7	58				
Obsessive Compulsive			5	42				
Panic			2	17				

Maternal Axis I diagnoses during pregnancy:			4	33	4	18	.41
Major mood disorders			1	8	1	5	1.00
Cannabis abuse/dependence			1	8	1	5	1.00
ADHD							
Antidepressant use during pregnancy	8	19	4	33	2	9	.15
Sertraline							
Fluoxetine	3	7	2	17	1	5	
Bupropion							
	3	7	1	8	1	5	
	1	2	1	8	0	0	

[a] *n=total number of infants who participated. This 43 infants include includes nine infants (five whose mothers did not participate in a psychiatric diagnostic evaluation and four subjects whose mother had a psychotic illness); the remaining 34 of these subjects were used for the following two columns comparing infants with and without prenatal exposure to anxiety.*

[b] *all statistical results are Fischer's exact test for categorical variables or Student's t for continuous variables unless otherwise noted*

[c] *A 4 month-old child born at 42 weeks gestation and a 4-month-old child born at 37 weeks gestation are both "full-term" and both are 4 months of age; however, the child born at 42 weeks is 5 weeks older. To adjust for this, age is adjusted for gestational age at birth to the equivalent of being born at 40 weeks gestation.*

[d] *n=23*

[e] *n=37*

[f] *n=8*

[g] *n=9*

[h] *n=10*

[i] *n=20*

[j] *The Socio-economic Index (SEI) is based on The Socioeconomic Index of Occupations.[25] 503 occupations are included and are scored in a potential range of 0-100. Managerial and professional occupations generally have scores above 60; technical, sales, and administrative support occupations generally score between 35 and 60; service, agricultural, and labor occupations generally have scores below 35. Scores are based on the highest occupation value achieved across an individual's life.*

[k] *Anxiety diagnoses total more 100% because many of the subjects had more than one diagnosis.*

Infants were seated upright in a car-seat strapped to a swivel-chair. Padding was placed around each infant's head to minimize head movements. Four-month-olds were seated 21 inches from the TV screen while six-month-olds were seated 29 inches away. A short video was played while the first experimenter adjusted the camera settings to optimize visualization of the eye. Then, a two-point calibration was completed using a series of images accompanied by music. These images started out large, then shrank down to a final size of one-inch-by-one-inch at each of the two calibration sites.

After calibrating, the stimulus appeared on the left side of the screen and blinked for two seconds while making a beeping noise to attract the infant's attention. If necessary, the second experimenter tapped on the screen during this time. Then, the dot moved horizontally across the screen at a constant speed of 9 degrees per second for a total visual angle of 15 degrees (for four-month-olds) or 20 degrees (for six-month-olds). While the dot was in motion, no sounds were made and the second experimenter's hands were removed from the area of the screen. After the dot reached its end location on the right side of the screen, it disappeared and started blinking again on the left.

This ramp was repeated a total of 10 times, at which point preliminary tracings were examined. If these were judged insufficient (either the infant did not engage in the task or the camera did not adequately record the eye's position), the process was repeated until sufficient data was obtained or until the infant got too fussy to continue (generally one to two times, but never more than five times per infant). When infants successfully completed the task at 9 degrees per second, the task was repeated at 12.5 degrees per second. If at any point during the experiment infants could not be successfully engaged, a break was taken, during which time mothers were permitted to interact with their babies. After such breaks, calibration was repeated. Infants who were unable to complete the task in the first session were brought back to try again another day.

2.4 Eye Tracking Analysis

All data were analyzed with a computer recognition pattern and confirmed by an evaluator, who was blinded to subject status. Data was smoothed using a five-point mean filter. Artifacts were removed by several criteria that were determined by having adults purposefully simulate head movements and blinks; for example, blinks are recorded by the system as has having two high velocity components in opposite direction. Artifacts lasting less than 50 ms (3 frames) were removed and interpolated (interpolated data was restricted to less than 5% of the total data). Once artifacts were removed, a ramp was considered valid if it contained greater than 500 ms of consecutive artifact-free data. A subject was considered to have sufficient data at a given speed if total data from all ramps added up to at least one second in duration.

Saccades were separated from smooth pursuit using velocity (calculated for each point by subtracting the raw position two frames ahead from the raw position two frames behind and dividing by 83.3 ms). An increase in velocity over one frame in duration was classified as a saccade if velocity exceeded 45 degrees per second. A velocity increase over two or more frames was considered a saccade if peak velocity exceeded 35 degrees per second. Points on either side of this peak velocity were considered part of the saccade if velocity remained above 30 degrees per second. If two saccades in the same direction had two frames or fewer between them, they were considered to be a single saccade. This definition of saccades has is similar to that used by other investigators [26,27]. Saccades were then subclassified into three categories: (1) forward saccades (those in the same direction as

target motion), (2) backward saccades (those in the opposite direction as target motion), and (3) square wave jerks (pairs of saccades in opposite directions 50-150 ms apart with a segment of smooth pursuit in between with a gain of >0.5).

Three established infant SPEM measures were assessed: (a) the percentage of time spent in smooth pursuit (calculated by dividing the time spent in smooth pursuit by the total artifact-free time including both smooth pursuit and saccades; (b) the frequency of forward saccades (number per second of artifact free recording); and (c) the longest duration of uninterrupted smooth pursuit the child was able to generate [24,28-30]. Fig. 1 shows a sample tracing.

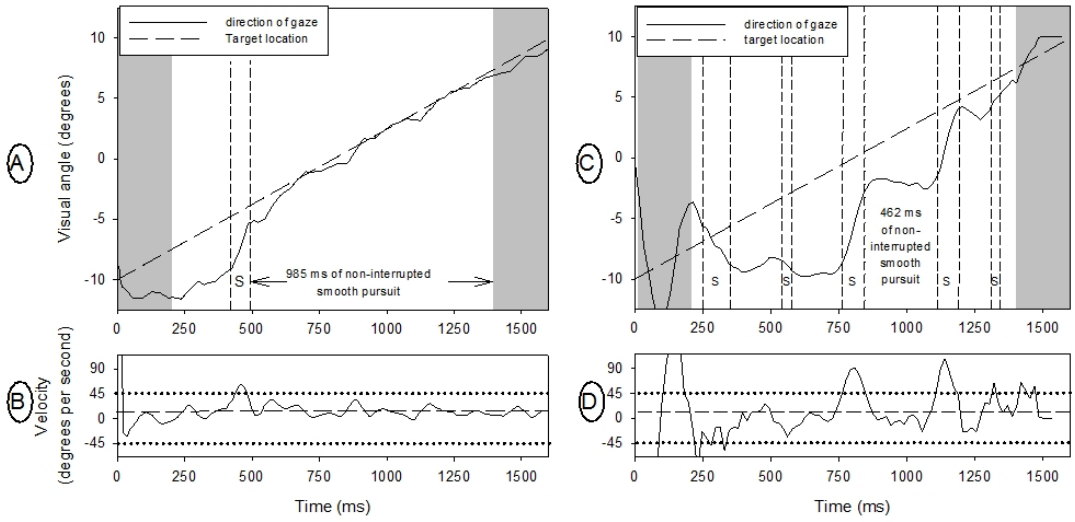

Fig. 1. Sample eye tracings from six-month old infants with a target velocity of 12.5 degrees per second. A) and C) are position tracings: The first and last 200 ms segments (noted in grey) are not included in the analysis; segments which consist of a saccade are noted with an "S." B) and D) are velocity tracings: the dashed line represents target speed; eye movements with a peak velocity greater than 45 degrees per second for one frame or greater than 35 degrees per second for two frames are classified as saccades. A) and B) are from a six-month old infant who spends most of the tracking time in smooth pursuit, has less frequent saccades, and longer periods of non-interrupted smooth pursuit. While engaged in smooth pursuit, this infant has eye movement velocities close to target velocity. Conversely, C) and D) are from a six-month old infant who spends a lower percentage of time tracking with smooth pursuit, has more frequent saccades, and shorter periods of non-interrupted pursuit. Smooth pursuit tracking velocities are often close to zero, with saccades utilized as the primary method for tracking the object.

2.5 Data Analysis

As an initial step, eye tracking measures were assessed for internal consistency. Specifically, since forward saccades compensate for smooth pursuit errors, the percentage of time spent utilizing smooth pursuit should be inversely correlated with the frequency of forward saccades. Similarly, since both percentage of time in smooth pursuit and longest

duration of uninterrupted smooth pursuit are felt to be global measures of SPEM performance, these two measures should correlated with each other. For analyses examining internal consistency, results from all available infants are included.

Because of the low number of children who participated at both time points, the primary analysis to assess the effect of age was cross-sectional. As a secondary analysis, for the 11 children who completed the 12.5 degrees per second task, a repeated measures ANOVA was completed.

The relatively low sample size also limits the power to detect more complex interactions such as those between prenatal exposure to anxiety, age, and target velocity; thus, global ANOVAs are difficult to interpret, even for main effects. Thus, for this initial study, examination of the effect of prenatal exposure on SPEM was limited to the 12.5 degrees per second task with a separate analysis of variance at each age for each variable. Because all 3 eye movement variables are hypothesized to measure global smooth pursuit performance, they are hypothesized to be highly correlated; correction for multiple testing may be overly conservative. An alpha <= 0.05 is considered significant. A family history of schizophrenia has a significant impact on smooth SPEM task performance [22], so infants whose mothers have a psychotic illness (n=4) were excluded from this analysis, as were infants whose mothers did not complete a diagnostic assessment (n=5). For the six-month-old recording, adjusted age at the time of recording differed between groups; however, for the six-month-old recording, adjusted age was not correlated with any eye tracking measure.

While maternal socioeconomic status and years of education, and infant gestational age and weight at birth did not differ between infants with and without maternal prenatal anxiety, these are potential confounding factors during prenatal development. Thus, all analyses were completed both with and without each potential confounding variable. When included, each confounder did not have a significant effect (p's >0.17) and results for the eye movement variables were similar. Only results without the covariates are reported here.

Statistical analyses are done using IBM Statistical Package for the Social Sciences (SPSS) version 21.0 [31].

3. RESULTS

3.1 Participants

In the total sample, forty-three infants participated. Twenty-three infants participated at four months of age; all (100%) participated with a target velocity of 9 degrees per second; 16 (70%) maintained attention long enough to also participate with a target velocity at 12.5 degrees per second. Thirty-seven infants participated at six months of age; 36 (97%) successfully completed participation with a target velocity of 9 degrees per second; 34 (92%) maintained attention long enough to also participate with a target velocity at 12.5 degrees per second. Seventeen infants participated at both four and six months of age. Of the 43 participating infants, five had mothers who did not participate in a diagnostic interview; four had mothers who had a psychotic illness. Of the remaining 34 infants, 12 (32%) had prenatal exposure to a mother with an active anxiety disorder (see Table 1 for additional demographic details).

3.2 Smooth Pursuit Performance: Relationship between Measures

There is a strong inverse correlation, at both ages and for both target velocities, between percent of time spent in smooth pursuit and frequency of forward saccades (Fig. 2). Similarly, at both ages and for both target velocities, there is a strong correlation between percent of time spent in smooth pursuit and duration of the longest period of uninterrupted smooth pursuit (r's between .512 and .569, all *P*'s $\leq$.033). At both four and six months of age, there is a correlation between performance in the 9 degree-per-second and 12.5 degree-per-second tasks for percentage of time spent in SPEM (Fig. 3), and for the duration of the longest period of uninterrupted smooth pursuit (r's between .439 and .582, *P*'s$\leq$.018), supporting the stability of performance across tasks.

3.3 Smooth Pursuit Performance: Impact of Age

For the 9 degree-per-second task, there was a strong impact of age with six-month-olds performing notably better than four-month-olds on all three measures (Table 2). For the 12.5 degree-per-second task, there was a strong impact of age on the longest duration of non-interrupted smooth pursuit with six-month-olds producing significantly longer durations than four-month-olds; however there was no significant effect of age on percentage of time spent utilizing smooth pursuit or frequency of forward saccades. Secondary analyses limited to the 17 children (11 for the 12.5 degree-per-second task) who participated at both ages, using repeated measures ANOVAs, showed similar findings: For the 9-degree-per-second task, 6-months olds performed better than four-month-olds on all three measures [percentage of time spent in smooth pursuit: $F(1,16)=21.6$, $p<.001$); frequency of forward saccades: $(F1,16)=22.0$, $p<.001$; longest duration of uninterrupted smooth pursuit: $F(1,16)=37.9$, $p<.001$)], while for the 12.5 degree-per-second task, significant effects of age were identified only for the longest duration of uninterrupted smooth pursuit [percentage of time spent in smooth pursuit: $F(1,10)=0.1$, $p<.719$); frequency of forward saccades: $(F1,10)= 0.0$, $p=.952$; longest duration of uninterrupted smooth pursuit: $F(1,10)=12.1$, $p=.006$)].

3.4 Impact of Prenatal Exposure to Maternal Anxiety

Six-month-old infants with a history of prenatal exposure to maternal anxiety, as compared to infants without such prenatal exposure, presented with a significantly lower percentage of time spent in smooth pursuit ($F=7.24$, $ndf=1$, $ddf=24$, $P=.013$), a significantly higher frequency of forward saccades ($F=14.77$, $ndf=1$, $ddf=24$, $P=.001$) and a significantly shorter duration of uninterrupted smooth pursuit ($F=6.27$, $ndf=1$, $ddf=24$, $P=.019$). The frequency of back-up saccades did not differ between groups ($F=.26$, $ndf=1$, $ddf=24$, $p=.62$). No significant effects were identified for four-month olds (all *P*'s > .37). Results are summarized in Fig. 4.

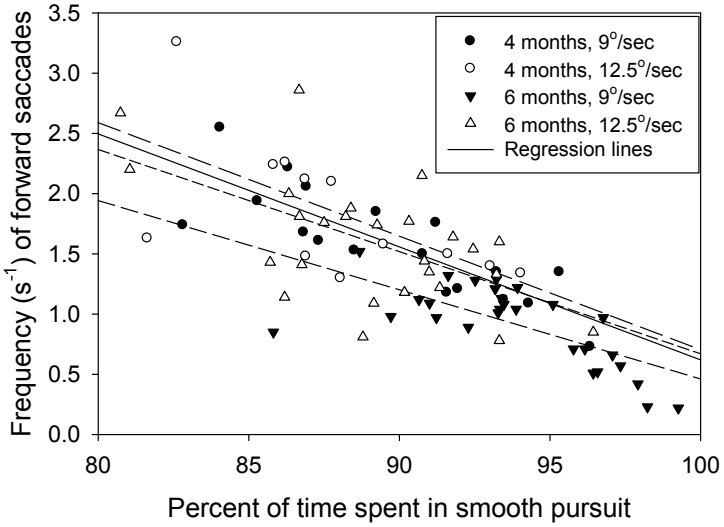

Fig. 2. The percent of time spent in smooth pursuit is inversely correlated with frequency of forward saccades for four-month-olds with a target velocity of 9 degrees per second (r=.-.855,*P*<.001) and 12.5 degrees per second (r=.-.667, *P*=005) and for six-month-olds with a target velocity of 9 degrees per second (r=.-.707, *P*<.001) and 12.5 degrees per second (r=.-.606, *P*<.001).

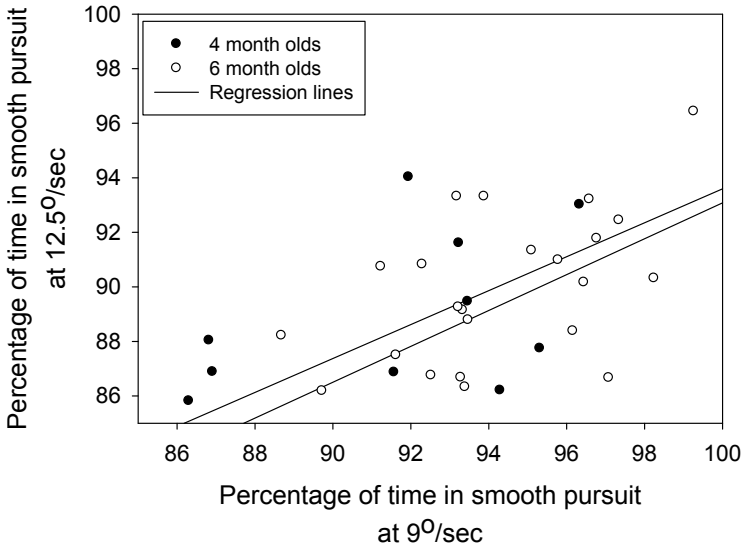

Fig. 3. The percentage of time spent in smooth pursuit when the target is moving at 9 degrees per second is correlated with the percentage of time spent in smooth pursuit when the target is moving at 12.5 degrees per second for both four- (r=.684, *P*=.003) and six-month-olds (r=.479, *P*=.005). Most children spend a lower percentage of time in smooth pursuit in the more difficult 12.5 degree-per-second task as compared to the less difficult 9 degree-per-second task

Table 2. Eye tracking performance for four- and six-month-old infants while tracking a target moving at a constant velocity. All results are mean ± S.D.

Age	4 months	6 months	t	*P*
Target moving at 9º/sec				
Percentage of time spent in smooth pursuit	90.1±4.0	94.0±2.9	t(57)=4.1	<.001
Frequency of forward saccades (s^{-1})	1.53±.49	.91±.32	t(57)=5.4	<.001
Duration of longest period of non-interrupted smooth pursuit (ms)	867±254	1389±312	t(57)=6.7	<.001
Target moving at 12.5º/sec				
Percentage of time spent in smooth pursuit	88.4±3.7	89.5±3.4	t(48)=1.0	.32
Frequency of forward saccades (s^{-1})	1.68±.61	1.57±.49	t(48)=0.7	.51
Duration of longest period of non-interrupted smooth pursuit (ms)	543±145	778±203	t(48)=4.1	<.001

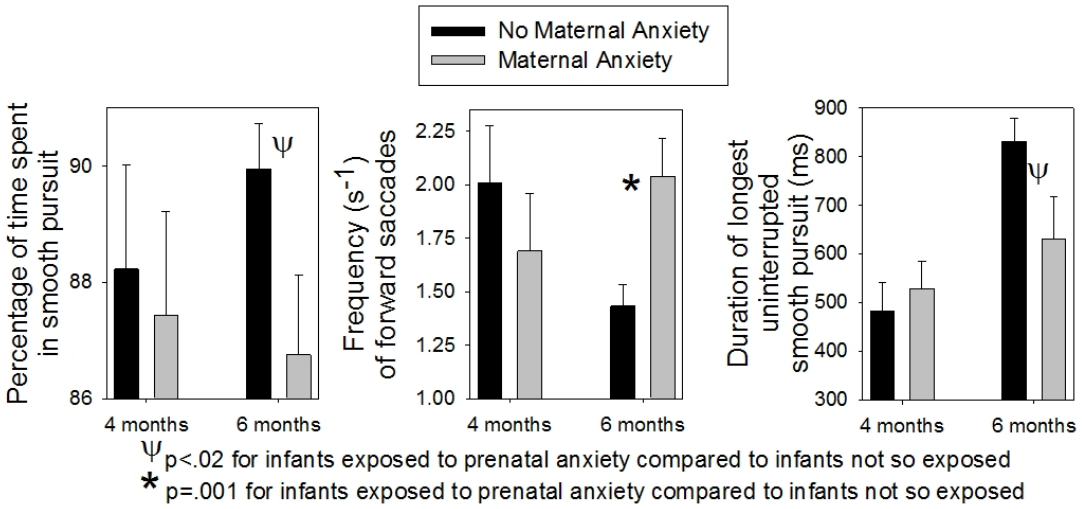

Fig. 4. Impact of prenatal exposure to maternal anxiety on infant SPEM measures at four and six months of age. All values are means ± S.E.M.

4. DISCUSSION

The percent of time spent in smooth pursuit, the frequency of forward saccades, and the duration of the longest period of uninterrupted smooth pursuit are highly correlated with each other suggesting that all three variables are reflective of overall task performance. For each age, there was a significant correlation across target speeds for percentage of time spent in smooth pursuit and duration of longest pursuit supporting the reliability of measurements across different levels of task difficulty.

V5, frontal eye fields and supplementary eye fields are considered central to smooth pursuit performance [13]. The large improvement in smooth pursuit performance on the 9 degree-per-second task between four and six months of age suggests rapid development of these brain regions over that time span. However, in contrast to previous work suggesting that the development of brain areas controlling SPEM is fairly mature by six months of age [24,28], the lack of an age effect and the finding that overall performance remains far below adult levels, even for six-month-olds, suggest that additional maturation of these brain regions remains.

The primary goal of this experiment was to focus on the use of smooth pursuit tasks to assess the impact of prenatal exposure to anxiety on infant brain development. One of the difficulties in this type of work is that the expression of vulnerability of any particular biomarker can occur for only limited time periods. For example, if relevant brain regions have not yet sufficiently developed, performance may not yet be affected. Conversely, after vulnerability is expressed, additional brain development may compensate, making the biomarker no longer effective. This paper provides preliminary evidence that the effect of prenatal maternal anxiety exposure on expression of brain developmental changes reflected in smooth pursuit tasks may not present until six months of age, and even then be limited to a narrow range of task difficulties (i.e. target velocities). Additional clarification of which target speeds at which ages are markers of prenatal anxiety exposure will be important for further investigation in this area.

Deficits in SPEM have already been shown to be a biomarker of risk for mental illness in adults and school-aged children, but this is the first suggestion that they are already present in infancy. Having biomarkers that are identifiable early in life allows researchers to directly measure the ability of early interventions to modify risk. Different biomarkers are reflective of different brain changes, and this biomarker adds to the arsenal of measures currently available.

4.1 Limitations

Maternal anxiety was characterized categorically based on established clinical criteria rather than on a dimensional basis. The question of whether dimensional or categorical characterization of symptoms offers the best way of considering psychopathology is a major issue in the field. Future efforts will need to explore the various benefits and costs of each of these diagnostic approaches.

The retrospective assessment of maternal prenatal anxiety diagnoses may have introduced some recollection bias and no post-natal anxiety information was obtained, so contributions of post-natal anxiety-related differences in parenting behaviors cannot be ruled out as an alternative explanation. Similarly, infants and their mothers often share genetic and epigenetic risk factors; thus the relationship between maternal prenatal anxiety and infant eye tracking may be due to shared genetic or epigenetic profiles rather that to the direct effect of maternal anxiety on fetal development. Sample size, particularly for infants participating at both time points, was low. Thus analyses were cross-sectional rather than longitudinal.

5. CONCLUSION

Mental illness is likely the result of decades-long interplay between genetics and environmental factors. A particularly salient window appears to be during the prenatal period, the time of greatest brain development. The availability of biological markers that are measurable during infancy and reflect relevant brain functions are critical to investigations seeking to clarify risk factors and identify disease mechanisms for mental illness. This study presents the first evidence suggesting that smooth pursuit tracking deficits are identifiable in infants exposed to a prenatal environmental risk factor. Additional imaging, genetic, and treatment work is needed to translate this biomarker into clinically-usable information.

CONSENT AND ETHICAL APPROVAL

Written informed consent was obtained from participating mothers and families were compensated $30 per visit as approved and monitored by a local Institutional Review Board: Colorado Multiple Institutional Review Board (C OMIRB) protocol # 03-888.

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COMPETING INTERESTS

The authors have no competing interests to report.

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