

Deviant smooth pursuit in preschool children exposed prenatally to methadone or buprenorphine and tobacco affects integrative visuomotor capabilities

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ABSTRACT

Background and aims Although an increasing number of children are born to mothers in opioid maintenance therapy (OMT), little is known about the long-term effects of these opioids. Previous studies suggest an association between prenatal OMT exposure and difficulties in eye movement control. Also, the effects of tobacco smoking on eye movements have been reported. The present study examined the influence of eye movements, i.e. smooth pursuit, on visuomotor capabilities in children of smoking mothers in OMT. **Design** The study comprised a 2 (OMT versus contrast group) × 2 (slow versus fast smooth pursuit) between-subject factorial design. **Setting** The cognitive developmental research unit at the University of Oslo, Norway. **Participants** Participants were 26 4-year-old children of tobacco-smoking women in OMT and 23 non-exposed 4-year-old children, with non-smoking mothers, matched by gender and age. **Measurement** Eye movements and smooth pursuit were recorded using a Tobii 1750 eyetracker. Visuomotor functions were examined by Bender test. **Findings** The OMT group tracked slowly moving objects with smooth pursuit in a similar manner to their non-exposed peers. When fast smooth pursuit was measured, the OMT group of children tracked the object more slowly than the contrast group, $P = 0.02$, $\eta_p^2 = 0.11$. A regression analysis showed that fast smooth pursuit predicted children's performance on a visuomotor task, $R^2 = 0.37$. **Conclusion** Impaired eye-tracking skills in 4-year-old children exposed to methadone or buprenorphine and tobacco prenatally could inhibit the development of some cognitive functions in later life.

Keywords Buprenorphine, cognitive, development, eye tracking, methadone, smooth pursuit, visuomotor.

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INTRODUCTION

Opioid maintenance therapy (OMT) by means of methadone and buprenorphine is a commonly used form of management of opioid-dependent pregnant women with illicit opioid abuse. Although complete detoxification from drugs before pregnancy is preferable, ceasing OMT during pregnancy is not recommended and might result in increased risk of relapse into heroin use and to spontaneous abortion and premature labour [1]. Despite evidence of beneficial effects, these drugs cross the placenta and can disrupt normal fetal development [2–4]. Approximately half of all infants exposed prenatally to OMT require medical treatment for neonatal abstinence syndrome (NAS [5]), but the literature regarding the

long-term developmental effects of OMT exposure is sparse and contradictory (for a review see [6]). While some studies report few or no long-term effects [7,8], others report disrupted cognitive performance [9–11]. For instance, prenatally exposed 4-year-old children performed worse than a comparison group on several executive function tasks and experienced further similar problems in everyday activities (Konijnenberg & Melinder, unpublished data).

Recently, impaired proactive goal-directed eye movements and fine motor skills (e.g. drawing a line) were found in children exposed prenatally to OMT, but these functions were not correlated [9]. This non-association is surprising, given the common expectation that goal-directed action is related to motor behaviour. However,

while goal-directed eye movements are dependent upon saccadic eye movement, fine visuomotor skills, such as those involved in drawing a line, might rather be related to the ability to follow a moving object or action, as in smooth pursuit.¹

SMOOTH PURSUITS AND SACCADDES

Foveation and the tracking of moving objects for acute perception is achieved by the coordination of smooth pursuit and catch-up saccades [13], enabling individuals to shift their gaze. While smooth pursuit allows the eyes to follow a moving object closely, saccadic eye movements are fast, and proceed simultaneously with both eyes in the same direction [14]. Pursuit helps to reduce the retinal motion of objects we look at, and may be either fast or slow, depending on the object's velocity [15].

The neural circuitry underlying smooth pursuit requires the coordination of multiple brain regions. Signals from the retina activate neurones in the primary visual cortex, which send target information to the middle temporal visual cortex; the processing of motion in this area is necessary for smooth pursuit responses. Areas in the frontal lobe respond to particular vectors of pursuit which, via the cerebellum, then project to optic motor neurones controlling the eye muscles [13,16,17]. The complexity of this process makes it particularly susceptible to impairment by a variety of factors, including the presence of teratogen substrates, such as tobacco, during the fetal period. Previous studies have found an association between prenatal exposure to methadone and nystagmus, suggesting that drug-exposed children may have difficulty controlling their eye movements [18,19]. In addition, difficulties with smooth pursuit have been found in individuals suffering from schizophrenia [20]. However, it is well known that tobacco smoking also induces a primary-position upbeat nystagmus [21] that might result in reduced smooth performance [22].

Furthermore, long-lasting opioids such as methadone and buprenorphine might influence neurotransmitters; in particular, decreased dopamine availability has been linked to impaired smooth pursuit performance [23,24].

Although visual capabilities are involved frequently in the integration of different modalities, few studies have investigated this association directly. In Konijnenberg & Melinder's study [9], although the prenatally exposed children demonstrated inferior performance in fine motor tasks compared to non-exposed children, these scores were surprisingly not related to proactive goal-directed eye movements that are dependent upon saccadic effi-

ciency. In the present study, we investigated whether visuomotor functions relied instead upon smooth pursuit. We included two measures of visual attention; one that tapped into visual attention only and one that examined the integrative capabilities of visual input and motor performance. Finally, we included one measure of everyday attention for ecological validity.

The study's aim was to relate smooth pursuit and saccadic eye movement to a visuomotor integration task in a sample of children exposed prenatally to OMT drugs. To accomplish this goal, we used infrared illumination of the pupil to track eye position. One hypothesis was proposed: poor smooth pursuit in the children of women in OMT affects the integration of visuomotor skills such as copying a figure.

METHOD

Participants

Forty-nine children participated in the study (see Table 1). Data from another 23 children (10 from the OMT and 13 from the contrast group, respectively) were excluded from the analyses owing to a failure to collect reliable eye-tracking data. To check whether these children differed from the participants who contributed eye-tracking data, a multivariate analysis of variance (MANOVA) was conducted using missing versus participating subjects as the factor. No significant differences appeared. Participants were recruited from a previous cohort study [25]. The opioid-dependent women were recruited from OMT centres throughout Norway during their pregnancy. The contrast group was recruited through health-care centres.

Apparatus

Eye movements were recorded using a Tobii 1750 eye tracker (Tobii Technology Inc., Stockholm, Sweden), which records the position of the eyes approximately every 20 ms (50 Hz). The stimuli movies were shown on a 17-inch TFT monitor that was integrated with the eye tracker. The signals from the eye tracker were transformed into eye positions using ClearView software (ClearView version 2.5.1; Tobii Technology Inc.). Percentages of invalid trials were computed (Tobii's reliability check) and checked against the OMT and contrast group.

Measures

Bender gestalt test II [26]

Bender is a widely used neurocognitive test for measuring fine motor development, perceptual discrimination and

¹We employ a head-unrestrained procedure to measure smooth pursuit, thus the saccadic system needs to keep track of several motor commands (e.g. the ocular smooth pursuit command, the vestibule-ocular reflex and the head movement command [12]).

Table 1 Demographic and birth characteristics of the contrast and OMT group.

	Contrast group <i>n</i> = 23		OMT group <i>n</i> = 26		<i>P</i>
	Mean	SD	Mean	SD	
NAS %, maintained on methadone	–		61% (<i>n</i> = 18)		NA
NAS %, maintained on buprenorphine	–		87% (<i>n</i> = 8)		NA
Age (months)	51.65	1.10	52.42	1.46	0.05
Gender % (females)	56%		50%		0.68
Mother's education, years	16.14	1.12	11.88	2.05	0.000 ^a
Employment, <i>n</i> (% employed)	22 (96)		13 (50)		0.000 ^b
Mean methadone dose at delivery, mg	–		85.00	64.9	NA
Mean buprenorphine dose at delivery, mg	–		13.13	5.9	NA
Cigarette use during pregnancy (% smoking)	0 (0.0)		26 (100)		0.000 ^b
Birth weight, g	3563	346.0	3104	658.6	0.004 ^a
Birth length, cm	50.6	1.4	47.7	3.3	0.000 ^a
Gestational age, weeks	39.87	0.7	38.95	2.95	0.15 ^a

^aUnivariate analyses of variance. ^bFisher's exact test (two-sided). OMT = opioid maintenance therapy; NAS = neonatal abstinence syndrome; NA = not applicable; SD = standard deviation.

integration skills. For the purpose of the present study, the subtests 'Copy' and 'Motor' were employed. The children were shown 10 different figures and asked to copy them onto a paper in the presence of the figures. The test battery provides standardized administration, raw scores and scoring norms from 4 years of age. Only raw scores will be used in further analyses.

Neuropsychological assessment (NEPSY) [27]

The NEPSY is a neuropsychological test for children aged 3–12 years. The battery has several subtests. In the present study the 'visual attention' subtest was employed to serve as a reliability check for results on the copy subtest (Bender).

Wechsler pre-school and primary scale of intelligence, revised (WPPSI-R) [28]

The WPPSI-R is one of the most-employed intelligence tests for preschool children. We used the raw scores from 'picture completion' and 'vocabulary' subtests, representing one performance subtask and one language-related subtest to index the children's general cognitive level.²

The Child Behaviour Checklist 1,5-5 (CBCL) [29]

The Child Behaviour Checklist 1,5-5 (CBCL [29]) is a parent-report questionnaire which assesses behaviour problems in 1.5–5-year-olds. The psychometric properties of the CBCL are exemplary (Cronbach's α = 0.90–0.97). For the purpose of the present study, *t*-scores were

calculated for one subscale (e.g. attention problems), where higher scores indicate more problems. This subscale was used to indicate parent-observed problems with everyday attention.

Stimuli of object motion [30]

Children watched a simulated multi-coloured ball rolling across a blue background (24° × 28°), with a 2.3° degree of visual angle. The ball accelerated to maximum speed, then moved with constant speed, then decelerated, and finally rolled in the opposite direction. Each child was shown two conditions of this task twice, one in which the ball rolled at a maximum speed of 13.2°/sec (the fast condition) and one in which the ball rolled at a maximum speed of 6.78°/sec (the slow condition). Two consecutive trials were run for each velocity, 7.5 and 15 sec, respectively. Thus, one trial equals one ball rolling back and forth (the ball can be seen eight times); in total, four trials per child.

Procedure

Each child and parent visited the laboratory once. Following a presentation of the study, informed written consent was obtained, after which the cognitive tasks were administered to the child in a quiet testing room. The child was invited to sit on a chair approximately 60 cm from the eye-tracker monitor. A five-point calibration procedure was started and repeated until measures of all five calibrations on points were obtained. The two stimulus conditions were then presented in a counterbalanced

²In WASI, for example, these two corresponding measures, plus two more from each group, compose the full-scale WASI, which is often used as a brief measure of intelligence.

Table 2 Behavioral, cognitive and gaze data by mean and standard deviation for the OMT and contrast groups.

Dependent measures	OMT (<i>n</i> = 26)		Contrast (<i>n</i> = 23)		<i>F</i>	<i>P</i>	η_p^2
	Mean	SD	Mean	SD			
CBCL, attention	53.92	5.27	50.68	1.92	7.45	0.01	0.14
Bender, copy	9.96	4.60	17.43	7.28	18.90	<0.001	0.30
NEPSY, attention	16.42	4.53	17.83	4.40	1.20	NS	0.02
WIPPSI, p.c. and voc.	32.19	5.56	34.68	5.06	2.59	NS	0.05
Looking time, sec	29.71	2.10	30.25	0.51	2.94	NS	0.03
Saccades sec, slow	1.27	0.60	1.22	0.41	0.25	NS	0.00
Saccades sec, fast	2.39	0.90	2.04	0.91	3.48	NS	0.04
Smooth, 6.78°/sec	77.84	12.20	79.49	11.18	0.24	NS	0.01
Smooth, 13.2°/sec	59.65	15.07	69.77	13.60	6.02	0.02	0.11

CBCL = Child Behaviour Checklist; NEPSY = neuropsychological assessment; NS = not significant; OMT = opioid maintenance therapy; SD = standard deviation; WIPPSI = Wechsler Preschool and Primary Scale of Intelligence.

order. At the end of the session, the child received a small gift (approximately €15). The study was approved by the local ethics committee (Regional Committee for Medicine and Health Research) and was conducted in accordance with the Declaration of Helsinki (1964).

Data analysis

Gaze data from the Tobii software were fed into a Matlab program for further analysis. First, invalid data (level 4 in Tobii software) were identified, and then the amount of invalid data as a proportion of the whole trial period was estimated. The number of saccades was calculated (>20 °/sec) from the gaze velocity profile, and the proportion of smooth gaze calculated by subtracting the saccades from the measured gaze. Thus, the smooth part was calculated as the ratio of gaze position without and with saccades from both eyes. Extreme differences in number of saccades or the proportion of smooth gaze between the eyes would indicate either extreme head movements or low coordination between the left and right eyes. For the lower velocity (slow), eight of 52 trials in the OMT group were excluded due to inattention or fuzziness. The corresponding number for the contrast group was one of 46. For the higher velocity (fast) trials, two of 52 were excluded in the OMT group and none in the contrast group.

All data were analysed using PASW statistics software (version 18; SPSS Inc., Chicago, IL, USA). Demographic, birth and substance exposure characteristics were investigated for statistical significance using Fisher's exact test. Scores on Bender and gaze data were compared using analysis of variance (ANOVA). A regression model was tested, with group (highest value = OMT) entered into the first model and smooth pursuit for slow- and fast-moving objects, respectively, added in addition to group in the second model. Normal distribution and homogeneity of

variances were verified by Shapiro–Wilk's and Levene's tests, respectively. Preliminary analysis revealed no gender differences; data from both sexes were therefore combined for subsequent analysis. Statistical significance was defined at an alpha level of 0.05. Given our sample size, we will have a 78% chance of detecting an effect corresponding to Cohen's *d* = 0.80, with an alpha of 0.05.

RESULTS

The presence of symptoms of abstinence and the amount of exposure (e.g. dose of OMT during pregnancy) did not correlate with performance on the visuomotor task, attention problems or with general cognitive function; all *Ps* > 0.29. This also held true when methadone and buprenorphine were analysed separately, except for the association between attention problems and exposure dose of buprenorphine; *n* = 8, *r* = -0.77, *P* = 0.02. NAS and exposure did not correlate with capability in either slow or fast smooth pursuit; all *Ps* ≥ 0.11, even when methadone and buprenorphine were analysed separately. Nineteen per cent of the OMT mothers reported having had emotional difficulties during the previous 30 days [range 3 (2%)–30 (8%)]. As can be seen from Table 1, children in the OMT group had lower birth weights and lengths, and their mothers had a lower education level and higher unemployment rate compared with the contrast group. Gestational age did not differ.

Children from the OMT group were considered generally to have more attention problems (CBCL) than the contrast group. Finally, a check of the children's general cognitive level (WIPPSI) evinced no differences between the groups. See Table 2.

Eye movement data

Looking time, recorded by length in seconds in the two trials, did not differ between the OMT and the contrast

group. Table 2 shows further that saccades per second in both slow and fast conditions did not differ significantly between the groups.

For smooth pursuit, we entered the percentage of the gaze which was smooth, calculated as the number of observations which showed smooth pursuit out of the total number of observations, for both slow and fast conditions, into two separate analyses of variance (ANOVAs). While slow-moving object presentation did not produce a significant difference between the OMT and the contrast group, a significant difference was produced between groups in the fast-moving object condition, which was still found when controlling [using analysis of covariance (ANCOVA) for mothers' employment ($P = 0.04$]. However, when mothers' education and children's birth weight were controlled for the difference disappeared ($P_s \geq 0.12$).

Scores from Bender (e.g. copy) and from NEPSY (e.g. visual attention) were compared to check reliability. Pearson's correlation ($n = 49$, $r = 0.39$, $P < 0.01$) confirmed a moderate association and we confidently entered raw scores for copy as our dependent measure into an ANOVA. Children in the OMT group performed significantly worse and with a moderate effect size [31] than children in the contrast group. This was also the case when motor skill, birth weight and mothers' education were controlled for ($P_s < 0.05$). However, when mothers' employment was controlled for, the difference disappeared ($P = 0.10$). None of these covariates were significant for the Bender result ($P_s \geq 0.15$) or fast pursuit ($P_s \geq 0.33$), and are not included in further analyses.

We then regressed children's scores on Bender into smooth pursuit. The first regression model had a significant squared multiple correlation of $R^2 = 0.29$, and (group) was a significant predictor [$B = -7.47$, standard error (SE) = 1.72, $\beta = -0.54$, $P < 0.001$] of scores on Bender. In the second model, $R^2 = 0.37$, $F_{(3, 45)} = 8.96$, $P < 0.001$, smooth pursuit for slow- and fast-moving objects, respectively, were added. Inclusion of these scores led to a significant change in explained variance, $\Delta R^2 = 0.09$, $F_{(2, 45)} = 3.13$, $P = 0.05$. Again, group was a significant predictor ($B = -6.00$, SE = 1.74, $\beta = -0.43$, $P = 0.001$), but smooth pursuit for fast-moving objects was also a significant predictor ($B = 0.14$, SE = 0.06, $\beta = 0.31$, $P = 0.02$).

DISCUSSION

Confirming our primary hypothesis, we found differences in smooth pursuit between the OMT and the contrast group. Secondly, we were able to link smooth pursuit to visuomotor performance. At a first glance this association may seem relatively obvious; copying a line is clearly dependent upon the ability to look at the same line while

drawing, just as tracking a moving object smoothly depends upon the same ability. We believe this relationship may represent a key factor in the picture of OMT children's difficulties.

Smooth pursuit requires the coordination of multiple brain regions which develop during pregnancy and the first years of life. Prolonged development of the brain makes the smooth pursuit function susceptible to influence from substrates operating during the fetal period. Previous studies have found an association between prenatal exposure to methadone and a condition of involuntary eye movements, which is assumed to interfere with the voluntary control needed in smooth pursuit [18,19]. In the present study we found evidence of deviant smooth pursuit that we may relate to fetal exposure to methadone or buprenorphine, perhaps mediated by decreased availability of dopamine. Of note, the type of exposure did not affect integrative and general cognitive functions differently. Environmental factors are certainly involved in shaping distinct functions later in development, but we are not aware of any postnatal drug abuse, child neglect or abuse that would result in an impaired smooth pursuit function. Supporting the conclusion that environmental influences were not likely to have contributed to the deviant smooth pursuit found are the results from the indexed general cognitive measure, in particular the vocabulary subtest, which showed no difference between the OMT and the contrast group.

However, smooth pursuit is dependent upon other cognitive mechanisms that might play a role in our findings. Importantly, the maintenance of accurate smooth pursuit requires continuous attention [32]. Problems with attention may therefore disrupt smooth pursuit. Visuomotor deficits could well be explained by the interacting effect of, on one hand, weaker smooth pursuit and, on the other hand, vulnerable attention capabilities. Fortunately, the present study can, to some degree, disentangle these factors. Results from the visual attention task (NEPSY) did not show differences between the groups of children ($P = 0.28$) when subjects were exposed to an attention task excluding the demanding integration of visual and motor capabilities. Thus, the OMT children struggle with smooth pursuit that affects integrative skills. It seems reasonable that the mutual influence of deviant smooth pursuit and faulty attention can create a cascading negative function observed in the OMT sample's inability to integrate modalities. Although it differs from the visual attention task (NEPSY) in terms of differences between the groups, the parents' ratings of children's attention problems (CBCL) further support the validity of our findings. This difference could be explained by the fact that CBCL is completed by the parents, whereas visual attention from NEPSY is a structured measure administered by a researcher. Another

explanation could be that CBCL asks for specific actions instead of 'pure' visual attention as does NEPSY and, as such, taps more closely into the same capabilities as Bender.

Saccades are not dependent upon an object to follow, but function according to a catch-up principle. In the present study we did not detect any differences between the OMT and the contrast group in terms of saccades. Thus, the 'saccadic explanation' for the deficits in proactive goal-directed eye movements found in the children of women in OMT has to be rejected (cf. [9]).

We found support for the hypothesis that worse smooth pursuit is related to poorer integrative visuomotor abilities, also seen when motor skills were controlled for. Thus, it is the integration of visual and motor skills that becomes deviant. Important visuomotor skills of this kind include the ability to track a line, copy a figure, follow a text and read fluently. Thus, deviant smooth pursuit has practical implications and could inhibit further development, including the development of social relations. For instance, a child with less efficient smooth pursuit might experience a different perception of a moving object or person compared with a child with more efficient smooth pursuit. A recent study showed that ability in smooth pursuit contributed to the brain's construction of holistic experiences, seamless behaviour and to talented sports performance [33]. Identifying deviant smooth pursuit early in development is important, therefore, as it affects the individual child's ability to reach further maturity in several domains.

Few studies have investigated how impairments in smooth pursuit can be corrected. However, experience has been found to enhance smooth pursuit performance. Specifically, it was found that playing certain video games improved smooth pursuit performance in healthy individuals [34]. It may therefore be possible to improve poor smooth pursuit skills by training people in visual tracking.

Our study has some noteworthy limitations. First, few subjects were included, which may affect the study's generalizability and ability to control for relevant confounders. To detect a moderate effect ($d = 0.5$) with an alpha of 0.05, we would have needed a sample of 60 individuals. However, all infants born during the sampling period were included, suggesting a high degree of representativeness. Findings are mixed with regard to the detrimental effect of tobacco on smooth pursuit [22], but tobacco smoking during pregnancy is related strongly to low birth weight, death from perinatal disorders, sudden infant death syndrome (SIDS) and altered lung development [35,36]. All OMT mothers used tobacco, whereas none did in the contrast group. Thus, the most we can say from the present study is that maternal OMT and cigarette smoking have detrimental effects on smooth pursuit,

which then influences visuomotor capabilities. Future studies should include smoking mothers not in OMT as controls to gain a more valid result.

It is also possible that level of maternal education and its influence on stimulating child learning created a further potential confounding variable. Another limitation is the inclusion of two types of opioids. However, we know from animal studies that prenatal exposure to either methadone or buprenorphine influences the depletion of dopamine, which is linked to impaired smooth pursuit performance [23,24]. As shown, except for the negative association between attention problems and exposure dose of buprenorphine, we did not find differences relating to type of exposure on any cognitive measure. As smooth pursuit relies upon attention ability, it is not obvious whether visual attention is harmed first by the opioids and so causes deviant smooth pursuit, or if the deficit in smooth pursuit is the first affected which then, in turn, affects the attention network. In any case, the effects might result in problems with integration and regulation of cognitive as well as emotional factors.

Parents generally regulate infants' behaviour, a function that is taken over subsequently by the child itself. Some of the most important functions for emotional and social regulation are the executive functions (EF). EFs are connected closely to attention and to environmental stimulation. Given the impaired smooth pursuit function in the OMT children influencing their integrative capacity, we suggest that later during development, when visual attentional demands become higher, the load on the cognitive system increases at the expense of EF.

This cascading development might be possible if we assume deviant smooth pursuit to result in worse attention, challenges with visual spatial integration and later less efficient EF. It is noteworthy that this depiction was recognized by the OMT parents, who rated their children as having greater difficulties with attention, compared with the contrast group of parents. However, the OMT mothers' educational level was lower than that of the contrast group, which might also have contributed to less relevant stimulation of their children, relevant to their EF.

Thus, a relatively small dysfunction could become a general problem with regulating physical distances to others, pre-reading training and writing. Failure in early stages of development, including maternal stimulation, might cause reduced experience with tasks that are important for higher-order cognitive functions. This, in turn, might result in less learning, less motivation to participate in further education and to a failure to cope with peers. Turning this negative developmental trajectory around through environmental support by means of training and sensitive stimulation is not simply a hope,

but a realistic approach that needs to be examined in future longitudinal intervention studies. As a concluding remark, it is worth mentioning again that the vast majority of the children included in our study still lived with their biological parents. This is especially remarkable, as children of substance-abusing parents (e.g. heroin abuse) are, as a general rule, placed into foster care early in life.

Declaration of interests

None.

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