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Theory of Mind Development is Impaired in 4-Year-Old Children with Prenatal Exposure to Maternal Tobacco Smoking

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Authors' contributions

This work was carried out in collaboration between all authors. All authors were involved in study design, statistical analysis, and manuscript preparation. All authors read and approved the final manuscript.

Research Article

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ABSTRACT

Aims: Theory of Mind (ToM) is an important component of social cognition. Deficits in ToM are found in various neurodevelopmental disorders and social and environmental factors have been found to influence ToM development. Little previous research has focused on effects of exposure to toxins; this report examines the impact of tobacco.
Place of Study: Department of Psychiatry, University of Colorado School of Medicine, between April 2006 – August 2012.
Methodology: 101 children, 18 with prenatal exposure to tobacco, underwent ToM testing at 40 (*n*=89) and 48 (*n*=77) months of age. Test questions received dichotomous pass/fail scores and percentage of correct responses was utilized as the primary dependent variable.
Results: At 40 months of age children were rarely able to correctly answer false belief questions and there were no significant differences according to prenatal tobacco exposure. At 48 months of age, there was a significant effect of prenatal tobacco exposure with non-exposed 48-month-olds correctly answering 45±40.6% of content false belief questions correctly, compared to 13.9±25.3% for 48-month-olds with prenatal tobacco exposure ($F=4.79$, $df= 1,73$, $p=.032$).
Conclusion: ToM abilities are rapidly developing between 40 and 48 months of age. Prenatal exposure to tobacco is associated with impairment at 48 but not 40 months of

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age. This finding supports consideration of nicotinic mechanisms as contributors to early development of social cognition.

Keywords: Social cognition; theory of mind; pregnancy; tobacco; smoking.

1. INTRODUCTION

There has been little work focused on how exposure to toxins may influence development of social cognition. This report is a first step to address that gap in the literature by examining the impact of tobacco, one of the most common toxins to which fetuses are exposed.

Social cognition – the ability to process, retain, and utilize information about other people – forms the foundation of the human ability to construct theories of others. It provides the foundation to attribute intent to others' actions, which is key to predicting behavior and establishing a causal framework to explain behavior in terms of internal, unobservable mental states. This allows individuals to self-organize, engage in social communication, regulate affect, and function in interpersonal relationships. A component of social cognition which has garnered great attention in recent years is Theory of Mind (ToM). ToM is the capacity to appropriately judge and attribute mental states of the self and others and to understand that other people have knowledge, beliefs, and desires which may differ from one's own. It has been described as a composite function which can require concurrent use of memory, joint attention, complex perceptual recognition (such as face and gaze processing), language, executive function, working memory, perspective-taking, and ability to recognize and process emotions such as empathy [1].

ToM normally develops between three and five years of age. It develops spontaneously as children begin to distinguish between mental and physical phenomena, e.g. thoughts and feelings are unobservable abstractions while objects and overt behaviors are visible and frequently tangible [2]. Children begin to associate causality with psychological states; for example, as described by Leslie, Friedman & German, "When somebody receives a present, they feel happy." The development of this ability allows children to begin to deduce motives and internal mental states of others [3]. Children thus learn to use unobservable phenomena to explain events, and with full development of a comprehensive ToM, are able to ascribe differing unobservable phenomena such as beliefs, knowledge, and desires to others and use them to explain actions and events. One form of this ability, to recognize that others retain and act on beliefs that are untrue, is termed false belief understanding and is an essential feature of ToM [3].

Before the age of three or four years, children make predictable and repeatable errors on false belief tasks which require them to take on the sets of beliefs or states of knowledge of other individuals. In normally developing populations, these errors disappear by five years of age. Persistent deficits in ToM have been associated with a variety of neurodevelopmental disorders, including autism [4,5], ADHD [6], and schizophrenia [7]. Family and environmental factors also influence ToM development. Factors associated with improved performance on ToM tasks include increased frequency of mothers' use of what Meins et al. have termed "mental state comments" used to refer to knowledge, thoughts, and desires – for example, "You know what that is, it's a ball," "I think you think it's a drum," and "Do you like the ball?" – along with increased child-adult interaction, increased amount of contact with older children (including siblings), and higher maternal education [8-11].

Despite the volume of literature which has examined ToM in relation to associated neurodevelopmental disorders and social and environmental factors, there is very little literature on biological influences on ToM development. In this paper we examine the effects of in utero exposure to tobacco through maternal smoking – the most common drug fetuses are exposed to in the United States. Given the impact of prenatal exposure to tobacco on social and cognitive development as demonstrated in studies examining behavioral problems [12-14], psychopathology [15;16], and neurocognitive deficits [17], we hypothesized that children of mothers who smoked during pregnancy would demonstrate deficits in ToM.

Mothers who smoke during pregnancy are more likely to suffer from mental health disorders [18] and maternal mental illness during pregnancy has adverse effects on offspring mental health outcomes [19]. The impact of maternal psychiatric illness during pregnancy on ToM development has not previously been explored, represents a potential confound, and thus is also included in the analysis.

2. METHODS

2.1 Participants

Participants were recruited through a letter sent from the Colorado State Department of Vital Statistics, with sampling appropriate to generate a testing group representative of the Denver metropolitan area. Participating children had birthdays between April 2006 and November 2009. Families were recruited and maternal psychiatric and substance use histories were completed within a few months after birth. ToM testing occurred between May 2010 and August 2012. 101 children underwent ToM testing; 18 of these children had prenatal exposure to tobacco as assessed by mothers' self-report of averaging at least 1 cigarette per day for at least 1 trimester during pregnancy. One mother had a history of alcohol abuse during pregnancy. ToM testing took place at 40 and 48 months of age. 89 children were assessed at 40 months of age and 77 were assessed at 48 months of age. Theory of Mind assessments were completed at both time points for 49 children. Measurements of children's IQ were obtained through completion of the Wechsler Preschool and Primary Scale of Intelligence [20] at 48 months of age and maternal mental health history was defined using a non-hierarchical best estimate approach after completion of the Structured Clinical Interview for DSM Disorders – IV [21] by an experienced research clinician. A mother was defined as having an Axis I psychiatric diagnosis if she either (a) met criteria for the illness during pregnancy, or (b) had symptoms prior to the onset of pregnancy and retained residual symptoms plus impairment of significant distress during pregnancy. Children with prenatal exposure to tobacco did not significantly differ from children with no such exposure in regard to age at testing, race and ethnicity, or prematurity; however, children with prenatal tobacco exposure were more likely than children without such exposure to also have prenatal exposure to maternal mental illness and to have lower IQs (Table 1). Parental consent was received for each child as monitored by the local Institutional Review Board.

Table 1. Demographic information for participants

Variable	Total (n = 101)	Prenatal tobacco exposure (n = 18)	No prenatal tobacco exposure (n = 83)	Statistic	p
Gender					
- Male	53 (52.5%)	11 (61.1%)	42 (50.6%)	χ^2=0.7	.418
- Female	48 (47.5%)	7 (38.9%)	41 (49.4%)		
Race/Ethnicity					
- Caucasian/Non-Hispanic	65 (64.4%)	10 (55.6%)	55 (66.3%)	χ^2=5.8	.056
- Caucasian/Hispanic	16 (15.8%)	1 (5.6%)	15 (18.1%)		
- Other/Mixed/Unknown	20 (19.8%)	7 (38.9%)	13 (15.7%)		
Premature birth	4 (4.0%)	2 (11.1%)	2 (2.4%)	χ^2=2.9	.145
Any prenatal maternal psychiatric diagnosis	22 (21.8%)	8 (44.4%)	14 (16.9%)	χ^2=6.6	.023
- Any Anxiety Disorder	17 (16.8%)	5 (27.8%)	12 (14.5%)		
- Agoraphobia	1 (1.0%)	0 (0.0%)	1 (1.2%)		
- Generalized Anxiety	10 (9.9%)	1 (5.6%)	9 (10.8%)		
- Obsessive-Compulsive	3 (3.0%)	1 (5.6%)	2 (2.4%)		
- Panic	2 (2.0%)	0 (0.0%)	2 (2.4%)		
- PTSD	7 (6.9%)	4 (22.2%)	3 (3.6%)		
- Any Mood Disorder	11 (10.9%)	6 (33.3%)	5 (6.0%)		
- Major Depression	5 (5.0%)	2 (11.1%)	3 (3.6%)		
- Bipolar Without Psychosis	4 (0.0%)	2 (11.1%)	2 (2.4%)		
- Bipolar NOS	2 (2.0%)	2 (11.1%)	0 (0.0%)		
- Any Psychotic Disorder	0 (0.0%)	0 (0.0%)	0 (0.0%)		
- Any Non-Nicotine Substance Use Disorder	1 (1.0%)	1 (5.6%)	0 (0.0%)		
- Eating Disorder	1 (1.0%)	0 (0.0%)	1 (1.2%)		
Maternal Years of Education	15.5±2.7	13.5±2.5	16.0±2.6	t=3.7	<.001
Child's IQ	105±13	96±13	106±13	t=2.5	.013

Values are numbers (percentages) or means (S.D.)

2.2 False Belief Tasks

There were four false belief tasks at each time point: two locations false belief tasks and two contents false belief tasks. The locations false belief tasks required children to predict where a protagonist would search for an object based on a false belief about the object's location. The contents false belief tasks required children to answer questions about the surprise contents of a mislabeled box. As in similar studies, tasks were presented in a standard order, as previous studies have failed to find order effects for false belief tasks [22].

2.2.1 Locations false belief tasks

The two locations false belief tasks were modeled after the original Wimmer and Perner Maxi task [23], as adapted by Bigelow and Dugas [24]. Children were introduced to a dollhouse, a mother doll, and a child doll named Maxi. For the first locations false belief task, children were told that Maxi and his mother were returning from the grocery store with some chocolate and the children watched Maxi put the chocolate in the cupboard of the dollhouse kitchen. They were then asked the control question, "Where did Maxi put the chocolate?" The children were told that Maxi then wanted to go outside to play, and watched as the mother doll moved the chocolate to the refrigerator while Maxi was out of the house. The children were asked the second control question, "Where is the chocolate now?" Maxi returned to the dollhouse for some chocolate and the children were asked the first of two locations false belief test questions, "Where will Maxi look for the chocolate? Will he look in the cupboard or in the refrigerator?"

The second locations false belief task was presented as a continuation of the same story, with Maxi receiving chocolate from his mother and then deciding to go outside to play once again. Children were told that Maxi first wanted to find his mittens, and it was explained that Maxi thought his mittens were under the bed but they were really in the closet. Then two control questions were asked: "Where are his mittens really?" and "Where does Maxi think his mittens are?" The children were then asked the second of two locations false belief test questions, "Where will Maxi look for his mittens? Will he look under the bed or in the closet?"

2.2.2 Contents false belief tasks

The contents false belief task was modeled after the original Perner, Leekam, and Wimmer "Smarties" task, as adapted by Razza and Blair [25]. In this task children were shown one of four mislabeled containers. The first container at the 40 month visit was an egg carton. The children were asked the first control question, "What do you think is in this container?" The researcher then opened the container, showing that the egg carton contained unexpected items, in this case pencils, and asked the children the second control question, "What is really in the container?" The researcher closed the container and asked the first contents false belief test question, "When you first saw this container, before I opened it, what did you think was inside?" followed by the second contents false belief test question, "If your friend came in and saw the container all closed up like this, what would s/he think was inside?" The procedure was repeated with a second container. At the 40 month visit the second container was a Band-Aid box with a roll of tape. At the 48 month visit the first container was a Crayon box with birthday candles and the second container was a Pringles can with tennis balls.

2.3 Data Analysis

Each test question received a dichotomous pass/fail score. Children were required to answer the control questions correctly in order to pass the test question. A summative score of the percentage of total number of correct locations false belief test questions (out of 2) and percentage of total number of correct contents false belief test questions (out of 4) at each time point was utilized as the primary outcome measure. Due to the non-normal distribution of percentage scores for locations and contents false belief questions, a non-parametric (distribution-free) analysis of covariance was applied to the total scores after a rank transformation [26] to estimate the association with maternal smoking and maternal mental illness. It has been shown that such a parametric analysis of covariance of the ranks is extremely well approximated by normal theory software after transforming the dependent variable to ranks [27]. As smoking rates are elevated in almost all psychiatric illnesses, the presence of prenatal maternal psychiatric illness was collapsed into a dichotomous variable (either yes or no). As all mothers who had a prenatal psychiatric illness had either prenatal anxiety or prenatal depression, results are identical whether the presence of psychiatric illness is limited to depression plus anxiety or to all Axis I psychiatric illnesses. No significant effect of gender was identified. All analytic results were similar whether gender was included as a variable or not. Results reported here are without gender as a variable. Results were similar whether all subjects were utilized or whether the analysis was limited to those from whom data was available at both time points. Results utilizing all subjects are reported here.

3. RESULTS

3.1 Location False Belief Tasks

Forty-month-old children correctly answered 5.5±15.7 (mean ± S.D.) percent of location false belief questions. Forty-eight-month-olds were somewhat more successful, answering 21.4±34.8% of location false belief questions correctly. There was no significant main effect for prenatal tobacco exposure or prenatal maternal mental illness or the interaction between the two at either age (Table 2 and Fig. 1).

Table 2. Results of a 2 x 2 ANOVA for percentage of questions answered correctly after rank transformation

False belief questions	Main effect of prenatal tobacco exposure	Main effect of prenatal maternal mental illness	Prenatal tobacco by prenatal maternal mental illness
40 months of age			
Location Questions	F (1,69) = 0.42, p = .518	F (1,69) = 0.18, p = .670	F (1,69) = 0.54, p = .464
Contents Questions	F (1,69) = 0.13, p = .721	F (1,69) = 0.41, p = .525	F (1,69) = 0.08, p = .778
48 months of age			
Location Questions	F (1,73) = 0.02, p = .898	F (1,73) = 1.71, p = .195	F (1,73) = 0.09, p = .768
Contents Questions	F (1,73) = 4.79, p = .032	F (1,73) = 0.05, p = .822	F (1,73) = 0.00, p = .989

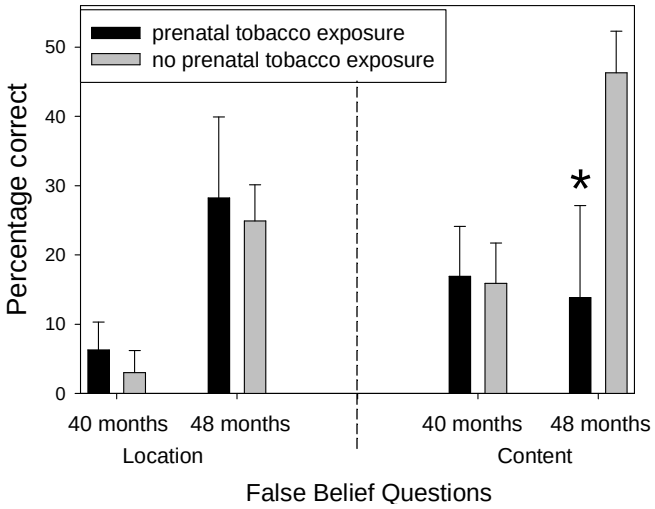

Fig. 1. Children were tested with Theory of Mind locations and contents false belief tasks at 40 and 48 months of age. Results are show as the marginal mean ± S.D. percentage of questions answered correctly. Analyses were based on a 2x2 (prenatal tobacco exposure by prenatal maternal mental illness) after rank order transformation
**p=.023.*

3.2 Content False Belief Tasks

Forty-month-old children correctly answered 19.2±28.1 (mean ± S.D.) percentage of correct responses. At 40 months of age, there was no significant main effect for prenatal tobacco exposure or prenatal maternal mental illness or for the interaction. Forty-eight-month-olds were more successful, answering 41.6±40.3% of content false belief questions correctly. There was no significant main effect of prenatal psychiatric illness nor was there a significant prenatal maternal mental illness by prenatal tobacco exposure interaction (Table 2). However, there was a significant effect of prenatal tobacco exposure with non-exposed 48-month-olds correctly answering 45±40.6% of content false belief questions correctly, compared to 13.9±25.3% for 48-month-olds with prenatal tobacco exposure (Fig. 1).

Because children with and without prenatal tobacco exposure differed in IQ, IQ was evaluated as a possible mediating factor for the relationship of prenatal tobacco with contents false belief performance at 48 months of age. Prenatal tobacco exposure and child IQ were strongly associated (t=2.53, d.f. = 75, p=.013) as was child IQ and performance on the contents false belief questions. (r=.337, d.f.=76, p=t.004). When IQ was utilized as a covariate, prenatal tobacco exposure no longer is significantly related to performance on the contents false belief task (F=1.36, d.f.=1, p=.250).

4. DISCUSSION

At 40 months of age, successful false belief responses were rare (around 5%) with slightly better performance on content questions (around 20%). This general inability to correctly answer false belief questions at 40 months of age is consistent with what has been previously reported [28]. At 40 months of age, there was no effect of either prenatal

exposure to either tobacco or mental illness on false belief task performance; however this likely reflects that almost all children had difficulty successfully completing the task.

Consistent with the literature [28], 48-month-old children were more successful at the task. Mean success on the content portion of the task approached 50%. Prenatal tobacco exposure is associated with poorer performance and appears to not be confounded by maternal prenatal mental illness. To our knowledge, only one other report has examined prenatal toxin exposure on ToM development. In their study, Rasmussen, Wyper, and Talwar found that children with fetal alcohol spectrum disorders demonstrated deficits in ToM [29]. It is unknown whether the deficits identified here in this study are transient and reflect developmental delay or are persistent over time. Additional evaluation at 60 months of age, when nearly all children should be able to complete the tasks, would help resolve this issue.

Maternal prenatal tobacco use was associated with infant IQ; infant IQ was associated with performance on the ToM tasks, and, when IQ was utilized as covariate, the relationship between prenatal tobacco and T0M tasks was no longer significant. This suggests that child IQ may be a mediator between prenatal tobacco and 48-month-old ToM performance.

Many studies suggesting a relationship between prenatal tobacco exposure and adverse developmental outcomes suffer from problems of maternal factors that covary with maternal smoking [30]. While the current study suggests that the relationship between prenatal tobacco and delayed development in social cognition is not due to comorbid maternal mental illness, a major limitation is that the sample size is too small to assess the impact of other potential confounding factors, including maternal IQ, education, and socioeconomic status. Additional research with larger sample sizes will be necessary to clarify these issues.

Historically, attempts to identify disease-specific etiologic factors have had little success. An alternative approach, focusing on identifying etiologic factors for impairments which cross diagnostic categories, has received significant recent attention [31]. For example, prenatal exposure to maternal tobacco smoking has been tied to later cognitive impairment [30;32;33], nicotinic mechanisms are now included in etiological models of cognitive development [34], and nicotinic agonists are currently being evaluated as primary prevention strategies [35]. Like cognition, social cognition is problematic across a number of psychiatric illnesses, including autism, schizophrenia, and ADHD. The finding that prenatal maternal tobacco smoking is associated with deficits in the development of social cognition suggests nicotinic mechanisms may also be appropriate as an area for research efforts in this symptom domain.

5. CONCLUSION

Understanding that others may act on beliefs that are untrue, a component of Theory of Mind, is a critical development step in social cognition. This component of Theory of Mind is relatively undeveloped at 40 months of age and the effects of prenatal tobacco exposure are not yet evident. By 48 months of age, this component of Theory of Mind is partially developed and children with prenatal tobacco exposure are demonstrating impairment. Prenatal tobacco exposure (the most common prenatal toxin exposure) is associated with a wide variety of neurocognitive and developmental delays. Theory of Mind should be added to this list as another cognitive function whose development is delayed by prenatal tobacco exposure.

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COMPETING INTERESTS

The authors declare that no competing interests exist.

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