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DRD2 Genotype and Prenatal Exposure to Tobacco Interact to Influence Infant Attention and Reactivity

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Introduction

➢**Prenatal tobacco exposure (PTE)** results in activation of nicotinic acetylcholine receptors, changing the timing of neurodevelopmental processes (e.g., premature shift to differentiation at the expense of replication), and alteration in function of dopaminergic/serotonergic circuits (e.g., Levin & Slotkin, 1998; Muneoka et al., 1997)

➢Previous studies have shown that PTE affects infant neurobehavior and temperament (Fried & Makin, 1987; Jacobson et al., 1984; Key et al., 2007)

➢Candidate genes related to dopaminergic neurotransmission have been implicated in individual differences in infant behavior/temperament (e.g., Auerbach et al., 2001; Lakatos et al., 2003; Laucht, Becker, & Schmidt, 2006).

➢The impact of PTE on childhood outcomes (e.g., ADHD) has been shown to interact with genetic risk factors (e.g., Becker et al., 2008; Kahn et al., 2003; Neuman et al., 2007)

➢**Does PTE interact with genetic risk in infancy?**

➢The TaqIA polymorphism is located within a kinase gene upstream from the coding region of the D2 dopamine receptor (DRD2) gene (Neville, Johnstone, & Walton, 2004)

➢Presence of the A1 allele (in A1A1 homozygotes or A1A2 heterozygotes, collectively referred to as the A1+ genotype) is associated with differences in DRD2 receptor expression and availability in striatum (Pohjalainen et al., 1998) and anterior cingulate activation when controlled attention is required (Fossella, Green, & Fan, 2006)

➢The present study examined the effects of **dopamine receptor D2 genotype** and **PTE status** on early infant neurobehavior

Method

➢The sample was comprised of 119 infants (*M* = 4.24 wks, range = 3.0 to 8.9 weeks)

➢Mothers were prospectively enrolled during pregnancy (most before the 16th week)

➢Prenatal tobacco exposure was quantified based on maternal self-report (timeline-followback interviews conducted at 16 weeks, 28 weeks, and 24-48 hours after birth), and verified by cotinine analysis of maternal urine and infant meconium

➢All infants were genotyped on DRD2 TaqIA allele

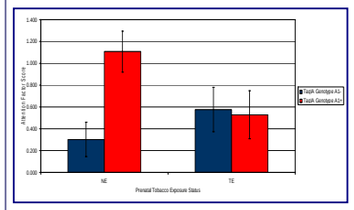
➢Infants were administered the Neonatal Temperament Assessment (NTA; Riese, 1983) when they were 4 weeks old

➢A principal components analysis of NTA rating scores yielded 3 summary component scores:

- Attention: (e.g., auditory orienting to voice or rattle, visual following of bulls-eye)
- Irritable Reactivity (e.g., irritability to visual/auditory stimuli, soothability after reflex elicitation)
- Dysregulation to Stress (responsiveness to soothing techniques, soothability after pacifier withdrawal)

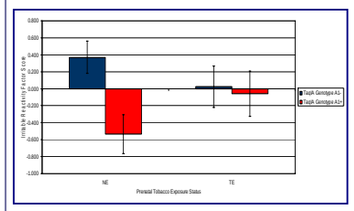
➢Component scores were analyzed using SAS's *proc mixed*, with PTE status, DRD2 allele, and their interaction entered as predictors, and covarying maternal education, sex, and age at assessment

Results



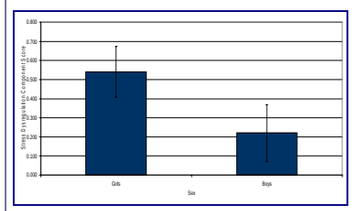
Attention

PTE: n.s.
DRD2: $p < .05$
PTExDRD2: $p < .05$
NE: A1+>A1-
TE: n.s.



Irritable Reactivity

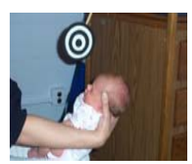
PTE: n.s.
DRD2: $p < .05$
PTExDRD2: $p < .05$
NE: A1+<A1-
TE: n.s.



Dysregulation to Stress

PTE: n.s.
DRD2: n.s.
PTExDRD2: n.s.

Sex: $p < .05$



Conclusions

➢Prenatal tobacco exposure appears to moderate the effect of genotype on infant attention and irritable reactivity

➢Infants with the A1+ genotype were more attentive and less reactive, but only in the absence of PTE

➢Infants with the A1+ genotype may have a heightened response to novelty (seen later in development: Berman et al., 2002), which could result in increased orienting and concomitant decreased irritability to novel stimuli

➢In PTE infants with the A1+ genotype, response to novelty may then be dampened, as has been found in rhesus monkeys exposed to perinatal tobacco smoke (Golub, Slotkin, Tarantal, & Pinkerton, 2007); however, infants with the A1- genotype (who evidenced intermediate levels of attention and irritability regardless of PTE status) may be less susceptible to PTE's effects

➢These results exemplify the interplay between genetic and environmental factors in infant development

➢Future studies should test these findings for replication and examine implications of early attention/orienting and irritability for later outcomes in samples with known prenatal histories and genetic risk

Acknowledgments

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Demographic variable	A1 Carriers (A1A1 $n = 4$; A1A2 $n = 40$)				A1 Non-carriers ($n = 75$)			
	Tobacco-exposed ($n = 21$)		Non-exposed ($n = 23$)		Tobacco-exposed ($n = 39$)		Non-exposed ($n = 36$)	
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
Infant sex (% female)	61.9	--	39.1	--	53.9	--	66.7	--
Birth weight (g)	3389.24	305.54	3276.83	485.82	3400.43 ($n = 37$)	475.25	3557.83 ($n = 35$)	449.29
Gestational age (weeks)	39.31	1.32	38.84	1.48	39.10	1.54	39.41	1.12
Age at NTA assessment (weeks)	4.17	0.51	4.06	0.50	4.42	1.27	4.20	0.47
Maternal age at delivery (years)	28.35	6.10	26.55	5.07	26.06	5.89	29.16	5.62
Maternal education (years) *	13.71	1.90	14.04	2.01	13.51	1.70	14.94	1.62
Self-reported smoking (cigarettes/day):								
Before last menstrual period *	8.76 ($n = 20$)	6.77	--	--	10.15 ($n = 38$)	7.90	--	--
16 weeks *	3.60 ($n = 15$)	5.58	--	--	3.85 ($n = 34$)	6.22	--	--
28 weeks *	2.39	3.78	--	--	2.93 ($n = 38$)	4.64	--	--
At delivery *	2.10	3.58	--	--	2.37 ($n = 38$)	3.93	--	--
Cotinine levels:								
16 weeks (maternal urine; ng/mL) *	434.50 ($n = 16$)	681.93	7.15 ($n = 20$)	20.63	358.51 ($n = 35$)	563.70	2.82 ($n = 28$)	11.66
28 weeks (maternal urine; ng/mL) *	331.81	604.03	5.87	12.24	330.54	545.46	10.22	22.50
At birth (maternal urine; ng/mL) *	82.33	179.03	6.73 ($n = 22$)	13.54	124.05	322.95	8.00	15.90
At delivery (infant meconium; ng/g) *	327.05	1073.80	0.00 ($n = 22$)	0.00	132.15 ($n = 33$)	537.99	1.64 ($n = 33$)	6.92

* = significant difference between TE and NE groups