Development and Psychopathology **30** (2018), 1333–1354

doi:10.1017/S0954579417001687

Maternal smoking during pregnancy and offspring executive function: What do we know and what are the next steps?

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Abstract

Children exposed to maternal smoking during pregnancy (MSDP) exhibit difficulties in executive function (EF) from infancy through adolescence. Due to the developmental significance of EF as a predictor of adaptive functioning throughout the life span, the MSDP–EF relation has clear public health implications. In this paper, we provide a comprehensive review of the literature on the relationship between MSDP and offspring EF across development; consider brain-based assessments, animal models, and genetically informed studies in an effort to elucidate plausible pathways of effects; discuss implications for prevention and intervention; and make calls to action for future research.

Adverse fetal environments can have pervasive negative consequences for developmental sequelae across the life span. One of the most common and preventable of these environments, maternal smoking during pregnancy (MSDP), not only impedes healthy child development, but also has major public health implications. Children exposed to MSDP are more likely to require support resulting from the well-documented physical, socioemotional, behavioral, mental, and neurocognitive consequences of exposure (see Ross, Graham, Money, & Stanwood, 2015, for a review). As such, MSDP increases the socioeconomic burden on healthcare, criminal justice, and educational systems. Due to its relevance to key developmental outcomes, such as academic success (e.g., McClelland & Cameron, 2011), and its repeated implication in most forms of psychopathology (see Snyder, Miyake, & Hankin, 2015, for a review), executive function (EF) has emerged as a fundamental neurocognitive outcome for studies of the effects of MSDP.

Defining EF

Children exposed to MSDP may exhibit decreases in later mental development and higher order capacities, such as EF, resulting from the early insult of MSDP to fundamental neurodevelopmental processes (Peterson et al., 2003). EF regulates and coordinates the internal and transactional processes that enable goal-directed thought, action, and emotion (Anderson, 2002; Zelazo, Müller, Frye, & Marcovitch, 2013), and facilitates a wide range of purposeful actions that allow us to fluidly approach novel behaviors and circumstances. EF is often theorized as multiple processes that function together as a supervisory system that is important for planning, reasoning, and the integration of thought and action (Shallice & Burgess, 1996; Stuss & Alexander, 2000).

EF has multiple layers of complexity (Jones, Bailey, Barnes, & Partee, 2016), and many abilities have been suggested as either critical components or supportive, more basic skills (e.g., attention and regulating eye movements; Garon, Bryson, & Smith, 2008; Johnson, 1995) that serve as building blocks for EF (Anderson, 2002; Miyake & Friedman, 2012; Snyder et al., 2015; Toplak, West, & Stanovich, 2013). However, the foundational and most commonly indexed domains of EF include (a) set-shifting, (b) inhibitory control, and (c) working memory (Best & Miller, 2010; Miyake et al., 2000). *Set-shifting* involves flexibly switching among multiple tasks to meet changing environmental demands and is leveraged in the real world when, for example, successfully writing 2018 on January 1 instead of 2017. *Inhibitory control* involves the suppression or delay of a prepotent, salient response for one that is less dominant to achieve a goal and is recruited to, for example, remove your foot from the gas pedal and apply the brake when approaching a yellow light. Inhibitory control is often differentiated into hot (i.e., emotionally laden) and cool (i.e., emotionally neutral) aspects (Zelazo & Müller, 2002). *Working memory* is required to manipulate information held in short-term memory and is exerted when, for example, creating a mental to-do list and prioritizing multiple activities. Studies of the structure of the foundational components of EF find that they show both unity and diversity (i.e., are correlated but separable) and that individual differences at the latent-variable level are almost entirely genetic in origin (e.g., Friedman et al., 2008).

Attention seems to play a critical role in the development of EF, as it allows children to control the internal and external

The first author is supported by Grant T32 DA016184 to Damaris J. Rohsenow.

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information that they process (see Posner & Rothbart, 2013, for a discussion of attention development in self-regulation, a broader construct that is subserved by EF; Hofmann, Schmeichel, & Baddeley, 2012). In fact, a core attention system has been proposed as a foundation upon which EF is built (Garon et al., 2008). Infants and young children become progressively more adept at regulating their emotions, thoughts, and behavior due to the increased connectivity of attentional control systems in the brain (Posner & Rothbart, 2013). Development of the rudimentary ability to focus attention across infancy and preschool enables children to be resistant to distractors (e.g., Richards, 1985). Although infants perform similarly to older children once in a state of focused attention, they are unable to sustain it for a long period of time (Garon et al., 2008); focused attention increases in duration from late infancy throughout the preschool period (e.g., Lansink, Mintz, & Richards, 2000). Children also become increasingly skilled at selective attention (i.e., flexible and voluntary shifts of attention) across early childhood due to the development of two attentional subsystems: the *orienting* and *anterior attention subsystems*. The orienting subsystem develops during the first year of life and allows children to orient to stimuli in their environment and shift attention (Colombo, 2001). The anterior attention subsystem emerges in late infancy and shows dramatic increases from ages 2 to 6 years (Rothbart & Posner, 2001). This subsystem selects and enhances the processing of stimuli and does so in part by operating on the orienting system (Ruff & Rothbart, 1996). Thus, the marked development of sustained attention across early childhood is thought to be due to the increased control of the anterior attention subsystem over the orienting subsystem (Ruff & Rothbart, 1996). Although substantial development in attentional systems occurs relatively early in life, development of prefrontal areas throughout adolescence and early adulthood subserves the maturation of attention (e.g., Kwon, Reiss, & Menon, 2002) and in turn increasingly successful performance on complex EF tasks.

Development of EF

EF skills manifest in different ways across development (Best & Miller, 2010); foundational skills appear earlier in development, and complex skills emerge later as children mature and acquire more advanced knowledge and abilities (see Jones et al., 2016, for a discussion of defining and measuring EE skills across development). For example, rudimentary developmental antecedents of EF emerge as simple behaviors, such as regulating eye movements and attending to and searching for hidden objects in early infancy (Diamond, 1990; Johnson, 1995; Wiebe, Fang, Johnson, James, & Espy, 2014). However, most research on EF focuses on sustained attention and the foundational components of EF during preschool and early school years (e.g., Garon et al., 2008), which reflects researchers' attempts to understand the manifestations of EF during a period of rapid development in EF. However, as previously noted, EF development is protracted into adolescence or early adulthood, and behavioral performance on EF tasks continues to improve across the adolescent years.

The protracted development of EF poses a challenge for understanding the effects of MSDP on EF, as there are nonlinear and variable developmental trajectories for some of the components of EF over time (Anderson, 2002; Best & Miller, 2010). For example, the development of inhibitory control shows large improvements across the preschool years, and modest, linear improvements during adolescence, whereas for working memory, development is linear from preschool through adolescence. The developmental trajectory for set-shifting is more complex. Age-related improvements in set-shifting continue throughout adolescence, but the ability to successfully shift among tasks also occurs through the development of other processes, such as metacognition (Best & Miller, 2010). There are multiple detailed papers that outline theories and frameworks for understanding the development EF (we direct the reader to Best & Miller, 2010; Diamond, 2006; Garon et al., 2008; Munakata, 2001; Posner & Rothbart, 2007; Zelazo et al., 2003). From these theories, we can extract a message that is particularly relevant to the current review: much of the story of the effects of MSDP on EF is lost by focusing on one developmental period. Thus, in order to provide a comprehensive picture of the effects of MSDP on EF, the present review considers the literature for each developmental period from infancy through adolescence.

State of the Literature

Existing reviews describe the effects of MSDP on child behavioral and neurocognitive outcomes (e.g., Clifford, Lang, & Chen, 2012; Ernst, Moolchan, & Robinson, 2001; Hermann, King, & Weitzman, 2008; Huizink & Mulder, 2006; Knopik, 2009; Lassen & Oei, 1998; Olds, 1997; Polańska, Jurewicz, & Hanke, 2015; Weitzman, Byrd, Aligne, & Moss, 2002), but a nuanced review of the literature on the effects of MSDP on child EF across development is lacking. EF does not entirely overlap with other neurocognitive constructs (e.g., Arffa, 2007). Therefore, scientific evidence associated with other neurocognitive constructs may not generalize to EF, and findings of an effect of MSDP on a single EF component, skill, or measure may not extend to other measures of EF (Jones et al., 2016; Toplak et al., 2013). Similarly, reviews that include limited studies of EF at isolated points in development may not generalize to different developmental periods. As such, the objectives of the current review are threefold. First, we aim to provide a comprehensive review of the literature on the relationship between MSDP and offspring EF from infancy to adolescence (see Table 1). For reviews specific to EF or its development, we direct the reader to excellent review by Best and Miller (2010). In the current review, we present the available knowledge on the association between MSDP and EF by developmental period. To accomplish this, we focus on the links between MSDP and the most commonly assessed components of EF (i.e., inhibitory control, set-shifting, and working memory). However, we

https://doi.org/10.1017/S0954579417001687 Published online by Cambridge University Press

Table 1. *Studies of maternal smoking during pregnancy and child executive function*

Reference	Sample Size & Age	Measure of Prenatal Exposure	Relevant Measure(s)	Domain(s) of EF Measured[a]	Brief Results (Exposed Children)	Strengths	Limitations
General Review and Brain Development							
Infancy/Toddlerhood (Birth–2 years)							
Chang et al., 2016	$N = 139$; 1 week–4 months	Maternal self-report on Substance Abuse Subtle Screening Inventory	Quantitative neurologic examination; diffusor tensor imaging	Brain study; not specific to EF	Lower fractional anisotropy in the anterior corona radiata of girls; lower axial diffusion in thalamus & internal capsule	Evaluated sex differences; longitudinal design	Potential skewedness of developmental trajectories; group differences in stability of social circumstances & stress may contribute to epigenetic reprogramming of fetal brain; exclusion of mothers with clinical depression may limit generalizability
Ekblad et al., 2010	$N = 232$; prenatal–2 years	Maternal self-report on questionnaire	Brain ultrasound examinations; head circumference; MRI	Brain study; not specific to EF	Smaller frontal lobes & cerebella	Detailed MRI analysis & assessment of brain volumes; rigorous control for potential confounds	Limited generalizability to full-term infants
Espy et al., 2011	$N = 304$; prenatal–1 month	Maternal self-report using structured TLFB method at 16, 28, & 40 weeks of pregnancy; biochemical measure of urine samples	Neonatal Temperament Assessment	Attention/orientation[a]	Poorer attention than controls 2 days postpartum; groups did not differ in attention at 4 weeks of age	Prospective, longitudinal design; demographic similarity among smoking & nonsmoking mothers; polysubstance use exclusion criteria	Possible ceiling effect in negative emotionality for MSDP-exposed neonates; strict exclusion criteria resulted in fewer heavier & more persistent smokers
Gaultney et al., 2005	$N = 63$; 6 & 9 months	Maternal self-report; maternal urine tests (during pregnancy & at birth); child urine & meconium analyses	Fagan Test of Infant Intelligence	Attention	Less focused attention during a novelty preference task; dosage effects at 9 months	Prospective, longitudinal design	Limiting sample to full-term infants may have excluded those with least effects of exposure; results tentative due to small sample size
Law et al., 2003	$N = 56$; 1–2 days old	Maternal self-report using TLFB; salivary cotinine	NICU Network Neurobehavioral Scale; Neonatal Behavioral Assessment Scale	Neurobehavioral functioning	More excitable & hypertonic; required increased handling; presented with stress/ abstinence signs in central nervous system	Prospective design; smoking & nonsmoking groups comparable on demographic & medical factors; findings not confounded by infant passive inhalation of 2nd-hand smoke	Maternal salivary cotinine only reflects recent cigarette use

Table 1 (*cont.*)

Reference	Sample Size & Age	Measure of Prenatal Exposure	Relevant Measure(s)	Domain(s) of EF Measured[a]	Brief Results (Exposed Children)	Strengths	Limitations
Richardson et al., 1989	$N = 373$; prenatal–24 hr	Maternal self-report at months 4 & 7 of pregnancy; 24 hr after delivery	Neonatal Behavioral Assessment Scale	Response decrement to visual, auditory, & tactile stimuli; irritability, self-quieting, & consolability; visual & auditory responsiveness to inanimate & animate stimuli (habituation); motor maturity; primitive reflexes	Altered habituation specific to 3rd trimester exposure	Prospective design; large sample size; polysubstance use exclusion criteria; standardized examination timeline	Exclusion of women >5 months pregnant at 1st prenatal visit eliminated those who had no prenatal care or began care late; tobacco use as categorical variable
Roza et al., 2007	$N = 7{,}042$; fetuses assessed early, mid, & late pregnancy	Maternal self-report in early, mid, & late pregnancy; categorized as "no," "until pregnancy was known," or "continued during pregnancy"	Head circumference, biparietal diameter; transcerebellar diameter, atrial width of lateral ventricles measured by ultrasound	Brain study; not specific to EF	Smaller head circumference, biparietal diameter, atrial width of lateral ventricle, & transcerebellar diameter throughout pregnancy	Prospective, longitudinal design; large sample size	Missingness in ultrasound data may not be random; growth variation before 1st measurement is 0, cannot measure MSDP effects on fetal growth early in pregnancy
Wiebe et al., 2014	$N = 218$; 6 months	Month-by-month maternal self-report of number of cigarettes smoked/day using a modified TLFB method at 14 weeks' gestation, 28 weeks' gestation, & delivery; maternal cotinine via urine	Arm restraint task; visual delayed response task; novel object habituation task; Fagan Test of Infant Intelligence	Emotion regulation in response to moderate frustration; reactivity; working memory; attention & dishabituation; novelty preference	More reactive while restrained & immediately following restraint; less focused attention	Prospective design; use of propensity scores to control for confounding risk factors	Sample at high sociodemographic risk may limit generalizability; observational measures of distress precludes separation of emotional reactivity & regulation
Willoughby et al., 2007	$N = 454$; 6–8 months	Retrospective maternal self-report of number of cigarettes smoked/day across trimesters	Adaptation of the Infant Behavior Record; Toy Reach Procedure	Attention; reactivity; irritability; stimulus approach; inhibition[a]	Boys had lower observer-rated attention than controls	Large, epidemiologically derived sample; use of propensity scores; infant behavior assessed in natural setting	Exclusion of infants for whom matched comparison could not be located; postnatal exposure not measured
Early Childhood (3–6 years)							
Chang et al., 2012	$N = 50$; 3–4 years	Maternal self-report of any prenatal cigarette use	MRI	Brain study; not specific to EF[a]	Subclinical abnormalities in glial development & regionally specific changes in other neurometabolites; greater alterations in girls	Strict exclusion criteria; examination of sex differences	Group differences in socioeconomic status, maternal IQ

Clark et al., 2016	$N = 296$; 5 years	Prospective, repeated maternal self-report interviews across prenatal & postpartum periods; bioassays of cotinine from urine samples	Nebraska barnyard; go/no-go task	Executive control (memory, inhibition)[a]	Poorer performance on memory & inhibition tasks	Prospective, population-based birth cohort study; repeated measures of MSDP	Lack of control for some confounds (e.g., parental IQ)
Daseking et al., 2015	$N = 71$; 5 years	Maternal self-report of number of cigarettes smoked/day	Behavior Rating Inventory of Executive Function—Preschool Edition	Inhibition; set-shifting; emotional control; working memory; plan/organize; EF composite	Poorer parent-rated inhibition & lower scores on general EF composite	Multiple raters of EF; multiple aspects of EF assessed	Sample size precluded multivariate analyses; did not examine 2nd-hand smoke exposure
El Marroun et al., 2014	$N = 226$; 6–8 years	Prospective maternal self-report; number of cigarettes smoked/day	MRI, Freesurfer Image Analysis (cortical reconstruction & volumetric segmentation)	Brain study; not specific to EF	Smaller brain volumes & cortical gray & white matter volumes; thinner superior frontal, superior parietal, lateral occipital, & precentral cortices	Prospective design; large sample size	Did not examine postnatal smoke exposure
Fried et al., 1992	$N = 126$; 6 years	Maternal self-report of number of cigarettes smoked/day during each trimester	Gordon Diagnostic System	Impulsivity; sustained attention[a]	A dose–response association between child's impulsive responding & levels of maternal smoking	Explored dose–response associations	Lack of control for potential postnatal confounds
Julvez et al., 2007	$N = 420$; 4 years	Maternal self-report (3rd trimester) of number of cigarettes smoked/day	McCarthy Scales of Children's Abilities	EF (authors do not specify constructs); working memory[a]	Poorer observer-evaluated working memory & EF	Population-based birth cohort study; repeated prospective surveys of parental smoking habits; large sample size	Lack of control for important covariates
Kristjansson et al., 1989	$N = 79$; 4–7 years	Nicotine score derived from multiplying maternal self-report of number of cigarettes smoked/day by nicotine content of brand used	Visual vigilance task (modified from CPT, auditory vigilance task)	Sustained attention (auditory & visual commission & omission errors)[a]	More errors of auditory commission; visual commission errors approached statistical significance	Low-risk sample (probability of detecting subtle effects enhanced)	Crude measure of environmental smoke exposure
Leech et al., 1999	$N = 608$; 6–7 years	Retrospective maternal self-report of usual no. of cigarettes smoked/day	CPT	Sustained attention (auditory & visual commission & omission errors)[a]	More errors of omission, but not commission, specific to 2nd & 3rd trimester exposure	Large sample size; controlled for postnatal environmental factors	Disadvantages of CPT measure (potential ceiling effects, single stimulus, types of commission errors, no reaction time)

Table 1 (*cont.*)

Reference	Sample Size & Age	Measure of Prenatal Exposure	Relevant Measure(s)	Domain(s) of EF Measured[a]	Brief Results (Exposed Children)	Strengths	Limitations
Noland et al., 2005	$N = 330$; 4 years	Maternal self-report; meconium assay	CPT for Preschoolers; picture deletion task for preschoolers (both modified); vigilance task	Selective attention	Greater commission errors	Prospective design; large sample size	Multiple exposures
Streissguth et al., 1984	$N = 452$; 4 years	Nicotine score derived from multiplying maternal report of no. of cigarettes smoked/day by nicotine content of brand used	Vigilance task	Attention (errors of omission, commission; orientation to stimulus)[a]	More attentional errors; oriented to target stimulus less frequently	Large sample size; multiple measures of attention	Multiple exposures; observer-rated attention
Wiebe et al., 2015	$N = 151$; 3 years	See Wiebe et al., 2014	Big-little Stroop task; preschool go/no-go; computerized shape school; Nebraska barnyard; snack delay; goody shelf	Inhibitory control (cool, hot); working memory	Poorer hot inhibitory control	Prospective sample; EF measurement; latent variable approach	Unmeasured confounding; power
			Middle Childhood (7–11 years)				
Boucher et al., 2014	$N = 186$; 11 years	Maternal self-report (yes/no), retrospective qualifications	Go/no-go; EEG	Response inhibition	Amplitude reductions in N2 & P3 components	Large sample size	Reliability of retrospective qualification of MSDP 10 years after delivery; yes/no qualification; no measure of parental psychopathology
Cornelius et al., 2001	$N = 593$; 10 years	Maternal self-report of no. of cigarettes smoked/day/trimester	Wisconsin Card Sort Task; Stroop; Trail Making Test; Pediatric Assessment of Cognitive Efficiency	Set-shifting; inhibitory control; sustained attention[a]	Increased perseverative responses on Wisconsin card sorting task	Assessed multiple components of EF	Generalizations of findings to higher socioeconomic status populations; potential underreporting of MSDP
Fried et al., 1998	$N = 131$; 9–12 years	Nicotine score derived by multiplying daily average of no. of cigarettes smoked by nicotine content of brand specified	Auditory working memory; Category Test; Gordon delay task; Gordon vigilance task	Working memory sentences & Gordon vigilance task; abstract reasoning & mental flexibility; impulsivity (noninhibited responding); sustained attention[a]	Poorer performance on auditory tasks (fluency & working memory)	Prospective design; assessed multiple components of EF; control for potential postnatal confounds (e.g., mother personality, home environment)	Multiple exposures

Huijbregts et al., 2008	$N = 40$; 8 years	Retrospective maternal self-report of no. of cigarettes smoked/day	Sustained attention dots task; delay frustration task	Sustained attention/ inhibitory control (cool); delay frustration (hot)	Poorer delay frustration	Hot vs. cool distinction	Lack of control for plausible confounds that may explain hot vs. cool findings (e.g., parental IQ, education); cool inhibitory control also elicited in hot EF measure
Naeye & Peters, 1984	$N = 9024$; 7 years	Prospective maternal self-report of no. of cigarettes smoked/ day	Duration of attention span	Attention span[a]	Shorter attention spans	Large sample; prospective design	Lack of control for important covariates; tester-rated attention
				Adolescence (12–18 years)			
Bennett (2009)	$N = 18$; 12 years	Maternal self-report of frequency & amount of cigarette use via semistructured interview prenatally or at time of birth (group assignment based on yes/no criteria)	fMRI; go/no go	Response inhibition	Greater activation in relatively large & diverse set of brain regions (left frontal, right occipital, bilateral temporal, parietal)	Rigorous control for environmental risks	Not powered to test for sex differences; increased neonatal health problems & environmental risks may limit generalizability; yes/no smoking criteria; limited generalization across racial or ethnic groups (African American sample)
Bennett et al., 2013	$N = 18$; 12 years	See Bennett et al., 2009	fMRI, N-back task	Working memory	Greater activation in inferior parietal region, right parietal lobe, right inferior frontal gyrus, & left middle frontal gyrus	Rigorous control for environmental risks	Modest sample size; not powered to test for sex effects; potentially limited generalization across modalities, memory tasks, racial or ethnic groups (African American sample)
Fried & Watkinson, 2000	$N = 146$; 9–12 years	See Fried & Watkinson, 1998	Trail Making Test	Set-shifting[a]	No group differences	Exploration of postnatal exposure effects	Multiple exposures
Fried & Watkinson, 2001	$N = 152$; 13–16 years	See Fried & Watkinson, 1998	CPT; Wisconsin Card Sorting Test; Stroop; Encode/Retain Memory Battery	Sustained attention (errors of omission, commission); set-shifting; inhibitory control; encode/retain (consistent with working memory)	For younger subjects only, noninhibited responding on CPT; more problems with encode/retain	Multiple components & measures of EF	Multiple exposures; lack of control for attentional deficits in parents

Table 1 (*cont.*)

Reference	Sample Size & Age	Measure of Prenatal Exposure	Relevant Measure(s)	Domain(s) of EF Measured[a]	Brief Results (Exposed Children)	Strengths	Limitations
Fried et al., 2003	$N = 145$; 13–16 years	See Fried et al., 1998	Wisconsin Card Sorting Test; Stroop Test	Set-shifting; inhibitory control[a]	No group differences	Multiple components of EF assessed	Multiple exposures
Kafouri et al., 2009	$N = 503$; 12–18 years	Maternal self-report of smoking ≥1 cigarette/day during 2nd trimester	Self-ordered pointing task; Ruff 2- & 7-Selective Attention Test; Stroop Test	Working memory; selective attention; inhibitory control[a]	No group differences	Multiple components of EF assessed; matched controls	Possible underreporting of MSDP
Liu et al., 2013	$N = 40$; 13–15 years	Maternal self-report	Conner's Continuous Performance Test II; structural MRI; Freesurfer (brain morphology)	Impulsivity (commission errors)	Those with more impulsivity had greater thalamic volumes	Matched controls	Imaging methods solely assessed brain volume, not reflective of cellular makeup of brain structures studied; dichotomized index of exposure
Piper & Corbett, 2012	$N = 357$; 5–18 years	Maternal self-report of no. of cigarettes smoked/day	Parent-report on Behavioral Rating Inventory of Executive Function	Global Executive Composite; Metacognition & Behavioral Regulation Indices	High exposure children had more problems with global composite score, metacognition index & initiate, plan/organize, & monitor scales; children with low exposure had more difficulties with Inhibit Scale than high exposure children; for emotional control, reverse was true	Large sample size; multiple components of EF assessed	Wide age range
			Animal Models				
Bryden et al., 2016	$N = 16$ male Long Evans rat pups	Nicotine added in increasing dosages across 3 weeks to 5 female rats' only source of drinking water (mothers consumed average of 5.93 mg/kg/day of nicotine during pregnancy)	Nose-poking task (go/no go); surgery & single unit recording	Inhibitory control	Poorer inhibitory control (i.e., more premature responses & errors on stop trials); disruptions in neural signals related to response encoding & conflict monitoring	Method of administration reduces potential stress effects	Did not explore sex effects

Schneider et al., 2011	$N = 73$ Lister Hooded rat pups	Nicotine added in increasing dosages across 3 weeks to 19 female rats' only source of drinking water (final concentration = 0.06 mg/ml of nicotine throughout pregnancy)	5-CSRTT; delay-discounting task; gene expression analysis	Sustained attention; impulsivity (noninhibited responding)	Problems with sustained attention & impulsivity; increase in *DRD5* mRNA expression in striatum	Multiple aspects of EF assessed; genetic variance controlled	Effects of prenatal exposure to nicotine cannot be distinguished from potential effects of dehydration & stress; effects may have involved learning process not specific to attentional tasks
Zhu et al., 2012	$N = 8$–12 C57BL/6 mice pups for each analysis	0.05, 0.1, or 0.2 mg/ml nicotine dissolved in 2% saccharin	Photobeam activity system; high-performance liquid chromatography; stereological estimation of regional brain volume	Spontaneous locomotor activity	Increased locomotor activity; reduced volume & radial thickness in cingulate cortex & decreased dopamine turnover in frontal cortex	Use of oral nicotine exposure reduces potential stress effects; inclusion of two control groups; explored sex effects	Cannot distinguish between intracellular & extracellular dopamine in frontal cortex
Genetically Informed Designs							
Micalizzi et al., in press	$N = 173$; 7–16 years	Retrospective maternal self-report; timing of exposure & no. of cigarettes smoked/day	Color-Word Interference Test	Inhibitory control	No differences following control for genetic & environmental confounds	Genetically informed; inclusion of detailed covariates (particularly maternal inhibitory control)	Unmeasured confounds that differ between siblings; did not include paternal confounds
Wiebe et al., 2009	$N = 98$; 4 weeks; $N = 58$; 4 years (cross sectional)	See Wiebe et al., 2014 for 4 weeks; parents completed a brief interview about smoking during pregnancy (4 years)	Neonatal Temperament Assessment (4 weeks); Preschool Trail Making Test (4 years); buccal samples	Attention-orientation (4 weeks); inhibitory control, set-shifting (4 years)[a]	No differences in attentive behavior between children with & without A1 allele at 4 weeks; increased inhibitory & shifting errors for children with A+ genotype at age 4	Multiple components of EF assessed; genetically informed; targeted recruitment & selective enrollment	Exploratory; wide age range in preschool sample

Note: For the purpose of this review, we only focus on the EF constructs reviewed in the text to be concise. CPT, continuous performance task; EF, executive function; fMRI, functional magnetic resonance imaging; MSDP, maternal smoking during pregnancy; TLFB, timeline follow-back.
[a]Studies also include additional measures to assess other constructs.

also present literature on the relationship between MSDP and key components or essential skills to EF (e.g., attention), which are thought to be important targets for intervention programs (Jones et al., 2016). We also consider the links between MSDP and impulsivity, as EF and impulsivity may be antipodes (i.e., impulsivity as executive *dys*function; Bickel, Jarmolowicz, Mueller, Gatchalian, & McClure, 2012). Second, we consider brain-based assessments, animal models, and genetically informed studies in an effort to elucidate plausible pathways of effects. Third, we discuss implications for prevention, intervention, and for future directions.

It is important to present these studies that follow with the note that in the field of MSDP–EF associations, the majority of the prior work that we outline below is primarily from the phenotypic point of view. These prior studies say very little, if anything, about how genetic factors may influence the reported associations between MSDP and offspring EF (discussed in detail below). The few studies that have considered genetic effects are reviewed toward the end of this section.

Offspring brain development relevant to MSDP and EF

MSDP has been suggested to modify genetically programmed fetal brain development (for a review, see Ekblad, Korkeila, & Lehtonen, 2015) that can impact later EF. Nicotine-induced alterations exert changes to cellular communication, neuronal pathfinding, mitosis, and synaptogenesis, among other key molecular and functional targets (for a review, see Slotkin, 2004; Wessler, Kirkpatrick, & Racké, 1998). Such alterations are hypothesized to be the primary mediators underlying the links between MSDP and neurobehavioral problems in offspring (e.g., Bublitz & Stroud, 2012). Further, behavioral gains in EF are consistent with development of the frontal lobe and myelination of prefrontal connections, processes that are protracted into adolescence (Anderson, 2002). As such, behavioral manifestations of brain alterations that result from exposure to MSDP may not emerge until the compromised area is recruited to support these behaviors later in development as trajectories of exposed and nonexposed children diverge (Goldman, 1974; Wiebe et al., 2015). That is, later developing EF skills may fail to develop normally due to early perturbation (Maurer, Monloch, & Lewis, 2007). Thus, at question is whether the impact of prenatal exposure to MSDP endures to compromise later prefrontal area development and in turn EF. This is an open empirical question, but it underscores the need for developmental designs to identify the potentially delayed emergence of such problems. We also review the literature on the links between MSDP and child brain development relevant to EF by developmental period as a preliminary step in evaluating the state of knowledge and identifying areas requiring future research attention.

MSDP and EF across development

Fetal period and birth. Notable neurobehavioral and physical precursors of later complex neurocognitive functioning are apparent in exposed offspring prior to and shortly after birth. MSDP is related to reduced fetal movement and variation in heart rate, disruptions in fetal habituation, and less reactivity during nonstress tests (Coppens, Vindla, James, & Sahota, 2001; Gingras & O'Donnell, 1998; Leader & Bennett, 1995; Oncken, Kranzler, O'Malley, Gendreau, & Campbell, 2002; Zeskind & Gingras, 2006). Atypical arousal patterns are characteristic of later neurocognitive abnormalities in children (e.g., Powell & Voeller, 2004) and may serve as early risk markers for subsequent adverse developmental outcomes (Zeskind & Gingras, 2006). Physical risk markers are also present. There is a dose–response relationship between MSDP and birth weight, with roughly a 5% reduction in relative birth weight per pack of cigarettes smoked per day (Kramer et al., 1990). Even when genetic effects are controlled for, the association between MSDP and low birth weight remains significant, suggesting a possible causal link between MSDP and birth weight (e.g., Knopik, Marceau, Palmer, Smith, & Heath, 2016; Kuja-Halkola, D'Onofrio, Iliadou, Langstrom, & Lichtenstein, 2010). Of note, low birth weight is one of the strongest predictors of future problems. For example, low birth weight is associated with poorer academic achievement, worse job performance, disruptive behaviors, and cognitive problems (for a review, see Chatterji, Lahiri, & Kim, 2014).

Infancy/toddlerhood (birth–2 years). There is evidence for atypical neurobehavior and poorer attention in infants who were exposed to MSDP. Exposed neonates were more excitable and hypertonic, required increased handling, presented with stress/abstinence signs in the central nervous system (Law et al., 2003), and showed altered habituation specific to third trimester MSDP exposure (Richardson, Day, & Taylor, 1989) 1 to 2 days after birth. Infants exhibited less orientation to and attentive tracking of auditory and visual stimuli than controls 2 days postpartum, but the groups did not differ in their attention at 4 weeks of age (Espy et al., 2011). These children exhibited a developmental "catch-up" to their peers, with an average growth rate more rapid than nonexposed neonates. The adverse effects of MSDP on attention persist later in infancy, as 6- to 8-month-old exposed boys had lower observer-rated attention than controls during a home visit (Willoughby, Greenberg, Blair, & Stifter, 2007). Similarly, 6- and 9-month-olds exposed to MSDP exhibited less focused attention than their nonexposed peers during a novelty preference task (Gaultney, Gingras, Martin, & DeBrule, 2005; Wiebe et al., 2014).

To our knowledge, no studies have examined the structural and functional neural moderators of the effects of MSDP on the developmental antecedents of EF in infants exposed to MSDP. However, assessments of early brain development that are not specific to EF do highlight differences between exposed and nonexposed infants. Although these studies are not specific to EF, they are included here to provide a comprehensive picture of links between MSDP and early brain development and to inform future research in this area. Fetuses exposed to MSDP had smaller head circumferences

https://doi.org/10.1017/S0954579417001687 Published online by Cambridge University Press

than unexposed fetuses, suggesting a global reduction in brain volumes (Roza et al., 2007). However, preterm infants exposed to MSDP had significantly smaller frontal lobes and cerebella (involved in motor control, language, and attention; Bublitz & Stroud, 2012), despite having typical head growth during the first 2 years of life (Ekblad et al., 2010). This evidence suggests that these brain areas may be vulnerable to the effects of MSDP and that regional volumetric changes can occur even in the absence of decreased head circumferences (Ekblad et al., 2010). This is an important consideration for identifying at-risk children, as it may not always be the case that head circumference is a marker of insult to brain development (Ekblad et al., 2010).

Differences in white matter development in infants exposed to MSDP have also been found. Diffusion tensor imaging of infants exposed to MSDP revealed lower fractional anisotropy in the female anterior corona radiata suggesting less coherent axons in the tract, potentially resulting from greater dendritic branching and spine densities, delayed myelination, and malformed axons (Chang et al., 2016). This finding, coupled with prior evidence for subclinical abnormalities in glial development and regionally specific changes in other neurometabolites related to MSDP in preschoolers (Chang et al., 2012) and reduced expression of myelin genes in periadolescent female rats with prenatal exposure (Cao et al., 2013), suggests that prenatal exposure to MSDP may result in epigenetic effects, such as reduced myelin gene expression and delayed white matter development in the anterior corona radiata (Chang et al., 2016). Further, there was lower axial diffusivity in the thalamus and posterior limb internal capsule of MSDP-exposed infants, potentially resulting from reduced myelination between compacted axons or greater dendritic branching and spine densities, as well as epigenetic alterations (e.g., upregulation of histone methylation complexes; Jung et al., 2016; Mychasiuk, Muhammad, Gibb, & Kolb, 2013). Taken together, these findings suggest that MSDP may alter white matter maturation in sex- and regionally specific manners (Chang et al., 2016) and result in epigenetic effects (Knopik, Maccani, Francazio, & McGeary, 2012).

There is a clear gap in studies of EF in children exposed to MSDP from 10 to 36 months of age. More advanced EF skills, such as holding representations in mind, inhibiting responses based on a rule held in mind, and suppressing motivated motor responses, build on the rudimentary EF skills across the first 3 years of life (Garon et al., 2008). Thus, this is a critical period in EF development. During periods of rapid developmental change, problematic behavioral manifestations resulting from early insult to EF processes may become increasingly apparent. Consequently, research attention is required to characterize MSDP-related EF problems during this period.

Taken together, the literature suggests that difficulties in the early developmental antecedents of EF (i.e., neurobehavior and attention) are potentially adversely affected by MSDP and that these issues persist across infancy. Of critical importance is the consideration that the negative impact of MSDP on EF in infancy may extend beyond the direct adverse effects of exposure. That is, children exposed to MSDP may elicit nonoptimal reactions from individuals in their environment through their own negative behaviors that further exacerbate the risk. For example, a child who is less attentive in infancy may elicit negative reactions from caregivers, creating a negative feedback loop that further impairs the child's development (Wiebe et al., 2014). It should be noted, however, that parent and child behavior is reciprocal, with each member of the dyad shaping the interaction (e.g., Micalizzi, Wang, & Saudino, 2015). Therefore, it is essential to consider the contributions of both dyadic partners to shaping the bidirectional interactions that may promote or hinder child development.

Early childhood (3–6 years). As previously noted, substantial development in attention occurs across early childhood. Consequently, it is important to assess the effects of MSDP on attention during this period. The continuous performance task (CPT) is a widely used measure of sustained attention that requires participants to stay vigilant to the serial presentation of a stimulus (or stimuli) over time and respond (e.g., press a button) when a particular stimulus is present and withhold the response when nontarget stimuli appear (Fried, Watkinson, & Gray, 1992). Commission errors on the CPT (i.e., false alarms) are thought to reflect impulsive (i.e., noninhibited) responding and poorer attention resulting from increased overall activity, whereas omission errors (i.e., misses) are thought to reflect inattentiveness (Fried et al., 1992). Four-year-olds exposed to MSDP made more attentional errors (i.e., errors of omission, commission, and the ratio of correct responses to total responses) in a visual vigilance paradigm, were oriented to the target stimulus less frequently compared to nonexposed children (Streissguth et al., 1984), and made more commission errors on the CPT and a visual search task (Noland et al., 2005). Four- to 7-year-old children exposed to MSDP made more errors of auditory commission, whereas visual commission errors approached statistical significance (Kristjansson, Fried, & Watkinson, 1989). Similarly, 6-year-old exposed children demonstrated more errors of impulsivity during a vigilance task (Fried et al., 1992) and made more errors of omission, but not commission, specific to second- and third-trimester exposure (Leech, Richardson, Goldschmidt, & Day, 1999).

Three-year-olds who were exposed to MSDP had lower levels of hot EF, assessed with tasks requiring children to wait for appealing snacks and toys (i.e., those that are highly motivating). MSDP was not associated with cool EF in the same sample (Wiebe et al., 2015). Exposed 4-year-olds had poorer tester-evaluated working memory and other components of EF, although the authors do not identify which (Julvez et al., 2007). Similarly, 5-year-olds had poorer parent-rated inhibition and lower scores on a general EF composite comprising inhibition, shifting, emotional control, working memory, and planning/organizing (Daseking, Petermann,

https://doi.org/10.1017/S0954579417001687 Published online by Cambridge University Press

Tischler, & Waldmann, 2015) and had poorer memory and inhibition (Clark, Espy, & Wakschlag, 2016).

To our knowledge, only one study has assessed the brain morphology of children exposed to MSDP during early childhood. Exposed children ages 6 to 8 years had smaller brain volumes and cortical gray and white matter volumes, as well as thinner superior frontal, superior parietal, lateral occipital, and precentral cortices relative to controls (El Marroun et al., 2014). Although these differences were not examined in the context of EF, they do provide evidence that the early volumetric changes related to MSDP observed in infancy (Ekblad et al., 2010) are not compensated by early childhood neuroplasticity (Huttenlocher, 2002).

Taken together, these findings suggest that MSDP may also negatively impact EF in early childhood. Given the rapid development of sustained attention across these early years, poorer attention may reflect a problem with the anterior attention subsystem exerting control over the orienting system, but this is an open empirical question that requires future research attention to elucidate this as a possible pathway of the effect of MSDP on EF. The current literature on the early childhood EF outcomes of children exposed to MSDP is primarily limited to sustained attention. The recent advent of developmentally appropriate measures of EF (e.g., NIH Toolbox Early Childhood Cognitive Battery; Zelazo et al., 2013) permits the assessment of all facets of EF during early childhood. Therefore, this is a call-to-action for future studies of the effects of MSDP on EF during this period to include measures of all foundational components of EF (i.e., set-shifting, inhibitory control, and working memory) to illustrate how widespread the adverse effects of MSDP are, as exposure may impact some, but not all, components or measures of EF (Toplak et al., 2013).

Middle childhood (7–11 years). Although substantial growth in EF occurs in early childhood, typically developing children become increasingly adept at leveraging EF skills across middle childhood. Children exposed to MSDP, however, exhibit clear difficulties relative to controls. Eight-year-old children exposed to MSDP had problems with hot but not cool inhibitory control (Huijbregts, Warren, de Sonneville, & Swaab-Barneveld, 2008). This is perhaps not surprising, as children exposed to MSDP are more likely to be diagnosed with attention-deficit/hyperactivity disorder (ADHD; see Langley, Rice, Van den Bree, & Thapar, 2005, for a review) and hot inhibitory control problems are commonly observed in this population (e.g., Yang et al., 2011). Ten-year-olds demonstrated increased perseverative responses in a set-shifting card-sort task, signifying less flexible problem solving (i.e., "cognitive rigidity" in persisting with an incorrect response and failure to attend to and learn from feedback; Cornelius, Ryan, Day, Goldschmidt, & Willford, 2001). Errors of commission were related to third-trimester tobacco exposure, but the association was attenuated when current maternal smoking was taken into account, highlighting the adverse effects of current secondhand exposure. Consistent with Huijbregts et al. (2008), cool EF was not related to MSDP, providing additional support for the notion that emotionally neutral EF may not be adversely affected by MSDP in middle childhood. In addition, sustained attention was not related to MSDP. The lack of an association may indicate a developmental shift away from the sustained attention deficits observed in early childhood, but is more plausibly a result of methodological considerations, as another assessment revealed that MSDP-exposed 7-year-olds had lower attention spans than their nonexposed peers (Naeye & Peters, 1984). Further, 9- to 12-year-old children exposed to MSDP performed more poorly than their nonexposed peers on auditory working memory (Fried, Watkinson, & Gray, 1998).

To our knowledge, the only study to assess functional brain activation specific to EF during middle childhood in children exposed to MSDP used an event-related potential design to examine the neurophysiological correlates of inhibitory control impairments in 11-year-old children (Boucher et al., 2014). Relative to nonexposed children, exposed children exhibited amplitude reductions in the N2 and P3 components. The no-go N2 component is thought to reflect conflict processes in the anterior cingulate cortex (e.g., Jonkman, Sniedt, & Kemner, 2007), and the no-go P3 component is an index of information processing that occurs when attentional resources are appropriately allocated to inhibit a response and involves regions of the prefrontal cortex (e.g., Smith, Jamadar, Provost, & Michie, 2013). These findings suggest that children exposed to MSDP have impairments in conflict processing and the attentional allocation required to inhibit prepotent responses (Boucher et al., 2014). Conflict is particularly relevant to EF. For example, inhibitory control requires overcoming conflict between a dominant and subdominant response. Similarly, set-shifting involves shifting to a new mental set that conflicts in some way with an existing mental set. As such, problems with conflict processing may be a pathway of the effect of MSDP on child EF.

Taken together, these results indicate that children exposed to MSDP exhibit hot inhibitory control, set-shifting, sustained attention, and conflict processing problems in middle childhood. Working memory was compromised in the only study that assessed it. It is important to note, however, that findings on auditory working memory may not extend to nonauditory working memory (e.g., visual working memory; Gevins & Cutillo, 1993). Children exposed to MSDP process auditory information differently than their nonexposed peers (e.g., Jacobsen et al., 2007). Therefore, observed MSDP effects on auditory working memory may reflect more basic auditory processing differences than a true EF problem, but that is an open empirical question.

These findings have important implications for MSDP-exposed children in formal schooling, where good EF promotes skills that are critically important to achievement. Teachers report that the most important determinants of school success are those abilities that are governed by EF: sitting still, paying attention, and following rules (McClelland et al., 2007). As such, children who have poorer EF as a result of exposure

https://doi.org/10.1017/S0954579417001687 Published online by Cambridge University Press

to MSDP may struggle in the classroom due to challenges with both behavioral regulation and academic content.

Adolescence (12–18 years). Behavioral gains in EF persist throughout adolescence in typically developing children, mirroring the development of frontal areas of the brain (e.g., Anderson, 2002). Children (5 to 18 years old) who were exposed to 10+ cigarettes per day had more problems with parent ratings of EF (including a global composite score, metacognition index, and initiate, plan/organize, and monitor scales) than nonexposed children (Piper & Corbett, 2012). For the behavioral regulation index, children with low nicotine exposure (i.e., 1–9 cigarettes per day) had significantly more difficulties on the inhibit scale than high exposure (i.e., 10+ cigarettes per day) children, whereas for emotional control, the reverse was true. In 13- to 16-year-olds, children exposed to MSDP had more problems with encoding/retaining (i.e., a construct that is consistent with working memory). For younger children only, noninhibited responding on the CPT was also related to MSDP (Fried & Watkinson, 2001). These findings suggest that there may be a developmental delay in inhibition for children who were exposed to MSDP, but that eventually, they "catch up" to their nonexposed peers, mirroring the developmental pattern of attention in early infancy (Espy et al., 2011).

However, not all studies find links between MSDP and EF. No group differences were observed in 9- to 12-year-olds during a set-shifting task once postnatal tobacco exposure was accounted for (Fried & Watkinson, 2000) or for set-shifting and inhibitory control in 13- to 16-year-olds (Fried, Watkinson, & Gray, 2003). Further, working memory, selective attention, inhibitory control, and set-shifting were not impaired in 12- to 18-year olds exposed to MSDP. The authors acknowledge that other key group differences between exposed and nonexposed children, such as cortical thickness and corpus callosum volume should preclude the interpretation that MSDP does not have adverse consequences for cognitive abilities (Kafouri et al., 2009). Nonetheless, these null findings highlight potentially confounding influences (e.g., postnatal secondhand smoke exposure) on the relation between MSDP and child outcomes and underscore the importance of accounting for these in design considerations.

Brain imaging of adolescents reveals structural and functional differences between the brains of children exposed to MSDP relative to their nonexposed peers (for a review, see Bublitz & Stroud, 2012). Differences relevant to EF have also been found. Adolescents who were exposed to MSDP and were more impulsive had greater thalamic volumes than their nonexposed counterparts (Liu et al., 2013). The thalamus is interconnected with the prefrontal cortex and basal ganglia and is responsible for integrating incoming sensory information, guiding attentional control, and coordinating behavioral responses (Newman, 1995). Consequently, the association between impulsivity and thalamic volume in this population is suggestive of a liability for top-down control problems (Liu et al., 2013).

Functional differences between exposed and nonexposed adolescents have also been observed. Twelve-year-olds who were exposed to MSDP showed greater and more diffuse activation across diverse regions (e.g., left frontal, right occipital, bilateral temporal, and parietal regions) in a go/no-go response inhibition task. Conversely, nonexposed children activated the cerebellum, a pattern that is indicative of better attention and motor preparation (Bennett et al., 2009). During a working memory task, adolescents who were exposed to MSDP showed greater activation in the inferior parietal region, right parietal lobe, right inferior frontal gyrus, and the left middle frontal gyrus, relative to unexposed children, who exhibited greater activation in inferior, middle, superior frontal regions, right and left inferior frontal gyrus, and the right middle frontal gyrus (Bennett et al., 2013). The activation differences occurred during correct working memory responses, suggesting that diverse brain regions are recruited across the groups when correctly leveraging working memory. The pattern of activation in nonexposed children is consistent with the appropriate developmental shift to increased and more efficient activation of frontal regions and better behavioral performance on working memory tasks. It is possible that, with time, the exposed children would also show more mature, focal brain activation, but that the process is simply delayed. This would be consistent with the behavioral findings of a pattern of developmental delay in attention in exposed children (Espy et al., 2011), but, again, this is an open question.

These studies provide preliminary evidence for structural and functional brain alterations in children exposed to MSDP relative to nonexposed controls, but more work is needed in this area. The components of EF can be dissociated neuroanatomically (Brocki, Fan, & Fossella, 2008). Thus, it is important for future studies to examine structural and functional differences between exposed and nonexposed children across all foundational EF components and periods of development to elucidate precise pathways that may serve as risk biomarkers and targets for intervention and prevention efforts.

Animal models

Rats with intrauterine prenatal nicotine exposure (PNE) exhibit postnatal neurocognitive and behavioral disturbances (e.g., Schneider et al., 2011). Consequently, rodent models are effective for investigating the pathways of MSDP exposure on EF. Rats with PNE displayed poorer inhibitory control (i.e., more premature responses and errors on stop trials) compared to controls in a rodent variant of the go/no-go task (Bryden et al., 2016). Further, exposed rats showed disruptions in neural signals that are related to response encoding and conflict monitoring, key components of inhibitory control, and overall firing in the medial prefrontal cortex (mPFC). There are similarities between the rodent mPFC and the human dorsolateral PFC (DLPFC; Kesner, 2000), potentially implicating this region in humans. Exposed rats exhibited increased locomotor activity, had reduced volume and radial thickness in the cingulate cortex, and had decreased

https://doi.org/10.1017/S0954579417001687 Published online by Cambridge University Press

dopamine turnover (i.e., a condition that may reflect decreased synaptic dopamine) in the frontal cortex relative to controls (Zhu et al., 2012). The cingulate cortex also plays a key role in attentional mechanisms in humans (e.g., alterations in the cingulate cortex are related to ADHD; Makris et al., 2010). If these regions are truly homologous across species, cingulate cortex volume may serve as a biomarker of attentional problems in humans exposed to MSDP.

PNE rats also presented for a delayed ability to learn a task with a high attentional load and had decreased accuracy, increased anticipatory responding, smaller number of earned rewards, and response time variability in the task, suggesting problems with sustained attention and impulsivity (Schneider et al., 2011). Further, there was a small increase in the dopamine receptor D5 (i.e., DRD5) mRNA expression in the striatum of exposed rats (Schneider et al., 2011), a finding that is consistent with molecular genetic studies that implicate dopamine system genes in EF in humans (e.g., Wiebe et al., 2009).

There is no question that animal work is vital to the study of human problems (for a transdisciplinary synthesis, see England et al., 2017). As demonstrated in this review, these animal studies provide valuable information about the effects of MSDP on EF. First, the observed mPFC hypoactivation related to PNE may generate a potential pathway through the DLPFC in humans for behavioral deficits in EF. Second, the cingulate cortex supports attentional mechanisms, indicating a potential biomarker for the attentional problems observed in offspring exposed to MSDP. Third, animal models provide further support for dopaminergic system involvement in the effects of MSDP on offspring outcomes.

There are clear strengths of animal models in terms of, for example, the ability to design studies that incorporate a controlled dose of a specific drug (e.g., nicotine). However, as noted above, the human condition is considerably more complex. In humans, MSDP results in fetal exposure not only to nicotine but also to a large number of other toxic components, such as carbon monoxide, ammonia, nitrogen oxide, lead, and other metals (Huizink & Mulder, 2006). Thus, one should not limit the effects of MSDP in humans to nicotine alone. In addition, the human brain is very different from the rodent brain. The effects of MSDP in humans often show up as higher level cognitive function, which are controlled by the prefrontal cortex (Knopik, 2009). Functional and structural differences in the region of rat brain traditionally considered homologous to the DLPFC in primates suggest that the rat may not have an equivalent region (Preuss, 1995). Therefore, while we can use the evidence of negative effects of prenatal nicotine exposure that we garner from animal work as a guide to narrow our focus on potential effects in humans, we cannot directly extrapolate from animal findings to the complex human condition (Knopik, 2009).

Genetically informed designs

It may be tempting at this point to assume causal effects of MSDP on EF. However, MSDP does not occur independent of other familial risk factors (Ellingson, Goodnight, Van Hulle, Waldman, & D'Onofrio, 2014). In addition to environmental risk, mothers who smoke during pregnancy are also more likely to confer *genetic risk* for poorer functioning to their offspring. For example, if children of mothers who smoke present for EF deficits, such problems may be caused by MSDP in a direct way, but this association is muddied by the fact that mothers who have EF deficits themselves may more commonly smoke during pregnancy. Thus, poor and inconsistent control for covariates, notably heritability, preclude concluding causal effects of MSDP on child outcomes (Knopik, 2009). Studies that account for specific, measured confounds (e.g., socioeconomic status and educational attainment) typically find the relations between MSDP and psychological outcomes attenuated, but still significant. Studies that account for general, unmeasured familial confounds (i.e., genetic and environmental), however, tell a more complex story with potentially causal MSDP effects for some birth (e.g., Knopik, Marceau, Palmer, et al., 2016; Kuja-Halkola, D'Onofrio, Larsson, & Lichtenstein, 2014) and behavioral outcomes (Gaysina et al., 2013, Knopik, Marceau, Bidwell, et al., 2016), and results suggest complete familial confounding for other behavioral and cognitive outcomes (e.g., Ellingson et al., 2014). The reasons for this inconsistent pattern of results are unknown but may be due, in part, to differences in sampling, outcome assessment (e.g., medical registry data vs. lab-based assessments), and MSDP measurement.

As such, genetically informed designs are required to disentangle genetic liability for poor developmental outcomes from true MSDP liability. To our knowledge, the only genetically informed study to assess the links between MSDP and EF found that the accounting for familial confounds fully attenuated the association between MSDP and child and adolescent cool inhibitory control (Micalizzi et al., in press). Although not specific to EF, a similar pattern emerged in two studies of the genetic and environmental influences on the cognitive abilities of MSDP-exposed children. A longitudinal sibling-comparison study (Ellingson et al., 2014) revealed that the links between MSDP and cognitive outcomes (i.e., digit span, math, reading, and receptive vocabulary; reading recognition was the exception) was fully attenuated when controlling for familial confounds. That is, familial factors caused the intergenerational transmission of many, but not all, adverse cognitive outcomes for children exposed to MSDP in early and middle childhood and adolescence. Another genetically informed study of cognitive abilities (i.e., academic achievement and general cognitive ability) found that when controlling for differential MSDP exposure across siblings, there was no significant association between MSDP and academic achievement or general cognitive abilities (Kuja-Halkola et al., 2014). Again, these results contest the notion of causal effects of MSDP on cognitive abilities, and instead suggest that the link is primarily due to familial effects that influence cognitive abilities in both generations. Taken together, these findings suggest that co-occurring vulnerabilities may act as more salient risk factors for some child

https://doi.org/10.1017/S0954579417001687 Published online by Cambridge University Press

outcomes than MSDP and may serve as effective targets for intervention (Micalizzi et al., in press).

Genetic and environmental effects do not occur in isolation, however. Complex interactions between genes and environments (i.e., Gene × Environment interactions [G × E]) shape human development. That is, certain genotypes are more responsive to environmental variation than others, for better or for worse. As for MSDP, it remains unclear whether the effects are the same for all children or if some children are more vulnerable than others, but the limited literature in this area provides preliminary evidence for the latter. A study of the interaction between the dopamine receptor D2 (*DRD2*) *Taq*1A genotype and MSDP in neonates revealed that nonexposed children with the risky A1+ allele (i.e., one that is related to higher levels of novelty seeking; Berman, Ozkaragoz, Young, & Noble, 2002) were more attentive to visual and auditory stimuli relative to those with the A1– allele (Wiebe et al., 2009). In exposed neonates, there were no differences in attentive behavior between children with and without the A1 allele. The authors suggest that MSDP may attenuate the novelty preference in children with the A+ genotype, resulting in no difference from the exposed children with the A1– allele. In the same study using a different sample of preschoolers, the effect of MSDP status was specific to children with the A1+ genotype. That is, children with the A1+ allele made more inhibitory and shifting errors than children with the A1– allele. These findings provide preliminary evidence for G × E interactions in the association between MSDP and EF, and also implicate the dopaminergic system in MSDP–EF links humans. That is, genetic factors may confer susceptibility for, or protection against, EF problems for children exposed to MSDP. This area requires future research attention as it has substantial public health implications; G × E may be used to identify MSDP-exposed individuals who are at risk for developing EF problems.

To our knowledge, this is the only G × E study of MSDP and EF, although there are G × E studies of MSDP and other outcomes, such as ADHD (e.g., Neuman et al., 2007). Further, G × E is not a static question, as the interaction between genes and environments may vary across development. As such, although requisite large sample sizes may pose a challenge for deep phenotyping, genetically informed developmental designs are essential to identify avenues for prevention and intervention.

Discussion

MSDP is linked to EF. However, as has been noted here and elsewhere (e.g., Clifford et al., 2012), the associations between the MSDP and cognitive parameters are not straightforward. Below, we outline trends and gaps in the literature in an effort to elucidate possible pathways of effects and make calls to action for future research.

Pathways of effects

Attention problems. The present review indicates that children exposed to MSDP demonstrate poorer attention than nonexposed children across a wide range of ages and measures. Children who were exposed to MSDP may present for EF problems because they do not adequately engage their attention to meet the demands of such tasks. EF is cognitively taxing, and physiological arousal facilitates EF by activating available attentional resources. For typically developing, nonexposed children in middle childhood, a single bout of physical activity (i.e., induction of physiological arousal) enhances children's immediate EF (Best, 2012). It is unknown whether the positive effects on EF persist past the immediate benefits of the intervention, but nonetheless, future research should explore if these findings extend to children who were exposed to MSDP. If so, this would provide a compelling avenue for a relatively easy, low-cost intervention to enhance EF in this population.

Hot inhibitory control deficits. The three studies that distinguish between hot and cool EF in early and middle childhood found that hot, but not cool, EF was related to MSDP (Cornelius et al., 2001; Huijbregts et al., 2008; Wiebe et al., 2015). Similarly, adolescents with high intrauterine nicotine exposure (i.e., 10+ cigarettes per day) had more problems with emotional control than children with low exposure (i.e., 1–9 cigarettes per day; Piper & Corbett, 2012). This suggests that one pathway of the effects of MSDP for EF may be through emotion and motivation. It should also be noted that, consistent with the well-documented association between MSDP and externalizing behavior problems, conduct problems and hyperactivity–inattention were also more common in children exposed to MSDP (Huijbregts et al., 2008).

Studies that parse EF into hot and cool components may shed light on mixed findings in the MSDP–externalizing behavior problems literature (Wiebe et al., 2015). MSDP has been repeatedly and robustly linked to disruptive behavior disorders such as oppositional defiant disorder and conduct disorder but shows inconsistent associations with ADHD (e.g., Nigg & Breslau, 2007). Motivation and emotion are recognized as core deficits in disruptive behavior disorders (e.g., Matthys, Vanderschuren, & Schutter, 2013). For ADHD, however, motivation and emotion are implicated in only a subset of children (Shaw, Stringaris, Nigg, & Leibenluft, 2015). Thus, if MSDP selectively impacts hot EF, then heterogeneity within children with ADHD may explain some of the inconsistent findings in studies of the MSDP–ADHD associations (Wiebe et al., 2015).

Delayed development. A trend that emerged across two behavioral studies of MSDP and EF is a pattern of developmental catch-up of exposed children to their nonexposed peers. For both attention in infancy (Espy et al., 2011) and noninhibited responding in adolescence (Fried & Watkinson, 2001), poorer performance in exposed children compared to nonexposed children is followed by a period of rapid development in exposed children, resulting in comparable performance later in development (Espy et al., 2011). Although not conclusive, these findings provide preliminary evidence that it may not be the case that exposed children never recover

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from the early insult, but instead exhibit developmental delays. It should be noted that the infancy study was completed shortly after birth, and it is possible that the poorer performance of exposed neonates was actually a function of immediate withdrawal from nicotine exposure and then a rebound following withdrawal (Espy et al., 2011).

Similarly, the few studies that assess brain structure and function related to EF in children who were exposed to MSDP suggest that delayed brain development may underlie the poorer behavioral performance in exposed children. Brain development proceeds from global and diffuse to articulated and focal (e.g., Durston et al., 2006). As such, the more diffuse brain activation in exposed children relative to nonexposed children indicates that children who were exposed to MSDP may have less mature brains than their nonexposed counterparts (Bennet et al., 2009, 2013). The cerebellar (Bennet et al., 2009) and inferior frontal (Bennet et al., 2013) hypoactivation observed in exposed adolescents during EF tasks relative to controls supports this notion. It may be the case that, with time, children exposed to MSDP also develop more mature brain activation, but this is an open question requiring future research attention and developmental designs.

Bennet et al. (2009) and Espy et al. (2011) also note that their findings may indicate a delay in maturation rather than pervasive effects of early perturbation; patterns that would suggest a self-correcting resilience over time. Because longitudinal studies of EF in children who were exposed to MSDP are lacking, it is unknown whether EF has the same developmental trajectory in exposed children relative to nonexposed children, from both behavioral and brain-based perspectives. As such, future studies should employ longitudinal designs, ideally with three or more time points to permit examination of growth trajectories. If it is the case that children who were exposed to MSDP lag behind their peers in EF development, it may be more appropriate to characterize these problems as "developmentally delayed" rather than "deficits," and interventions should strive to close the developmental gap.

The dopaminergic system. Another potential pathway that emerged in both rodent (Zhu et al., 2012) and human (Wiebe et al., 2009) models is the involvement of the dopaminergic system in the relation between MSDP and EF. This may not be surprising, as polymorphisms in the dopaminergic system are independently linked to EF humans (Congdon, Constable, Lesch, & Canli, 2009; Congdon, Lesch, & Canli, 2008; Krämer et al., 2009), and MSDP alters dopamine release in humans (Changuex, 2010; Muneoka et al., 1997) and rats (Drew, Derbez, & Werling, 2000). Nonetheless, future molecular genetics studies of G × E interactions in the association between MSDP and EF should focus their efforts in identifying risky alleles on the dopaminergic system.

Directions for future research

Timing of exposure to MSDP. One question that emerged in reviewing the literature surrounds sensitive periods (i.e., those of increased vulnerability to disturbances) to MSDP, as independent evidence supports the adverse effects of both early (Kafouri et al., 2009) and late (Leech et al., 1999) exposure. It is reasonable to expect that exposure to MSDP at any point in fetal development would be harmful to EF. For example, nicotinic acetylcholine receptors are critical for proper early brain development and are present within the first 2 months of gestation. Chronic exposure to nicotine causes long-term changes in the function of the receptor and adversely impacts neonatal outcomes (see Ekblad et al., 2015, for a description of this mechanism). However, during the second and third trimesters, density of nicotonic receptor binding sites begin to increase (Roy, Andrews, Seidler, & Slotkin, 1998; Slotkin, McCook, & Seidler, 1997), and insult during this period may disrupt this process.

A study of reaction time in MSDP-exposed children ages 5 to 7 years explored whether performance differed between children whose mothers quit smoking early in pregnancy compared to those whose mothers smoked throughout (Mezzacappa, Buckner, & Earls, 2011). Children whose mothers smoked throughout the duration of their pregnancies had slower reaction times compared to children whose mothers quit early in their pregnancies, suggesting that exposure to MSDP later in pregnancy has more negative consequences for reaction time. It should be noted that mothers who quit early in pregnancy also tended to smoke fewer cigarettes per day relative to those who continued to smoke, thus it is unclear whether this is indicative of an association with smoking later in pregnancy or magnitude of exposure in the early stages (Clifford et al., 2012). Nonetheless, designs of this type can be utilized to address this question. If it is the case that the second and third trimesters are periods of increased vulnerability to MSDP, it would underscore the importance of continuing smoking cessation interventions for pregnant mothers throughout the duration of the pregnancy.

Further, it may be that epigenetic alterations (i.e., changes in gene expression that are not caused by changes in the sequence of DNA; Bird, 2007) may moderate the link between MSDP and neurocognitive outcomes, such as EF (see Knopik et al., 2012, for a discussion of the epigenetics of MSDP and effects on child development). Both epigenome-wide association studies (EWAS) and gene-specific methylation studies yield significant associations between MSDP and placental methylation patterns. Epigenome studies assess the methylation status of cytosine nucleotide–phosphate–guanine nucleotide (CpG) loci across the entire genome (see Maccani & Maccani, 2015, for a comprehensive review of genes in which one or more CpG sites show differential methylation associated with MSDP). In addition, EWAS using cord blood as the tissue of interest have also been conducted and suggest that prenatal smoke exposure may alter the epigenome resulting in global DNA hypomethylation (when considering all CpG sites across the genome; Ivorra et al., 2015). In one of the largest EWAS studies to date, Joubert et al. (2012) screened 1,062 newborn cord blood samples and found significant methylation changes at four genes.

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Similar patterns of methylation changes due to prenatal smoke exposure were also recently found in an independent sample of 3- to 5-year-old children, suggesting that that prenatal-exposure driven methylation changes persist and are still detectable in later childhood (Ladd-Acosta et al., 2016). Taken together, these findings highlight the importance of looking across tissue types and understanding the level of gene expression in various tissues when examining the effects of MSDP, while also considering the important facts that there are epigenetic changes that occur as a natural and normal part of development and that gene expression is tissue dependent (i.e., that epigenetic changes found in placental tissue or cord blood may or may not correlate with epigenetic signatures present in brain tissue). This generates an interesting question surrounding how environmental exposures during sensitive periods of development, such as intrauterine exposure to MSDP, could induce epigenetic moderations that have consequences on the developing fetus, fetal programming, and thus, long-term developmental outcomes, such as EF. Longitudinal studies capable of measuring within-individual changes in DNA methylation in a variety of tissues over time will yield important data informative of the intragenerational plasticity of DNA methylation in various tissue types (Knopik et al., 2012).

Assessing EF. There are clear gaps in the MSDP–EF literature. To our knowledge, there are no studies of MSDP and EF during toddlerhood, limited longitudinal studies of MSDP–EF associations, no studies of brain development specific to EF in children who were exposed to MSDP before middle childhood, and very few studies of MSDP and working memory across all ages. As previously discussed, because EF is multidimensional, it cannot be assumed that EF problems that are related to MSDP will be universal across all components. In addition, evidence suggests that performance-based and behavioral ratings of EF are not interchangeable; these measures correlate marginally and appear to assess different aspects of cognitive functioning (Toplak et al., 2013). As such, future studies should include measures of all foundational components of EF when assessing the relation between MSDP and EF and to be cautious in generalizing findings across EF components and measures. Further, the protracted development of EF underscores the importance of examining the association between MSDP and EF from a developmental perspective, as deficits may emerge at different developmental stages and in different components of EF. Although most of the studies reviewed here do find EF impairments related to MSDP, most of these studies are contemporaneous, and preclude examining trajectories of developmental change.

These findings may also shed light on studies of the structure of EF (e.g., Miyake et al., 2000) and genetic and environmental contributions to individual differences in EF (Friedman et al., 2008, 2016). In this prior work by Friedman et al., the covariance between the three primary components of EF (i.e., inhibitory control, set-shifting, and working memory) was almost entirely due to genetic influences. While findings from this review suggest that MSDP or correlated risks may differentially impact the components of EF, this is not inconsistent with Friedman et al. (2008, 2016). Even though Friendman et al. (2008, 2016) report that the covariance among and the individual differences in the components EF were almost entirely genetic in origin, this does not preclude the latent variables or individual task measures for each EF component itself from having residual variance (i.e., genetic or nonshared environmental) that cannot be attributable to genetic influences that are common among the components of EF. Each individual task measure of EF in the Freidman et al. studies is influenced by unique (i.e., measure specific) nonshared environmental effects. That measure-specific nonshared residual variance includes measurement error as well as environments/events that twins do not share (e.g., differential exposures). In addition, both the working memory ("updating" in Friedman et al., 2008, 2016) and set-shifting latent variables have genetic influences that are independent from those genetic influences on the common EF factor. As such, effects of MSDP on EF may be genetic or nonshared and unique to each component of EF. It is difficult to determine how the MSDP findings around the hot/cool inhibitory control distinction maps onto these studies because Friedman et al. (2008, 2016) do not include measures of hot inhibitory control. Future genetically informed studies should include both cool and hot measures of EF to explore sources of genetic and environmental covariance, an approach that may shed light on potential targets for MSDP interventions. If MSDP effects are specific to hot EF, it would emerge as unique (i.e., construct specific) influences on hot, but not cool, EF.

Consideration of genetic and environmental confounds

Confounds muddy the MSDP–EF literature. Several studies indicate that MSDP is not an isolated risk factor for child outcomes (Ellingson, Rickert, Lichtenstein, Långström, & D'Onofrio, 2012). That is, MSDP may be a false correlate of a causal relationship between characteristics of women who smoke during pregnancy and the environments in which they live (Wakschlag et al., 1997). For example, women who smoked during pregnancy may differ from those who do not on personality traits (e.g., depression, antisocial traits, and self-care; Ramsay & Reynolds, 2000), demographics (e.g., socioeconomic status; Wakschlag et al., 1997), parenting (e.g., use of harsh discipline and parental supervision; Wakschlag et al., 1997), physical characteristics (e.g., age and weight; Ernst et al., 2001; Weitzman et al., 2002), drug use (e.g., smoking intensity and other drug use; Ernst et al., 2001), and cognitive functioning (e.g., IQ; Ernst et al., 2001). All of these may reflect a familial vulnerability for later disorders. Despite this, there is a surprising lack of examination of the joint roles of environmental factors (e.g., MSDP) and genetic transmission of risk in studies of MSDP and child outcomes. The quasi-experimental studies of MSDP and cognitive abilities

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discussed here (Ellingson et al., 2014; Kuja-Halkola et al., 2014; Micalizzi et al., in press) and other studies of externalizing behavior (D'Onofrio et al., 2008; Knopik, Marceau, Bidwell, et al., 2016; Marceau et al., 2017) and academic achievement (D'Onofrio et al., 2010; Lambe, Hultman, Torrång, MacCabe, & Cnattingies, 2006) underscore the importance of including potentially confounding genetic variables in the study of the relation between MSDP and EF.

There is also a surprising lack of control for seemingly robust contextual confounds, such as postnatal secondhand smoke exposure. Exposure to secondhand smoke is inversely associated with child and adolescent cognitive functioning (see Chen, Clifford, Lang, & Anstey, 2013, for a review), including EF (Julvez et al., 2007). In the United States, approximately 41% of children ages 3–11 years were exposed to secondhand smoke during 2011–2012 (Homa et al., 2015), and state-specific prevalence for postpartum women who relapsed to cigarette smoking within 4 months after delivery ranged from 4.1% to 37.5% in 2010 (Tong et al., 2013). As such, it is important to account for postnatal exposure, as a failure to may artificially create or inflate suspected links between MSDP and child EF (Knopik, 2009).

Therefore, it is evident that the association between MSDP and offspring outcomes are confounded by co-occurring risks. However, it is extremely difficult to parse these variables in human studies. We must consider the likelihood that multiple risks contribute additively or interactively to child outcomes and that mothers who smoke during pregnancy differ substantially from control groups. Therefore, a direction for future research is not solely to control for confounds, but instead to examine how they might serve to mediate, exacerbate, or diminish the effects of MSDP. It is unlikely that a single study design will provide the answer to the complex nature of the association between MSDP and EF (Knopik, 2009). Instead, a multimethod approach is likely to contribute a more complete picture.

Efficacy of EF interventions for MSDP-exposed children

Interventions aimed at attenuating the effects of MSDP on EF can take three forms. Of course, the most straightforward interventions can occur at the ground level, targeting smoking cessation in pregnant mothers. Evidence suggests that a woman-centered approach to smoking interventions increases intrinsic motivation, overall well-being and self-efficacy, and may be the most effective means of promoting sustained change (Huizink, 2015). Other opportunities for intervention may be those aimed at modifiable correlated factors of MSDP, for example, the smoking status of the partner (Knopik et al., 2005), parenting, or the rearing environment.

Another avenue for prevention and intervention efforts may be to target EF in children. EF is malleable and responsive to intervention in typically developing children (see Diamond & Lee, 2011). Because such little is known about the developmental trajectory of EF in children exposed to MSDP, two important questions surrounding EF interventions in this population remain. First, will children who were exposed to MSDP also benefit from such interventions? Second, because children exposed to MSDP may have developmental delays in EF, would the established windows for interventions in this population be the same as those for typically developing children?

Conclusion

Good EF is required for nearly all activities that allow us to be productive members of society. As such, it is critical to isolate if there are direct adverse effects of MSDP on EF independent of familial risk. While questions about the causal nature of the association remain (Herrmann et al., 2008), we are approaching a clearer understanding of the impact of MSDP on child EF due to advances in conceptualizing and measuring EF coupled with the integration of findings from brain-based perspectives, animal models, and genetically informed designs. Taking a multimethod, interdisciplinary approach holds great promise to increase our understanding of the consequences of MSDP on child behavior and to translate these findings into clinical and public health policy (see Weitzman et al., 2002, for suggestions). Many developmental and behavioral researchers do not consider the prenatal environment as a critical period that can affect some of the most well-studied outcomes later in life (e.g., EF, ADHD, and academic performance variables). This is a call-to-action for developmental psychologists and prenatal exposure researchers to come together to address gaps in the literature to obtain a more complete understanding of the developmental consequences of MSDP on EF.

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