Review

Maternal Smoking During Pregnancy and Offspring Brain Structure and Function: Review and Agenda for Future Research

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Abstract

Introduction: Maternal smoking during pregnancy (MSDP) has been associated with long-term neurobehavioral and cognitive deficits in offspring. Animal models demonstrate alterations in brain structure and function following prenatal nicotine exposure. However, few studies have assessed the relationship between MSDP and brain development in humans. Therefore, the aims of this review are (a) to synthesize findings from the small number of human studies investigating effects of MSDP on offspring brain development and (b) to outline an agenda for future research in this nascent area.

Methods: We searched MEDLINE and Psychinfo databases for human studies of MSDP and offspring brain structure and/or function.

Results: Eleven studies meeting our search criteria were identified; 6 studies investigated effects of MSDP on brain structure; 5 examined effects on brain function. Across studies, MSDP was associated with decreased volume/thickness of the cerebellum and corpus callosum, increased auditory brainstem responses, and lack of coordination across brain regions during information and auditory processing.

Conclusions: Results from the small number of human studies revealed effects of MSDP on brain structure and function, highlighting potential neural pathways linking MSDP and offspring neurobehavioral and cognitive deficits. Given the limited amount of research in this area, we propose an agenda for future research. Gold standard studies would utilize longitudinal designs, integrated biological and maternal report measures of MSDP, and repeated measures of brain structure/function and neurobehavioral deficits across key developmental periods.

Introduction

Prenatal nicotine exposure via maternal smoking during pregnancy (MSDP) has been described as “the most widespread

prenatal drug insult in the world” (Levin & Slotkin, 1998). Despite pervasive medical and societal sanctions against smoking during pregnancy (Logan & Spencer, 1996), it is estimated that between 11% and 30% of women continue to smoke during pregnancy in the United States (Martin, Hamilton, Ventura, Menacker, & Park, 2002). Although inconsistent reports have emerged, a growing body of literature has demonstrated associations between MSDP and offspring neurobehavioral and cognitive deficits, including attention deficit hyperactivity disorder (ADHD), externalizing disorders, conduct disorder (CD), nicotine dependence and substance abuse (SA), and cognitive deficits (Cornelius & Day, 2009; Ernst, Moolchan, & Robinson, 2001; Herrmann, King, & Weitzman, 2008; Langley, Rice, van den Bree, & Thapar, 2005; Pauly & Slotkin, 2008). Dose response relations have been shown (Fergusson, Horwood, & Lynskey, 1993; Slotkin, 2008).

However, although numerous studies have documented associations between MSDP and offspring neurobehavioral deficits, there is a dearth of studies in humans that identify alterations in neural pathways (structures and function) that may underlie this relationship. Studies that specify alterations in neural structure and function from MSDP are critical in that they may elucidate neural pathways that may serve as targets for identification, intervention, and prevention efforts for offspring neurobehavioral deficits from MSDP. Such studies could also help to elucidate inconsistencies in the literature linking MSDP with long-term neurobehavioral deficits. We and others (Baler, Volkow, Fowler, & Benveniste, 2008; Cornelius & Day, 2009; Ernst et al., 2001) propose alterations in brain structure and function as key candidate mediators underlying links between MSDP and offspring neurobehavioral deficits in humans. In support of this hypothesis, disorders and deficits associated with exposure to MSDP in humans (e.g., ADHD, CD, SA, cognitive deficits) have been consistently linked to alterations in brain structure and function. In addition, a large body of research in animal models has revealed prenatal nicotine as a potent neuroteratogen, with evidence for disruption of key neurobiological pathways in offspring following prenatal exposure to

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nicotine (Slotkin, 1998, 2008; Slotkin, Pinkerton, Tate, & Seidler, 2006). Identification of neural mediators may also help to (a) inform early prevention efforts with exposed offspring, (b) inform development of personalized treatment for exposed offspring with neurobehavioral deficits, and (c) lead to novel therapeutic targets for protecting exposed fetuses.

The majority of prior research investigating effects of MSDP on neural structure and function has been conducted using animal models. Results from animal studies demonstrate a robust association between prenatal nicotine exposure and upregulation of nicotinic acetylcholine receptors (nAChRs) across a wide array of brain regions as early as first trimester. Upregulation of nAChRs leads to inhibition of DNA synthesis and, ultimately, disruption of brain cell replication and differentiation (Slotkin, 1998). Prenatal nicotine has also been associated with dysregulation of cholinergic, catecholaminergic, serotonergic, and other neurotransmitter systems. Furthermore, unlike the majority of teratogens, effects of prenatal nicotine on offspring brain development have emerged even in the absence of effects on somatic growth, suggesting that nicotine specifically targets the fetal brain and central nervous system (CNS) (Slotkin, 1998).

While animal models have demonstrated profound alterations of brain development by prenatal nicotine, it is not clear whether these findings can be directly translated to human brain development. First, intermittent exposure to tobacco in the human fetus differs from the continuous nicotine dosing employed in animal models (Slotkin, 2008). Second, there are dramatic differences in brain structure and function between rodents and humans (i.e., humans display an enlarged prefrontal cortex, distinct hippocampal structure, and higher density of synaptic connections as compared to rodents). Third, animal studies have primarily focused on perinatal exposure to nicotine alone, whereas human studies necessarily focus on cigarettes and tobacco products, which include nicotine in addition to a numerous other potential neuroteratogens (e.g., arsenic, acetone, and formaldehyde). Finally, the third trimester of human pregnancy corresponds to the postnatal rather than perinatal period in the rodent (Dwyer, McQuown, & Leslie, 2009). Thus, prior animal studies that have modeled effects of prenatal exposure are not able to provide insight into neural effects of human prenatal exposure in the third trimester. Given these differences, it is critical to investigate effects of MSDP on offspring brain development in humans.

Previous comprehensive reviews have summarized studies investigating associations between MSDP and offspring neurobehavioral deficits and disorders from both the human and the animal literatures (Cornelius & Day, 2009; Ernst et al., 2001; Herrmann et al., 2008; Langley et al., 2005; Pauly & Slotkin, 2008). These reviews have reported relatively consistent links between MSDP and neurobehavioral deficits but highlight the difficulty in establishing causal associations given the number of potentially confounding factors, ethical impossibility of experimental designs in humans, and obstacles in translating findings from animal models to human neurobehavioral outcomes. Previous reviews have also summarized associations between MSDP and offspring neural development with focus on both animal and some human studies (Baler et al., 2008; Blood-Siegrfried & Rende, 2010; Dwyer et al., 2009; Shea &

Steiner, 2008; Slotkin, 1998). These reviews suggest that dysregulation in the development of receptor, neurotransmitter, and basic synaptic systems by maternal smoking/prenatal nicotine could lead to functional and structural brain changes and neurobehavioral/cognitive impairments in offspring. However, the reviews relied heavily on findings from animal studies and did not provide a comprehensive review of human studies of brain structure and function. Therefore, our aims in the current review are (a) to systematically summarize and critique the small number of human studies of MSDP and brain structure and function and (b) to propose an agenda for future research in this nascent area.

Methods

We performed searches of MEDLINE and Psycinfo databases (1980–2011) for original research investigating effects of MSDP on structure or function of the human brain using search terms “pregnancy, maternal, and prenatal”; “tobacco, cigarette, and smoking”; and “brain, imaging” as well as backward searches of reference lists and forward searches of article citations. Numerous studies (i.e., Gray et al., 2010; Kallen, 2000) that investigated effects of MSDP on fetal and infant head circumference were not included in this review as results have been highly consistent (MSDP associated with decreased fetal and infant head circumference) and because the studies do not provide insight into specific structural or functional alterations of the brain.

Our search yielded 11 empirical articles published between 2006 and 2010. Of these, six investigated effects of MSDP on offspring brain structures and five considered effects of MSDP on brain function. Description, results, and limitations of these studies are presented in Table 1 and summarized below. Studies are organized by focus on brain structure versus function and across development (fetal period to adolescence).

Results

Brain Structure

Six studies examined effects of MSDP on offspring brain structures. Two focused on regional brain volumes during late gestation and early infancy. Roza et al. (2007) examined effects of MSDP on growth of fetal brain regions across pregnancy in a population-based prospective pregnancy cohort (Generation R Study). Regional brain growth was measured by ultrasound, a validated mode of regional brain measurement (Endres & Cohen, 2001). Sonographers were blind to participants' smoking status, and high intra- and interobserver reproducibility was reported. MSDP was measured by prospective maternal report. 5,675 participants (1,199 exposed) contributed to analyses of cerebral hemispheric growth (atrial width, i.e., the widest diameter of the atrium of one of the lateral ventricles of the cerebrum and a marker of abnormal brain growth); 3,071 participants (1,199 exposed) contributed to analyses of the cerebellum (structure involved in motor control, language, and attention). Exposure was associated with smaller atrial width of lateral ventricular and smaller transcerebellar diameter across pregnancy. Ekblad et al. (2010) investigated associations between MSDP and infant regional brain volumes in 232 very low birth weight

Table 1. Summary of Reviewed Studies of Effects of MSDP On Brain Structures and Function

Authors	N (% exposed)	MSDP measure ^a	Brain measure	Offspring age (characteristics)	Results (region, findings in exposed vs. unexposed)	Design limitations
Brain structures						
Roza et al. (2007)	7,042 (17)	Prospective; Categorical; No biomarker	Ultrasound	Fetal period	Cerebellum, ventricular system (Smaller volume)	MSDP measure
Ekblad et al. (2010)	232 (18)	Retrospective; Categorical; No biomarker	MRI	Newborns at term	Frontal lobe, cerebellum (Smaller volume)	Sample selected for low birth weight, low gestational age
Rivkin et al. (2008)	35 (49)	Retrospective; Categorical; No biomarker	MRI	10–13 years	Cerebral cortex (Reduced gray matter volume)	Sample selected for prenatal cocaine exposure
Jacobsen, Picciotto, et al. (2007)	67 (49)	Retrospective; Categorical; No biomarker	DTI	13–18 years (current smokers and nonsmokers)	Corpus Callosum; Internal Capsule (Altered white matter microstructure)	MSDP measure
Toro et al. (2008)	314 (49)	Retrospective; Categorical; No biomarker	MRI	12–18 years	Frontal, temporal, parietal lobes (Thinning [results stronger in females])	MSDP measure
Paus et al. (2008)	300 (49)	Retrospective; Categorical; No biomarker	MRI	13–17 years	Corpus callosum (Smaller volume [exposed females only])	MSDP measure
Brain function						
Peck et al. (2010)	40 (25)	Prospective; Categorical; Cotinine	ABR	2 days	Brainstem (Increased auditory brainstem responses)	Small N
Kable et al. (2009)	172 (67)	Retrospective; Continuous; Cotinine	ABR	6 months	Brainstem (Increased auditory brainstem responses)	MSDP measure
Bennett et al. (2009)	18 (39)	Retrospective; Categorical; No biomarker	fMRI	12 years	Frontal, temporal, parietal lobes, cerebellum (Greater activation to response inhibition task)	Small N
Jacobsen et al. (2006)	13 (54)	Retrospective; Categorical; No biomarker	fMRI	16–18 years (current smokers)	Temporal lobe (hippocampus; Greater activation during smoking abstinence to visuospatial encoding and recognition tasks)	Small N
Jacobsen, Slotkin, et al. (2007)	63 (52)	Retrospective; categorical; No biomarker	fMRI	16–18 years (current smokers and nonsmokers)	Temporal, occipital lobes (Greater activation to auditory attention tasks)	MSDP measure

Note. ABR = auditory brainstem response; DTI = diffusion tensor imaging; fMRI = functional magnetic resonance imaging; MRI = magnetic resonance imaging; MSDP = maternal smoking during pregnancy.

^aProspective measure of MSDP = measured in pregnancy; Retrospective = measured after pregnancy; Categorical = compared exposed versus unexposed offspring; Continuous = exposure examined as a continuous measure.

(<1,500 g) or very low gestational age (<32 weeks) infants (42 exposed) at term. MSDP-exposed infants showed smaller frontal lobes and cerebellar volumes measured by magnetic resonance imaging (MRI). Given the links between ADHD and reduced overall brain volume, cerebellar volume, and growth in the lateral ventricular system (Castellanos et al., 1996), Roza et al. (2007) and Ekblad et al. (2010) speculate that the MSDP-related decreases in brain volume in these regions may serve as promising neural pathways linking MSDP to offspring neurobehavioral deficits.

Four studies focused on regional brain volume and microstructure in older children and adolescents. Rivkin et al. (2008) investigated effects of MSDP in a sample of 35 children ages 10–14 years (17 exposed) selected based on exposure or nonexposure to prenatal cocaine. MSDP was measured retrospectively via maternal self-report; volumetric MRI was performed to determine regional volumes of gray and white matter (neuronal cell bodies and myelinated axons, respectively). Rivkin et al. (2008) found significantly reduced cerebral cortical gray matter and total parenchymal volume in exposed children but no evidence for exposure-induced alterations in white matter or subcortical gray matter. Jacobsen, Picciotto, et al. (2007) used diffusion tensor imaging (DTI) to examine effects of MSDP on white matter microstructure in 67 adolescent smokers and nonsmokers, ages 13–18 years (33 exposed). MSDP was measured by retrospective maternal self-report. DTI is a measure of diffusion of water within brain tissue and provides information about fractional anisotropy (FA or degree of directionality), myelination, and density of connections between brain regions. Both MSDP and current offspring smoking were associated with increased FA in anterior cortical and subcortical brain regions involved in communication of auditory information (genu of the corpus callosum [CC], right superior longitudinal fasciculus, and right internal capsule). Current adolescent smoking was associated with stronger effects on FA than prenatal exposure, with no evidence for additive effects of prenatal and adolescent exposure.

Two investigations from the Saguenay Youth Study found associations between MSDP and reduced regional brain volumes, particularly in female offspring. MSDP was measured via retrospective maternal report; unexposed offspring were matched to MSDP-exposed offspring based on maternal education. Regional brain measurements were assessed by MRI. Toro et al. (2008) examined regional thickness of the cerebral cortex in a sample of 314 adolescents ages 12–18 years (155 exposed; findings also reported in Loftipour et al., 2009). They found thinning of a number of areas of the frontal, temporal, and parietal regions (including lateral orbitofrontal, middle frontal, and parahippocampal cortices—areas with high density of nicotinic receptors). Effects were strongest in exposed females for all regions except the parahippocampal cortex and parietal areas. As well, thinning of the orbital frontal cortex (OFC) was negatively associated with an index of competence and social connection, suggesting that thinning of the OFC may be a link between MSDP and poorer social development. In a study of 300 adolescents ages 13–17 years (146 exposed), Paus et al. (2008) investigated effects of MSDP on volume and degree of myelination of the CC. They found reduced volume in the middle and posterior regions of the CC in MSDP-exposed female adolescents only. No significant effects of MSDP on myelination of the CC emerged, suggesting that MSDP is associated with de-

creased number of axons but not axonal diameter/myelination. Given evidence for reduced CC size in ADHD, Paus et al. highlight alterations in the CC as a potential neural mechanism linking effects of MSDP and ADHD.

Brain Function

Four studies considered effects of MSDP on brain function in human offspring. Two investigated effects of MSDP on auditory brainstem responses (ABRs) in infants. ABRs are electrical signals evoked from the brainstem by presentation of a sound such as a click, typically measured by surface electrodes. ABRs serve as indicators of CNS development and auditory functioning. Greater or more rapid ABRs in infants are indicative of impaired ability to encode auditory information, which could in turn lead to the emergence of language and learning impairments later in childhood (Marler & Champlin, 2005). Peck et al. (2010) assessed effects of MSDP, measured by prospective maternal report and urinary cotinine (i.e., a nicotine metabolite and common biomarker for exposure to tobacco; 16- to 19-hr half-life) during first trimester, on rate of ABRs in 40 two-day-old infants (10 exposed). Infants of mothers with the highest prenatal cotinine concentrations (>1,000 mg/ml) or who smoked 10+ cigarettes/day showed 3+ times increased rate of ABRs relative to unexposed infants. Kable, Coles, Lynch, and Carroll (2009) investigated associations between MSDP and ABRs in 172 six-month-old infants (115 exposed). MSDP was measured prospectively over pregnancy; blood samples were collected for maternal cotinine after delivery. Controlling for perinatal complications and maternal alcohol use, MSDP was associated with increased rate of ABRs, especially in offspring of heavy smokers.

Finally, three studies utilized functional magnetic resonance imaging (fMRI) technology to examine effects of MSDP on adolescent brain function. Bennett et al. (2009) investigated effects of MSDP on brain function during a response inhibition task (Go/No-go) in 18 twelve-year-olds (7 exposed). The Go/No-go task consists of pressing a button when one stimulus type is shown but withholding response when another stimulus type is shown. MSDP was measured by maternal report at delivery. MSDP-exposed adolescents displayed greater activation in a diverse set of brain regions (left frontal, right occipital, bilateral temporal and parietal regions, and cerebellum) and made 31% more errors than unexposed adolescents, while unexposed adolescents showed greater activation in the medial regions of the cerebellum and the occipital lobe. Bennett et al. suggest that increased activation of diverse brain regions may indicate inefficient recruitment of relevant brain regions resulting in impaired response inhibition, a core deficit in individuals diagnosed with ADHD and externalizing disorders. Jacobsen, Slotkin, Westerveld, Mencl, and Pugh (2006) investigated effects of MSDP on fMRI response to verbal and visuospatial memory tasks performed during ad libitum smoking and 24-hr abstinent periods in 13 adolescent smokers ages 16–18 years (7 exposed, measured via retrospective maternal report). Within the abstinence period only, prenatally exposed smokers showed increased activation of regions of the hippocampus (left parahippocampal gyrus and bilateral hippocampus; structures involved in long-term memory) during memory tasks, whereas activation in these structures decreased in unexposed adolescents. No effects of MSDP emerged during the ad libitum condition. Jacobsen et al. (2006) propose that prenatally exposed

adolescents may smoke in order to overcome MSDP-related cognitive deficits (i.e., memory deficits). [Jacobsen, Slotkin, et al. \(2007\)](#) also investigated effects of MSDP on fMRI response to auditory and visual attention tasks in a sample of 63 adolescent smokers and nonsmokers ages 16–18 years (33 exposed, measured by retrospective maternal report). MSDP (with and without adolescent smoking) was associated with greater temporal lobe activation (bilateral superior temporal gyrus) during an auditory attention task. MSDP in nonsmokers was associated with greater activation in the occipital lobe (bilateral lingual gyrus). Both regions are critical for processing auditory and visual information. In contrast to [Jacobsen et al. \(2006\)](#), they found additive effects of MSDP and adolescent smoking on regional activation, indicative of poor coordination among brain regions during auditory attention tasks.

Discussion

Our review revealed a small number of recently published studies highlighting significant alterations in offspring brain structure and function following exposure to MSDP. Structural brain studies in late gestation and early infancy revealed associations between MSDP and reduced frontal lobe, lateral ventricular system, and cerebellar volume. In adolescence, MSDP was associated with reductions in volume of cortical gray matter, cerebellum, and CC; thinning of regions in the frontal, temporal, and parietal lobes; and alterations in white matter microstructure of several major connective tracts. Importantly, alterations in these in brain regions have also been linked to deficits in cognitive abilities, auditory processing, social development, and ADHD. Results from the Saguenay Youth Study ([Paus et al., 2008](#); [Toro et al., 2008](#)) revealed stronger effects in female offspring, highlighting the importance of examining gender differences in links between MSDP and offspring outcomes in future studies.

Studies of brain function highlight links between MSDP and increased rate of ABRs in infant offspring. Increased rate of ABRs may lead to interruptions in auditory processing and deficits in speech and language development, which may serve as potential mediators between MSDP and cognitive deficits. fMRI studies in adolescents suggest associations between MSDP and inefficient recruitment of task-relevant brain regions, including the temporal lobe, hippocampus, and cerebellum during response inhibition, attention, and memory tasks. As well, additive effects of MSDP and current smoking during adolescence were seen on temporal lobe activation ([Jacobsen, Slotkin et al., 2007](#)), suggesting that MSDP may potentiate effects of adolescent smoking on brain functional deficits. Of note, however, additive effects of current and prenatal exposure on brain function were in contrast to structural findings, which showed stronger effects of current exposure relative to prenatal exposure and no additive effects of current and prenatal exposure on white matter microstructure.

While all studies included in this review are recent and identify promising neural regions linking MSDP to long-term neurobehavioral outcomes in humans, these initial studies have some limitations that suggest directions for future research. In general, the current body of literature is very small, and although each study involved unique analyses, several of the 11 studies involved analyses within overlapping participant samples ([Jacobsen et al., 2006](#); [Jacobsen, Picciotto et al., 2007](#);

[Jacobsen, Slotkin et al., 2007](#); [Paus et al., 2008](#); [Toro et al., 2008](#)). Thus, integrated findings are based on only eight unique samples. In terms of exposure, most studies measured MSDP through retrospective maternal report with no biochemical verification of smoking status or level (see [Table 1](#)). Furthermore, most studies examined brain differences in exposed versus unexposed offspring; only one study examined dose–response MSDP/cotinine levels ([Kable et al., 2009](#)). Finally, MSDP is highly confounded with multiple indicators of low socioeconomic status (SES). While all studies in this review included one or more indicators of SES as statistical covariates, only two studies ([Paus et al., 2008](#); [Toro et al., 2008](#)) matched exposed and unexposed offspring on SES, allowing for assessment of unique effects of MSDP independent of SES.

In terms of offspring outcomes, there are several gaps in the current literature. First, all studies were conducted during either the fetal period/early infancy or the middle childhood/adolescence. No longitudinal studies of brain development have been published, and no studies have examined effects of MSDP on brain structure or function in offspring between 6 months and 10 years of age. While the perinatal/early infancy and adolescent stages represent periods of rapid brain development, given that cognitive, attention, and externalizing deficits emerge in early and middle childhood, it is critical to investigate brain structure and function across additional key periods of development. Furthermore, studies of MSDP and offspring brain function have primarily focused on tasks associated with cognitive, auditory, and attention deficits. However, MSDP is also linked to offspring externalizing behaviors and smoking uptake/nicotine dependence—disorders associated with altered response to emotional processing tasks and altered activation of emotion regulatory regions of the brain (i.e., amygdala, ventral striatum, orbitofrontal cortex, anterior cingulate cortex). Finally, no studies have prospectively investigated links between offspring brain development and long-term offspring neurobehavioral deficits (i.e., ADHD, CD, SA).

Future Directions

More research is needed to determine whether reliable and consistent associations exist between MSDP and altered brain structure and function and whether alterations in brain structure and function mediate effects of MSDP on long-term neurobehavioral and cognitive deficits. Thus, we propose an agenda for future research. First, we will describe the “gold standard” study that is likely to yield the most definitive results regarding neural mechanisms linking MSDP to offspring clinical disorders (see [Box 1](#)). Next, we offer suggestions for smaller scale cross-sectional studies that would also yield important contributions to our understanding of the effects of MSDP on brain structure and function. Finally, we provide a detailed discussion of measurement issues that arise when conducting these studies.

In order to best understand potential neural mechanisms linking MSDP to offspring disorder, the “gold standard” study would include prospective assessment of MSDP and maternal cotinine over pregnancy and prospective assessment of promising brain structures and function over gestation, infancy, early and middle childhood, and adolescence, as well as concurrent behaviors indicative of emerging clinical disorders over these key developmental periods. Prospective measures of MSDP would include quantity and frequency of smoking at multiple points over pregnancy integrated with multiple measures of

Box 1. Gold Standard Study Design

Study design:

- Longitudinal, prospective
- Repeated measures
- Novel designs to address environmental/genetic confounds
- Offspring gender as key variable

Measurement of maternal smoking during pregnancy:

- Multiple measures over pregnancy
- Detailed measure of cigarette quantity/frequency [e.g., Time Line Follow Back (TLFB)]
- Biochemical verification (e.g., maternal saliva cotinine)
- Statistical integration of self-report and biological measures over pregnancy

Offspring brain structure and function:

- Multiple measures over development
- Structural and functional MRI methodology
- Regions of interest:
 - a) Replication of prior studies: corpus callosum, cerebellum, cerebral cortex
 - b) Conceptually promising: limbic structures, mesocortical dopamine system, cerebral cortex, basal ganglia, anterior cingulate cortex, orbitofrontal cortex
- Potential fMRI tasks: working memory (e.g., reading span, N-back), impulsivity/ inhibition (e.g., stroop, go/no-go), reward processing (e.g., monetary incentive delay), emotion processing (i.e., face-emotion labeling task), and risk-seeking behaviors (i.e., Balloon Analog, Wheel of Fortune task)

Neurobehavioral deficits/clinical disorders:

- Multiple measures over development
- Corroborating interview and behavioral observations
- Diagnostic and symptom severity measures

maternal cotinine, allowing analyses of MSDP on brain development on both exposure status and levels (dose–response), as well as novel analyses focused on effects of timing of MSDP exposure on brain development.

The “gold standard” study would collect structural and functional brain measures during pregnancy and across critical stages of development (i.e., infancy, early and middle childhood, and adolescence; [Chugani, 1998](#)). In pregnancy, brain growth/development would be measured via fetal ultrasound. Throughout childhood and adolescence, the “gold standard” study would utilize fMRI techniques to detect regional brain activity in response to attention, response inhibition, reward processing, and risk-seeking behavior tasks in brain regions previously associated with ADHD and externalizing disorders. Regions of interest would include limbic structures (amygdala, hippocampus, limbic cortex), structures associated with the mesocortical dopamine system (ventral tegmental area, nucleus accumbens), cerebral cortex (particularly frontal regions), basal ganglia (striatum, globus pallidus, substantia nigra), anterior cingulate cortex, and the orbitofrontal cortex.

Along with prospective measures of brain structure and function, the “gold standard” study would prospectively assess symptoms and diagnoses of ADHD, CD, and SA over childhood and adolescence utilizing interview and behavioral observations from parents, teachers, and children across development to determine associations between brain function and symptom severity. In late childhood and adolescence, offspring smoking assessments would be conducted to further elucidate the nature and specificity of brain deficits from MSDP versus adolescent current smoking.

Finally, the “gold standard” study would be designed to disentangle confounding effects of genetic and environmental factors on links between MSDP and offspring clinical disorders, including SES, parent and/or child psychopathology, maternal age, other drug use in pregnancy, secondhand smoke exposure, and clinical disorders in the parent (i.e., ADHD). SES is particularly important to account for in future studies as it has been associated with both MSDP and offspring disorders. Possible designs that take into account SES could include matching of exposed and unexposed offspring based on SES, especially given the known associations between low SES and externalizing disorders (see [Lucas-Thompson, Goldberg, & Prause, 2010](#) for a recent review). Alternatively, there may be qualitative differences between low SES mothers who smoke versus low SES mothers who do not smoke. Thus, another option would be a discordant sibling design (exposed vs. unexposed siblings or differential levels of exposure between siblings), allowing control of socioeconomic and genetic factors. Finally, given preliminary evidence for gender differences in effects of MSDP on regional brain volumes and preclinical and human studies revealing gender differences in effects of prenatal smoking/nicotine, the “gold standard” study would be adequately powered to investigate gender differences in associations between MSDP and alterations in neural structure and function/clinical disorders.

By identifying key neural structural and functional alterations associated with MSDP, pharmacological and behavioral interventions could be tailored to meet the unique needs of prenatally exposed offspring at risk for neurobehavioral deficits or clinical disorders. Greater understanding of alterations in task-specific brain function in exposed offspring may lead to education efforts

for parents and teachers regarding the most effective modes for working with exposed offspring (e.g., auditory vs. visual information, number of repetitions for memory tasks, need for response inhibition or emotion regulation techniques). Very early interventions for at-risk offspring (i.e., infancy and early childhood) could be developed that are aimed at improving memory and concentration while the brain is in a stage of rapid development. Identifying key neural changes could also lead to novel medication targets for exposed offspring who have developed clinical disorders.

While the “gold standard” study outlined above would provide the most comprehensive and rigorous assessment of potential neural mechanisms linking MSDP to clinical disorders, we also propose several options for preliminary studies that would make meaningful contributions to this emerging literature and offer promise for identifying at-risk children and guiding intervention efforts. First, following the approach of Jacobsen et al. (2006, Jacobsen, Slotkin, et al., 2007; Jacobsen, Picciotto, et al., 2007), a cross-sectional approach could be used to investigate the effects of MSDP on brain structure/function in individuals diagnosed with clinical disorders (ADHD, CD, nicotine dependence). Such studies could lead to differential intervention approaches in exposed versus unexposed patients. Second, studies could involve the addition of measures of offspring brain structure and function in ongoing prenatal/birth cohort studies in which MSDP was measured prospectively or at birth, allowing prospective assessment of effects of MSDP on offspring brain development. For example, Roza et al. (2007) examined fetal brain structures in the Generation R Study, a population-based pregnancy cohort involving prospective measurement of MSDP. Measures of brain structure and function in older children and adolescents from ongoing cohort studies would also be informative. Discordant sibling designs could also be utilized to investigate effects of MSDP on brain structure and function in ongoing cohort studies (Gilman, Gardener, & Buka, 2008; Obel et al., 2010). Third, following the approach of Loftipour et al. (2009; Saguenay Youth Study), preliminary studies could evaluate whether associations between MSDP and clinical disorders (e.g., SA) are mediated by structural or functional changes in neural regions (e.g., thinning in the orbitofrontal cortex), allowing insight into links between MSDP-induced neural changes and offspring clinical risk.

Key Issues in Design of Gold Standard and Preliminary Studies

MSDP Measurement

One of the challenges in understanding associations between MSDP and neural structure and function in humans is the accurate measurement of MSDP. Most ideal would be multiple MSDP measurements across gestation, including both detailed maternal report of quantity and frequency of smoking and repeated biochemical measures of smoking exposure. For example, the Time Line Follow Back (TLFB) interview is a calendar-based recall method aimed to minimize recall bias (Shiffman, Kassel, Paty, Gnys, & Zettler-Segal, 1994), which has been adapted for MSDP in several prior studies (Law et al., 2003; Stroud et al., 2009). Validated biochemical measures of tobacco exposure over gestation can be measured in maternal saliva, urine, hair, nails, and plasma or serum nicotine/cotinine (Benowitz, Hukkanen, & Jacob, 2009). Previous research has shown salivary cotinine to be the most sensitive test of MSDP (Russell, Crawford, & Woodby, 2004). Of note, metabolism of nicotine/cotinine is in-

creased in pregnancy due to increased circulating sex hormones (Benowitz et al., 2009). Consequently, cotinine concentrations per cigarette are lower during pregnancy, which may be important for researchers to consider if comparing pre- and postnatal cotinine values. At the time of birth, an infant's first stool (i.e., meconium) can be assayed for cotinine/nicotine as an integrated measure of tobacco exposure over third trimester (Marin, Christensen, Baer, Clark, & McMillin, 2011). Cord blood, neonatal saliva, urine, and plasma/serum may also be assayed for nicotine/cotinine to measure acute levels of tobacco exposure at birth. Statistically, it is critical for longitudinal studies including multiple assessments of MSDP over time to appropriately account for clustering and correlated self-report and biochemical data, for example, using hierarchical models or generalized estimating equations (e.g., Louis et al., 2006).

Timing of Exposure

Given differential development of fetal brain regions across pregnancy, elucidating effects of timing of MSDP would be informative. Findings from animal models suggest that nicotine exposure in the first trimester is most likely to result in premature development and subsequently altered neuronal activity in the brainstem (locus coeruleus) and midbrain (substantia nigra and ventral tegmental area) structures, while second and third trimester exposure is linked to persistent abnormalities in neuronal maturation and decreased cell size in the cerebral cortex, hippocampus, and cerebellum. The gold standard study and preliminary studies involving prospective MSDP measurement would utilize integrated measures of MSDP (including biochemical markers) at multiple points across gestation to investigate whether timing effects from animal models translate to humans. Mothers who quit smoking over pregnancy (typically in the first or second trimester) may offer unique insight into the influence of timing of tobacco exposure (early vs. late gestation) on offspring neural structure and function.

Brain Structures

Gold standard and preliminary studies should include state-of-the-art measurement of key brain structures shown to be associated with MSDP-related clinical disorders. Common brain regions associated with clinical outcomes of ADHD include the prefrontal cortex, caudate nucleus, frontal lobe, basal ganglia, dorsal anterior cingulate cortex, and putamen. Regions associated with CD include the amygdala, ventral striatum, orbitofrontal cortex, temporal lobes, and the anterior cingulate cortex. Brain regions implicated in nicotine dependence include the ventral tegmental area and the nucleus accumbens. Therefore, while previous research has investigated effects of MSDP on the CC, cerebellum, hippocampus, occipital, and temporal lobes, many brain regions theoretically linked to MSDP-related clinical disorders have yet to be examined. As suggested for the “gold standard” study outlined above, promising brain areas for future research include limbic structures (amygdala, hippocampus, and limbic cortex), the mesocortical dopamine system (ventral tegmental area and nucleus accumbens), the cerebral cortex (particularly frontal regions), basal ganglia (including striatum, globus pallidus and substantia nigra), anterior cingulate cortex, and the orbitofrontal cortex.

Brain Function Measurement

We propose that, as a next step in this developing area of research, gold standard studies utilize fMRI techniques. While

other imaging techniques (e.g., positron emission tomography, DTI, event-related potential) would allow researchers to generate additional assessments of connectivity, receptor density, and brain activity in relation to MSDP. fMRI offers the possibility of investigating contextually based markers of brain function with increased relevance for the “real world.” fMRI also offers potential for investigating alterations in brain activation in response to processes associated with MSDP-related clinical disorders (ADHD, CD, SA).

Gold standard and preliminary fMRI studies would elucidate regional brain responses to key processes in clinical disorders associated with MSDP by implementing tasks that target processes associated with attention deficits, including working memory (i.e., reading span, N-back tasks) and impulsivity/inhibition (i.e., Stroop, Go/no-go, Stop signal, Eriksen flanker tasks), and processes associated with externalizing disorders, such as reward processing (i.e., monetary incentive delay task), emotion processing (i.e., face-emotion labeling task), and risk-seeking behaviors (i.e., Balloon Analog, Wheel of Fortune task). Tasks should also be selected that correspond to the participants’ developmental stage. For example, for 4-year-old participants, the face-emotion labeling and Balloon Analog fMRI tasks are likely to be more developmentally appropriate than the reading span or Stroop tasks due to variability in reading comprehension. For children/adolescents who are current smokers, neural function could be assessed utilizing fMRI tasks above under smoking ad libitum and abstinence conditions, thus elucidating combined effects of MSDP and current smoking.

Genetically Informative Designs

When possible, future studies could utilize innovative genetically informative designs (e.g., siblings discordant for MSDP exposure, children of twins, children of adult siblings discordant for MSDP exposure; D’Onofrio et al., 2008) in order to better understand the unique effects of MSDP on offspring disorder. For example, discordant sibling designs have been utilized to investigate effects of MSDP on offspring behavioral outcomes and have allowed more clear partitioning of genetic effects, which could also be utilized to investigate effects of MSDP on brain structure and function in ongoing cohort studies (Gilman et al., 2008; Obel et al., 2010). A recent study by Thapar et al. (2009) utilized a novel “natural experiment” design in which they assessed ADHD risk in MSDP-exposed offspring who were or were not genetically related to the mother due to in vitro fertilization. Future studies using these and other genetically informative designs could include neural measures to determine whether MSDP predicts changes in brain function independent of genetic risk.

Conclusions

MSDP is consistently associated with neurobehavioral and cognitive deficits including attention problems, impulsivity, subtle intellectual deficits, hyperactivity, and substance use in offspring, yet 11%–30% of women continue to smoke during pregnancy. Animal studies report causal dose–response associations between MSDP and altered neural development that may serve as mechanisms linking MSDP to offspring cognitive and behavioral disorders. However, few studies of MSDP-related neural changes have been conducted in humans. In this review, we summarized findings from the small number of human

studies designed to investigate potential neural mechanisms linking MSDP and offspring neurobehavioral deficits. MSDP was associated with reductions in volume and thickness of various cortical regions and the CC, reductions in cortical gray matter, and alterations in white matter microstructure. MSDP was also associated with increased ABRs and impairments in brain region coordination during memory and attention tasks. However, given the small body of literature on MSDP effects on the human brain, we provide an agenda for future research in this nascent area. The “gold standard” study would prospectively assess MSDP and maternal cotinine, neural structure, and function and offspring behavior from gestation through infancy, childhood, and adolescence. Preliminary studies could include comparison of exposed and unexposed participants with clinical disorders associated with MSDP and studies of brain structure and function in cohorts with prior measures of MSDP.

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Declaration of Interests

None declared.

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