Prenatal tobacco exposure predicts differential brain function during working memory in early adolescence: A preliminary investigation

Prenatal tobacco exposure predicts differential brain function during working memory in early adolescence: A preliminary investigation

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Abstract

Children prenatally exposed to tobacco exhibit higher rates of learning and emotional-behavioral problems related to worse working memory performance. Brain function, however, among tobacco exposed children while performing a working memory task has not previously been examined. This study compared the brain function of tobacco-exposed (n = 7) and unexposed (n = 11) 12-year-olds during a number N-back working memory task using an event-related functional magnetic resonance imaging (fMRI) design. Prenatal alcohol exposure, neonatal medical problems, environmental risk, and sex were statistically controlled. Tobacco-exposed children showed greater activation in inferior parietal regions, whereas unexposed children showed greater activation in inferior frontal regions. These differences were observed in the context of correct responses, suggesting that exposed and unexposed children use different brain regions and approaches to succeed in working memory tasks. Implications for future research and intervention are discussed.

Key words: Prenatal Tobacco Exposure; Working Memory; fMRI; Brain Imaging

Prenatal tobacco exposure is a common risk factor as a quarter of pregnant women in the United States smoked at some point during their pregnancy, with 16% having smoked in the last month of their pregnancy (Arria et al., 2006; SAMHSA, 2009). High rates are also found in other nations, particularly for young, low SES mothers (Lee et al., 2011; Mohsin & Bauman, 2005; Schneider, Maul, Freerksen, & Potschke-Langer, 2008). Prenatal tobacco exposure harms the developing fetus by increasing carboxyhemoglobin and placental vascular resistance and by decreasing uterine blood flow, possibly leading to chronic fetal hypoxia (Herrmann, King, & Weitzman, 2008). Animal models suggest that prenatal nicotine exposure prematurely stimulates neuronal differentiation, exerts cholinergic effects on cellular communication, neuronal pathfinding and mitosis, and affects neurotransmission by increasing adrenergic receptor binding while reducing dopaminergic activity and serotonin uptake (Herrmann et al., 2008).

Prenatal tobacco exposure appears to be an important risk factor for poorer working memory performance. Children prenatally exposed to tobacco have been found to exhibit worse performance on working memory tasks from preschool age to adolescence (Fried & Watkinson, 2001; Fried, Watkinson, & Gray, 1998; Julvez et al., 2007). Working memory involves the temporary storage and simultaneous processing of information that is critical for complex cognitive tasks such as learning, language comprehension, and reasoning (Baddeley, 1992). Working memory and its risk factors are important to study given that children with poor working memory are at increased risk for learning problems as well as for emotional and behavioral problems (Brunnekreef et al., 2007; Gathercole, Pickering, Knight, & Stegmann, 2004; Maehler & Schuchardt, 2009).

Imaging studies further suggest that prenatal tobacco exposure affects the developing brain, with children exposed to tobacco having thinner parahippocampal, middle frontal, and orbitofrontal cortices (Toro et al., 2008), reduced cortical gray matter and parenchymal volumes, a smaller head circumference (Rivkin et al., 2008), and increased fractional anisotropy (FA) in anterior cortical white matter but decreased FA in supplementary motor area and premotor cortex, suggesting that exposure affects white matter maturation (Jacobsen, Picciotto, et al., 2007; Liu, Cohen, Gongvatana, Sheinkopf, & Lester, 2011).

Prenatal tobacco exposure may be associated with differential brain function during working memory performance, with multiple brain regions implicated in working memory including the dorsolateral prefrontal

cortex (DLPFC, particularly Brodmann areas 10 and 46), inferior parietal lobe (IPL), inferior frontal lobe (IFL), and anterior cingulate cortex (ACC) (Casey et al., 1995; Hurt et al., 2008; Owen, McMillan, Laird, & Bullmore, 2005). At present, however, it is unknown whether tobacco-exposed children exhibit distinct patterns of brain function during working memory. Given that prenatal tobacco exposure tends to co-occur with other risk factors, most notably prenatal alcohol exposure, less than optimal neonatal health, and low socioeconomic status (DiFranza, Aligne, & Weitzman, 2004; Pickett, Wilkinson, & Wakschlag, 2009), any attempt to examine tobacco exposure effects should consider the potential effects of these risk factors. Prenatal alcohol exposure has been associated with differential brain activation during working memory tasks, including increased activation in regions suggestive of less efficient frontal-parietal processing (Astley et al., 2009; O' Hare et al., 2009; Roussotte et al., 2011), while neonatal health problems and environmental risk have each been related to poorer working memory in childhood (Evans & Schamberg, 2009; Luciana, Lindeke, Georgieff, Mills, & Nelson, 1999). Sex differences in activation, brain structure, and performance on cognitive tasks also have been observed in response to tobacco exposure (Bell, Willson, Wilman, Dave, & Silverstone, 2006; Jacobsen, Slotkin, Mencl, Frost, & Pugh, 2007; Toro et al., 2008). As such, the potential effects of prenatal alcohol exposure, neonatal health, environmental risk, and sex were controlled when examining the effects of prenatal tobacco exposure on working memory in the current study.

The purpose of this study is to examine the brain function of tobacco-exposed children during the N-back task, which is commonly used to assess working memory (Owen et al., 2005). We hypothesized that brain regions associated with working memory would show differential activation between exposed and unexposed groups. The specific regions of interest selected were the DLPFC (including Brodmann areas 10 and 46), the IPL, IFL, and ACC as these regions have typically been activated during working memory tasks in prior research (Casey et al., 1995; Hurt et al., 2008; Owen et al., 2005). These differences were observed in the context of correct responses to ensure that brain activation differences between groups could not be attributed to performance differences(J. Lee, Folley, Gore, & Park, 2008).

Methods

Participants

Eighteen 12-year-olds (M = 12.6 years, SD = 0.2), all African American, were recruited from an ongoing longitudinal study of prenatal substance exposure. Seven children were prenatally exposed to cigarettes

(2 boys, 5 girls; PTE group) and 11 were unexposed (5 boys, 6 girls; Control group). Participants were right handed with the exception of one left-handed participant in each group. Imaging was conducted at the Temple University Hospital imaging center in Philadelphia.

Participants in the longitudinal study were initially recruited at or prior to birth through hospital-based prenatal clinics or newly delivered women at a university affiliated hospital in Philadelphia. Prenatal tobacco exposure was assessed by maternal report at the time of birth, which has been shown to be a valid measure of maternal smoking during pregnancy (Campbell, Sanson-Fisher, & Walsh, 2001). Cocaine, cannibinoids, opiates, and phencyclidine exposures were screened using meconium assay and maternal report at birth. Potential subjects with prenatal cocaine or marijuana exposure were excluded because children with exposure to these substances have been found to exhibit poorer working memory or differences in brain activation during a working memory task (Bennett, Bendersky, & Lewis, 2002; Smith, Fried, Hogan, & Cameron, 2006). In addition, children were excluded from the longitudinal study if they were prenatally exposed to opiates or phencyclidine, born prior to 32 weeks of gestation, required special care or oxygen therapy for more than 24 hours, exhibited congenital anomalies, or if their mothers were infected with HIV. No participants were taking stimulant medication at the time of the imaging study.

While 33 children and their parents were approached, 26 agreed to participate. Eight children who agreed to participate, however, were not included as: four were scheduled but did not keep their appointments, two became uncomfortable upon seeing the MRI scanner and decided not to participate, one had a metal plate in his body, and one fell asleep in the scanner during the working memory task. No significant differences were found between children who participated and those who did not in age, sex, prenatal tobacco exposure, prenatal alcohol exposure, environmental risk, or IQ as assessed by the Stanford-Binet Intelligence Scale, Fourth edition (Thorndike, Hagen, & Sattler, 1986) (effect sizes ranged from $d = 0.02$ for IQ to $d = 0.74$ for neonatal health, with a median effect size of $d = 0.38$). As seen in Table 1, no significant differences were observed between the prenatal tobacco exposed and control groups on the measures of prenatal alcohol exposure, current second hand smoke exposure (assessed by the mean of child and parent report on a questionnaire adopted from (Iribarren, Darbinian, Klatsky, & Friedman, 2004), environmental risk, and neonatal health problems. Nonetheless, these variables were included as covariates in analyses of the imaging data in the event that modest relations exist

between these variables and brain function during working memory that could not be detected with current statistical power. The study was approved by the institutional review boards of the Drexel University College of Medicine, Robert Wood Johnson Medical School, and Temple University School of Medicine. Parental consent and participant assent were obtained at the time of the screening interview for the imaging study. Participants were paid $40 in vouchers for use at local stores.

Measures

Environmental risk. Several environmental risk variables were assessed by maternal interview at the 4, 18, 54, 84, 102, and 120 month visits of the longitudinal study. At each age, the 9 individual risk variables were standardized (T-score), reverse coded if necessary so that higher scores reflected greater risk, and then averaged into a composite T-score (Bendersky & Lewis, 1998). The 9 variables were: maternal life stress (based on the Social Environment Inventory (Orr, James, & Casper, 1992); maternal social support network size (Norbeck Social Support Questionnaire (Norbeck, Lindsey, & Carrieri, 1981); number of regular caregivers (greater number = higher risk); irregularity of the child's schedule (Family Chaos Scale; R. Seifer, personal communication); instability of the child's surroundings (Family Chaos Scale; R. Seifer, personal communication); single parent household (living alone with children = higher risk); maternal education (years of education); maternal race (minority status, i.e. non-European American = higher risk); and public assistance status (public assistance as main source of income = higher risk). The mean T-score from each of the six ages was used to estimate environmental risk throughout each adolescent's lifetime.

Neonatal health problems. Prenatal and neonatal medical data were abstracted by nurses from hospital records shortly after birth. They were used to complete a neonatal medical risk scale consisting of 35 possible complications (Hobel, Hyvarinen, Okada, & Oh, 1973). Variables included general factors (e.g., low birth weight, fetal anomalies, and feeding problems), respiratory complications (e.g., congenital pneumonia, apnea, and meconium aspiration syndrome), metabolic disorders (e.g., failure to gain weight and hypoglycemia), cardiac problems (e.g., murmur and cardiac anomalies), and CNS problems (e.g., CNS depression and seizures). The total number of neonatal health problems ranged from 0 to 13 in the current sample.

Prenatal tobacco and alcohol exposure. Substance use during pregnancy was obtained through a semi-structured interview conducted prenatally or in the mother's room on the maternity ward postnatally

(Bendersky, Alessandri, Gilbert, & Lewis, 1996). The interview contained questions about the frequency and amount of cigarette and alcohol use, as well as use of cocaine, marijuana, opiates, and phencyclidine. Participants were assigned to the tobacco exposure group if their mothers reported any cigarette smoking during pregnancy. The average number of cigarettes per day smoked by mothers throughout pregnancy in the tobacco exposure group was 6.09 (SD=6.92), with a range of 1 to 20 per day. Alcohol exposure, a covariate, was based on maternal report of the average number of alcoholic beverages (i.e., 12 oz. beer, 5 oz. wine, or 1 shot of liquor) consumed throughout pregnancy, with a range of 0.00 to 0.28 drinks per day.

Design/Paradigm

An event-related fMRI design was used to assess brain activation during the N-back task. Prior to entering the imager, children briefly practiced 0-, 1-, and 2-back trials to ensure that they understood the procedure. Children made responses by pressing a button on a keypad with their dominant hand. Once in the imager, numbers were presented one at a time for 1000 msec followed by a 1000 msec ISI for each condition. In the 0-Back condition, participants were to respond whenever a "5" appeared. In the 1-Back condition, participants were to respond whenever a number repeated itself (e.g., “8-8”). In the 2-Back condition, participants were to respond only when a number repeated itself following an intermittent number (e.g., "7-4-7"). Participants were told that each of the three conditions would be repeated once, and that an image on the screen would cue them as to the new condition. The 0-Back condition was administered first (25 trials with 8 targets), followed by the 1-Back (29 trials with 7 targets) and 2-Back (28 trials with 7 targets) conditions. A picture (e.g., of a computer screen with “7-4-7” to prompt the child that a 2-back series was about to begin) was present for 6000 msec to let participants know that a different N-back condition was about to begin. Each condition was then repeated a second time using a different set of numbers and with the same number of trials, but with 8 targets presented in the 1-Back and 2-Back conditions. The 2-Back minus 1-Back contrast was used for the present analyses as this contrast best reflects higher-order working memory executive processing (Haberecht et al., 2001; Ragland et al., 2002; Tan et al., 2006) and may be the most sensitive to behavioral performance differences among prenatally exposed children (Astley et al., 2009). Furthermore, prenatal drug exposure effects may be most visible under increased cognitive demands (Savage, Brodsky, Malmud, Giannetta, & Hurt, 2005) such as required in the 2-Back condition.

fMRI Recording Apparatus

Functional MRI (fMRI) provides a method to non-invasively observe differences in brain function during cognitive or motor tasks such as the N-back (Braver et al., 2001). Scanning was performed using a 1.5 Tesla General Electric Scanner with a gradient echo-EPI sequence and an eight channel head coil. Participants were positioned supine on the gantry of the scanner with the head midline in the coil. In addition to instructions to limit head motion, foam pads within the head coil helped secure head fixation and prevent motion. Scanning began with a standard spin echo T1-weighted sequence positioned parallel to the line of the anterior and posterior commissures covering the whole brain. This yielded 24 axial slices of the brain for analyses as the high resolution structural images. Imaging parameters were matrix size = 256*256; TR = 3000 ms; TE = 60 ms; FOV = 22 cm; NEX = 1; slice thickness = 5 mm, interleaved with no skip. fMRI images were acquired using a T2*-weighted echo planar imaging (EPI) gradient echo sequence (matrix size = 64*64; TR = 2000 ms; TE = 50 ms; FOV = 22 cm; slice thickness = 5 mm, with no skip) covering the same brain regions and in the same plane as the T1-weighted sequence. The N-back stimuli were presented using MRI compatible 3D video goggles (Resonance Technologies, Inc.), which had 180,000-pixel resolution and a 30° field of view. All stimuli were delivered using Neurobehavioral Systems Presentation software (www.neurobs.com). An MR compatible response keypad was used to measure the responses participants made to the visual displays.

Image Processing

The post-acquisition preprocessing and statistical analysis was performed using SPM2 (K. Friston, 2003), run under the Matlab environment (The Mathworks, Inc., Natick, MA). Images were converted from DICOM format into ANALYZE (AnalyzeDirect, Inc., Lenexa, KY) format adopted in the SPM package. Slice timing correction was performed to compensate for delays associated with acquisition time differences among slices during the imaging. A 3D automated image registration routine (six-parameter rigid body, sinc interpolation; second order adjustment for movement) was applied to the volumes to realign them with the first volume of the fMRI series used as a spatial reference (i.e., immediately before subjects viewed the cross-hair for 18 sec). The functional volumes collected at this time are closest in sequence to the acquisition of the high resolution structural images. All functional and anatomical volumes were then transformed into the standard anatomical space using the T2 EPI template and the SPM normalization procedure (Ashburner & Friston, 1999;

Friston et al., 1995). This procedure uses a sinc interpolation algorithm to account for brain size and position with a 12 parameter affine transformation, followed by a series of non-linear basic function transformations seven, eight, and seven nonlinear basis functions for the x, y, and z directions, respectively, with 12 nonlinear iterations to correct for morphological differences between the template and given brain volume. Next, all volumes underwent spatial smoothing by convolution with a Gaussian kernel of 8 cubic mm full width at half maximum (FWHM), to increase the signal-to-noise ratio (SNR) and account for residual intersession differences.

Individual subject-level statistical analyses were performed using the general linear model in SPM2, restricting analyses to trials in which subjects responded correctly. The two condition events and the baseline were modeled using a canonical hemodynamic response function. Working memory effects were examined via linear contrasts to the parameter estimates for the correct N-back two minus correct N-back one trials contrast, resulting in a contrast map for each participant.

A region of interest (ROI) analysis was performed on predetermined regions identified in the literature as involved in working memory (Casey et al., 1995; Hurt et al., 2008; Owen et al., 2005), controlling for environmental risk, neonatal health problems, and prenatal alcohol exposure. These regions were: bilateral DLPFC, bilateral IPL, bilateral IFL, and the ACC. The BOLD activation in each of these regions was masked using WFU PickAtlas software (The Functional MRI Laboratory, Wake Forest University School of Medicine). The ROI analysis was conducted at the group level, and not at the individual level. All of the interpretations were done after a random effects analysis (RFX) of the group data. Cluster probability of an uncorrected value of $p \leq 0.001$ was applied to the regions of interest and the surviving voxels were retained for further analysis. The volumes of these surviving clusters within the ROI's were calculated using MarsBaR software (Brett, Anton, Valabregue, & Poline, 2002).

Results

Task Performance. The measures obtained were omission errors, i.e. neglecting to hit the button when a target stimulus appeared, and commission errors, i.e. hitting the button when a non-target stimulus was present. Exposed and unexposed children did not differ significantly in the mean number of total omission errors ($M_{Exposed}$=11.4 (*SD*=7.1) vs. $M_{Controls}$=8.1 (*SD*=4.9), *t*(16)=1.15, *p*=.27) or commission errors ($M_{Exposed}$=2.7

(*SD*=2.0) vs. $M_{Controls}$=4.9 (*SD*=5.0), *t*(16)=1.09, *p*=.29). Likewise there were no significant group differences in the number of omission or commission errors when examining the 2-, 1-, and 0-back conditions separately ($p > .15$ for each).

Whole Brain Results. Figures 1 and 2 present SPM anatomical images showing brain activations based on exposure group during correct responses. Table 2 presents significant ($p \leq .001$; Z scores ≥ 3.00) activation differences between exposure groups from the whole brain analysis during correct responses. Exposed children showed greater activation primarily in the inferior parietal region. In contrast, the unexposed children primarily showed greater activation in inferior, middle, and superior frontal regions.

ROI Results. Table 3 presents significant ($p \leq .001$) activation differences between exposure groups from the ROI analyses during correct responses. Exposed children showed greater activation in the right parietal lobe (BA7 and BA40), right inferior frontal gyrus (BA11), and left middle frontal gyrus (BA46). In contrast, the unexposed children showed greater activation in the right and left inferior frontal gyrus and, to a lesser extent, the right middle frontal gyrus. A similar number of voxels was found to be activated for each group in the left inferior parietal region. No activation was observed in the ACC.

Discussion

The current study is the first to examine imaging differences in working memory as a function of prenatal tobacco exposure. Consistent with prior research using the N-back task, activation was observed in frontal and parietal regions (Owen et al., 2005). Children prenatally exposed to tobacco showed greater activation in inferior parietal regions, whereas unexposed children showed greater activation in bilateral inferior frontal regions during a working memory task. These differences were observed in the context of correct responses, suggesting that exposed and unexposed children use somewhat different brain regions when correctly utilizing working memory.

The greater activation of the inferior frontal region exhibited by controls is consistent with a developmental shift in which frontal regions are increasingly used across late childhood and adolescence during working memory (Casey et al., 1995; Scherf, Sweeney, & Luna, 2006). This increased activation during working memory coincides with the development of increased myelination in non-cortical white matter circuitry in prefrontal regions during childhood and adolescence (Barnea-Goraly et al., 2005). Increased fractional

anisotropy in the inferior frontal lobe in children and adolescents, believed to reflect the extent of myelination in white matter, has been associated with greater working memory performance (Nagy, Westerberg, & Klingberg, 2004). Such increased myelination suggests that more efficient, mature working memory performance is dependent in part on improved functional connectivity between frontal and parietal regions (Edin, Macoveanu, Olesen, Tegner, & Klingberg, 2007; Scherf et al., 2006). In addition, children who were not exposed to tobacco exhibited increased left inferior frontal activation in Brodmann area 45. Activations in this region, which was also found to be activated in controls but not children prenatally exposed to alcohol in response to an N-Back task (Diwadkar et al., 2012), is believed to involve response organization (e.g., verbal rehearsal of the stimulus)(Chein, Fissell, Jacobs, & Fiez, 2002) and raises the possibility that controls may have used verbal rehearsal to a greater extent.

The N-back task involves multiple underlying executive processes, including active maintenance of the last N items, an update of new items to be maintained, a rapid ordering of items to match the current item with the N-back item, and resistance to proactive interference arising from non-N lag items (Barbey, Koenigs, & Grafman, 2011) The N-back task also requires participants to quickly decide whether a target stimulus is present and, if not, to refrain from pressing a button (i.e., behavioral inhibition). Working memory performance is closely linked to inhibition (McNab et al., 2008). The ability to inhibit responding is associated with greater inferior frontal activation, which increases during successful response inhibition from age 10 years to adulthood (Booth et al., 2003; Rubia, Smith, Taylor, & Brammer, 2007). The N-back task also requires one to expel previous information from working memory when the information (i.e., a specific number) is no longer relevant (i.e., cognitive inhibition). The left inferior frontal cortex has been repeatedly found to be activated in response to tasks assessing such cognitive inhibition (Jonides & Nee, 2006). Thus, the inferior frontal region is involved in both behavioral and cognitive inhibition. Adolescents with ADHD, which is more common among tobacco exposed youths (Abbott & Winzer-Serhan, 2012; Froehlich et al., 2009; Galera et al., 2011), also exhibit less inferior frontal activation as well as poorer performance during response inhibition tasks (Cornelius et al., 2011; Rubia, Smith, Brammer, Toone, & Taylor, 2005). Furthermore, while diagnoses of ADHD were not made in the current study, children with ADHD have been found to exhibit poorer working memory performance, consistent with the notion that attentional systems are central to working memory (Baddeley, 1992; Martinussen, Hayden,

Hogg-Johnson, & Tannock, 2005). Collectively, these findings suggest that children prenatally exposed to tobacco (and the social-genetic environment in which tobacco use occurs during pregnancy) may have less mature behavioral inhibition, cognitive inhibition, and attentional systems, which in turn may affect their working memory ability.

While exposed children exhibited less inferior frontal activation, they exhibited greater inferior parietal activation, which is associated with memory maintenance and inhibitory control, in the right hemisphere (Geier, Garver, Terwilliger, & Luna, 2009; McNab et al., 2008). This finding is somewhat surprising in that IPL activation, like IFL activation, has been found to increase from childhood to adolescence and adulthood during working memory tasks (Geier et al., 2009; Scherf et al., 2006). However, right IPL activation is associated with sustained attention (Singh-Curry & Husain, 2009). Given that prior studies have found tobacco exposed children to exhibit poorerworking memory than unexposed children (Fried & Watkinson, 2001; Fried et al., 1998; Julvez et al., 2007), the increased right parietal activity does not necessarily indicate more mature brain function, but may instead indicate a less automatic, less efficient use of the IPL in sustaining attention during a working memory task. This interpretation is consistent with research finding that tobacco exposed children exhibit deficits in sustained attention (Leech, Richardson, Goldschmidt, & Day, 1999). Alternatively, IPL activation has been found to increase in response to memory load (Kirschen, Chen, Schraedley-Desmond, & Desmond, 2005; Nyberg, Dahlin, Stigsdotter Neely, & Backman, 2009), suggesting that it is central to storage in working memory. This raises the possibility that children prenatally exposed to tobacco found the N-back task to be more challenging than their peers, even for trials that they completed successfully, as they exhibited greater utilization of regions involved in storage. IFL activation, however, also increases with memory load (Kirschen et al., 2005), limiting the specificity of this interpretation. A third possible explanation pertains to the IPL's involvement in number processing, as stimuli used in the current N-back task were Arabic numbers. The right IPL, in particular, is involved in the conceptual processing of numbers (Cappelletti, Lee, Freeman, & Price, 2010), raising the possibility that children with tobacco exposure are less efficient in number processing. While the underlying processes are unclear, our findings do suggest similarities between prenatal tobacco and alcohol exposure given that children with fetal alcohol syndrome have been found to exhibit greater parietal activation whereas unexposed children were found to primarily recruit left inferior frontal regions during an N-back task in

a study by Diwadkar and colleagues (Diwadkar et al., 2012), paralleling our findings of children with tobacco exposure.

The anterior cingulate, which is related to increased effort, task complexity, conflict monitoring, and error monitoring (Duncan & Owen, 2000; Kerns et al., 2004; Kiehl, Liddle, & Hopfinger, 2000), did not show activation or differences in activation as a function of tobacco exposure. Differences in the anterior cingulate may have been more observable had we included incorrect rather than correct responses, as the anterior cingulate may not be activated during correct trials (Kiehl et al., 2000). Alternatively, the anterior cingulate may play a greater role in working memory later in adolescence and adulthood (Scherf et al., 2006), making it difficult to observe activation differences at the age of the current participants during early adolescence.

Activation of the dorsolateral prefrontal cortex, including the inferior frontal region, is believed to reflect executive or control processes, including those related to rehearsal (Smith & Jonides, 1997, 1999). In contrast, activation in posterior parietal regions, including the inferior parietal region, is believed to reflect working memory storage (Smith & Jonides, 1997, 1999). Longitudinal research is needed to examine whether the differences in activation of these regions observed among Tobacco-Exposed youth persists into adolescence, or whether the brain function of exposed youths becomes more similar to that of their unexposed peers at some point. It will also be important to identify the effects of tobacco exposure on brain function at multiple time points, as there are regional variations in the timing of changes (e.g., myelination and synaptic pruning) that may affect brain development, particularly in the protracted development of prefrontal cortex regions such as the inferior frontal region (Best, Miller, & Jones, 2009). The effects of cigarette smoking during adolescence may also affect brain development and function (Jacobsen, Picciotto, et al., 2007). Given that children prenatally exposed to tobacco may show greater executive function deficits when emotionally aroused (Huijbregts, Warren, de Sonneville, & Swaab-Barneveld, 2008), future research should also examine working memory performance under "hot" as well as "cold" cognition contexts among children prenatally exposed to tobacco. Finally, while the current study found exposure differences in frontal and parietal lobe function, research is needed to examine possible differences in the connectivity of the fronto-parietal network.

Several limitations deserve mention. First, prenatal tobacco exposure classification was based on maternal report. Although it is unlikely that mothers in the tobacco exposure group reported smoking when they

did not, it is possible that mothers in the unexposed group may have smoked. Second, our sample size was relatively modest and the current findings need to be replicated in a larger sample. Similarly, sex was covaried as our sample size did not allow for the examination of sex effects, including tobacco exposure by sex interactions which have been inconsistently found in prior research (Coles, Kable, & Lynch, 2012). Third, while working memory involves activation of common regions regardless of the modality or type of stimulus presentation (Baldo & Dronkers, 2006; Owen et al., 2005), modality- and stimulus-specific differences are sometimes observed and as such the current findings do not necessarily generalize to other modalities (e.g., oral presentation) or stimuli (e.g., spatial). Likewise, it should be noted that the N-back task assesses different aspects of working memory than do memory span tasks (Miller, Price, Okun, Montijo, & Bowers, 2009; Oberauer, 2005) and our findings may not generalize to other measures of working memory. While complex span tasks demand serial recall in which participants retrieve items using only self-generated cues, the N-back task demands recognition as participants discriminate target items from familiar foils (Kane, Conway, Miura, & Colflesh, 2007). Fourth, we were unable to control for genetic factors and specific environmental or familial factors (e.g., ADHD) that may increase risk for both maternal smoking and differential patterns of children's activation during working memory. This is particularly important given that ADHD, for example, has a strong genetic basis (Faraone, Perlis, Doyle, Smoller, Goralnick, Holmgren, & Sklar, 2005) and is associated with increased cigarette smoking (Kollins, McClernon, & Fuemmeler, 2005), Finally, our sample consisted solely of African American children and the results may not necessarily generalize to children of other racial or ethnic groups.

This is the first study to identify differences in brain function during working memory related to prenatal tobacco exposure. Our findings suggest that tobacco exposed vs. unexposed youths differentially employ inferior frontal and inferior parietal regions during working memory. To the extent that tobacco exposed youths actually exhibit poorer working memory, it will be important to examine whether such performance can be improved with intervention (Holmes, Gathercole, & Dunning, 2009) and whether changes in parietal and frontal regions result from such training. Recent research, for example, has found that the amount of working memory training was related to increased fractional anisotropy of fiber tracts in the white matter regions adjacent to the intraparietal sulcus, suggesting that such training may increase myelination in this

region (Takeuchi et al., 2010). Pharmacological interventions may also enhance working memory for children showing poor working memory (Holmes et al., 2010). Such improvements in working memory may lead to improved academic and behavioral performance for children (Roberts et al., 2011).

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Table 1
Means (and standard deviations) of covariates

	Tobacco-exposed (n = 7)	Unexposed (n = 11)	t value (16 df)	p
Environmental Risk	53.51 (10.2)	51.80 (5.4)	0.47	0.65
Neonatal Health Problems	1.80 (2.5)	0.89 (1.1)	1.07	0.30
Prenatal Alcohol Exposure	0.04 (0.1)	0.01 (0.0)	1.01	0.33
Prenatal Tobacco Exposure	4.18 (3.4)	0.00 (0.0)	4.15	0.0007
Second Hand Smoke Exposure	1.14 (1.3)	1.21 (1.22)	0.13	0.90

Note. Prenatal alcohol exposure refers to the mean number of alcoholic beverages per day consumed throughout pregnancy. Prenatal tobacco exposure refers to the mean number of cigarettes smoked per day throughout pregnancy.

Table 2

Whole brain analysis: Areas showing significant group differences in activation during working memory (i.e.,correct 2-back minus 1-back trials)

Region	BA	Radiological Coordinates (3mm Range) x	y	z
Greater activation for Exposed group				
Parietal lobe				
R inferior parietal lobe	40	37	-58	45
		42	-39	44
		53	-34	24
		44	-33	35
L inferior parietal lobe	40	-44	-36	48
		-67	-28	31
		-40	-33	33
		-55	-31	42
		-50	-31	35
		-46	-43	28
		-51	-45	39
		-36	-50	45
		-42	-42	44
Sub-lobar				
R insula	13	48	-39	26
Greater activation for Control group				
Frontal Lobe				
R inferior frontal gyrus	47	40	17	-6
	47	32	25	-6
	9	48	3	20
	46	-44	39	4
L inferior frontal gyrus	9	-53	15	36
	44	-61	12	16
	45	-51	22	15
R middle frontal gyrus	9	44	13	36
	9	44	11	27
	11	46	36	-12
	11	36	34	-15
	46	48	42	15
	46	48	30	21
R superior frontal gyrus	10	26	52	-3
Parietal Lobe				
R inferior parietal lobe	40	46	-48	52
L inferior parietal lobe	40	-55	-44	43
Sub-lobar:				
R insula	13	34	23	3

Note. All areas significant at $p \leq .001$ and with Z scores ≥ 3.00.

Note. BA = Brodmann's area.

Table 3

Region of interest analyses: Number of activated voxels by group during working memory (correct 2-back minus correct 1-back trials)

Region of Interest	Number of Activated Voxels	
	Unexposed Group	Exposed Group
1. Inferior frontal gyrus, Left (BA 47)	985	0
2. Inferior frontal gyrus, Right (BA 9, 45 & 46)	555	0
3. Inferior frontal gyrus, Right (BA 11)	0	17
4. Inferior parietal lobe, Left (BA 40)	214	179
5. Inferior parietal lobe, Right (BA 40)	0	267
6. Inferior parietal lobe, Right (BA 7)	0	23
7. Middle frontal gyrus, Left (BA 46)	0	17
8. Middle frontal gyrus, Right (BA 9)	11	0