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Early Risk, Attention, and Brain Activation in Adolescents Born Preterm

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Abstract

The relations among early cumulative medical risk, cumulative environmental risk, attentional control, and brain activation were assessed in 15 – 16-year-old adolescents who were born preterm. Functional magnetic resonance imaging found frontal, temporal, and parietal cortex activation during an attention task with greater activation of the left superior-temporal and left supramarginal gyri associated with better performance. Individual differences in early cumulative risk are related to patterns of brain activation such that medical risk is related to left parietal cortex activation and environmental risk is related to temporal lobe activation. The findings suggest that early risk is related to less mature patterns of brain activation, including reduced efficiency of processing and responding to stimuli.

Studies of the developmental outcome of low-birth-weight survivors have shown deficits in cognitive ability and school achievement through young adulthood (e.g., Bhutta, Cleves, Casey, Craddock, & Anand, 2002; Breslau et al., 1996; Hack et al., 2002). However, many preterm children show none of these deficits, and therefore it is necessary to consider other factors that covary with prematurity, particularly neonatal medical complications and the social environment in which these at-risk infants are raised (Bendersky & Lewis, 1994, 1995; Lewis & Bendersky, 1989). There is now ample evidence to indicate that cumulative neonatal medical complications scores (MCS) are negatively related to subsequent development that includes cognitive and motor deficits, achievement, and behavioral problems at school age (Cohen & Parmelee, 1983; Cohen et al., 1996; Klebanov, Brooks-Gunn, & McCormick, 1994; Leonard et al., 1990; Rose, Feldman, Rose, Wallace, & McCarton, 1992; Thompson et al., 1997;

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Werner, Simonian, Bierman, & French, 1967). Similarly, the pre- and postnatal environment plays a prominent role in subsequent development, and cumulative environmental risk scores (ERSs) have repeatedly been shown to be related to cognitive and social development (Atzaba-Poria, Pike, & Deater-Decker, 2004; Bendersky & Lewis, 1994, 1995, 1998; Cohen et al., 1996; Deater-Decker, Dodge, Bates, & Pettit, 1998; Lee & Barratt, 1993; Luciana, 2003; McGauhey, Starfield, Alexander, & Ensminger, 1991; Sameroff, Seifer, Baldwin, & Baldwin, 1993; Sameroff, Seifer, Barocas, Zax, & Greenspan, 1987; Sameroff, Seifer, Zax, & Barocas, 1987; Shraeder, Heverly, & O'Brien, 1996; Stanton, McGee, & Silva, 1991).

Preterm birth appears to affect the development of the brain. Neuroimaging studies have identified diffuse abnormalities of the brain and reduced brain volumes at age 8 years in preterm children compared with controls in several regions, including sensorimotor, premotor, parietal – occipital, and midtemporal cortices, while controlling for size of head, body, and brain (Peterson, 2003). Regional volumes were related to gestational age at birth. In addition, there are smaller volumes of basal ganglia, corpus callosum, amygdala, and hippocampus for preterms at age 8 years, even after excluding cases that had intraventricular hemorrhages. Magnetic resonance imaging (MRI) has shown that the gray to white matter ratio is lower in preterm than term adolescents (Allin et al., 2004; Nosarti et al., 2002).

The changes in the structural development of the brain resulting from preterm birth are also related to subsequent deficits in cognitive functioning. Voxel-based morphometry analyses of MRI scans show that IQ scores are related to areas in the temporal and parietal regions in adolescents who were born pre-term and classified as neurologically normal (Isaacs et al., 2004). Higher IQ scores were associated with less gray matter and more white matter in the parietal lobe regions of the angular gyrus and intraparietal sulcus. Moreover, IQ at age 8 years is associated with the volumes of sensorimotor, mid-temporal, and parietal – occipital regions (Peterson et al., 2000). In general, correlations have been found between brain structure and IQ, for total brain volume (see Gray & Thompson, 2004, for a review) and for gray matter volume (Thompson et al., 2001; Wilke, Sohn, Byars, & Holland, 2003).

In a long-term study of preterm infants, Bendersky and Lewis (1994, 1995) found that specific outcomes were related to different cumulative risk scores. A cumulative MCS predicted motor performance at ages 2 and 3 years, whereas a cumulative ERS predicted cognitive and language outcomes. These findings suggest that cortical areas involved in motor function, including the parietal lobe, are sensitive to the effects of neonatal medical complications (Murphy et al., 2001; Platt & Glimcher, 1999). Unlike the cumulative neonatal MCS, which impacts early central nervous system (CNS) development, the cumulative ERS continues to affect development over time. Reducing environmental risk has been shown to improve neurobehavioral functioning in preterm infants, and, in particular, to decrease the MRI T2* signal (indicating greater maturation) in frontal white matter and occipital lobe compared with the control group (Als et al., 2004). It also improves the coherence of electroencephalogram (EEG) signals between left frontal regions and occipital and parietal regions (Als et al., 2004). These findings suggest that frontal and posterior brain regions, which are integrally involved in language, attention, and cognitive function, may be more specifically impacted by environmental factors.

Studies of brain activation during attention tasks have shown increases in posterior areas that are mediated by parietal and anterior cingulate cortices (Cabeza & Nyberg, 2000; Pugh et al., 1996). A study of auditory vigilance shows an auditory attention network consisting of the right ventrolateral frontal cortex, the right parietal cortex, as well as the orbitolateral and dorsolateral frontal cortex (Paus et al., 1997). A network that includes the prefrontal and parietal regions serves to regulate directed attention and executive functioning (Booth et al., 2003; Bunge, Dudukovic, Thomason, Vaidya, & Gabrielli, 2002; Daffner et al., 2003; Davis, Bruce,

Snyder, & Nelson, 2003; Klingberg, Forssberg, & Westerberg, 2002; Posner & Dehaene, 1994).

Little is known about the impact of preterm birth on brain activation during cognitive tasks. There are few studies to date that have looked at whether individual characteristics of preterm children systematically affect the brain-behavior relation. For example, preterm infants with higher cumulative MCS and cumulative ERS might show poorer performance and different brain activation during an attention task than those with less risk. A review of the literature on cognitive development in preterm children indicates that few studies follow cohorts in young adulthood, and that many research reports have not considered environmental risk (Luciana, 2003). In addition, many neuroimaging studies emphasize the consistency of activation across subjects; therefore, a focus on the variability across subjects, rather than the consistency, may provide a basis for the variability in performance on cognitive tasks, and especially in attention tasks (Cabeza & Nyberg, 2000).

In the present study we examine attention in a group of adolescents who were born preterm. Because we found in preterms that a cumulative MCS and a cumulative ERS differentially affect later development (Bendersky & Lewis, 1994, 1995; Lewis & Bendersky, 1989), we examined these two risk scores as they relate to patterns of brain activation using functional magnetic resonance imaging (fMRI) during performance in an attention task. Moreover, as morphological abnormalities are shown in the parietal and temporal cortex in preterm infants and children (Peterson, 2003), and these brain regions are involved in a broad network that supports selective attention (Pugh et al., 1996), performance on the attention task should be related to activation of parietal and temporal regions. Furthermore, on the basis of the EEG and MRI findings with NICU infants, higher cumulative ERS should relate to decreased brain activation in temporal lobes and increased attention errors (Als et al., 2004). On the other hand, higher cumulative MCS would reduce brain activation in parietal areas and increase response times in an attention task.

Method

Participants

Ten participants (15 – 16-years-old; 7 females) served as volunteers. All were born preterm (gestational ages ranged from 28 to 35 weeks, $M = 32.1$, $SD = 2.5$) with birth weight ranging from 1,100 to 2,050 g ($M = 1612$, $SD = 336$). None showed intraventricular hemorrhage (IVH) as evaluated by ultrasound scanning performed at the bedside at 4 and 24 hr as well as 7 days after birth (Bendersky & Lewis, 1994). Two were African-American and eight were European-Americans. This sample of 10 adolescents was a subset of the 74 infants born preterm without IVH (Bendersky & Lewis, 1995). Using a series of *t* tests, no differences were found between the sample and the larger group of 74 preterm infants without IVH in several measures including gestational age, birth weight, medical complications, environmental risk, full-scale intelligence quotient at age 3 years, or the four subscales of Stanford – Binet.

fMRI Recording Apparatus

Scanning was performed with a 1.5 T GE Signa System (General Electric, Milwaukee) with an echo gradient-EPI sequence and a standard quadrature 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. Participants were run with eyes open to reduce their anxiety levels, and ambient light from a window allowed for visual orientation to the room. Scanning began with a standard spin echo T1-weighted sequence positioned parallel to the line of the anterior and posterior commissures covering most of the brain in nine slices from vertex to tentorium. This

yielded horizontal slices of the brain for analyses. Imaging parameters were matrix size = 256×256 ; TR = 400 ms; TE = min; FOV = 21 cm; NEX = 1; slice thickness = 10 mm, with 1 mm skip. T2*-weighted images were acquired using echo planar imaging (EPI) gradient echo sequence (matrix size = 128×128 ; TR = 3000ms; TE = 60ms; FOV = 40cm; flip angle = 90; slice thickness = 10mm, with 1mm skip) covering the same brain regions and in the same plane as the T1-weighted sequence.

Procedure

Participants performed an attention task while fMRI data were collected in a block design. They were to squeeze a bulb when the letter A was heard and to inhibit the squeeze when letters other than A were heard. Letters were presented at the rate of 500 ms per letter with an interstimulus interval of 1,000 ms, which is a presentation rate that has been used with children aged 9 – 11 years (Casey et al., 1995). The task took 300 s to complete 10 blocks of 30 s each. For the first block of 30 s, no letters were presented allowing accommodation to the scanner noise. During the second, fourth, seventh, and ninth blocks of 30 s, 20 letters were presented randomly, of which 15 were the letter A and 5 were letters other than A. For the third, fifth, eighth, and tenth blocks of 30 s, 20 letters other than A were presented randomly. Participants wore headphones connected to a PC using software (E-Prime) that presented instructions and the auditory stimuli, and recorded participants' responses.

Measures

Brain activation—Brain regions were analyzed slice by slice for activation with the Analyses of Functional Neuroimages Package (AFNI; Cox, 1996; Cox & Hyde, 1997) running under UNIX software. The data were realigned to minimize motion-related artifacts. A cross-correlation analysis was applied to determine if hemodynamic activity changed proportionally with the changes in the auditory stimuli, from blocks with the letter A to blocks with letters other than A. A synthesized boxcar waveform corresponding to the stimulus presentation was cross-correlated with all voxel time courses on a voxel-by-voxel basis to identify stimulus-locked responses. All voxels that passed the statistical threshold (p value = 0.01, uncorrected) in the task-activated data sets were considered activated. In this way, we identified the voxels that correlated with the changes in task from the blocks when the letter A was present to the blocks when the letter A was not present. We combined blocks of trials into two sets. The first set of blocks combined the BOLD signal in blocks 2 and 4 and compared it with the combined BOLD signal in blocks 3 and 5 to identify voxels that were active during the attention task. Similarly, the second set of blocks combined the BOLD signal in blocks 7 and 9 and compared it with the combined BOLD signal in blocks 8 and 10 to identify active voxels.

The active voxels were assigned to brain regions. Twenty-two regions were selected based on previous studies of auditory selective attention (Booth et al., 2003; Pugh et al., 1996). The extents of the regions were determined by the gyri and sulci patterns as defined in the Harvard Whole Brain Atlas (Johnson & Becker, 1999). The regions were identified on the right and left sides for (a) superior frontal, (b) middle frontal, (c) inferior frontal, (d) anterior cingulate, (e) superior temporal, (f) middle temporal, (g) inferior temporal, (h) superior parietal, (i) angular gyrus, (j) supramarginal gyrus, and (k) inferior parietal. These brain regions were defined as active for a participant if four or more contiguous pixels were activated (Forman et al., 1995). As the BOLD signal was analyzed twice for each participant, once for each set of blocks, activation scores for each brain region were either 0 (no activity on either set), 1 (active on either the first or second set), or 2 (active on both sets).

Concurrent performance measures—Participants' behavioral performances on the task were measured both by their response time to the appearance of the letter A and by their accuracy in identifying the letter A. Response time was measured in milliseconds from the

onset of the letter presentation until the bulb squeeze. Two types of errors indicated accuracy. Type 1 errors were responses when letters other than A were presented. Type 2 errors were failures to respond when the letter A was presented. Each type of error reflects different processes. Type 1 errors are inhibitory errors as they represent failures to suppress an incorrect response, whereas Type 2 errors reflect attentional failures because they indicate missing responses to targets. Given the small sample size, a combined performance score (CPS) was used for comparison with the fMRI data. A CPS was calculated by adding z-score transformations for response times and Type 2 errors. There were too few Type 1 errors to include them in the combined score. Concurrent intelligence was assessed within 4 weeks of the fMRI with the Wechsler Intelligence Scale for Children-Version 3 (WISC-3).

Cumulative risk measures—Aggregate variables of risk are more stable than any individual measure, and there is increased power to detect effects because errors of measurement decrease as scores are summed and degrees of freedom are preserved (Burchinal, Roberts, Hooper, & Zeisel, 2000; Wachs, 1991). Cumulative risk measures have been found to explain more variance in children's outcomes than single factors (Atzaba-Poria, Pike, & Deater-Decker, 2004; Bendersky & Lewis, 1994, 1998; Deater-Decker et al., 1998; Sameroff et al., 1993; Sameroff, Seifer, Barocas et al., 1987; Sameroff, Seifer, Zax et al., 1987; Stanton, McGee, & Silva, 1991). Cumulative measures of environmental risk have been shown to be associated with subsequent developmental outcomes (Bendersky & Lewis, 1994, 1995; McGauhey et al., 1991; Sameroff, Seifer, Barocas et al., 1987; Sameroff, Seifer, Zax et al., 1987; Sameroff et al., 1993).

Prenatal and perinatal medical histories for the participants were available from our longitudinal study (Bendersky & Lewis, 1994, 1995). The cumulative MCS was derived by summing the following common complications of prematurity: 1- and 5-min Apgar scores less than six, respiratory distress syndrome, mechanical ventilation for longer than 1 week, apnea greater than 2 weeks, hyper-bilirubinemia (bilirubin level greater than 10), metabolic disorder (hypoglycemia, hypocalcemia, hyper- or hyponatremia, or other metabolic disorder detected in at least one blood test), seizures, sepsis requiring treatment for more than 7 days, meningitis, hypoxia, shock, anemia at admission (hematocrit <40), acidosis (pH <7.2 on at least one occasion), bronchopulmonary dysplasia, and patent ductus arteriosus. A cumulative ERS included the following items: parental education and occupation, family status, life stress, social support, minority status, and the mother – child interaction (see Bendersky & Lewis, 1994, for more details). ERS data were available for the participants in this study at 3 months, 1 year and 3 years of age. A single ERS score was obtained by averaging the standard scores over the three ages.

Although different risk scores have different consequences, a composite risk score was obtained to determine if multiple risks affect brain activation. A combined risk score (CRS) was calculated by adding z-score transformations for MCS and for ERS. Finally, an overall competence score (OCS) was obtained in order to compare individual subject's overall competence with brain activation. This OCS was computed by combining response times, Type 2 errors, IQ, the MCSs, and the ERSs. There were too few Type 1 errors to include them in the combined score. The OCS allows for maximizing power given our sample size, and the number of comparisons necessary given the number of variables under examination.

Results

Analyses were performed on the brain activation patterns, performance, and the two risk scores. Brain activity then was examined as a function of performance, risk, IQ, and competence.

Overall Brain Region Activation

An analysis of activation of the motor cortex yields a manipulation check on the sensitivity of the fMRI to detect changes when participants respond. The BOLD signal changed during responses in the supplementary motor area for all participants on the right side and for 80% of the participants on the left side. In addition, all participants showed activation of the postcentral gyrus on the right side and 50% of participants showed left side activation. Therefore, the BOLD response indicates activation of the motor cortex for all participants consistent with hand activity during the response.

Over all participants, there was activation in the frontal lobe, in particular the superior- (75% on left side, 70% on right side), middle- (75% left, 60% right), and inferior- (70% left, 85% right) frontal regions, and anterior cingulate (50% left, 60% right). In addition, there was activation in the superior- (35% left, 60% right) and inferior- (65% left, 85% right) parietal lobules, angular gyrus (35% left, 50% right), and supramarginal gyrus (55% left, 90% right). Finally, activation was found for the group in superior-temporal (60% on the left side, 75% right), medial-temporal (35% left, 35% right), and inferior-temporal (25% left, 25% right) regions. In general, the activation in the right was greater than in the left side. These group results are consistent with the activation patterns reported in tasks of auditory selective attention (Pugh et al., 1996) and inhibitory control (Casey et al., 1997). The appendix lists the levels of activation in brain regions by individual participants and for the group.

Individual Differences

Table 1 presents the performance measures of response times, Type 2 errors, standardized CPS scores ($M = -0.05$, $SD = 1.59$), IQ ($M = 102.1$, $SD = 17.62$), MCSs ($M = 4.20$, $SD = 3.08$), standardized ERSs ($M = 0$, $SD = 1.00$), CRS scores ($M = 0$, $SD = 1.81$), and OCS scores ($M = 0.13$, $SD = 3.96$). The mean scores of the sample on the subtests of the WISC-III that assess attention and concentration were 11.4 (arithmetic), 10.2 (digit span), and 13.0 (coding), compared with normative scores of 10.0 for the general population. On the basis of these results, the sample did not have attentional deficits relative to the normal population.

Of interest is whether an individual subject's performance and early risk scores are reflected in differences in their brain activation. In order to examine these associations, we first examine performance and its relations to risk scores and IQ. Next, the relation between brain activation and individual differences in performance, risk, and IQ are examined.

Errors and response times—Participants made few Type 1 errors (1%), that is, they rarely responded to a letter other than the letter A. There was some variability in Type 2 errors (0–10%, $M = 2\%$), those errors associated with not responding to the letter A when it was presented. Because of the variability in Type 2 errors, these errors were used in subsequent analyses. The average response times for correct detections of the letter A ranged from 794–1,106 ms ($M = 907$ ms). There was a positive but nonsignificant relation between Type 2 errors and response times such that more errors were associated with longer response times ($r = .47$). Although this correlation is not significant in this small sample ($N = 10$), these data suggest that 25% of the variance in these two variables is shared. Because of this association, a CPS was computed that combined the z -score transformations for response times and Type 2 errors.

Relation among Type 2 errors, response times, MCS, ERS, and IQ—The cumulative MCS is positively related to the ERS ($r = .63$, $p < .05$). Risk is also related to task performance in that higher MCS and ERS scores are associated with Type 2 errors ($r = .19$; $r = .71$, $p < .05$, respectively) and longer response times ($r = .35$; $r = .27$, respectively). The relation between the combined risk (MCS and ERS) and combined performance (Type 2 errors and response times) measures indicated that the higher the CRS, the poorer the task

performance ($r = -.78, p < .01$). IQ scores are negatively related to the CRS ($r = -.49$) and positively related to the combined performance scores (CPS; $r = .52$) such that higher IQ is associated with lower risk scores and better performance.

Relations among brain activation, OCS, CPS, CRS, and IQ—We examine the relation between brain activation and OCS (the summary measure including MCS, ERS, performance errors, response times, and IQ) as well as CRS and CPS, and IQ. These relations are seen in Table 2. For the OCS, there is a significant relation such that higher competence is related to greater activation in parietal and temporal lobes but not to activation of the cingulate region or frontal lobes. For the CRS, the same relation was found, namely the higher the CRS, the less activation in the parietal and temporal lobes. Moreover, the CPS is related to the parietal and temporal lobes such that the better the performance, the greater the activation in these two areas. The same findings hold for IQ with higher scores related to greater activation, significantly so for the parietal lobe association.

The OCS as well as the CRS, the CPS, and IQ are related to activation in the parietal and temporal lobes but not to activation in the cingulate region or the frontal lobes. Interestingly, there are no relations between frontal lobe activation and the OCS, CRS, CPS, or IQ. The activation of inferior-frontal gyri on both the left and right sides is associated with faster response times ($r = -.70, p < .05$; $r = -.78, p < .01$, respectively), a finding also reported by others (Casey et al., 1997; Durston et al., 2002).

Table 3 presents the activation of the left and right sides for specific regions within the parietal and temporal lobes as they relate to OCS, CRS, CPS, and IQ. When we look at the parietal lobe as a whole, as well as the specific regions in regard to the measures of overall competence, risk, and performance, there is evidence that activation of the left lobe as opposed to the right lobe is associated with competence. The inferior lobule and supramarginal gyrus are the specific regions showing the most significant activation.

Examination of the individual risk scores reveals that MCS is associated with activation of the parietal lobe; specifically, lower MCSs are related to increased activation of the angular gyrus and left supramarginal gyrus ($r = .66, p < .05$; $r = .65, p < .05$, respectively), whereas there is little relation to the ERSs. IQ scores are directly related to levels of activation of the left inferior-parietal lobule as well as the left superior-temporal gyrus.

A somewhat different pattern emerges when looking at the brain activation of the temporal lobes. There is little evidence of asymmetrical activation being associated with individual differences in risk and performance scores for the temporal lobe as a whole. However, the specific region that is associated with overall competence, risk, performance, and IQ is the left superior-temporal gyrus. Examination of the individual risk scores reveals that ERS is largely associated with temporal lobe activation, in particular lower ERSs are related to increased activation in both the left and right superior-temporal gyri ($r = .79, p < .01$; $r = .69, p < .05$ respectively), while there is little activation relative to the MCSs.

Discussion

This study of attentional control in adolescents who were born preterm is relatively unique in its emphasis on individual differences in the relation between brain function and task performance. Although all participants were preterm, there was in fact a range of risk, both medical and environmental. These early cumulative risk factors are related to subsequent performance, including IQ, as well as brain activation. A focus on individual differences in the brain-behavior relation is particularly important in understanding long-term effects of early risk factors on subsequent cognitive processing and brain activity.

Our results are consistent with the hypothesis that performance on an attention task will be better, and IQ will be higher, with lower medical and environmental risk scores in the child's early years. Moreover, brain activation appears to be related differentially to both types of risk scores. In particular, lower MCSs are associated with greater activation of the left parietal region and lower ERSs are related to greater activation of both right and left temporal regions. Consistent with our findings, others have reported that activation of the left parietal region is also associated with better performance by children (Bunge, Dudukovic, et al., 2002).

Brain regions that were activated in the attention task by most subjects included superior-, middle-, and inferior-frontal gyri, the anterior cingulate, superior- and inferior-parietal lobules, angular gyrus, supramarginal gyrus, and superior-temporal gyrus. These same regions are activated by adult subjects in selective attention tasks (Pugh et al., 1996), suggesting that the adolescents in the current study recruited similar regions. Moreover, and interestingly, there is a similar pattern of activation to that reported for inhibitory control tasks with children and adolescents (Bunge, Dudukovic, et al., 2002; Casey et al., 1997, 1998; Casey, Giedd, & Thomas, 2000; Durston et al., 2002, 2003). This suggests that both attentional and inhibitory tasks recruit similar brain regions: specifically, the inferior frontal, anterior cingulate, and parietal regions.

In addition to the findings of common areas of activation for the group, we also found individual differences in recruitment of the left superior-temporal gyrus and left supramarginal gyrus that are related to performance on the task itself. In addition, concurrent IQ scores are directly related to activation of the left inferior-parietal lobule and left superior-temporal gyrus. Consistent with these findings are reports that activation levels of the left parietal region increase with age on both the Stroop task (Adelman et al., 2002) and working memory tasks (Klingberg et al., 2002). Adults recruit the left parietal cortex more than children during working memory tasks (Bunge, Hazeltine, Scanlon, Rosen, & Gabrieli, 2002; Nelson et al., 2000), and high performing adults use a left hemisphere sub-network, involving inferior-parietal lobule, to succeed on working memory tasks whereas low performers use a right hemisphere network (Glabus et al., 2003). Myelination of the parietal cortex continues through adolescence (Klingberg et al., 2002) and adulthood (Sowell et al., 2003). As the fronto-parietal network matures, its function presumably becomes more efficient, enabling less effortful frontal and more automatic posterior control of a variety of tasks that require cognitive processes. Our findings on the attention task suggest that adolescence represents the transition from the child pattern of brain activation to the adult pattern. Early risk factors appear related to the rate of change from the child pattern to the adult pattern in that those adolescents having lower risk scores show a more mature pattern of brain activation than those adolescents having higher risk scores.

Evidence from several other lines of research supports the idea that the maturation of white matter pathways between temporo-parietal regions and frontal regions is related to performance. Using histological studies, Selemon and Goldman-Rakic (1988) identified common efferent pathways between dorsolateral prefrontal and posterior parietal association cortices that are involved in attention and memory. Diffusion tensor magnetic resonance imaging (DT-MRI) has been used to identify the microstructure of white matter in adults with poor or normal reading abilities. Using DT-MRI, a correlation was found between reading scores and the maturation of the left temporo-parietal region, and no correlation was found between reading scores and the homologous region on the right, indicating that white matter underlying the left temporo-parietal cortex plays a critical role in reading ability (Klingberg et al., 2000).

Although subjects experienced preterm birth, it is clear that there are differences in both patterns of brain activation and performance that are related to the levels of medical risk at

birth and environmental risk during the first 3 years of life as well as to current IQ. The present findings extend the effects of early risk from infancy into adolescence to include brain activation, performance, as well as IQ. Similar findings have been reported in preterm children. For example, Nelson and colleagues (Curtis, Lindeke, Georgieff, & Nelson, 2002; Luciana, Lindeke, Georgieff, Mills, & Nelson, 1999) have reported a relation between cognitive performance and neonatal risk. At 7 – 9 years, greater neonatal risk was associated with subsequent working-memory deficits on cognitive tasks, and by 11 – 12 years, greater neonatal risk was related to lower IQ (Luciana et al., 1999).

We concluded that the sample represented the larger group of preterm children we had followed based on the similarities between groups on a number of measures of medical and environmental risk factors and cognitive performance. The measures included gestational age, birth weight, medical complications, environmental risk, full scale IQ, and the four subscales of the Stanford– Binet at age 3 years. In addition, we found that the attention abilities of the sample were similar to those of the general population based on inspection of the subtest scores of the WISC-III in adolescence. Specifically, the adolescents in our sample had mean scores on the subtests of arithmetic, digit span, and coding that were above the average of the standardization sample. Therefore, we believe that our sample did not have attentional deficits relative to the general population. Finally, the size of the sample in this study is typical of the pediatric sample sizes in neuroimaging studies (Casey et al., 1995; Durston et al., 2002), although it is small relative to behavioral and cognitive studies. Therefore, the correlations we report among the measures of risk, performance, and brain activity should be considered suggestive given the sample size. We were interested in knowing the impact of early risk, both medical and environmental, on later cognitive ability and brain activity. To that end, we selected a group of subjects, all born preterm, who had a range of medical and environmental risks, and found that the variations in early risk variables are related to performance on the cognitive task and to brain activity.

The question all these studies raise is whether these early risk factors are themselves related to subsequent deficit directly through impaired brain structures or processes or whether these early risk factors impact or interact with other environmental risks to produce the later deficits. In the present work, both neonatal and environmental risk scores have an effect on subsequent IQ and on brain activity and performance. This is consistent with the work of Bendersky and Lewis (1995) who, in studying preterm infants, reported that environmental risk itself, controlling for medical complications, is related to subsequent IQ at a younger age. These data do not allow us to conclude whether it is early environmental risk or the continuing risks of the environment in which the children are raised that is related to the observed deficits. It is clear that IQ does not mediate the effect of early environmental risk on subsequent ability, even though IQ itself is related to earlier environmental risk.

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Appendix

Table A1

Brain Activation by Lobes and Regions for Each Participant (10 Participants)

Lobes	Regions	S1	S2	S3	S4	S5	S6	S7	S8	S9	S10	Sum of region	Percent activation in regions
Frontal	Right inferior	2	2	2	1	2	2	2	2	1	1	17	85
	Left inferior	2	2	2	2	1	1	2	2	0	0	14	70
	Right middle	2	1	2	1	2	0	2	1	1	0	12	60
	Left middle	2	1	2	1	1	1	2	2	2	1	15	75
	Right superior	2	2	1	1	2	0	2	2	2	0	14	70
	Left superior	2	1	2	1	2	1	2	2	2	0	15	75
	Right ACC	0	1	1	2	0	1	2	2	2	1	12	60
	Left ACC	0	2	1	0	1	0	2	2	2	0	10	50
Temporal	Right inferior	1	0	0	1	0	0	0	2	0	1	5	25
	Left inferior	1	0	0	1	0	0	0	2	0	1	5	25
	Right middle	1	1	0	0	0	1	1	1	1	1	7	35
	Left middle	1	1	0	1	0	0	1	2	1	0	7	35
	Right superior	2	2	1	2	2	1	2	1	0	2	15	75
	Left superior	2	1	0	2	1	1	2	2	0	1	12	60
	Right superior	2	0	0	2	1	2	1	2	2	0	12	60
	Left superior	1	0	0	1	1	1	0	2	1	0	7	35
Parietal	Right inferior	2	1	2	2	2	2	2	2	1	1	17	85
	Left inferior	2	0	0	1	2	2	2	2	1	1	13	65
	Right angular gyrus	1	1	0	0	0	2	1	2	2	1	10	50
	Left angular gyrus	1	0	0	0	0	1	1	2	1	1	7	35
	Right supramarginal gyrus	2	2	2	1	2	2	2	2	1	2	18	90
	Left supramarginal gyrus	2	1	0	1	1	1	1	2	1	1	11	55

Note. Cell entries are the number of sets of blocks showing activation in no set (0), one set (1), or both sets of blocks (2).

Table 1

Concurrent Measures of Response Time (RT), Type 2 Errors, Combined Performance Score (CPS), IQ, Medical Complications (MCS), Environmental Risk (ERS), Combined Risk (CRS), and Overall Competence (OCS)

Participant	RT (ms)	Type 2 errors	CPS	IQ	MCS	ERS	CRS	OCS
1	812	0	0.84	101	3	0.03	-0.36	1.27
2	822	0	1.14	87	5	-0.36	-0.10	0.38
3	980	0	-0.49	110	10	-0.18	1.70	-1.52
4	795	1	1.74	109	1	-0.71	-1.74	4.09
5	805	1	2.05	106	0	-1.12	-2.48	4.93
6	834	1	0.70	133	4	-0.03	-0.09	2.99
7	990	1	-0.17	122	3	-0.59	-0.98	2.27
8	924	2	-1.77	80	7	1.61	2.52	-5.62
9	1106	2	-1.24	94	2	-0.59	-1.30	-0.33
10	1005	6	-2.85	79	7	1.95	2.86	-7.11

Table 2

Correlations Among Activation of General Brain Regions and Overall Competence (OCS), Combined Risk (CRS), Combined Performance (CPS), and Intelligence Quotient (IQ)

Brain region	OCS	CRS	CPS	IQ
Cingulate region	.36	-.33	.36	.21
Frontal lobes	.26	-.04	.36	.32
Parietal lobes	.90**	-.83**	.80**	.67**
Temporal lobes	.72*	-.68*	.69*	.44

*
 $p < .05$.

**
 $p < .01$.

Table 3

Correlations of Activation in Specific Brain Regions with Overall Competence (OCS), Intelligence Quotient (IQ), Combined Performance (CPS), Combined Risk (CRS), Medical Complications (MCS), and Environmental Risk (ERS)

Brain region	Side	OCS	IQ	CPS	CRS	MCS	ERS
Parietal lobe	L	.64 [*]	.44	.54	-.64 [*]	-.65 [*]	-.50
	R	.49	.30	.53	-.41	-.49	-.24
Inferior lobule	L	.70 [*]	.75 [*]	.49	-.60	-.60	-.49
	R	.43	.61	.42	-.18	-.10	-.29
Superior lobule	L	.33	.17	.33	-.32	-.29	-.29
	R	.21	.27	.24	-.08	-.06	-.08
Angular gyrus	L	.41	.12	.34	-.51	-.66 [*]	-.26
	R	.14	-.20	.21	-.24	-.44	.00
Supramarginal gyrus	L	.72 [*]	.37	.66 [*]	-.73 ^{**}	-.65	-.67 [*]
	R	.59	.23	.55	-.66 [*]	-.74 [*]	-.46
Temporal lobe	L	.64 [*]	.42	.65 [*]	-.58	-.35	-.66 [*]
	R	.75 [*]	.40	.67 [*]	-.79 ^{**}	-.57	-.86 ^{**}
Superior gyrus	L	.82 ^{**}	.76 [*]	.76 [*]	-.62	-.34	-.79 ^{**}
	R	.57	.58	.45	-.47	-.15	-.69 [*]
Middle gyrus	L	.32	.14	.45	-.21	-.13	-.26
	R	.31	-.07	.35	-.41	-.55	-.19
Inferior gyrus	L	.45	.13	.41	-.55	-.41	-.58
	R	.45	.13	.41	-.55	-.41	-.58

* $p < .05$.

** $p < .01$.