Altered Gray Matter Volume and School Age Anxiety in Children Born Late Preterm

Cynthia E. Rogers, MD[1,2], Deanna M. Barch, PhD[1,3,4,5], Chad M. Sylvester, MD, PhD[1], David Pagliaccio, MS[5], Michael P. Harms, PhD[1], Kelly N. Botteron, MD[1,3], and Joan L. Luby, MD[1]

Objectives To determine if late preterm (LP) children differ from full term (FT) children in volumes of the cortex, hippocampus, corpus callosum, or amygdala and whether these differences are associated with anxiety symptoms at school-age.

Study design LP children born between 34 and 36 weeks gestation and FT children born between 39 and 41 weeks gestation from a larger longitudinal cohort had magnetic resonance imaging scans at school-age. Brain volumes, cortical surface area, and thickness measures were obtained. Anxiety symptoms were assessed using a structured diagnostic interview annually beginning at preschool-age and following the magnetic resonance imaging.

Results LP children (n = 21) had a smaller percentage of total, right parietal, and right temporal lobe gray matter volume than FT children (n = 87). There were no differences in hippocampal, callosal, or amygdala volumes or cortical thickness. LP children also had a relative decrease in right parietal lobe cortical surface area. LP children had greater anxiety symptoms over all assessments. The relationship between late prematurity and school-age anxiety symptoms was mediated by the relative decrease in right temporal lobe volume.

Conclusions LP children, comprising 70% of preterm children, are also at increased risk for altered brain development particularly in the right temporal and parietal cortices. Alterations in the right temporal lobe cortical volume may underlie the increased rate of anxiety symptoms among these LP children. These findings suggest that LP delivery may disrupt temporal and parietal cortical development that persists until school-age with the right temporal lobe conferring risk for elevated anxiety symptoms. *(J Pediatr 2014;165:928-35)*.

Preterm birth is a major public health problem with well-established high risk for adverse medical and developmental outcomes in survivors.[1] These poor outcomes may be mediated by a greater risk for altered brain development associated with prematurity including decreased volumes of gray matter, white matter,[2] and in particular regions like the hippocampus[3] and the corpus callosum.[4] These regional alterations have been found during the neonatal period with evidence of persistence into school-age,[5,6] adolescence,[7,8] and adulthood[9,10] especially in those born prior to 34 weeks gestation. Global and regional reductions in gray and white matter volumes have even been found in school-age preterm children that were considered at low risk for neurodevelopmental deficits based on their gestational age (GA) and lack of significant medical complications.[11]

Studies of volumetric brain changes in children born preterm, however, have been limited to a focus on very preterm infants, even though late preterm (LP) infants, born between 34 and 36 weeks gestation, comprise approximately 70% of preterm births.[12] LP infants may also be at elevated risk for disrupted brain development. Underscoring the significant brain development that occurs between 34 and 40 weeks, the 34-week brain weighs only 65% of the full term (FT) brain, and the cortical volume is only about one-half that of what it will be at 40 weeks.[13] One study that evaluated neonatal brain volumes of LP infants at term-equivalent age found that they had significantly smaller gray matter volumes and percentage of gray matter volume than term-born infants.[14] Conversely, a study focused on corpus callosum volume, did not find differences in callosal volumes at adolescence between 11 children born LP and 53 FT

CAPA	Childhood and Adolescent Psychiatric Assessment
FT	Full term
GA	Gestational age
GAD	Generalized anxiety disorder
LP	Late preterm
MDD	Major depressive disorders
MRI	Magnetic resonance imaging
PAPA	Preschool-Age Psychiatric Assessment
PTSD	Post-traumatic stress disorder
VAN	Ventral attention network

From the Departments of [1]Psychiatry and [2]Pediatrics, and [3]Department of Radiology, Mallinckrodt Institute of Radiology, Washington University School of Medicine; and [4]Department of Psychology and [5]The Program in Neuroscience, Washington University in St. Louis, St. Louis, MO

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controls.[15] Given the high prevalence of LP birth, the suggestion of structural differences in LP infants and the steep trajectory of brain development during these final gestational weeks, further investigation of structural brain outcomes in LP children is clearly indicated.

Prematurity is also associated with increased rates of psychiatric disorders including anxiety disorders.[16,17] Indeed, increased rates of anxiety symptoms among those born very preterm (prior to 30-32 weeks gestation) have been reported at both childhood and adulthood,[1,16,18] although findings have been mixed.[19] Although there is less evidence in the LP population, available evidence supports an increased rate of psychiatric symptoms in LP children as well, including "emotional," and anxiety symptoms.[20,21] We have also previously noted increased rates of psychiatric disorders, including a 4-fold risk for anxiety disorders, at preschool age among LP children in the cohort to be examined in the analyses presented here.[22] Elevated rates of generalized anxiety disorder (GAD) and separation anxiety disorders were found in this group. Although we found these early childhood anxiety disorders in LP children were mediated by maternal depression, underlying neurodevelopmental differences could confer additional risk.

There has been a burgeoning literature investigating whether altered brain development associated with preterm birth is associated with the increased risk of psychiatric symptoms, with links noted between both global and regional brain differences and childhood psychiatric symptoms[23-25] including anxiety symptoms.[1,26] Given the primary focus of the prior research on children born at earlier GAs, it remains unclear whether abnormalities in brain development are also found at an increased rate among LP children. It is also unknown if these brain alterations could underlie an increased risk of anxiety disorders. To address these research gaps, the current study aimed to assess whether children born LP differed from FT children in regions previously associated with preterm birth (hippocampus, corpus callosum) or anxiety (amygdala), in volume of cerebral gray matter or white matter, or in cortical surface area and thickness, and to determine whether any structural differences were related to differences in anxiety symptoms at school age between LP and FT children.

Methods

Data for this analysis was obtained from 108 children born between 34 and 36 weeks GA (LP) or between 40 and 41 weeks (FT) from a larger sample enrolled in a 10-year longitudinal study investigating preschool depression (n = 306).[22] The larger sample was recruited from day cares and preschools around metropolitan St. Louis using a screening checklist to oversample preschoolers with depressive and disruptive symptoms and to include healthy controls. Preschoolers with chronic medical or neurologic problems, intellectual disability, or autistic spectrum disorders were also excluded from the larger longitudinal study. As previously described, children and their caregivers participated in 3-6 comprehensive annual diagnostic and developmental assessments prior to their first neuroimaging session.[27] Participants were screened for standard imaging contraindications. In addition, children with a history of head injury, ischemic insults or stroke or other brain injuries, seizure disorders, history of mechanical ventilation, or focal neurologic deficits on neurologic examination were also excluded. Of the 210 LP (n = 40) and FT (n = 170) children eligible for the imaging study, 122 had a magnetic resonance imaging (MRI) scan at school-age (6-12 years). Forty-eight children or families refused, 12 cancelled or did not keep appointments repeatedly, 20 had MRI contraindications, 2 were deceased, and 6 were lost to follow-up/lived out of state. Children also returned for 1 to 3 annual diagnostic assessments after the MRI scan. All study procedures were reviewed and approved by the institutional review board at the Washington University School of Medicine in St. Louis. Written informed consent was obtained from parents, and assent was obtained from children. Children with poor image quality were also excluded (n = 14) leaving a final sample of 108 children for inclusion in the analyses that follow.

Preterm Birth

GA at birth (completed weeks) was reported by the child's primary caregiver. GA groups were categorized as follows: LP (34-36 weeks), and FT (40-41 weeks). The focus of this analysis was on the LP population because of our prior findings of increased risk of psychopathology in this group compared with the FT children in this sample.[22]

Anxiety Symptoms

Trained staff conducted annual behavioral/developmental assessments of children and their parents/guardians. Prior to age 8, the Preschool-Age Psychiatric Assessment[28] (PAPA) was administered to assess psychopathology. The PAPA is an interviewer-based diagnostic assessment with empirically established test re-test reliability that covers a broad range of psychiatric symptoms and impairment. The Childhood and Adolescent Psychiatric Assessment (CAPA)[29] was used after age 8, and it also includes a child-report interview. All interviews were audiotaped for quality control and group calibration. In addition to diagnoses, both the PAPA and CAPA provide dimensional counts of symptoms. For this analysis, an anxiety symptom domain score was created for each annual assessment by summing the symptom counts for GAD, post-traumatic stress disorder (PTSD), and separation anxiety disorder. There are 6 possible GAD symptoms, 17 possible PTSD symptoms, and 8 possible separation anxiety disorder symptoms, for a maximum possible anxiety dimensional score of 31. Only symptoms from these anxiety disorders were included as they are assessed both on the PAPA and the CAPA.

MRI Acquisition

Two 3-dimensional T1-weighted magnetization-prepared rapid gradient echo scans were acquired on a Siemens 3.0-T Tim Trio scanner (Siemens, Maryland Heights, Missouri)

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