

## Preterm Birth and Adolescent Social Functioning—Alterations in Emotion-Processing Brain Areas

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**Objective** To investigate the relationship between preterm birth, adolescent, and adult psychosocial outcomes, and alterations in gray matter volume.

**Study design** Individuals (n = 73) born at <33 weeks of gestation (very preterm) and 49 controls completed the Child Behavior Checklist (CBCL) at age 15 years to identify 'social immaturity' (SI) cases. Voxel-based morphometry was used to investigate gray matter volumes according to CBCL-SI 'caseness.' The Clinical Interview Schedule-Revised (CIS-R) was administered at age 19 years.

**Results** Very preterm adolescents were almost 4 times more likely to reach CBCL-SI 'caseness' compared with controls. Ex-preterm SI 'cases' had increased gray matter volume in the fusiform gyrus bilaterally (Talairach coordinates: x = 60, y = -27, z = -30; Z = 3.78; x = -61, y = -35, z = -27; Z = 3.56, after correction for multiple comparisons) compared with ex-preterm SI 'noncases.' Left fusiform volume displayed a stronger correlation with ipsilateral orbitofrontal cortex in SI 'cases' (x = -15, y = 22, z = -26; Z = 3.64). CIS-R total scores were slightly higher in ex-preterm individuals compared with controls. In the whole sample, SI 'cases' in midadolescence also had higher CIS-R scores in adulthood compared with 'noncases' (SI 'cases': mean = 5.7, 95% CI = 4.0-7.4; SI 'noncases': mean = 2.7, 95% CI = 1.1-4.3; F = 6.4, df = 74; P = .013).

**Conclusions** Ex-preterm adolescents had increased socialization problems in adolescence, which were associated with volumetric alterations in an emotion-processing brain network. Atypical social development is linked to an increased vulnerability to psychiatric disorder. (*J Pediatr* 2013;163:1596-604).

There is an association between very preterm (VPT) birth and behavioral and psychiatric abnormalities in childhood and adolescence.<sup>1-4</sup> Furthermore, individuals born VPT are at increased risk of developing psychiatric disorders as adults, including schizophrenia, bipolar affective disorder, anxiety disorder, and depression.<sup>5-7</sup>

The evaluation of increased social threat, social defeat, and chronic stress may underlie an increased risk for psychiatric disorder.<sup>8</sup> Animal and human models have shown a relationship between abnormal aspects of social functioning and later development of psychopathology.<sup>9,10</sup> Studies of children and adolescents at risk for psychosis have demonstrated atypical social development,<sup>11</sup> increased social anxiety,<sup>12</sup> and decreased social competence.<sup>13</sup> Socialization difficulties in individuals who were born VPT have been reported as early as the first year of life,<sup>14</sup> and an increased liability to autism spectrum symptomatology has been found in childhood.<sup>15</sup> Furthermore, ex-preterm adolescents have been described as being at increased risk of experiencing socialization difficulties and deficits in social competence.<sup>16,17</sup>

Adolescence is a critical stage of development, associated with a magnitude of dynamic brain developmental changes that rivals only infancy, during which several brain regions underlying psychosocial and high order cognitive functions reach maturity. During this developmental stage, social communication becomes increasingly sophisticated, and the social networks in which adolescents operate become more complex. Social acceptance and the achievement of social dominance are central to enable access to an array of resources including romantic partners. Furthermore, during adolescence, important changes in social affiliations occur, such as a shift of influence from primary caregivers to peers.<sup>18</sup> Pre-existing vulnerability in socialization is, thus, likely to become more evident during this period, which is associated with the emergence and early expression of several psychiatric disorders.<sup>19</sup> Social rejection and bullying are important risk factors for a range of adverse psychopathology outcomes both in adolescence<sup>20</sup> and early adulthood.<sup>21</sup>

Despite evidence for a strong association between preterm birth and social vulnerability, preterm birth and adult psychopathology, and socialization problems and psychiatric disorders, the underlying biological mechanisms linking preterm birth,

ASD	Autism spectrum disorder
CBCL	Child Behavior Checklist
CIS-R	Clinical Interview Schedule-Revised
FWE	Family wise error
MRI	Magnetic resonance imaging
SES	Social economic status
SI	Social immaturity
VPT	Very preterm

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Supported by the Sir Jules Thorne Trust and the Wellcome Trust (to R.M. and L.R.). The authors declare no conflicts of interest.

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social vulnerability, and adult psychopathology remain unknown. Structural alterations in the amygdala<sup>22</sup> and the occipito-temporal cortex including the fusiform gyrus<sup>23</sup> were described in preterm samples but have not been directly linked to behavioral abnormalities. These regions, together with the orbitofrontal cortex and the superior temporal sulcus, form an emotion-processing network.<sup>24</sup> Therefore, alterations in an emotion-processing network might represent the underlying biological mechanism linking preterm birth, social vulnerability, and adult psychopathology.

To test this hypothesis, we evaluated the relationship between VPT birth, adolescent and adult psychosocial outcomes, and alterations in an emotion-processing brain network. We investigated a cohort of individuals who were born VPT (<33 weeks of gestation) and controls, who had been followed-up from birth to age 19 years in a longitudinal study brain-behavior correlates of socialization problems.

## Methods

In 1983-1984, 253 infants born at less than 33 weeks gestation and admitted within 5 days of birth to the neonatal intensive care unit at University College Hospital London survived until term; they were then enrolled for long-term follow-up ( $n = 147$ ). At 14-16 years, all those born at 28 completed weeks of gestation or less were selected for assessment ( $n = 78$ ), as well as a random sample of 1 in 4 of those born from 29-33 weeks of gestation ( $n = 69$ ). This selection was necessitated by an expansion in capacity of the neonatal intensive care unit at University College Hospital London in 1983, which prevented inclusion of the entire consecutive series because of limited research resources. In midadolescence, 111 (75.5%) of these individuals were assessed, 90 (61.2%) had a magnetic resonance imaging (MRI). A control group of 71 adolescents was recruited from the community through advertisements in the local and national press. Inclusion criteria were full-term gestation (38-42 weeks), birth weight >2500 g, no history of neurologic conditions, intracranial infection, and head injury.<sup>23</sup>

VPT- and term-born adolescents had neurocognitive, mental health assessments, and MRI at the Institute of Psychiatry, King's College London. Written informed consent for the assessment including MRI was obtained from an accompanying parent and verbal consent was from the young people. Ethical approval was granted by the Institute of Psychiatry at the Maudsley Ethical Committee (Research) (Ref 111/98).

Parent-completed Child Behavior Checklist (CBCL)<sup>25</sup> scores and structural brain MRI data of sufficient quality to be used for voxel-based morphometry analysis were available for 73 VPT-born adolescents and 49 controls; these are the subjects on whom the current analyses were carried out. Of these individuals, 47 VPT-born individuals and 28 controls completed the Clinical Interview Schedule-Revised (CIS-R)<sup>26</sup> in early adulthood, at age 19 years (64% and 57% of the initial sample, respectively).

## Behavioral, Cognitive, and Parental Psychosocial Assessment

**Midadolescence Assessment.** The CBCL is an empirically derived, valid, and reliable parent checklist of problems in children's psychological adjustment; there are 20 competence items and 120 items on behavioral and emotional problems. Summing the responses to each problem item derives a number of broad-band scales (internalizing, externalizing) and 8 narrow-band scales, one of which concerns social problems. This scale includes items such as "acts too young," "too dependent," "does not get along with peers," "gets teased," "not liked by peers," "clumsy," "overweight," and "prefers younger kids." The scale has a maximum score of 16. As a parent-completed measure, the CBCL provides a common metric across patients and studies that is free from clinician interpretation. Many of the research groups who have explored childhood and early adolescent outcomes of preterm birth/low birth weight have employed the CBCL as an outcome measure.<sup>27</sup> We used the CBCL social problems scale to identify the subgroups of VPT-born and term-born adolescents who had social problem scores at or over the 90th percentile of scores of term-born controls ( $\geq 2$ ). These young people were referred to as 'socially immature' (VPT,  $n = 37$ ; term-born = 9).

The Wechsler Intelligence Scale for Children-Revised<sup>28</sup> is a test of intelligence, defined as an aggregate of mental aptitudes or abilities, which includes 12 subtests divided into verbal and performance parts. Verbal scale subtests include vocabulary, information, similarities, arithmetic, comprehension, and digit span; performance scale subtests include block design, picture completion, picture arrangement, object assembly, coding, and mazes. Each subtest yields a raw score, which is converted into a standard score, with a mean of 10 and a SD of 3. The Wechsler Intelligence Scale for Children-Revised test estimates full-scale IQ, as well as verbal and performance IQ, resulting from sums of scaled scores; the IQs are actual standard scores with a mean of 100 and standard deviation of 15.

A 5-item index of environmental adversity derived from the Child and Adolescent Psychiatric Assessment, a standardized, investigator-based parent interview,<sup>29</sup> was used to quantify psychosocial adversity. The index was similar to the 6-item psychosocial index created by Rutter et al; however, the item placement in foster homes was not included, as none of the individuals had been placed out of home.<sup>30</sup> Any instance of interparental violence was used as a proxy for 'severe marital discord.' Social economic status (SES) was based on father's/male caregiver's occupation or, if this was not available, on mother's occupation; if the head of the household was not working, their last occupation was used to assign SES. 'Low SES' was defined as being in social class III-manual IV, V, or unclassified.<sup>30</sup> 'Large family size' was defined as 5 or more children. 'Parental criminality' was indexed by a history of contact with the police for any offence other than a minor traffic offence. 'Parental mental disorder' was measured as either parent having had treated psychiatric disorder. These 5 variables were summed to create a total psychosocial adversity score.

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