Cognitive Abilities in Preterm and Term-Born Adolescents

Luke A. Schneider, PhD[1], Nicholas R. Burns, PhD[2], Lynne C. Giles, PhD[3], Ryan D. Higgins, BSc[1], Theodore J. Nettelbeck, PhD[2], Michael C. Ridding, PhD[1], and Julia B. Pitcher, PhD[1]

Objective To investigate the influence of a range of prenatal and postnatal factors on cognitive development in preterm and term-born adolescents.

Study design Woodcock-Johnson III Tests of Cognitive Abilities were used to assess general intellectual ability and 6 broad cognitive abilities in 145 young adolescents aged approximately 12.5 years and born 25-41 weeks gestational age (GA). To study potential links between neurophysiologic and cognitive outcomes, corticomotor excitability was measured using transcranial magnetic stimulation and surface electromyography. The influence of various prenatal and postnatal factors on cognitive development was investigated using relative importance regression modeling.

Results Adolescents with greater GA tended to have better cognitive abilities (particularly general intellectual ability, working memory, and cognitive efficiency) and higher corticomotor excitability. Corticomotor excitability explained a higher proportion of the variance in cognitive outcome than GA. But the strongest predictors of cognitive outcome were combinations of prenatal and postnatal factors, particularly degree of social disadvantage at the time of birth, birthweight percentile, and height at assessment.

Conclusions In otherwise neurologically healthy adolescents, GA accounts for little interindividual variability in cognitive abilities. The association between corticomotor excitability and cognitive performance suggests that reduced connectivity, potentially associated with brain microstructural abnormalities, may contribute to cognitive deficits in preterm children. It remains to be determined if the effects of low GA on cognitive outcomes attenuate over childhood in favor of a concomitant increase in the relative importance of heritability, or alternatively, if cognitive development is more heavily influenced by the quality of the postnatal environment. *(J Pediatr 2014;165:170-7)*.

In developed countries, 6%-12% of all births annually are preterm (ie, <37 completed weeks gestation).[1] A plethora of studies have shown associations between preterm birth and later suboptimal neurodevelopmental outcomes. In terms of identifying the actual effects of reduced gestational age (GA) on neurodevelopment, most have arguably been confounded by not differentiating GA from birthweight percentile (BW%), and/or including children with clinical histories of brain lesions or other neurosensory impairments, and rarely including late preterm children (33-37 weeks GA), who comprise over 70% of all preterm births. Compared with their term-born peers, the late preterm exhibit a high prevalence of low severity motor, cognitive, and behavioral impairments.[2-6] They account for up to 74% of the total burden of dysfunction because of preterm birth,[7] a greater need for special education,[2,8,9] lower net income, and a reduced likelihood of completing a university education.[7] These outcomes are not explained by perinatal brain lesions that affect <1% of children (<10% in those born <32 weeks GA), but more likely by microstructural brain abnormalities not readily detected with standard magnetic resonance imaging (MRI).[10-13]

Using transcranial magnetic stimulation (TMS), we previously showed relationships between preterm birth and reduced corticomotor excitability, neuroplasticity, and functional motor development in early adolescence.[4,14] The motor cortex (M1) contributes to at least some cognitive functions[15,16] and a basic TMS measure of corticomotor excitability, the resting motor threshold (rMT), also correlates with cortical white matter maturation and integrity.[17] Here, we investigated if there are also links between GA, corticomotor excitability, and cognitive abilities, in adolescents born across a range of GAs but without known brain lesions or neurosensory disabilities. We hypothesized that increased

BW%	Birthweight percentile
GA	Gestational age
GIA	General intellectual ability
IRSD	Index of relative socioeconomic disadvantage
M1	Motor cortex
MRI	Magnetic resonance imaging
rMT	Resting motor threshold
SES	Socioeconomic status
TMS	Transcranial magnetic stimulation
WCH	Women's and Children's Hospital

From the [1]Research Center for Early Origins of Health and Disease, Robinson Institute, School of Pediatrics and Reproductive Health, [2]School of Psychology, and [3]Discipline of Public Health, University of Adelaide, Adelaide, Australia

Supported by the National Health and Medical Research Council of Australia (565344 and 299087 both to J.P.), the South Australian Channel 7 Children's Research Foundation, the Women's and Children's Hospital Research Foundation, and the Faculty of Health Sciences, University of Adelaide. The authors declare no conflicts of interest.

http://dx.doi.org/10.1016/j.jpeds.2014.03.030

cortical excitability is associated with increased cognitive performance. To better characterize any associations, we also examined the influence of a range of pre- and postnatal variables known to influence cognitive abilities, including fetal growth[18] and socioeconomic factors.[19] Preliminary results have been presented in abstract.[20]

Methods

Stratified recruitment was used to recruit 145 early adolescents (78 males) with parent/primary caregiver written informed consent (Table). GAs ranged from 25-41 weeks (34.5 ± 3.5 weeks) and the mean uncorrected age at assessment was 148.7 ± 9.3 months (ie, 12 years and 5 months, range: 128-168 months). All preterm adolescents (N = 101) were born between January 1996 and December 1997 at the Women's and Children's Hospital (WCH), Adelaide, Australia. Term-born adolescents (N = 44) were recruited from the preterm children's schools and from community newspaper advertisements. Exclusion criteria were any abnormality on perinatal cranial ultrasound (no MRI available), any genetic or chromosomal disorder, an identifiable syndrome, or physical or intellectual disability that rendered participants unable to follow simple instructions, in addition to the exclusion criteria recommended for the safe use of TMS.[21] Ineligible children were screened and removed from the database lists prior to recruitment. Ethical approval was provided by local WCH, university, government, and Catholic education human research ethics committees. All procedures were performed in accordance with the Declaration of Helsinki (2008 revision).

As this study was part of the broader Preterm Motor and Cognitive Development study,[14] all data collection was performed by investigators blinded to GA, BW%, etc. Each child's current height, weight, and percentage of body fat, determined using bio-impedance scales (body composition analyzer, Tanita, Kewdale, Australia) were recorded. Characteristics pertaining to each preterm (and some term) participant's birth were obtained from WCH Perinatal Statistics collection with parental written consent. Gestation Related Optimal Weight software[22] was used to calculate each child's actual birthweight relative to their predicted optimal term weight adjusted for GA, sex, maternal size, ethnicity, and parity. This BW% is a marker of fetal growth. The Australian Bureau of Statistics' index of relative socioeconomic disadvantage (IRSD) was calculated for the address each child went home to following their birth (1996 National Census; $IRSD_{birth}$) and for their current address (2006 National Census; $IRSD_{current}$). This composite measure, which includes educational attainment, occupation, employment, and income, is a summary of economic and social conditions of people and households within small geographic areas (ie, census districts).

Cognitive Abilities Assessment

The age-normed Woodcock-Johnson III Tests of Cognitive Abilities[23] were administered to each participant according to standardized procedures.[24] The Woodcock-Johnson III Tests of Cognitive Abilities is explicitly linked to the Cattell-Horn-Carroll theory, which provide a model of the structure of cognitive abilities.[25] We included tests 1-9 from the standard and test 14 from the extended batteries (see www.assess.nelson.com/pdf/asb-7.pdf for more specific test details). Combinations of the subtests contribute to

Table. Characteristics and cognitive abilities of the participants by GA group

	Early preterm, ≤32 wk GA (*N* = 38)	Late preterm, 33-36 wk GA (*N* = 63)	Term, 37-41 wk GA (*N* = 44)	Total (*N* = 145)
GA (wk)	29.7 ± 2.2*,†	34.8 ± 1.1*	38.1 ± 1.5	34.5 ± 3.5
BW%	37.7 ± 33.0*	37.1 ± 31.5*	56.2 ± 30.0	43.3 ± 32.4
Sex				
Males	19 (50%)	36 (57%)	23 (52%)	78 (54%)
Females	19 (50%)	27 (43%)	21 (48%)	67 (46%)
Parity	0.8 ± 1.3	0.8 ± 0.9	1 ± 1	0.8 ± 1
Birth head circumference (cm)	27.8 ± 2.3*,†	32.4 ± 1.9*	34.8 ± 3.5	31.8 ± 3.7
Birth length (cm)	39.0 ± 3.4*,†	45.9 ± 2.6*	48.5 ± 4.5	44.8 ± 5
Apgar score 1 min	6.6 ± 1.8*,†	7.9 ± 1.5	8.1 ± 1.1	7.6 ± 1.7
Apgar score 5 min	8.6 ± 1.4*,†	9.1 ± 0.7	9.2 ± 0.6	9 ± 1
Child weight at assessment (kg)	40.8 ± 11	44.6 ± 10.4	45.8 ± 11.4	44 ± 11
Child height at assessment (m)	1.5 ± 0.1*,†	1.5 ± 0.1	1.5 ± 0.1	1.5 ± 0.1
Child % body fat at assessment	20.6 ± 8.8	20.4 ± 6.6	21.2 ± 7.9	20.7 ± 7.6
IRSD score birth	996.2 ± 109.3	960.8 ± 109.3	995.7 ± 88.5	980 ± 104.8
IRSD score current	1006.5 ± 76	1007.1 ± 88.5	993.0 ± 91.6	1002.7 ± 86.1
GIA	93.8 ± 13†	100.7 ± 14.2	99.3 ± 11.2	98.5 ± 13.2
Verbal ability	97.3 ± 10.3	99.5 ± 9.9	97.0 ± 11.9	98.2 ± 10.6
Thinking ability	99.8 ± 14.1	104.8 ± 14	104.3 ± 12.2	103.3 ± 13.6
Cognitive efficiency	89 ± 13.9†	98.1 ± 15.6	94.7 ± 16.8	94.7 ± 15.9
Auditory processing	106.3 ± 14.5	110.7 ± 13.4	111.2 ± 16	109.7 ± 14.6
Phonemic awareness	102.5 ± 16.2	106.3 ± 18.4	107.1 ± 17.6	105.5 ± 17.6
Working memory	94.8 ± 13.4*,†	102.3 ± 15.2	102.5 ± 12.7	100.4 ± 14.3

Data are mean ± SD for each GA group, except for sex *N* (%) of sample in each GA group.
*Denotes $P < .05$ compared with the term-born group.
†Denotes $P < .05$ compared with the late preterm group.