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Cognitive Deficits in Prematurely Born Adults are Associated with Reduced Basal Forebrain Integrity

Darrick T. Balu, Ph.D.[1,2]

[1]Department of Psychiatry, Harvard Medical School, Boston, MA USA 02115

[2]Translational Psychiatry Laboratory, McLean Hospital, Belmont, MA, USA 02478

It is well known that individuals born prematurely have increased risk for adverse long-term outcomes, including neurocognitive deficits. In this issue, Grothe et al. (1) investigate whether the impairments in the development of the cholinergic basal forebrain (cBF) contributes to cognitive deficits in premature born individuals during adulthood.

Premature births occur at a worldwide rate of 10% and are associated with a host of adverse long-term outcomes, including higher morbidity, growth failure, and impaired neurocognitive development (2). Those born with very low birth weight (VLBW; < 1500 g) and/or very preterm (VP; gestational age, < 32 weeks) have a significantly increased risk for adverse outcomes (3). The neuronal perturbations following premature birth could be due to a higher propensity for brain injury as a result of perinatal stressors (i.e., ischemia, hypoxia, and inflammation).

Perinatal brain injury affects primarily forebrain white matter, although with increasing severity of injury, white matter impairments extend to gray matter (4). Thus, the cBF may be of particular interest because in animal models, proper cBF development is extremely sensitive to perinatal stressors that lead to long-lasting structural and functional impairments (5). The cBF is highly relevant for cognitive functioning and intellectual capabilities (6), possibly linking perinatal brain injury to lasting effects on neurocognitive development. Therefore, owing to the higher risk for perinatal stressors in prematurely born humans, the authors hypothesized that cBF integrity might be specifically involved with the impaired neurocognition associated with premature birth.

To this end, Grothe *et al.* leveraged recent developments in stereotactic mapping of cBF nuclei in the human brain, which allows magnetic resonance imaging (MRI)–based volumetric assessments, thereby providing an *in vivo* marker of cBF structural integrity. They recruited study participants from a geographically defined whole-population sample of neonatal at-risk infants born in southern Bavaria (7). The study sample consisted of 99 VP (gestational age < 32 weeks) / VLBW (< 1500 g) individuals and 106 demographically matched term-born individuals that served as controls. Before, and independent from, the

*Corresponding author: Darrick T Balu, Harvard Medical School, McLean Hospital, 115 Mill Street, Belmont, MA 02478, USA., dbalu@mclean.harvard.edu, Tel.: 617-855-2329, Fax: 617-855-2705.

DISCOLOSURES

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MRI examination, controls and subjects in the at-risk neonatal cohort were assessed for global cognitive functioning at 26 years old. The assessment included a short version of the German version of the Wechsler Adult Intelligence Scale–III, that allows for the computation of full-scale IQ (FIQ), verbal IQ (VIQ), and performance IQ (PIQ). After MRI imaging and extraction of individual gray matter volumes, the authors measured the entire volume of the cBF, including all cholinergic subdivisions, as a marker for overall cBF system integrity.

The VP/VLBW adult subjects, who had significantly lower birth weights and gestational age compared to controls, also displayed significantly lower IQ scores compared with term-born control subjects. Very interestingly, this study found that compared with control subjects, the cBF volumes in VP/VLBW adults were reduced by a highly significant 4.5%. Their smaller cBF volumes were significantly correlated with a higher intensity of neonatal treatment index (INTI; a measure of neonatal complications). However, there was no significant difference between global GM and white matter volumes (WM) between the two groups. This suggests that structural abnormalities observed in VP/VLBW subjects in other cortical and subcortical brain regions might normalize during late development. Among VP/VLBW adults, smaller cBF volumes were significantly associated with a lower FIQ, VIQ, and PIQ, while neither global GM nor WM volume was associated with any IQ measure. Importantly, in controls, neither cBF volume nor GM or WM volume was significantly associated with any other IQ measure. Among VP/VLBW adults, the INTI score was significantly associated with a lower VIQ and FIQ, but not with a lower PIQ. Notably, the reduced cBF volume mediated the association between neonatal complications and adult cognitive problems.

The results of this study provide the first evidence in humans that the cBF is involved in long-term adverse effects of premature birth. Their results are in line with the widely supported role of the cBF system in higher cognitive functions and may reflect an impaired cholinergic innervation of cognition-relevant cortical circuits (6). As neuroimaging studies have identified associations between reduced cBF integrity and cognitive deficits in neurodegenerative conditions (8), the findings presented in this article suggest that reduced cBF integrity could be associated with cognitive deficits across multiple disorders.

Preclinical and clinical evidence suggest that it is possible that cBF deficits could be responsive to pharmacologic interventions for reducing adverse consequences of premature birth. In animal models of increased vulnerability to cholinergic deficits, perinatal choline supplementation protects the integrity of this system (9). Early postnatal dietary interventions have been shown to mitigate the adverse effects of preterm birth on cognitive and brain volumetric outcome variables in adolescents (10). In VP/VLBW adults, pharmacological interventions with pro-cholinergic drugs, such as acetylcholinesterase inhibitors or nicotinergic agonists, might be able to reverse their enduring cognitive deficits.

Although this study presents very interesting and novel findings, several limitations need to be taken into account. Since volumetric cBF measurements are only an indirect marker of cholinergic system integrity, it cannot be ruled out that the volumetric perturbations might also be due to changes in other noncholinergic neuronal (i.e. cortically projecting gamma-

aminobutyric acid (GABA) neurons) or astrocytic populations. This study also focused on high-risk premature birth, as defined by the VP/VLBW criteria. As these criteria consist of numerous factors, it is difficult to determine which medical or prematurity factors, or combinations thereof, might be the most influential for cBF volume and IQ in adulthood. Finally, the study sample consisted of VP/VLBW adults with relatively lower neonatal complications and higher IQ because individuals with more severe impairments were more likely to be excluded in initial MRI screening or were not willing to participate in the neuroimaging. Therefore, the reductions in cBF volume in VP/VLBW adults might actually be considered a conservative estimate.

In sum, Grother *et al.* provide for the first time compelling evidence that reduced cBF volume is associated with the long-term cognitive deficits caused by complications arising from premature birth. Future studies utilizing functional imaging of the cBF combined with pharmacological challenges would further strengthen the link between cBF disruption and cognitive impairments.

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