Commentary: The neonatal brain and the challenge of imaging biomarkers, reflections on Batalle et al. (2018)

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This review of neonatal imaging by Batalle et al. (2018) comes at an important time in the field. As the authors point out, perinatal imaging has matured to a point that important questions can now be asked in a more definitive way. Understanding the prenatal and early childhood origins of cognitive ability, behavior, and risk of neuropsychiatric disorders is now possible. The authors have done an excellent job summarizing the challenges of neonatal imaging, as well as the advances in image acquisition, motion correction, and image analysis that have made studies at this important age feasible and meaningful. There are a few points that deserve consideration and emphasis.

One of the important questions that can now be addressed is how different aspects of the developing brain influence each other, how does the maturation of white matter, gray matter and functional connectivity relate to one another, how do they influence each other? This is beginning to be elucidated (Gilmore, Santelli, & Gao, 2018). Studies indicate that major white matter tracts are in place at the time of birth, and white matter networks already exhibit mature properties, including small worldness and 'rich club' structure. Myelination and microstructure maturation of white matter proceeds very rapidly in the first year of life. While primary sensorimotor functional networks are relatively mature at birth, most other functional networks mature significantly in the first year or two of life. Components of cortical gray matter, including cortical thickness and surface area grow rapidly in the first year of life, and there is evidence that cortical gray matter networks mature later than resting state networks. These early studies suggest a model in which white matter connectivity sets the stage for functional network development, which in turns shapes and refines cortical gray matter growth. Future studies in humans and animal models are needed to flesh out how different components of the developing brain influence each other.

The authors point out that differences related to developmental age are often greater than inter-individual differences in early childhood. Age is a critical variable for studies in early childhood, and especially in the first year of life, when there are significant changes in size, intensity, and contrast of brain structures. Age-specific atlases and segmentation protocols, as well as age-specific MR head coils are important approaches to this problem. However, their use makes it much more difficult to make meaningful comparisons across ages, especially in longitudinal studies. It is also important to note that that early studies suggest

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that structure – cognitive function relationships change with age in early childhood. For example, white matter factional anisotropy is significantly related to Mullen Composite Score at age 1, but not at age 2 (Lee et al., 2017). Analyses have to take these potential age-related differences in structure-function relationships into account and one should avoid analyses that group subjects with wide age ranges together.

White matter microstructure is highly correlated across white matter tracts in early childhood (Lee et al., 2017), making it difficult to identify tract-specific relationships with cognitive function or behavior. The apparent specificity of any hypothesized tract-cognition/behavior or tract-outcome relationship must be evaluated using several control tracts.

One of the major hopes of early childhood imaging is the identification of imaging biomarkers of later cognitive function, behavior, and risk for neuropsychiatric disorders. This would allow early identification and intervention, potentially normalizing suboptimal developmental trajectories during periods of rapid development and plasticity in early childhood. At this time it is not clear what the interventions would be, though imaging biomarkers may help identify brain targets and sensitive time periods for potential intervention (i.e. behavioral, neuromodulatory, pharmacologic). The authors acknowledge that large effect sizes are not expected; so far, the ability of current structural and functional imaging approaches to predict later cognition and behavior is rather modest. This is true, for example, in studies of white matter at multiple levels, including voxel based clusters within white matter, individual white matter tracts, principle components of white matter, and more recently machine-learning analysis of white matter networks. Often, clinical and demographic variables have stronger correlations with outcomes than current imaging biomarkers (Gabrieli, Ghosh, & Whitfield-Gabrieli, 2015).

The identification of imaging biomarkers has many challenges. These include small effect sizes, a lack of specificity of a region of interest with the functional aspects of the neurons that underlie it, and the involvement of a distributed network of brain regions with a specific cognitive function or disease risk (Woo, Chang, Lindquist, & Wager, 2017). The advanced machine-learning approaches highlighted in this review offer a way forward. It will also be important to determine if combining multiple components of brain structure and functional connectivity will provide better predictive ability and if so, how it is influenced by development (Braun et al., 2018; Seidlitz et al., 2018). Finally, as emphasized in the review, large longitudinal cohorts will be necessary to parse the interaction of potential imaging biomarkers with multiple environmental and genetic influences in the prediction of heterogeneous outcomes.

Acknowledgements

References

Batalle D, Edwards AD, & O'Muircheartaigh J (2018). Annual Research Review: Not just a small adult brain: understanding later neurodevelopment through imaging the neonatal brain. Journal of Child Psychology and Psychiatry, 59, 350–371. [PubMed: 29105061]

Braun U, Schaefer A, Betzel RF, Tost H, Meyer-Linden-berg A, & Bassett DS (2018). From maps to multi-dimensional network mechanisms of mental disorders. Neuron, 97, 14–31. [PubMed: 29301099]

Gabrieli JDE, Ghosh SS, & Whitfield-Gabrieli S (2015). Prediction as a humanitarian and pragmatic contribution from human cognitive neuroscience. Neuron, 85, 11–26. [PubMed: 25569345]

Gilmore JH, Santelli RK, & Gao W (2018). Imaging structural and functional brain development in early childhood. Nature Reviews Neuroscience, 19, 123–137. [PubMed: 29449712]

Lee SJ, Steiner RJ, Yu Y, Short SJ, Neale MC, Styner MA, … & Gilmore JH (2017). Common and heritable components of white matter microstructure predict cognitive function at 1 and 2 y. Proceedings of the National Academy of Sciences of the United States of America, 114, 148–153. [PubMed: 27994134]

Seidlitz J, Vasa F, Shinn M, Romero-Garcia R, Whitaker KJ, Vertes PE, … & Bullmore ET (2018). Morphometric similarity networks detect microscale cortical organization and predict inter-individual cognitive variation. Neuron, 97, 231–247. [PubMed: 29276055]

Woo C-W, Chang LJ, Lindquist MA, & Wager TD (2017). Building better biomarkers: Brain models in translational imaging. Nature Neuroscience, 20, 265–377.