Cerebellum (2013) 12:776–777
DOI 10.1007/s12311-013-0483-x

LETTER TO THE EDITOR

The Cerebellum in Autism: Pathogenic or an Anatomical Beacon?

Mark N. Ziats · Owen M. Rennert

Published online: 21 April 2013

To The Editor:

In the September 2012 issue of *The Cerebellum*, Fatemi et al. presented a comprehensive literature analysis of the putative role of the cerebellum in autism pathogenesis [1]. While this is an important work, which synthesizes the main findings of cerebellar research in autism spectrum disorders (ASD), we believe there is an alternative hypothesis to the role of the cerebellum in autism that is more parsimonious.

The conclusion that the cerebellum is pathogenic in ASD is predicated on the notion that the cerebellum functions in the cognitive processes disrupted in autism, although such pathways remain undiscovered. While the cerebellar contribution to higher cognition has been debated for decades [2], a clear mechanistic understanding of how the cerebellum may integrate with processes affected in autism, such as theory of mind, is not well established—as Fatemi et al. noted. Human studies that have consistently implicated the cerebellum in ASD do so mostly on the basis of volumetric imaging studies, or postmortem histologic and molecular changes, including our own work [3]. However, as opposed to the notion that these changes are pathogenic—which would require an as yet undiscovered mechanism for the cerebellum in the higher cognitive functions affected in ASD—we propose instead that the unique anatomy, physiology, and development of the cerebellum may result in an exaggerated manifestation of the brain-wide pathologic changes that underlie autism, without being causal for the clinical phenotype. In this sense, then, the cerebellum in autism may be acting as an "anatomical beacon" of more subtle changes in other brain regions where the functional pathology actually rests.

The unique anatomy, physiology, and development of the cerebellum make it a distinct part of the human brain. The cerebellum has the highest cell density of any brain area, approximately four times that of the neocortex [4, 5], and cerebellar Purkinje cells have more synapses than any other cell type by orders of magnitude [6]. As building synapses requires the appropriate molecular "toolkit," the cerebellum's molecular complexity of transcripts [7, 8] and proteins [9, 10] rivals that of the cerebral cortex. Underlying the heightened synaptogenesis of the cerebellum is the need for energy to carry out this process, resulting in oxidative metabolic demand that is similar to the cerebral cortex as well [11]. The implications of these well-recognized cerebellar properties to autism are profound. The ASD phenotype is considered to ultimately result from synaptic dysfunction [12], which derives from underlying genetic changes that manifest in aberrant RNA and protein production [13, 14]. Additionally, autism has a strong and growing association with related problems in oxidative metabolism [15]. Is it possible that cerebellar pathology in ASD is more evident than other brain areas purely because the cerebellum contains more of the components that are disrupted in autism?

If the molecular and cellular processes that are abnormal in ASD are dysfunctional throughout the brain, then these observations suggest that the cerebellum may have properties that result in an exaggerated manifestation of ASD pathology compared to other brain regions. Therefore, we hypothesize that the cerebellum may not be etiological in the pathogenesis of autism spectrum disorders; rather its unique

M. N. Ziats (✉) · O. M. Rennert
Laboratory of Clinical and Developmental Genomics, National Institute of Child Health and Human Development, National Institutes of Health, 49 Convent Drive, Building 49, Room 2C08, Bethesda, MD 20814, USA
e-mail: ziatsm@mail.nih.gov

O. M. Rennert
e-mail: rennerto@mail.nih.gov

M. N. Ziats
Baylor College of Medicine MSTP, Houston, TX, USA

M. N. Ziats
NIH-University of Cambridge Biomedical Scholars Program, Cambridge, UK

anatomic and physiologic properties may accentuate the mechanisms that are aberrant throughout the autistic brain. Consequently, investigations into autism pathology may be more readily observed in the cerebellum because the changes are more obvious than the concomitant changes in other brain areas responsible for the clinical phenotype.

This hypothesis does not diminish the potential importance of the cerebellum to autism research. Harnessing this unique property has serious implications in diagnostic testing, for example with neuroimaging. Diagnostic tests may be able to identify biological changes in ASD patients earlier in life, which is known to correlate with improved patient outcomes [16, 17], by focusing on the cerebellum. While cerebellar changes may not directly cause the cognitive deficits of ASD, they could serve as an "internal biomarker" for the more subtle alterations that must therefore be ongoing in other brain areas but would require more sensitive techniques to detect.

Until it is understood how the cerebellum functions in the higher cognitive processes that are abnormal in autism, the field must consider the alternative hypothesis that changes found in the cerebellum of autistic patients are not pathogenic, but rather are collateral manifestations of the cellular and molecular deficits that are present throughout the autistic brain. The distinctive nature of the cerebellum may exaggerate changes that are more subtle in other brain areas, without being causal of the ASD phenotype. However, such an interpretation does not diminish the importance of cerebellar research in autism, as this unique characteristic may make the cerebellum an ideal diagnostic target.

Acknowledgments The intramural research program at the National Institute of Child Health and Human Development supported this work. MNZ was also supported by Baylor College of Medicine MSTP and the NIH-University of Cambridge biomedical scholars program. The funders had no role in decision to publish or preparation of the manuscript.

Conflict of Interests The authors declare that they have no conflicts of interest to disclose.

References

1. Fatemi SH, Aldinger KA, Ashwood P, Bauman ML, Blaha CD, Blatt GJ, et al. Consensus paper: pathological role of the cerebellum in autism. Cerebellum. 2012;11(3):777–807.
2. Frings M, Maschke M, Timmann D. Cerebellum and cognition: viewed from philosophy of mind. Cerebellum. 2007;6(4):328–34.
3. Ziats MN, Rennert OM. Aberrant expression of long noncoding RNAs in autistic brain. J Mol Neurosci. 2013;49(3):589–93.
4. Herculano-Houzel S. The human brain in numbers: a linearly scaled-up primate brain. Front Hum Neurosci. 2009;3:31.
5. Herculano-Houzel S. The remarkable, yet not extraordinary, human brain as a scaled-up primate brain and its associated cost. Proc Natl Acad Sci USA. 2012;109 Suppl 1:10661–8.
6. Kandel ER, Schwartz J, Jessell T, Siegelbaum S, Hudspeth AJ. Principles of Neural Science. 5th ed. New York: McGraw-Hill Education; 2012. p. 966.
7. Mazin P, Xiong J, Liu X, Yan Z, Zhang X, Li M, et al. Widespread splicing changes in human brain development and aging. Mol Syst Biol. 2013;22(9):633.
8. Kang HJ, Kawasawa YI, Cheng F, Zhu Y, Xu X, Li M, et al. Spatio-temporal transcriptome of the human brain. Nature. 2011;478(7370):483–9.
9. Fountoulakis M, Juranville JF, Dierssen M, Lubec G. Proteomic analysis of the fetal brain. Proteomics. 2002;2(11):1547–76.
10. Martins-de-Souza D, Guest PC, Guest FL, Bauder C, Rahmoune H, Pietsch S, et al. Characterization of the human primary visual cortex and cerebellum proteomes using shotgun mass spectrometry-data-independent analyses. Proteomics. 2012;12(3):500–4.
11. Howarth C, Gleeson P, Attwell D. Updated energy budgets for neural computation in the neocortex and cerebellum. J Cereb Blood Flow Metab. 2012;32(7):1222–32.
12. Zoghbi HY. Postnatal neurodevelopmental disorders: meeting at the synapse? Science. 2003;302(5646):826–30.
13. Voineagu I. Gene expression studies in autism: moving from the genome to the transcriptome and beyond. Neurobiol Dis. 2012;45(1):69–75.
14. Maurer MH. Genomic and proteomic advances in autism research. Electrophoresis. 2012;33(24):3653–8.
15. Rossignol DA, Frye RE. Mitochondrial dysfunction in autism spectrum disorders: a systematic review and meta-analysis. Mol Psychiatry. 2012;17(3):290–314.
16. Howlin P, Magiati I, Charman T. Systematic review of early intensive behavioral interventions for children with autism. Am J Intellect Dev Disabil. 2009;114(1):23–41.
17. Levy SE, Mandell DS, Schultz RT. Autism. Lancet. 2009;374(9701):1627–38.