

S.09. Autism spectrum disorders: current advances on physiopathological mechanisms

S.09.01 Whole-brain structural MRI of autism-associated neuroanatomical features

D. Murphy^{1*}. ¹*Institute of Psychiatry King's College London, Forensic and Neurodevelopmental Sciences, London, United Kingdom*

Autistic Spectrum Disorder (ASD; comprising 'typical' autism, and Asperger syndrome) is associated with a significant healthcare burden.

There is increasing evidence that children with ASD have differences in brain growth trajectory. However, the neurobiological basis of ASD in adults is poorly understood.

Recently we reported evidence that brain aging people with ASD is significantly different as compared to controls – so that in adulthood they no longer have a significantly larger overall brain volume, but they do have anatomical and functional abnormalities in frontal lobe, basal ganglia and the limbic system (1).

There are, however, many unanswered questions. For example, a) what is the cellular and/or neurochemical associates of these gross anatomical and functional differences, and b) can we use brain imaging to aid diagnosis? Hence we studied neuronal integrity using proton magnetic resonance spectroscopy (¹H MRS), and reported that in adults with ASD abnormalities in frontal lobe were related to repetitive behaviours and social communication deficits (2). Also we have now carried out further studies using MRS, fMRI (with tryptophan depletion), and SPET to study (respectively) glutamate and GABA, brain blood flow during executive function and emotion processing tasks, and 5HT_{2A} receptor binding. Our results suggest that differences in brain maturation and function in people with ASD may be related to abnormalities in the glutamatergic and serotonergic systems. Lastly, we demonstrated that (3) can be used to 'categorise' people as having, or not having, autism. Hence sMRI may become a diagnostic aid in young adults with ASD.

References

- [1] Autistic-spectrum disorders: lessons from neuroimaging. Toal F, Murphy DG, Murphy KC. *Br J Psychiatry*. 2005 Nov;187:395–7.
- [2] In Vivo ¹H-Magnetic Resonance Spectroscopy Study of Amygdala-Hippocampal and Parietal Regions in Autism. Page L, Schmitz N, Simmons A, Daly E, Toal F, Deeley Q, Russell A, McAlonan G, Murphy DGM. *Am J Psychiatry*. 2006 Dec;163(12):2189–92.
- [3] Investigating the predictive value of whole brain structural MR scans in Autism: A pattern classification approach. Ecker C, Rocha-Rego V, Johnston P, Mourao-Miranda J, Marquand A, Daly AM, Brammer MJ, Murphy C; Murphy DGM, AIMS Consortium. *Neuroimage* 2009. Epub ahead of print.

S.09.02 Environment and vulnerable physiology in autism

M.R. Herbert^{1*}. ¹*Massachusetts General Hospital, TRANSCEND/Pediatric Neurology Harvard Medical School, Charlestown MA, USA*

Active pathophysiological processes such as inflammation and oxidative stress have been identified in autism spectrum disorders (ASD) [1]. These findings challenge deeply held assumptions

about ASD which are embodied in a classical model framing ASD as a problem of genes, brain and behavior – i.e., as a genetically determined developmental disorder of the brain whose main manifestation is behavioral alterations based upon an indelible static encephalopathy; this model would not have predicted the growing documentation of pathophysiological disturbances. An emerging pathophysiology-centered model of autism is more inclusive in that it can subsume genes, brain and behavior but can also include much more [2]. Prior evidence can be reread from this vantage point to support the framing of ASD as (1) not only developmental but also a chronic condition based on active pathophysiology, (2) not only behavioral but also having somatic and systemic features that are not secondary but rather intrinsic consequences of underlying mechanisms, (3) not only genetic but also environmental [3], (4) not a static encephalopathy but a dynamic, recalcitrant encephalopathy, and (5) not a set of discrete behavioral features neatly mapping to specific genetic mechanisms but a set of emergent properties dynamically arising from pathophysiological systems whose parameters have been dramatically and interactively perturbed. It is argued that a research program based upon this approach will incorporate the strengths of the classical model, will encourage many more routes to investigations with practical and treatment applications, and may lead much more rapidly to helping affected individuals and their families.

References

- [1] Herbert, M. R. 2009. Autism: The centrality of active pathophysiology and the shift from static to chronic dynamic encephalopathy in Autism: Oxidative stress, inflammation and immune abnormalities. A Chauhan, V Chauhan, and T. Brown. Taylor & Francis/CRC Press, Chapter 18, 343–387.
- [2] Herbert, M. R., M. P. Anderson. 2008. An Expanding Spectrum of Autism Models: From Fixed Developmental Defects to Reversible Functional Impairments. *Autism: Current Theories and Evidence*. ed. A Zimmerman, Humana Press. 429–463.
- [3] Herbert, M. R. 2010. Contributions of the environment and environmentally vulnerable physiology to autism spectrum disorders. *Curr Opin Neurol* 23:103–10.

S.09.03 Neurotrophic factors in autism

R. Riikonen^{1*}, I. Makkonen¹, J. Kuikka², W. Kaufmann³, U. Turpeinen⁴, R. Vanhala⁵, H. Kokki⁶. ¹*University of Kuopio, Children's Hospital, Kuopio, Finland;* ²*University of Kuopio, Imaging Center, Kuopio, Finland;* ³*Kennedy Krieger Institute, Neurology and Neuroscience, Baltimore, USA;* ⁴*University of Helsinki, Laboratory, Helsinki, Finland;* ⁵*University of Helsinki, Child Neurology, Helsinki, Finland;* ⁶*University of Kuopio, Anesthesiology, Kuopio, Finland*

Neurotrophic factors are important for neuronal growth, survival, and synaptic formation. Increased cerebral volume or brain weight is found across the studies. Pathological brain growth and premature developmental arrest are suggested to be restricted to the first year of life. In autism there seems to be a disruption of normal neurobiological mechanisms due to "premature growth without guidance".

1. We found a correlation between CSF IGF-1 and head growth in patients with autism but not in the controls [1]
2. At an early stage of the CSF IGF-1 concentrations of IGF-1 was lower than in the control [1]. This suggests a disruption of normal neurobiological mechanisms at an early age. IGF-2 was normal.
3. We also found disturbed SERT binding in patients with autism. Early decrease of serotonergic innervation might lead to low