Research Open

Psychology Journal: Research Open
Volume 6 Issue 6

Commentary

Commentary: Implications of Critical Periods in the Development of Autism

George Ayoub*

Psychology, Santa Barbara City College, Santa Barbara, CA 93109, USA

***Corresponding author:** George Ayoub, Psychology, Santa Barbara City College, Santa Barbara, CA 93109, USA

Received: December 20, 2024; **Accepted:** December 27, 2024; **Published:** January 03, 2025

Autism spectrum disorder (ASD, or autism) is a collection of developmental disorders with an increasing diagnosis rate. The most recent data compiled by the CDC (Centers for Disease Control and Prevention [1]) show a prevalence of 2.76% of 8 year olds in the US as diagnosed autistic in 2020, compared with 1.47% in 2010 and 0.67% in 2000. A new report [2] provides some guidance on factors that may contribute which, in combination with other recent studies, gives direction on what can be done to help mitigate this rise.

The report reviews determining factors of folate and of inflammation in the development of autism and observes that there are multiple critical periods in ASD where these factors play essential roles.

Critical Periods

The concept of critical periods was first demonstrated in the visual system, showing that the absence of light during a key period in visual cortex development determined the ultimate pathways made in the visual cortex, and that even normal exposure to light following this critical period was insufficient for the pathways to develop if they had not had light stimulation during the critical period. Wiesel and Hubel named this a critical period in the visual cortex, earning them the Nobel Prize in physiology or medicine in 1981 for this central understanding of the development of key brain functions [3]. The report [2] assesses that autism has multiple critical periods, and lists factors involved in at least two of these critical periods. In so doing, they point to a means to potentially reduce the diagnosis rate of ASD possibly other neurodevelopmental disorders (ADHD in particular comes to mind due to several overlapping symptoms in focus and attention).

Folate and Autism

Several clinical trials have shown that in the autistic population, about 70% make an autoantibody to the folate receptor [4,5]. Production of this folate receptor autoantibody (FRAA) seems to be triggered by dairy products in someone's diet [6] and results in a cerebral folate deficiency (CFD, or folate deficiency in the brain). If CFD is not corrected by dosing with natural folate (the form used is folinic acid, trade name *leucovorin*), or by removing the FRAA antigen (presumably by eliminating all dairy products from the diet), the ASD symptom of poor social communication firms up during the critical period, and even if correction is made later, neurotypical behavior cannot be fully restored and the ASD behavior is not abbreviated.Thus, a critical period is the need for natural folate (folate in its reduced form), and an abundance of synthetic folate (folate in its oxidized form) cannot help those with FRAA. Indeed, excess oxidized folate (folic acid) may be detrimental, as there is increasing evidence that unmetabolized folic acid (UMFA) can outcompete natural folate at the folate receptor, creating a CFD despite measured high plasma folate [7].

Oxidative Stress

Similarly, there is now abundant evidence that oxidative stress can alter neurotypical development, as documented [8] and postulated in that oxidative stress during critical periods in development will result in a decrease in microglial cells in the brain [2]. Microglia serve as part of the brain's immune system, since the lymphocytes (B cells and T cells) cannot cross the blood brain barrier. These microglia scavenge and clean out discarded or unused cell structures during development, most specifically for ASD, they remove unused synapses during the process of synaptic pruning. Synaptic pruning follows neurogenesis, when there is a proliferation of neuronal birth and synaptic contacts made, with only the active synapses retained later to create neurotypical brain pathways. If the excess synapses are not pruned, the report contends this gives rise to the ASD symptom of inability to focus on a task as well as explains a possible neural mechanism for the documented extraordinary memory for detail seen in ASD. Thus, this reduction in synaptic pruning can explain the excellent memory but also the inability to focus on a task that is seen in autism.

What are the causes of oxidative stress in neurodevelopment? Oxidative stress can be caused by inflammation from infection, emotional stress, under nutrition or exposure to foreign compounds [8,9]. The foreign chemicals include the usual litany of pesticides and persistent compounds from the environment (such as "forever chemicals") [10] as well as heavy metal ions such as lead exposure [11] but also include a number of pharmacological drugs. While drug side effects are often well established, their impact on a developing fetus or infant can often be overlooked. Thus, even well-tolerated psychopharmacological medicines may need to be reconsidered during pregnancy, putting them in a category perhaps similar to alcohol or caffeine, which are not typically discontinued during pregnancy and nursing due to the potential lasting impact of such depressants and stimulants on neurodevelopment.

In addition to these known agents of oxidative stress, we may need to add micro- and nanoplastics to the list, as these are reported to be embedded in every human organ, with documented effect on cardiovascular system, development and the microbiome, according to a report from the December 2024 hearing on health impacts of plastics held in Korea [12]. Indeed, this report reminds us that the microbiome is the essential processing zone for all nutrients, and alterations to someone's microbiome can have broad impacts.

Reducing Damage

While the report also reveals the mechanism of oxidative stress in the development of ASD, it also reveals the ways to minimize its effect. Oxidative stress depletes microglia nutrients, particularly N-acetyl cysteine and taurine. Increasing the intake of these nutrients should limit the damage to the microglia and support neurotypical development. Significantly, these small molecule nutrients are present in many foods (especially fish and seafood) and these are no reports of adverse effects of using supplements to restore these nutrients during periods of oxidative stress. Similarly with folate, many foods (including legumes, leafy greens, eggs and citrus) have high levels of this vitamin, and there is also a prescription source of natural folate available in leucovorin. Leucovorin has successfully been used in the ASD clinical trials mentioned above, and there are decades of its use in cancer treatment, where it is used to replenish the vitamin B-9 that is depleted by certain chemotherapies, so it is known to have no adverse effects.

Intriguingly, a new preprint [13] shows extra folate during pregnancy can reduce the impact of metabolism disrupting chemicals on a child. Thus, folate may be quite central to two mechanisms of neurotypical development.

Vaccine Impact

An intriguing aspect that comes out of the 2024 report [2] gives credence to the continued concern of vaccines and autism. In previous decades (until the 1980s), the pertussis vaccine was made from whole cells, which could be very inflammatory in up to one percent of children receiving the vaccine, causing brain fever. Now that we have an understanding about critical periods in autism development, we can see that if this inflammation occurred during such a critical neurodevelopmental period, there may be a lasting effect that could increase the risk of ASD. The most common pertussis vaccine used now no longer uses whole cells, and this acellular version does not cause such inflammation. Also, the timing of the vaccine is adjusted now to minimize developmental impact. However, the lingering concern among some parent groups about this vaccine is linked to a reality that is has passed. Originally, the vaccine used, DPT (for diphtheria-pertussis-tetanus) was problematic for neurodevelopment of an estimated 3 children per million vaccinations, while the newer version, the DTaP (for diphtheria-tetanus-acellular pertussis, or Tdap which is used for booster vaccinations) does not have this detrimental effect. This should be comforting news for parents, as they can continue to protect their children from these deadly diseases while no longer raising the risk for such children to have a neurological disorder.

Conclusion

Critical periods help us understand neurotypical as well as autistic development. The knowledge that those at higher risk due to inflammation and/or the presence of FRAA can help mitigate these risks with functional or lifestyle medical actions of modifying diet to include more foods with folate and with N-acetyl cysteine or taurine, along with getting regular exercise. Indeed, this may be an optimal treatment for someone at higher risk of ASD, further supporting use of a Mediterranean diet, which provides these nutrients, and also benefits the microbiome. Given the overabundance of ultra-processed foods (UPF) in many contemporary diets, we may have chosen a side of increased neurological disorders with the convenience of these fast foods. A comparison of neurodegenerative disorders in matched communities with UPF diets compared with blue zone diets may help provide confirmation that the increasing ASD diagnoses may be in part due to dietary changes made by families in the past half century.

References

1. https://www.cdc.gov/autism/data-research/index.html
2. Ayoub G (2024) Neurodevelopment of autism: critical periods, stress and nutrition. Cells. 13: 1-11. [crossref]
3. Wiesel TN: Nobel Lecture. NobelPrize.org.
4. Frye RE, Slattery J, Delhey L, et al. (2016) Folinic acid improves verbal communication in children with autism and language impairment: a randomized double-blind placebo-controlled trial. Mol Psychiatry. 23: 247-256. [crossref]
5. Renard E, Leheup B, Guéant-Rodriguez RM, Oussalah A, Quadros EV, et al. (2020) Folinic acid improves the score of Autism in the EFFET placebo-controlled randomized trial. Biochimie. 173: 57-61. [crossref]
6. Ramaekers VT, Sequeira JM, Blau N, Quadros EV (2008) A milk-free diet downregulates folate receptor autoimmunity in cerebral folate deficiency syndrome. Dev Med Child Neurol. 50: 346-352. [crossref]
7. Akiyama T, Kuki I, Kim K, Yamamoto N, Yamada Y, et al. (2022) Folic acid inhibits 5-methyltetrahydrofolate transport across the blood–cerebrospinal fluid barrier: Clinical biochemical data from two cases. JIMD 63: 529-535. [crossref]
8. Usui n, Kobayashi H, Shimada S (2023) Neuroinflammation and oxidative stress in the pathogenesis of autism spectrum disorder. In J Mol Sci. 24: 5487 [crossref]
9. Ahmavaara K, Ayoub G (2024) Stress and folate impact neurodevelopmental disorders. J Health Care & Res 5: 1-6.
10. Parenti M, Slupsky CM (2024) Disrupted prenatal metabolism may explain the etiology of suboptimal neurodevelopment: a focus on phthalates and micronutrients and their relationship to autism spectrum disorder. Adv Nutri. 15: 3-19. [crossref]
11. McFarland 2024 https://doi.org/10.1111/jcpp.14072
12. Moulun AG (2024) Quel impact des micro- et nano-plastiques sur la santé humaine? Medscape.
13. India-Aldana S et al. (2024) Metabolism-Disrupting Chemical Mixtures during Pregnancy, Folic Acid Supplementation, and Liver Injury in Mother-Child Pairs. medRxiv. [crossref]

Citation:

Ayoub G (2024) Commentary: Implications of Critical Periods in the Development of Autism. *Psychol J Res Open* Volume 6(6): 1-2.