Published in final edited form as:

J Am Acad Child Adolesc Psychiatry. 2013 October ; 52(10): 993–994. doi:10.1016/j.jaac.2013.07.015.

Human brain development in a dish

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Here: In This Issue

This issue of the *Journal* draws our attention to the interactions between poverty, nutrition, and the developing brain.

Comorbid psychopathology is common in children with Autism Spectrum Disorder (ASD), but little is known about how environmental factors contribute to psychopathology in this population. Midoudas and colleagues (p.XX) used data from 209 children with ASD in the Millenium Cohort Study (MCS) to examine whether psychopathology was influenced by family poverty or parenting characteristics. Problem behaviors were identified at 3, 5, and 7 years old using caregiver ratings on the Strengths and Difficulties Questionnaire. Parent warmth and involvement, as well as household chaos, were assessed by questionnaires at 3 years old. As expected, in comparison with the 13,737 MCS children without ASD, children with ASD had higher parent-reported general psychopathology symptoms at all three ages, with an increase over time (all P-values < 0.001). Family socioeconomic disadvantage (SED), a 4-item index of poverty, predicted higher general psychopathology symptoms ($t = 2.95$, $P < 0.01$), but this effect was not significant after correcting for maternal warmth. General symptoms were predicted by lower maternal warmth ($t = -7.98$, $P < 0.001$), with greater impact at younger ages.

Diet is well-known to impact both physical and mental health, but our understanding of this effect is based largely on either extreme cases, like famine, or on short-term effects in adolescents or adults. Jacka and colleagues (p.XX) used data from the Norwegian Mother and Child Cohort Study (MoBa) to examine the longitudinal effects of diet in children born to 23,020 women who were followed from pregnancy through 5 years of age. Mothers completed a food frequency questionnaire (FFQ) about their own diet during pregnancy and their child's diet at 1.5 and 3 years of age, which was used to identify 'wholesome' and 'unhealthy' dietary patterns. A shortened version of the Child Behavior Checklist (CBCL) was used to evaluate internalizing and externalizing behaviors at 1.5, 3, and 5 years of age. Externalizing behaviors were predicted by both prenatal (intercept factor 0.036, $P < 0.01$) and early postnatal (0.057, $P < 0.01$) exposure to an unhealthy diet, even after correction for

Disclosure of Biomedical Financial Interests and Potential Conflicts of Interest: Dr. Veenstra-VanderWeele has had research funding from Seaside Therapeutics, Novartis, Roche Pharmaceuticals, Forest Research Institute, and SynapDx, and has consulted with Novartis and Roche.

maternal depression, sex of the child, and several other factors. In contrast, internalizing behaviors were predicted by a wholesome prenatal diet (intercept factor 0.046, $P < 0.01$); whereas a wholesome postnatal diet was protective (-0.048 , $P < 0.01$). An unhealthy postnatal diet was associated with internalizing factors as well (intercept factor 0.110, $P < 0.01$), but this impact attenuated with age (slope factor -0.028 , $P < 0.01$). For comparison, most of the effects of diet were less than half of the effect of prenatal or early postnatal maternal depressive symptoms.

The brain must contribute to the development of anorexia nervosa (AN), but the resulting starvation could also impact brain function. Frank and colleagues (p.XX) performed structural MRI and diffusion tensor imaging (DTI) in 19 adolescent girls with AN and 22 controls. Importantly, the girls with AN were scanned shortly after inpatient hospitalization and followed a defined meal plan to avoid acute effects of starvation or dehydration. Neither total gray matter volume or white matter volume differed between the AN and control groups. Paralleling data in adults with AN, girls with AN had increased gray matter volume in the left orbitofrontal cortex (OFC, $P = 0.009$) and right insula ($P = 0.047$) in comparison to controls. Remarkably, OFC volume correlated negatively with ratings of pleasantness after tasting a sucrose solution ($r = -0.498$, $P < 0.03$) in the AN group but not in the control group. White matter integrity by DTI also differed in the AN group, including higher fractional anisotropy in the left fornix, where similar findings were previously reported in adults.

There: Abstract Thinking

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For many of our physician colleagues, a careful examination of cells from a biopsy is critical to making a solid diagnosis. As child psychiatrists, though, our best tool is an interview or examination. The closest we get to our cells of interest, barring the unfortunate instance of a postmortem study, is a black-and-white picture of tens of billions of neurons, sometimes overlaid with patterns of blood flow. This is not to disparage our tools – they represent careful clinical science and can yield life-changing treatments – but they are far from a biopsy of the developing brain.

A recent advance promises a glimpse into the early brain development of living patients. By reprogramming skin biopsies, blood cells, or even tooth pulp, scientists have managed to recreate stem cells from human tissue. These *induced, pluripotent stem cells* (iPSCs) can become neurons and glia. While they do not literally form brains in a dish, these induced neurons, when placed in a suspension for 10 weeks, can form layered cortex with some similarity to the same period in fetal development¹.

Studies in two rare genetic syndromes highlight the promise of iPSCs for understanding and potentially treating disorders of brain development. The Muotri lab reported that iPSC-derived neurons from patients with Rett Syndrome (RS) are smaller, form fewer synapses, and show signaling deficits in comparison to controls². Paralleling work in mice, this abnormality could be partially rescued by insulin-like growth factor 1 (IGF-1), which is the most promising mechanism now being explored in human treatment studies. The Dolmetsch

lab studied induced neurons from patients with Timothy Syndrome (TS), an extremely rare disorder associated with autism and cardiac abnormalities due to a mutation in the *CACNA1C* gene causing decreased inactivation of an L-type calcium channel subunit. They found a shift in gene expression and an increase in induced neurons expressing tyrosine hydroxylase (TH), the rate-limiting enzyme in the synthesis of dopamine and norepinephrine³. It was not altogether surprising that a calcium channel antagonist, roscovitine, decreased TH expression. In contrast, it was quite surprising that dendrites shrink, rather than expand, when induced neurons from TS patients are stimulated, regardless of whether the calcium channel is blocked⁴.

Thus far, most human iPSC studies have confirmed or extended our understanding of pathophysiology from cellular or animal models, rather than yielding independent breakthroughs. As reprogramming efforts are better able to differentiate specific neuronal subtypes, however, we can expect new knowledge to emerge that allows treatments to be tried on developing neurons in a dish before being tested on fully formed humans. We can begin to imagine a day when we test for medication response in a child's induced neurons before writing the initial prescription.

Acknowledgments

This work was supported in part by NIH grant R01-MH094604. Dr. Veenstra-VanderWeele would like to thank Dr. David Hong for editorial suggestions.

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