frontiers | Frontiers in Science

TYPE Frontiers in Science Editorial
PUBLISHED 28 February 2023
DOI 10.3389/fsci.2023.1148127

Check for updates

OPEN ACCESS

APPROVED BY
Frontiers Editorial Office,
Frontiers Media SA, Switzerland

REVIEWED BY
Arti Ahluwalia,
University of Pisa, Italy

*CORRESPONDENCE
Rémi Quirion
remi.quirion@frq.gouv.qc.ca

RECEIVED 19 January 2023
ACCEPTED 28 January 2023
PUBLISHED 28 February 2023

CITATION
Quirion R. Brain organoids: are they for real? *Front Sci* (2023) 1:1148127. doi: 10.3389/fsci.2023.1148127

COPYRIGHT
© 2023 Quirion. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Brain organoids: are they for real?

Rémi Quirion[1,2]*

[1]Quebec Chief Scientist, Montreal, QC, Canada, [2]President, International Network for Governmental Science Advice (INGSA), Montreal, QC, Canada

KEYWORDS

artificial intelligence, microphysiological systems, synthetic biology, bioengineering, organoid intelligence, Alzheimer's disease

An Editorial on the Frontiers in Science Lead Article

Organoid intelligence (OI): the new frontier in biocomputing and intelligence-in-a-dish

Introduction

In 1965, Gordon E. Moore, the co-founder of Intel, observed that the number of transistors on a single microchip doubles approximately every two years, while the cost of computers roughly halves during that timeframe; this became known as "Moore's Law." This increase in computational power was the bedrock of the Fourth Industrial Revolution and all the societal change it drove. Engineers continue to find seemingly impossible ways to pack even more transistors onto chips, even though logic tells us we have been nearing physical size limits for years. How can science and society prolong these welcome waves of progress?

Perhaps biology could offer the solution. From the very beginning, computers have been designed to model the human brain. The mathematician John von Neumann was a pioneer of the computer age. His unfinished book, *The Computer and the Brain*, first published in 1958, discussed important differences between brains and the computers of his day and suggested directions for future research. This strongly influenced the efforts of generations of innovators to make computers increasingly brain-like.

In their fascinating article, Smirnova et al. (1) now propose doing the exact opposite: making brain cultures more computer-like. In June 2022, Hewlett Packard's Enterprise Frontier (OLCF-5) supercomputer at the U.S. Department of Energy Oak Ridge National Laboratory surpassed the estimated computing power of a single human brain (1 exaFLOPS). However, there is a dramatic difference in efficiency: a human brain weighs around 1.4 kg and consumes 20 W of power, whereas Enterprise Frontier takes up 680 m^2 and consumes 21 MW. Notably, the supercomputer also cost an estimated $600 million to build, not to mention its running costs. On a smaller scale, Apple's current MacBook also weighs about 1.4 kg and claims to deliver 10 teraFLOPS of performance – that is, 100,000 times less than a human brain. In other words, if Moore's Law holds, it would take approximately 33 more years for a laptop to reach brain performance.

Although these comparisons are purely notional, they help to illustrate the enormous potential of biological computing. The big challenge for Smirnova et al. and other researchers in this field is: can they grow the next supercomputer in a cell culture lab?

Organoid intelligence: Achievements and challenges

The field of artificial intelligence (AI) is at an impasse, requiring exponentially larger amounts of power and data to yield only incremental gains. One key problem is that AI systems must build a new model every time data is added, whereas the human brain uses progressive learning. Some years ago at the American Association for the Advancement of Science's Annual Meeting, and more recently at the 2022 EuroScience Open Forum in Leiden, the Netherlands, I have seen how Johns Hopkins University is leading a revolution in bioengineering and brain cell culturing that aims at a new generation of AI. In their latest article (1), Smirnova and colleagues, based at Johns Hopkins and other institutions, explain how standardized human brain organoids are now being produced with the aim of harnessing them *via* pioneering interface technologies and machine learning toward the development of biological computers and "organoid intelligence" (OI), or *intelligence-in-a-dish*.

While much of the work remains hypothetical, substantial progress has certainly been made since the first description of human brain organoid cultures in 2013 (2). Standardized brain cell cultures are successfully being produced with the incorporation of glial helper cells, which are critical for cognitive functions such as learning and memory. These are being supported by microphysiological systems that attempt to recreate brain architecture and functionality on a micro-scale, including organoids, organ-on-chip, and multi-organ-on-chip models. Other microphysiological systems are already achieving breakthroughs for COVID-19 and autism research and are also being applied to space research. For the first time, the U.S. Food and Drug Administration has approved an investigational drug candidate to move into human trials based on microphysiological testing – without animal efficacy data (3).

Major challenges remain to realizing OI, including the development of techniques to supply input to brain organoids and measure their output. Recently, some of Smirnova's co-authors have made advances in electroencephalograph (EEG) technology that allows the electrical activity of brain organoids to be assessed (4). Other co-authors are currently pioneering truly fascinating studies to assess learning in brain cell cultures, such as training brain organoids to play the computer game Pong (5) or to control the movements of a robot (6). Unquestionably, there is still a long way to go, but this multidisciplinary community of researchers has reached the critical mass necessary to tackle these and other challenges.

A "man-on-the-moon"-style ambition is necessary

Biomedicine depends on models to understand both standard physiology and disease processes – such knowledge is prerequisite for the development of treatments and cures. Current models, based on, for example, human tumor cell lines and human cells from surgical materials, have well-known limitations. Brain organoids may provide a human model that allows researchers to recreate physiological and pathophysiological processes without the drawbacks of conventional models. Innovative technologies such as OI will shape the advancement of biomedical research – even if not everyone is brave enough to get on board.

Unless there is a joint effort to champion reliable, evidence-based policymaking on issues relating to the brain and brain research, we risk a dangerous slide into the realm of policy-misinformed evidence. While I agree with the "precautionary principle," there are times when the "innovation principle" should hold sway – and this might just be one such time. Not only could brain organoid research benefit biological computing, it could also have significant public health benefits. The incidence of neurological disorders, mental illnesses, and addictive behaviors has increased markedly in recent decades owing in part to demographic and lifestyle changes. For example, based on 2016 data (which likely understates current numbers), neurological diseases are the leading cause of disability and the second leading cause of all deaths worldwide (7). In the United States, around one in six children is born with some form of neurodevelopmental disorder (8) and around one in 44 children has autism (9). At the other end of the life cycle, 6.5 million Americans aged 65 and older are currently living with Alzheimer's disease, and the US Centers for Disease Control and Prevention projects this number will reach 12.7 million by 2050 (10).

Despite large, worldwide investments in brain research, truly novel therapeutic approaches and effective treatments for central nervous system disorders remain remote. The recent development of the monoclonal antibody lecanemab (11) is an important step forward in the treatment of Alzheimer's disease, but there is much more to do. To tackle these silent pandemics, we need new, "outside-the-box" research tools and strategies. A human-based model of learning and memory, potentially built from a patient's own cells to incorporate the individual's specific genetic elements, could become a crucial tool for better understanding neurological diseases and developing cures. If we succeed in creating models that are capable of learning and remembering, we will be able to study the fundamental physiology of brain function in a dish. Combining a brain cell culture with AI and enabling crosstalk might elucidate how the brain changes in response to external factors and disease states, and hence how these affect its function. This will potentially allow us to take a significant but limited step in our understanding of what is going wrong in neurodevelopment toward cognition.

Smirnova et al. are driving toward such a model to help us improve our understanding of how cognitive functions are established and how our genes and our environments (enviro-genomics) play a role. This could be game changing for public health. Everyone – from policymakers and funding bodies to scientists, pharmaceutical companies, and the public – should give the innovative approach of OI a chance to succeed. These studies are still in their infancy, and they need our support.

The ethics of brain research

There was a time when people who were "different" were simply locked up alongside criminals and debtors. Out of sight was out of

mind; caring for such individuals was costly. Today, society strives to do more to help everyone – from children to elderly people – suffering from life-limiting or life-threatening conditions. However, the extent of societal intervention is frequently limited by legal boundaries, which are often informed by the hotly contested interests of ethics and religion, as well as by a fear of the unknown. As a neuroscientist, and as Quebec Chief Scientist, I have seen firsthand how topics involving the brain – and even more so the mind – can divide individuals, scientists, and policymakers. Recent advances toward OI give me great hope that, with the proper engagement of all stakeholders, we can establish a successful set of ethics and principles to inform this crucial work at the boundary between science, society, and policy – while avoiding the unfortunate pitfalls experienced with genetically modified organisms (GMO), for example.

There is a whole new arena for debate around OI, posing questions about when sentience or consciousness start, or about the relationship of a patient to their organoid, and/or what it perceives and computes. The way we address these compelling questions is critical to societal acceptance of any new treatments or technologies that may result from brain organoid research. Scientists should promote the innovation principle at levels, whether at the dinner table or the gas station, when informing national policy, and *via* networks such as the International Network for Government Science Advice (INGSA) (12). We should vigorously encourage and pursue detailed discussions among experts in various disciplines, as well as from various cultural and ethnic backgrounds. Such discussions are one of the best ways to ensure that the new discipline of OI thrives and generates breakthroughs in the understanding of brain functions and diseases. The authors must be applauded for their efforts to address these questions from the outset, with the help of leading ethicists.

Watch this space

I believe we will hear much more about this new field of OI in the months and years to come. It will not be easy – the saying "it takes a village (to raise a child)" well applies to such a multidisciplinary, long-term mission. However, a wave of global interest is already helping to build it, including an upcoming series of world summits and an international society. The authors have judiciously begun forming such a community, including through the "Baltimore Declaration toward the exploration of organoid intelligence" (13). In February 2022, they held an initial workshop at which 50 eminent participants explored the latest scientific, technological, and ethical developments and challenges in this area (14). It is tempting to compare this workshop with the workshop at Dartmouth College in the summer of 1956 that established AI as a scientific field. Only time will tell if OI lives up to this comparison – wouldn't it be tremendous if these discussions were the seminal moments marking the birth of OI? I wouldn't miss it for the world.

Author contributions

The author confirms being the sole contributor of this work and has approved it for publication.

Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Smirnova L, Caffo BS, Gracias DH, Huang Q, Morales Pantoja IE, Tang B, et al. Organoid intelligence (OI): the new frontier in biocomputing and intelligence in-a-dish. *Front Sci* (2023) 1:1017235. doi: 10.3389/fsci.2023.1017235

2. Lancaster MA, Renner M, Martin CA, Wenzel D, Bicknell LS, Hurles ME, et al. Cerebral organoids model human brain development and microcephaly. *Nature* (2013) 501(7467):373–9. doi: 10.1038/nature12517

3. Rumsey JW, Lorance C, Jackson M, Sasserath T, McAleer CW, Long CJ, et al. Classical complement pathway inhibition in a "human-on-a-chip" model of autoimmune demyelinating neuropathies. *Adv Ther (Weinh)* (2022) 5(6):2200030. doi: 10.1002/adtp.202200030

4. Huang Q, Tang B, Romero JC, Yang Y, Elsayed SK, Pahapale G, et al. Shell microelectrode arrays (MEAs) for brain organoids. *Sci Adv* (2022) 8(33):eabq5031. doi: 10.1126/sciadv.abq5031

5. Kagan BJ, Kitchen AC, Tran NT, Parker BJ, Bhat A, Rollo B, et al. *In vitro* neurons learn and exhibit sentience when embodied in a simulated game-world. *Neuron* (2022) 110(23):3952–69. doi: 10.1016/j.neuron.2022.09.001

6. Schley L. *Meet the scientists connecting lab-grown "mini brains" to robots* (2018). Available at: https://www.discovermagazine.com/mind/meet-the-scientists-connecting-lab-grown-mini-brains-to-robots.

7. GBD 2016 Neurology Collaborators. Global, regional, and national burden of neurological disorders, 1990–2016: A systematic analysis for the global burden of disease study. *Lancet Neurol* (2019) 18(5):459–80. doi: 10.1016/S1474-4422(18)30499-X

8. Zablotsky B, Black LI, Maenner MJ, Schieve LA, Danielson ML, Bitsko RH, et al. Prevalence and trends of developmental disabilities among children in the united states: 2009–2017. *Pediatrics* (2019) 144(4):e20190811. doi: 10.1542/peds.2019-0811

9. Maenner MJ, Shaw KA, Bakian AV, Biller DA, Durkin MS, Esler A, et al. Prevalence and characteristics of autism spectrum disorder among children aged 8 years – autism and developmental disabilities monitoring network, 11 sites, united states, 2018. *MMWR Surveill Summ* (2021) 70(11):1–16. doi: 10.15585/mmwr.ss7011a1

10. Matthews KA, Xu W, Gaglioti AH, Holt JB, Croft JB, Mack D, et al. Racial and ethnic estimates of alzheimer's disease and related dementias in the united states

(2015–2060) in adults aged ≥65 years. *Alzheimers Dement* (2019) 15(1):17–24. doi: 10.1016/j.jalz.2018.06.3063

11. van Dyck CH, Swanson CJ, Aisen P, Bateman RJ, Chen C, Gee M, et al. Lecanemab in early alzheimer's disease. *N Engl J Med* (2023) 388(1):9–21. doi: 10.1056/NEJMoa2212948

12. International Network for Governmental Science Advice (InGSA). INGSA. Available at: https://ingsa.org/.

13. Hartung T, Smirnova L, Morales Pantoja IE, Akwaboah A, Alam El Din D-M, Berlinicke CA, et al. The Baltimore declaration toward the exploration of organoid intelligence. *Front Sci* (2023) 1:1068159. doi: 10.3389/fsci.2022.1068159

14. Morales Pantoja IE, Smirnova L, Muotri AR, Wahlin KJ, Kahn J, Boyd JL, et al. First Organoid Intelligence (OI) workshop to form an OI community. *Front Artif Intell* (2023) 6:1116870. doi: 10.3389/frai.2023.1116870