

An Ethical Exploration of Brain Organoid Models in Biomedical Research

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What Are Organoids?

Organ-oid = “resembling an organ” or “Organ-like” (3D)

Defined (generally) by three fundamental characteristics:

1. Self-arrangement and self-development *in vitro*.
2. 3D structure (<-> stem cells).
3. Consist of multiple celltypes found in their organ counterpart, and have some of the functions normally carried out in the organ counterpart.

Examples of Organoids

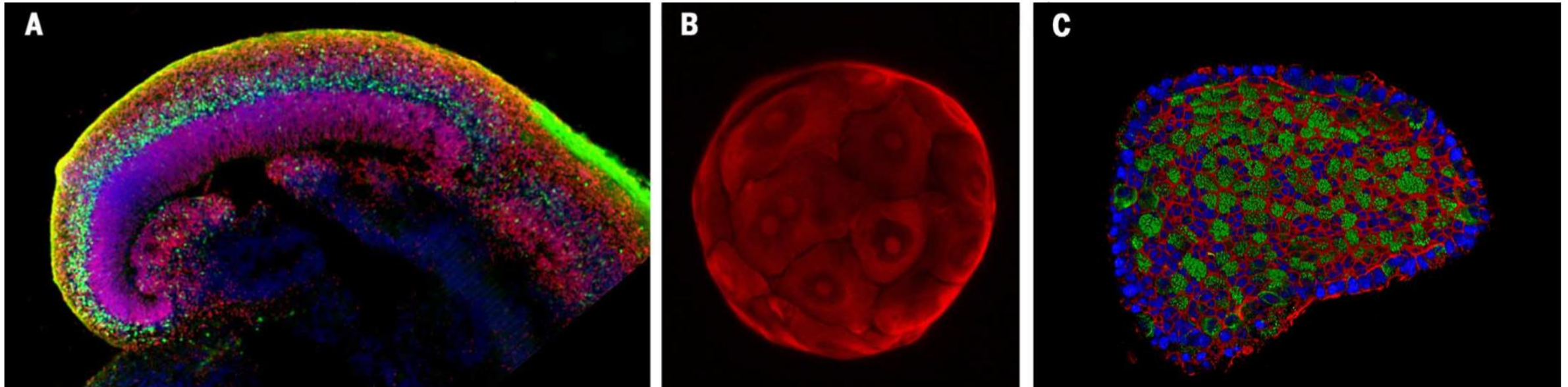


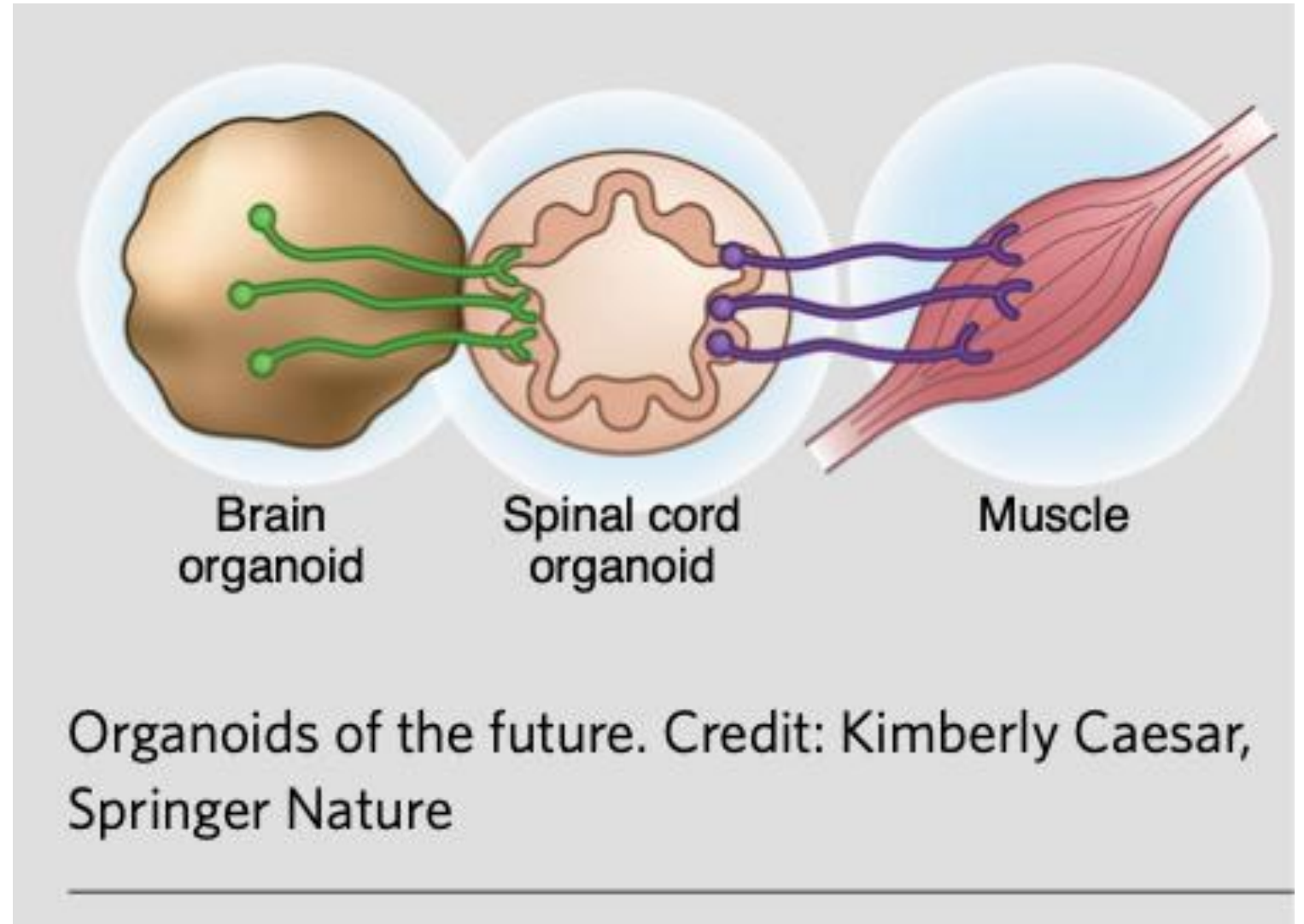
Fig. 1. Examples of organoid models. (A) Human brain organoid displaying complex morphology. Heterogeneous regions containing neural progenitors (SOX2, red) and neurons (TUJ1, green) are visible. [Courtesy of M. Lancaster] (B) Human liver organoid (actin cytoskeleton in red, blurred). [Courtesy of H. Gehart] (C) A human airway organoid (nuclei in blue, actin cytoskeleton in red, and cilia in green). [Courtesy of N. Sachs]

Bredenoord *et al.*, *Science* **355**, eaaf9414 (2017) 20 January 2017

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Organoids of the Future?

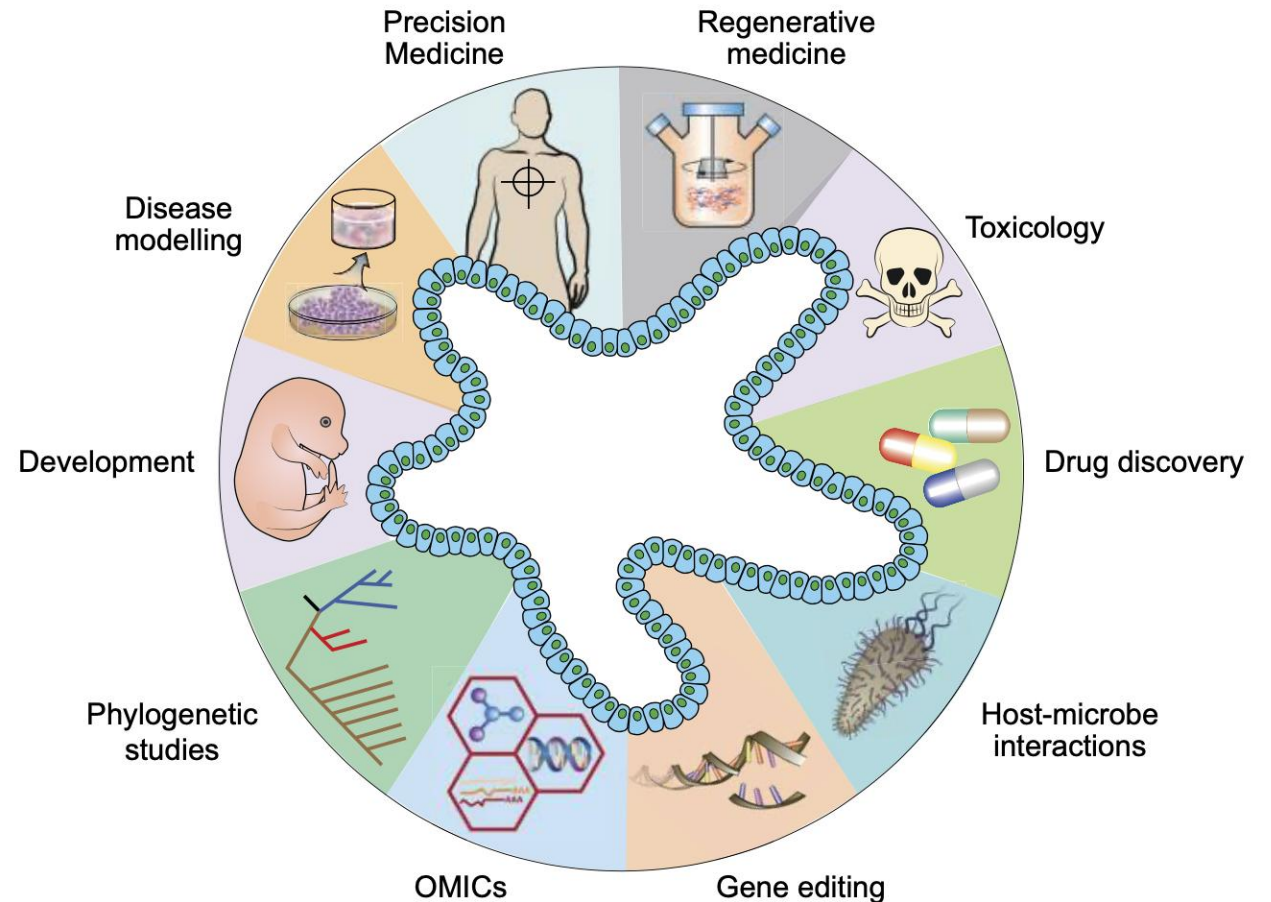
Maybe in the future we can combine or fuse multiple kinds of organoids together (*assembloids*)



Vogt, N. (2021). Assembloids. *Nature Methods*, 18(1), 27. <https://doi.org/10.1038/s41592-020-01026-x>

Why make an organoid?

- Alternatives to Animal Models
- Disease Modeling
- Living Biobanks
- Precision Medicine
- Regenerative Medicine
- Developmental Modeling
- Transplantation
- Etc.



Corrò, C., Novellademunt, L., & Li, V. S. W. (2020). A brief history of organoids. *American Journal of Physiology-Cell Physiology*, 319(1), C151–C165. <https://doi.org/10.1152/ajpcell.00120.2020>

REVIEW ARTICLE

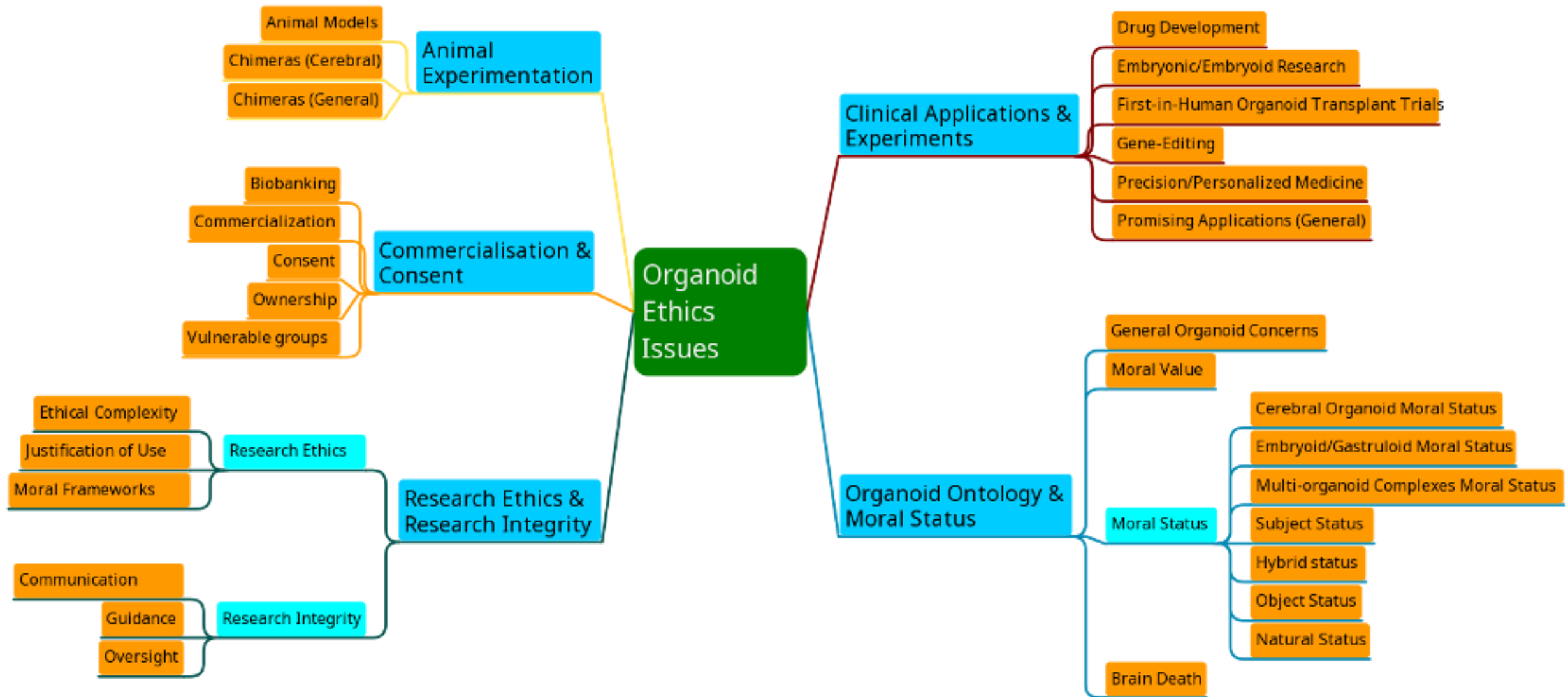


The Many Moral Matters of Organoid Models: A systematic review of reasons

Andrew J. Barnhart¹  · Kris Dierickx¹

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Human brain organoids

- WHAT?

- Human brain organoids can be described as self-organizing structures
- that follow the neurodevelopmental blueprint
- to form three-dimensional tissue architectures.

These 3D structures mimic several features of the developing fetal brain, including cellular composition and tissue organization.

- TODAY AND TOMORROW

Given the rapid progress in brain organoid research, it is important to consider not only the ethical issues we face today, but also those we may encounter in the future.

Human brain organoids ... and ethics

Three clusters of ethical challenges:

1. Ethical issues raised by the in-vitro brain organoid itself
2. Ethical issues raised by transplanting brain organoids
3. Ethical issues related to research ethics and governance

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THEME 1:

ethical issues raised by the in-vitro brain organoid itself

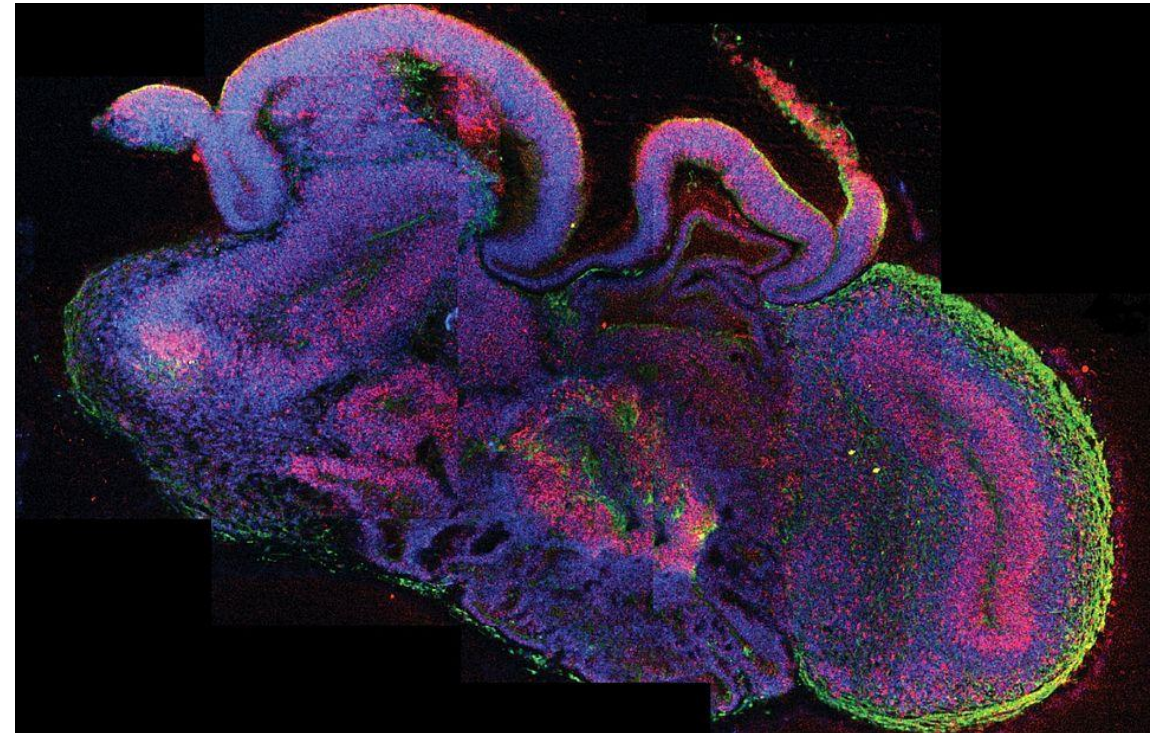
- Cerebral organoids raise unique questions about
 - **moral status**,
 - particularly concerns about their potential to develop some form of **consciousness**, or the ability to feel **pleasure or pain**.
- Images of “**brains in a dish**” often come to mind, prompting worries that scientists might be crossing moral boundaries by creating life in a dish.



Brain Organoid Ontology & Moral Status

Cerebral Organoid Moral Status ?

- *Do brain organoids require special moral considerations?*
- *Potential consciousness (cf also next slide)?*
- *Measuring this? Needed? Possible?*



BRAIN ORGANOIDS & CONSCIOUSNESS?

(if something has consciousness -> has significant moral weight)

How will we know if a brain organoid develops consciousness? (**empirical**)

What kind of consciousness does a brain organoid need in order to have moral significance? (**philosophical**)

What is minimal consciousness? Is it different from morally significant minimal consciousness? (**ethical**)

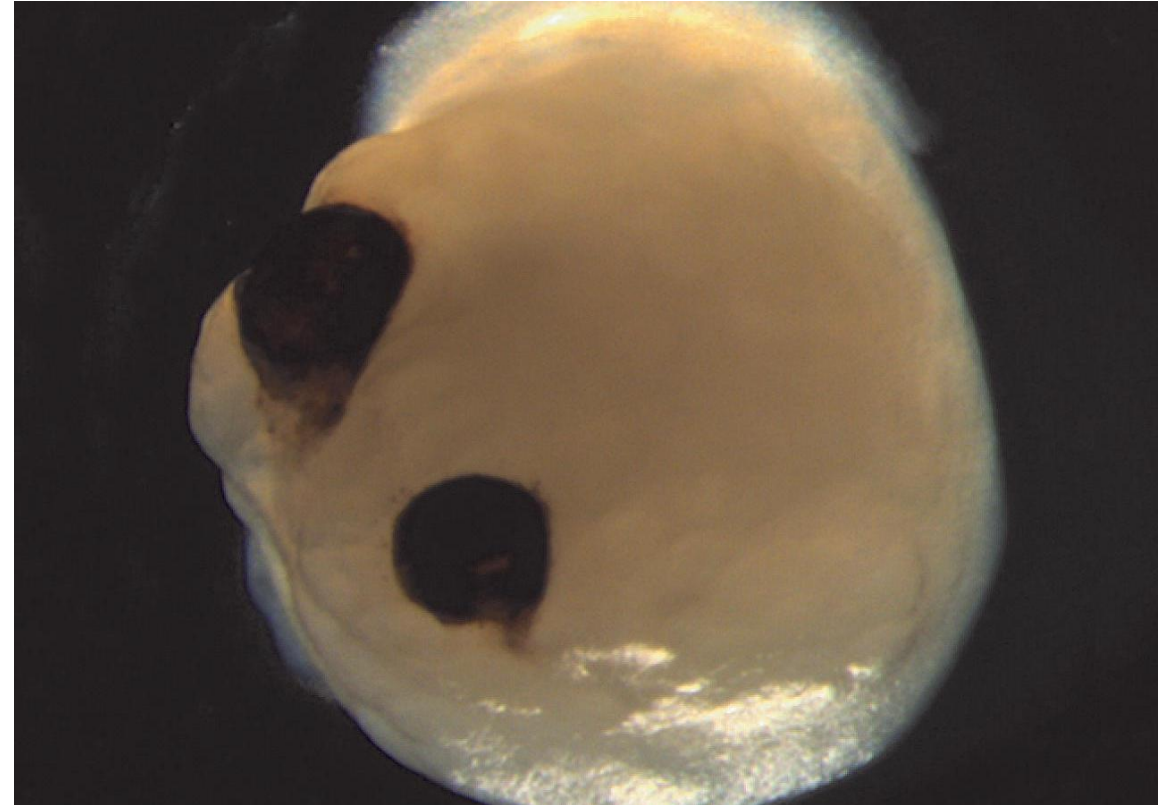


Image Credit: Elke Gabriel

Consciousness: More than one definition?

- **Access Consciousness** – A state of consciousness that has global access to information and a kind of availability of information contents.
- **Phenomenal Consciousness** – Characterized as a subjective experience with qualitative content such as pain, pleasure, and perception.
- **Self-Consciousness** – Having the concept of self and being able to use this concept when thinking about the self.
- **Monitoring Consciousness** – a reflexive or second order capacity of examining what is happening in one's own mind

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<https://doi.org/10.1080/21507740.2025.2519459>



TA <https://doi.org/10.1080/21507740.2025.2519459>

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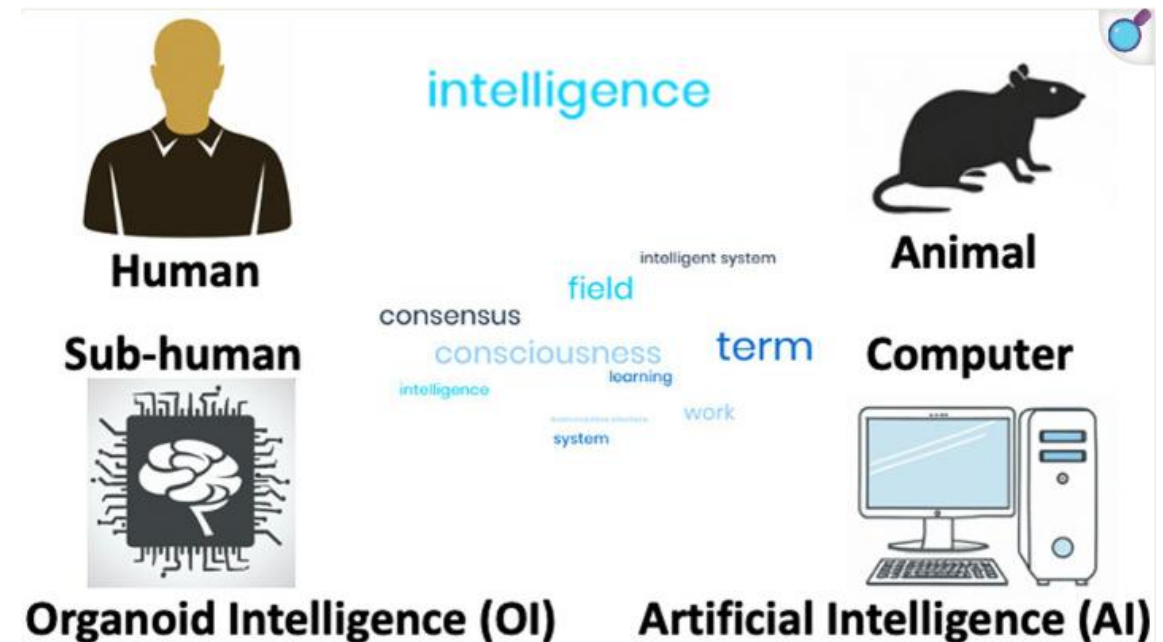


Consciousness and Human Brain Organoids: A Conceptual Mapping of Ethical and Philosophical Literature

Aileen Van Gyseghem^a , Kris Dierickx^a and Andrew J. Barnhart^b

Can brain organoids think?!

- Short answer: Extremely unlikely, little cause for concern.
- Some brain waves detected similar to 19 to 24 week fetus.
- Synchronous activity across cellular clusters.
- Not much else to show significant enough activity to correlate to consciousness... ***for now.***



Brain organoids: how close is too close?

- As brain organoid models become more advanced, they could become closer in resemblance to their *in vivo* counterparts. That will elevate these ethical concerns.
- So... how close is too close?
 - How close should organoids model their *in vivo* organ counterparts?
 - To what extent should they be allowed to mature? Is there a limit? If so, how do we define it?

Human brain organoids ... and ethics

Three clusters of ethical challenges:

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THEME 2: ethical issues raised by transplanting brain organoids

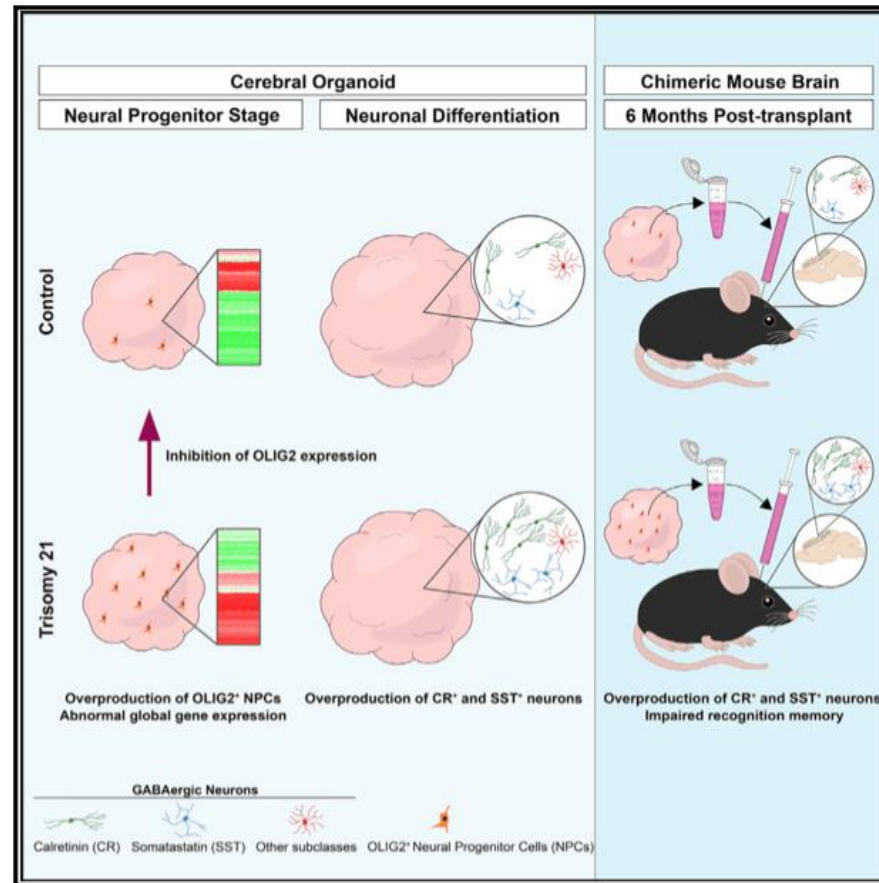
2a) Transplanting more advanced human brain organoids into animals may result in chimeric animals.

- These animals could potentially develop types of consciousness or cognitive abilities not seen in untransplanted animals.



OLIG2 Drives Abnormal Neurodevelopmental Phenotypes in Human iPSC-Based Organoid and Chimeric Mouse Models of Down Syndrome

Graphical Abstract



Authors

Ranjie Xu, Andrew T. Brawner, Shenglan Li, ..., Ronald P. Hart, Ying Liu, Peng Jiang

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In Brief

Using Down syndrome (DS) human iPSC brain organoid and neuronal chimeric mouse brain models, Xu et al. demonstrate that upregulated expression of OLIG2 in DS neural progenitors causes overproduction of subclass-specific GABAergic interneurons. Reducing OLIG2 expression restores interneuron differentiation and improves recognition memory in DS chimeric mice.

THEME 2:

ethical issues raised by transplanting brain organoids

Two specific ethical issues :

* The first is: **(human) dignity??**

Some argue that if animals acquire psychological or mental abilities that only humans possess(moral humanization), this would **violate human dignity** and should be considered morally problematic

Others argue that creating a human-animal chimera actually creates a **new form of dignity** => no human dignity is violated.



THEME 2:

ethical issues raised by transplanting brain organoids

Two specific ethical issues :

*The second issue is **animal enhancement**.

Fear that transplanting brain organoids into animal brains could alter the animals' normal capabilities in unintended ways.

Instead of enhancing them, it might **compromise their natural functioning and health**.



THEME 2:

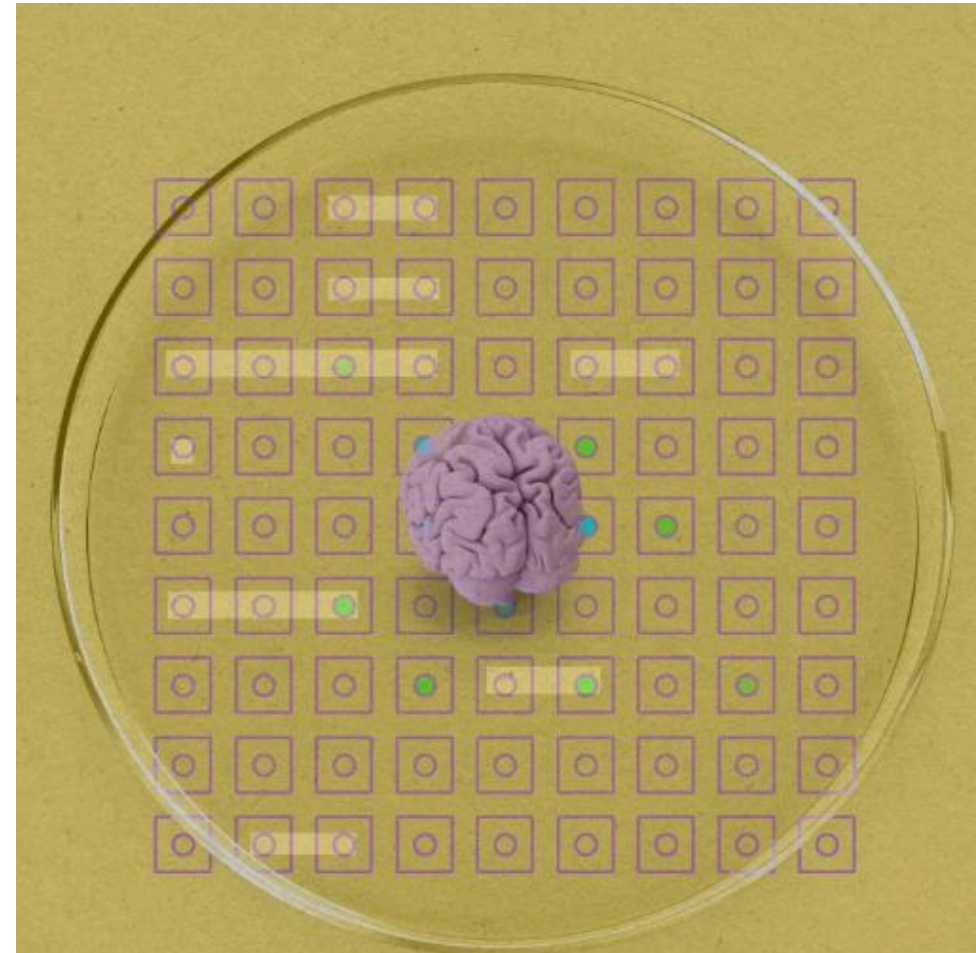
ethical issues raised by transplanting brain organoids

2b) Transplanting human brain organoids into non-living systems

- E.g. robots, artificial intelligence

?= In the future, combining brain organoids with living or non-living systems could lead us to regard these hybrids as human individuals? New moral status?

If higher cognitive abilities => precautionary principle => restrictions on these hybrid studies?



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THEME 3:

Ethical issues of research ethics and governance

Can there ever be an overarching (brain) organoid ethics framework?

Probably not...

The **Paradox** of Constructing an Organoid Ethics Framework:

Think of all the different organoids there are.

Many have unique morally problematic properties.

Think of all the different applications of organoids.

Many have unique morally relevant contexts.

The more relevant moral contexts the ethical framework tries to incorporate, the more abstract and less useful the organoid-framework becomes.



THEME 3:

Ethical issues of research ethics and governance

Context is key!

- Organoid ethics inherently demands context.
- Proposal to use context-dependent or context-grounded approaches to ethics!
 - Collaborative ethics
 - Embedded ethics
 - Parallel Ethics Research

No need to re-invent the ethics wheel specifically for organoids.



THEME 3:

Ethical issues of research ethics and governance

What about research ethics committees?



- no dedicated ethical oversight committees specifically for organoid research.
- Existing Embryonic & Stem Cell Committees? RECs?
- Discuss governance with fields of AI and robotics
- Develop international guidelines for scientific research practices
 - Under the auspices of WHO?
 - Research institutions + governments + public + ...

Extra: views of organoid experts

- Empirical turn bioethics:
 - From deductive -> inductive (cf descriptive ethics)
 - Empirical methods: interviews, focus groups, surveys, ...
 - Ongoing challenge: is/descriptive-> ought/normative
- Semi-structured interviews with experts (n=19)
 - Different organoid experts+ Geographic distribution
 - (basic) researchers & clinical researchers
- SMEC, PRET, COREQ

Interview results: 5 themes

1. Attitudes of **Uncertainty**

- Uncertainty stemmed from a lack of consensus on (1) the **moral status** of organoids, (2) the **rapid advancements** in organoid technology, and (3) the **unforeseen ethical challenges** that may arise in the future.
- Need for **guidelines** and ethical framework
- Participants have **limited knowledge** of organoid types outside their area of expertise

2. Research **Animal Welfare**

- Expressed sentiments of moral obligation, focusing on using organoids to **reduce animal models & enhance scientific validity** (organoids more closely resemble human tissue)
- Lack of consensus on the use of chimera models.

Interview results: 5 themes

3. Precision Medicine Positives

- Optimism. Acknowledge the benefits of using organoids to develop personalized treatments, improve drug testing, and enhance **the understanding of disease mechanisms** at the individual level. The potential for organoids to **revolutionize patient care** and ultimately improve health outcomes was seen as a significant positive aspect of this research area.
- Challenge of **equitable access** to healthcare
- **Line between research and clinical care** (even more) blurred

Interview results: 5 themes

4. Controversial Organoid-Entity Concerns

- Apprehensive about the potential for **brain organoids** to develop consciousness (how to measure?), experience pain, or exhibit human-like properties. Concerns were raised about **potential misuse** of these organoids

5. Informed Consent & communication

- Stress on **importance** of proper informed consent...
- ... but participants often did **not have full understanding** of current consent processes
- Need of dynamic consent models (having a saying)
- Emphasized the need for **ongoing communication** and engagement with patients or donors.
- Risk of overhyping

Conclusion interviews: Epistemic Gap

- A disparity or **lack of knowledge and understanding** among individuals or **groups** regarding a specific subject or issue.
- **Participants** often admitted their **limited knowledge of organoid types or research outside their area of expertise**.
 - Possibly due to *hyper-specialization* in research, early-stages of scientific careers, or encountering organoid research for the first time.
 - Researchers and clinicians may *not be aware* of organoid ethical issues beyond their own scientific domain.
- **Disparities of moral views may develop:**
 - E.g. Brain organoid researchers see no causes for moral concern relating to consciousness, while non-brain organoid researchers do.

Videos from Sakaguchi Lab

Stem Cell Reports Article



OPEN ACCESS

Self-Organized Synchronous Calcium Transients in a Cultured Human Neural Network Derived from Cerebral Organoids

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<https://doi.org/10.1016/j.stemcr.2019.05.029>

Synchronous activity across brain organoid cellular clusters:
This synchronous activity could be the basis of basic elements of consciousness.

Thank you !!

Dr Andrew Barnhart & Dra Ayleen Van Gyseghem

Q & A



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