Les organoïdes cérébraux : perspectives juridique et éthique
Brain organoids: legal and ethical perspectives

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Le cadre juridique de la recherche sur organoïdes

Les différents régimes juridiques applicables aux organoïdes *[legal regimes applicable]*

En fonction de l'origine des cellules *[origin of cells]*

- **Cellules humaines** *[human cells]*
- Cellules animales *[animal cells]*

En fonction des processus appliqués aux organoïdes *[processes applied]*

- OGM *[GMO]*

En fonction de l'usage final des organoïdes *[final use]*

- **Recherche fondamentale** *[basic research]*
- Recherche pré-clinique *[pre-clinical]*
- Recherche clinique *[clinical]*
- Application thérapeutique *[therapeutic]*
- Usages de bioproduction ou industriels *[industrial]*

Régime du corps humain en droit *[human body in french law]*

Code civil (CC) *[Civil code]*

- Art. 16 : **primauté de la personne**, interdiction de toute atteinte à la **dignité** de la personne, garantie du respect de l'être humain dès le commencement de sa vie. *[Primacy of the person, human dignity]*
- Art. 16-1 : **respect** et **inviolabilité** du corps humain. **Non-patrimonialité** du corps humain, ses éléments et ses produits. *[Respect, inviolability and non-ownership of the human body]*
- Art. 16-3 : atteinte à l'intégrité du corps qu'en cas de **nécessité médicale** pour la personne ou à titre exceptionnel dans l'intérêt thérapeutique d'autrui. Obligation d'obtenir le **consentement** préalable. *[Medical necessity, consent]*
- Art. 16-4 : Protection de **l'intégrité de l'espèce humaine**. Interdiction des pratiques eugéniques et du clonage reproductif. *[Integrity of the human specie, prohibition of eugenism and cloning]*
- Art. 16-6 : **interdiction de rémunération** pour une personne se prêtant à une expérimentation. *[Prohibition of remuneration]*
- Art. 16-8 : **anonymat** du donneur et receveur, sauf en cas de nécessité thérapeutique. *[Anonymity]*

Principes applicables à la recherche sur les éléments et produits du corps humain *[research on elements of the human body]*

<u>Code de la santé publique (CSP)</u> ***[Public health code]***

- Titre Ier du livre II de la première partie
  - Art. L1211-1 : finalité médicale ou scientifique de la recherche *[medical or scientific purpose]*
  - Art. L1211-2: consentement préalable au prélèvement + révocable à tout moment + utilisation ultérieure à d'autres fins possible, mais après information du donneur *[revocable consent, subsequent uses necessitate information of the donor]*
  - Art. L1211-5 : anonymat du don *[anonymity]*

Régime de la recherche sur cellules souches [*stem cell research*]

Interdictions générales (art. L2151-1 à -4) ***[general prohibitions]***	**Recherche sur CSEh (art. L2151-6)**	**Recherche sur CSPih (art. L2151-7)**
• Clonage *[cloning]* • Conception d'embryon par fusion de gamètes à des fins de recherche *[creating embryo by fusing gamètes for research purposes]* • Création d'embryon humain chimérique *[creating human chimera embryo]*	• Déclaration à l'Agence de Biomédecine *[Declaration to the Biomedicine Agency]* • CSEh obtenues conformément aux dispositions sur la recherche sur embryon *[hESC obtained in conformity with embryo research legislation]* • Finalité médicale ou viser à améliorer la connaissance de la biologie humaine *[medical purpose or increase knowledge of human biology]* • La pertinence scientifique doit être établie *[scientificaly relevant]* • Respect les principes du CC et du CSP *[respect of previous obligations in the Civil and Public health codes]*	• Pas de déclaration préalable à l'ABM, sauf pour les « cas sensibles » *[No declaration to the Biomedicine Agency except for sensitive cases]* • Respect des principes du CC et du CSP *[respect of previous obligations in the Civil and Public health codes]*

« Cas sensibles » : différenciation en gamètes, obtention de modèles de développement embryonnaire in vitro, insertion de cellules dans un embryon animal pour le transférer chez la femelle
[*sensitive cases : differentiation into gametes, embryo models, chimeric embryos*]

L'encadrement (futur) de la recherche sur organoïdes cérébraux [*(future) legal framework applying to organoids*]

- **Pas d'encadrement particulier des protocoles d'organoïdes cérébraux**
  - Évolution à l'avenir avec la complexification des modèles?
  - Chimères aux capacités cognitives altérées?

  [specific regulation for brain organoids and chimeras in the future?]
- Droit dur français et Droit souple international [*french hard law and international soft law*]

Legal and ethical questions raised by brain organoid research

Overview of the main ethical and legal challenges

Review | Open access | Published: 23 July 2022

Organoids: a systematic review of ethical issues

Dide de Jongh, Emma K. Massey, the VANGUARD consortium & Eline M. Bunnik

Stem Cell Research & Therapy **13**, Article number: 337 (2022) | Cite this article

10k Accesses | **19** Citations | **58** Altmetric | Metrics

- Informed consent
  - Challenges (possible uses change rapidly, many parties involved, how donors relate to different uses of their samples)
  - Revise informed consent forms?
- Anonymity
  - De-identification (not necessarily desirable, perhaps not even possible)
- Clinical use
  - Personalised medicine and healthcare system
  - Transplantation in human, first-in-human tests
- Concerns regarding sub-types of organoids

Brain organoids and international guidelines

ISSCR Guidelines for Stem Cell Research and Clinical Translation

INTERNATIONAL SOCIETY FOR STEM CELL RESEARCH

ISSCR recommendations concerning brain organoids

- Most *in vitro* organoid research should be exempt from review by a specialized oversight process

ORGANOID RESEARCH

At this time, there is no biological evidence to suggest any issues of concern, such as consciousness or pain perception with organoids corresponding to CNS tissues, that would warrant review through the specialized oversight process. However, researchers should be aware of any ethical issues that may arise in the future as organoid models become more complex through long-term maturation or through the assembly of multiple organoids (Hyun *et al.* 2020).

Brain organoids and the study of consciousness

Assumptions made regarding brain organoids and consciousness

- Thinking on a **longer time-scale**
- Basic mental states might emerge in sufficiently complex neural structures that are man-made
  - without the complexity of the whole brain
  - without having to be connected to a body in the traditional sense?
- Strong **empirical commitment**
  - Data to take **informed decisions**
  - Navigating **epistemic uncertainty and risk**

Brain organoids and the study of consciousness

Consciousness understood as the presence of any minimal phenomenological experience, any subjective mental states, i.e. sentience.

Current limitations

- Size and complexity
- Lack embodiment
- No unified theory of consciousness
- No standardized and validated tool to measure consciousness

Brain organoids and the study of consciousness

A way beyond these limitations?

- Size and complexity: degrees of sentience already arise in relatively small brains
- Embodiment: Is the whole body necessary to reproduce a single sensory modality? Synthetic embodiment?
- Strategies for vascularization, multi-regional and multi-organ assembloids, interfacing with robotics and software
  - What if we achieve much greater control over neural morphogenesis, finer modelling of sensory pathways (intero- and exteroception)
- Theories of consciousness and measuring consciousness
  - ongoing work, brain organoids might help in elucidating the necessary conditions for the emergence of consciousness
  - propositions such as adapting the PCI index or developing neuroanatomical and neurophysiological indicators of consciousness

Not being able to measure consciousness does not mean it cannot be created in vitro

Policy suggestions in the literature concerning brain organoids

Policy	Summary
Legal endorsement of existing research best practices	Even highly developed brain organoids do not and should not have a legal status comparable to that of embryos or born human being. Current best practices must be passed in law (Taupitz, 2022).
"20 weeks" threshold	Applications of 3R principles to human brain organoids that are equivalent to 20 weeks' *in vivo* brain development or more. For brain organoids with the potential to develop advanced cognitive capacities additional considerations apply (Koplin and Savulescu, 2019).
Graded spectrum of caution	The emergence of cortical structures, the generation of cortical neural oscillations and the response to the "Zap & Zip" test warrant caution. The more milestones incorporated the higher the chances to achieve consciousness (enabling structures, input & output, embodiment) (Jeziorski et al, 2022).

Brain organoids and chimeras

Ethical problems with brain organoids in chimeras

- Demonstrated **functional integration** of brain organoids
- **Alteration of cognitive functions** in the host
- « Enhancement » of animal cognitive abilities – especially in great apes
- A matter of animal ethics
  - Animal welfare and reducing their suffering
- And human ethics
  - What value for the boundary between species?

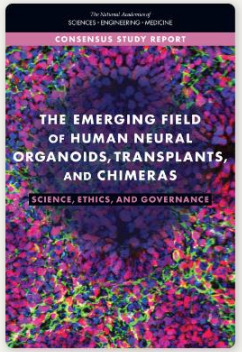
Brain organoids and chimeras

Recommendations from the ISSCR

- Pre-natal implantation protocols
  - **Animal research oversight committee** with an expertise in stem cell or developmental biology
  - Set **timepoints** to assess degree and scope of chimerism
  - Favor strategies of **targeted chimerism**
  - **Should exclude great and lesser apes**
- Post-natal implantation protocols
  - broadly consistent with common animal research review standards
  - traditional animal research oversight

Brain organoids and chimeras

NATIONAL ACADEMIES Sciences Engineering Medicine



The Emerging Field of Human Neural Organoids, Transplants, and Chimeras

Science, Ethics, and Governance

(2021)

Recommendations from the consensus report from the US national academies

- **Precautionary approach**
  - pausing research when changes from species-typical behaviour
  - assess the qualitative changes and whether it has an ethical significance
- Monkey chimeras
  - More sensitive due to evolutionary proximity
  - More likely to be seen as violating human dignity and boundaries between species

Merci pour votre attention!

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