

## Neural organoids in research: ethical considerations



### EXECUTIVE SUMMARY

#### INTRODUCTION

- Organoids are small, lab-grown three-dimensional structures that are made from stem cells to model different aspects of an organ or tissue, such as the liver, gut, kidney and brain.
- This briefing note focuses on *neural* organoids, and particularly human neural organoids, which are used to model different aspects of the developing brain. Any reference to neural organoids in the text presupposes that they are made from human cells, unless indicated otherwise.

#### ABOUT THIS WORK

- The aim of this briefing note is to provide an evidence-based and balanced summary of the main ethical considerations in neural organoid research and the ethical issues that might arise in the future as research progresses.
- We describe the main advances in neural organoid research, their current and future applications, and possible research directions. Next, we give an overview of regulation and guidance relevant to organoid research. Lastly, we present and discuss the main ethical considerations in neural organoid research.
- Our work is informed by relevant academic and grey literature, as well as input from expert stakeholders who attended short interviews and/or commented on earlier versions of this document.<sup>1</sup>

## CONCLUSIONS

- Neural organoids are promising research tools that could have important applications in the future, improving our understanding of a range of brain conditions and treatment options.
- Neural organoid research is, however, still in its infancy and its potential is yet to be fully explored. There is still uncertainty around future possibilities, research directions, likelihood of success, and the extent to which neural organoids currently resemble, and will be able to resemble, the human brain.
- Research is moving at pace, and it is difficult to predict when significant developments will take place. It is important, therefore, for policy makers to work with scientists, ethicists, and publics to ensure that the ethical and regulatory questions are fully explored, in order to ensure that appropriate guidance and regulations will be in place to facilitate innovation and address ethical considerations.
- Relevant ethical considerations in neural organoid research include:
  - whether or not more tailored ethical guidance and oversight is needed;
  - what might be appropriate consent procedures and processes for tissue donors;
  - the potential for neural organoid research to benefit human and non-human animals;
  - the importance of balanced and accurate communication of neural organoids' current and potential future capabilities; and
  - the possibility of neural organoids developing capacities increasingly similar to the developing human brain, such as sentience and consciousness, if indeed they ever do.
- Areas where further ethical guidance, policy, and regulatory decisions are needed include:
  - appropriate consent processes that can account for the fast-paced developments and unpredictable direction of research;
  - what appropriate, future-looking, and proportionate regulation of these models might look like – if needed – considering developments in assembloids, neural organoid transplantation and other, more advanced technologies; and
  - what anatomical or functional 'hallmarks' might be used as criteria to attribute consciousness to neural organoids and what the implications for their moral significance might be as a result.

Further exploration of these themes is needed to better understand potential ethical issues raised by this research and possible future advances.

The Nuffield Council on Bioethics (NCOB) intends to facilitate future discussions around these important issues, which should involve scientists, ethicists, potential regulators, publics and all those involved in making decisions around neural organoid research.

Clear, accurate communication, as well as meaningful engagement with publics, will be important to ensure that we all benefit from neural organoid research and future advances.

## ADVANCES IN NEURAL ORGANOID

### WHAT ARE NEURAL ORGANOID?

Human neural organoids are small lab-grown, three-dimensional tissue cultures which are developed by researchers as a model of the developing human brain. They are small 'balls' of tissue, roughly the size of a pea, with cellular and

molecular characteristics which resemble those of a fetal human brain up to about six months after conception. Electrical activity has also been detected in mature organoids cultured for eight months. They have also been observed to respond to light stimulation when connected with retinal tissue.<sup>2</sup>

## BOX1: GUIDE TO TECHNICAL TERMS

- **Cell culture or tissue culture** is the process by which cells are grown under controlled conditions in a lab.
- **Stem cells** are a particular type of cell which can be found in humans and other animals. They have the ability to self-renew (to divide and give rise to identical cells) but also to continuously develop into other types of cells found in the body (by dividing and giving rise to more differentiated cells). Some stem cells are **pluripotent**, which means that they can differentiate into many different cell types. Others, like multipotent stem cells, have a more limited ability to give rise to other cells. Stem cells can sometimes be used to repair damaged tissue in the brain and other organs.
- **Embryonic stem cells (ESCs)** are pluripotent stem cells found in early-stage embryos. ESCs are extracted from donated embryos from in vitro fertilisation procedures.
- **Induced pluripotent stem cells (iPSCs)** are made from adult cells, usually taken from the skin, hair, or blood, and then reprogrammed to become pluripotent and to have properties similar to those of ESCs. iPSCs can be made from person-specific cells and have the same DNA of the person from whom they were created.
- **Fetal stem cells** are extracted from donated fetuses following a termination of pregnancy. They are not pluripotent but their potential to differentiate into different cell types appears to be greater than that of adult stem cells.
- There are two main types of neural organoid: **guided organoids** model specific brain regions, such as the cerebral cortex, hippocampus, and cerebellum, while **unguided or minimally guided organoids** model many regions of the brain at the same time.<sup>3</sup>
- **Biobanks** store biological samples, such as tissue or bodily fluids, for use in research.

### HOW ARE NEURAL ORGANOIDs MADE?

Human neural organoids, like other organoids, are made from human stem cells. These are typically embryonic stem cells (ESC) or induced pluripotent stem cells (iPSC), but fetal stem cells can also be used (see Box 1 for a definition of ESC, iPSC and other stem cells). These stem cells self-assemble and organise into brain-like structures with the help of nutrients and other substances, such as growth factors administered by researchers.<sup>4</sup> Once created, neural organoids can be cultured in petri dishes and kept indefinitely, provided that they are regularly supplied with the necessary nutrients to survive, although they stop growing after reaching a certain size (about 4 millimetres) due to a lack of a vascular system.

### WHY ARE NEURAL ORGANOIDs MADE?

Both unguided and guided organoids (see Box 1 for their definition of these) provide researchers

with the opportunity to study different aspects of the human brain in ways that would raise both ethical and practical complications in living brains inside human bodies. The use of human neural cultures to model the human brain is not new. Before the first neural organoid was created a little more than a decade ago, 2D cultures were used in brain research and are often still used today. Human organotypic brain cultures – slices of human brain tissue that can be removed via a surgical procedure and kept in culture for weeks – can also be used to study aspects of the human brain.<sup>5</sup> 3D organoids are more complex than 2D cultures, and have more features similar to the structure and functionality of the human brain. For these reasons, they are generally considered to be better models of the brain.<sup>6</sup> At the same time, it is important to note that there are a number of differences between today's neural organoids and the living human brain, for example in size and in number of neurons.

## RESEARCH AND CLINICAL APPLICATIONS OF NEURAL ORGANIDS

### MODELLING NEURODEVELOPMENT

Because of their similarities to the fetal brain, neural organoids have been used to study neurodevelopment. For example, researchers have developed and studied neural organoids affected by Zika virus to explain how Zika infection of pregnant people leads to the development of microcephaly.<sup>7</sup> A number of research groups, including in the UK, have started to use neural organoids to investigate the developmental origins of autism, aiming to identify changes occurring during early embryonic stages of development that might lead to specific forms of autism.<sup>8</sup>

### MODELLING CONDITIONS THAT AFFECT OUR BRAINS

While neural organoids are most similar to the fetal brain, studies suggest that organoids could also be used to study conditions affecting the adult brain and better understand treatment options. By using patient-derived stem cells, scientists have grown neural organoids to model glioblastoma, a form of brain cancer, to study its development and progression.<sup>9</sup> Organoids are also being used to study neurodegenerative disorders, for example, by creating models of Parkinson's disease.<sup>10</sup>

Mental health research via organoids is still in its infancy but studies are already underway to investigate the physiological mechanisms associated with schizophrenia, depression, and bipolar disorder.<sup>11</sup> Some authors have pointed out that it is still too early to understand the capacity of neural organoids to model conditions occurring in adults. Therefore, findings from such studies should be interpreted with caution, particularly in the case of age-related neurodegenerative conditions.<sup>12</sup>

### PRE-CLINICAL RESEARCH

Organoids developed by using stem cells derived from individuals with specific conditions can provide a human cell-based platform for drug testing. Current studies are underway investigating the suitability of neural organoids to act as experimental subjects in pre-clinical studies testing the effects of potential therapeutics on humans. For example, neural organoids derived from individuals with Alzheimer's disease have been used to identify drugs that were initially developed for other purposes, but that could also be used to alleviate symptoms of the disease.<sup>13</sup> There are hopes that organoids could replace, or lead to a reduction in, non-human animal testing in the future. The ethical concerns associated with the use of non-human animal models in pre-clinical studies will be explored in subsequent sections in more depth.

### STUDYING HUMAN EVOLUTION

Scientists are also using neural organoids to study brain evolution and compare brain development in human and non-human animals, including in animals from which brains are rarely available due to ethical, legal, and practical restrictions (such as primates).<sup>14</sup> For example, organoids from different species of apes have been compared with the aim of identifying cells and molecules that might account for the differences in brain growth and number of neurons between species.<sup>15</sup> Such studies may improve understanding about the basis of human brain formation and discover features that are uniquely present in humans, apes and other animals.

# THE FUTURE OF NEURAL ORGANOID RESEARCH: NOVEL ORGANOID-RELATED TECHNOLOGIES AND POSSIBLE RESEARCH DIRECTIONS

## TRANSPLANTATION OF HUMAN NEURAL ORGANOIDS IN NON-HUMAN ANIMALS

Due to the lack of a vascular system for oxygen and nutrient supply, organoids can only grow up to a certain size when cultured in the lab – currently about 4 millimetres.<sup>16</sup> To overcome this limitation and allow for growth and maturation, researchers have recently tried to transplant human neural organoids into the brains of other animals, in the hope that the host brains would give organoids an environment in which to grow, as well as a body and an external environment with which to interact.<sup>17</sup> In 2018, human neural organoids were first transplanted into the brains of adult mice and, in 2022, into newborn rats.<sup>18</sup> The human organoids were able to mature and establish connections with the host brain. In the case of newborn rats, the level of integration of the human organoid with the host brain was higher than seen in adults, and scientists working on the experiment also reported that activity within the organoid could influence the rats' behaviour.<sup>19</sup>

## ASSEMBLOIDS

The study of connectivity between brain areas and other body parts is important in understanding how the brain works. The neural organoids described so far currently lack these long-range connections.<sup>20</sup> This has led to the creation of neural assembloids, which are formed by two or more organoids linked together.<sup>21</sup> A neural organoid can be linked to another neural organoid or to a different organoid, depending on how the model is intended to be used. Since the first neural assembloid was developed in 2017, others have been created. For example, a model integrating organoids representative of the cerebral cortex, spinal cord, and skeletal muscle has been created to study neural connections during voluntary movement.<sup>22</sup> Researchers found that stimulating the assembloid at the level of the cerebral cortex caused the muscle tissue to twitch.<sup>23</sup> In the future, it is possible that more complex types of assembloids will be created, which may connect different neural regions or connect neural organoids with organoids modelling other body parts. Such assembloids

could potentially more closely model different aspects and capacities of the human brain.<sup>24</sup>

## NEURAL ORGANOIDS-ON-CHIPS

Organoids-on-chips (OOCs) are small systems containing cultured tissue grown inside microfluidic chips, which are small devices with patterns of microchannels that allow for the manipulation and control of tiny amounts of fluids. In these devices, fluids can be manipulated to control the environment surrounding cells with the aim to better mimic human physiology.<sup>25</sup> Combining organoids or assembloids and OOC technology could therefore facilitate blood-like circulation, delivery of oxygen and nutrients, and provide a realistic environment for organoids to grow and mature. This approach could have pharmaceutical applications and has recently been used to closely observe how prenatal nicotine exposure affects brain development.<sup>26</sup> Microfluidic devices may also provide a platform to grow more complex assembloids. Looking to a more distant future, those working on this technology hope that advances in OOCs will facilitate the linkage of multiple microfluidic devices to enable the connection of distinct organoids, forming multi-assembloids-on-chips.<sup>27</sup>

## FUTURE PHARMACEUTICAL APPLICATIONS AND PERSONALISED MEDICINE

Advances in the areas of OOC technology, transplantation, and assembloids are making neural and other organoids much more complex, mature, and representative of human physiology. It is therefore possible that they may become more widely used in pre-clinical studies to test efficacy and toxicity of new therapeutics. By using induced pluripotent stem cells from patients with recognised health conditions, personalised organoid models that mimic the genetic background and microenvironment of individual patients could also be developed. These models could be used for personalised drug screening, the modelling of disease progression, or predicting how well a patient might respond to specific treatments.<sup>28</sup>

## HUMAN TRANSPLANTATION

Human transplantation of neural organoids for therapeutic purposes could also be possible in the future. For example, with their self-renewal and self-organisation properties, transplanted organoids could help replace damaged brain tissue in people affected by Parkinson's disease or spinal muscular atrophy (SMA). Using neural organoids instead of the cells used in traditional neural stem cell therapy could lead to better results; because organoids can self-organise and contain many different types of neural cells, they may have a better chance of surviving and forming correct connections with the host brain.<sup>29</sup> This hypothesis was tested on mice in 2023. Researchers transplanted human neural organoids into a damaged area of mice brains which had been previously lesioned to induce a stroke. They found that the transplanted organoids repaired the damaged tissue and eliminated symptoms caused by the stroke. When repeating the procedure with dissociated single stem cells taken from organoids, the cells failed to repair the damage, suggesting that the use of organoids could lead to better results.<sup>30</sup>

## DEVELOPMENT OF BIOCOMPUTING TECHNOLOGY

Future uses of neural organoids could extend beyond clinical applications. Research is underway to develop a new biocomputing technology using neural organoids. The aim is to create devices in

which organoids are connected with sensors and output mechanisms and are continuously trained to respond to electrical stimulation via AI/machine learning and other methods. In these systems, neural activity would be recorded through microelectrodes and processed via AI/machine learning and other computational methods. The organoid would then receive feedback through electrophysiological stimulation and 'learn' to adjust its activity accordingly.<sup>31</sup>

Research in this emerging field is still in its infancy and important scientific breakthroughs, including advances in organoid technology, big data, and AI will be needed to be able to create these systems.<sup>32</sup> An early version of such a device, which used 2D neural cell culture rather than 3D organoids, was recently built as a proof of concept. If developed, such biocomputing systems could overcome some of the limitations of current computers and AI. Advances in this field could also lead to the development of more complex neural organoids, capable of receiving inputs, generating outputs, and processing some level of information about their surrounding environment. Some have used the term "organoid intelligence" to refer to this area of research. The behaviour exhibited by the cell cultures in the proof-of-concept experiment has also been referred to as "sentient" and "intelligent".<sup>33</sup> This has generated controversy, and some scientists have expressed concerns about the "unsupported use of these terms".<sup>34</sup>

## REGULATION AND GOVERNANCE OF NEURAL ORGANOID IN THE UK

There is no regulatory authority that governs the development and use of neural and other organoids for lab research in the UK. There is, however, regulation that covers the sourcing of the original material (stem cells), the development of clinical therapies, and non-human animal brain research.

### REGULATION RELEVANT TO THE SOURCING OF STEM CELLS TO DEVELOP ORGANOID AND ORGANOID USE IN LABORATORY RESEARCH

The Human Fertilisation and Embryology Authority (HFEA) regulates research using human embryos and the derivation of human embryonic stem cell lines, but it does not regulate research

with organoids made from embryonic stem cell lines. Once an embryo has been dissociated, HFEA's remit ceases.<sup>35</sup>

Under the Human Tissue Act 2004, the Human Tissue Authority (HTA) regulates and licences establishments that remove, store, and use "relevant material" for research purposes. "Relevant material" under this Act is material, other than gametes, which consists of or includes human cells and so the removal, storage and use of tissue involved in creating induced pluripotent stem cell (iPSC) lines, for example, would fall within the HTA's regulatory remit.<sup>36</sup> Material created outside the human body which consists of, or includes human cells, is explicitly excluded from the HTA's remit and so neural organoids

would not fall within the statutory definition of “relevant material”.<sup>37</sup> In short, while the material used to create neural organoids is subject to HTA regulation, the actual neural organoids are not.

### **REGULATION RELEVANT TO THE USE OF HUMAN TISSUES AND CELLS FOR THERAPEUTIC PURPOSES**

The HTA also licenses and inspects establishments that undertake the procurement, testing, processing, storage, distribution, import, and export of human tissues and cells for human application, or that carry out any associated donor testing.<sup>38</sup> Medicines made from tissues and cells for use in humans are known as Advanced Therapy Medicinal Products (ATMPs). The procurement of human tissues and cells to be used as starting material to create an ATMP falls under the HTA’s remit, but any subsequent processing, storage or distribution is regulated by the Medicines and Healthcare products Regulatory Agency (MHRA). The MHRA and the Health Research Authority (HRA) regulate clinical trials involving ATMPs, and the MHRA licenses the manufacture and import of ATMPs in the UK.

### **GUIDANCE RELEVANT TO STEM CELL RESEARCH**

There is existing guidance on the use of stem cells in research, but no specific guidance has so far been developed to address neural organoids or organoids more generally (with the exception of an initiative which aims to develop a code of practice for research involving stem cell-based embryo models in the UK, expected to be published in 2024).<sup>39</sup> One of the most comprehensive sets of ethical recommendations and guidance for the use of stem cells in research is provided by the International Society for Stem Cell Research (ISSCR), a leading international scientific organisation in stem cell research. Their most recent (2021) guideline documents included a series of statements on neural organoids and organoids more generally, and concluded that while there is currently no evidence to suggest any “issues of concerns” – for example in relation to the possibility of neural organoids developing consciousness – 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.”<sup>40</sup>

Since this statement was issued, neural organoid research has progressed rapidly and more sophisticated models with advanced capabilities have been created, as seen in previous sections. Some authors, including ethicists, scientists, and legal scholars have suggested that, in the future, new forms of oversight and regulatory bodies may be needed to govern neural organoids.<sup>41</sup>

### **REGULATION RELEVANT TO NON-HUMAN ANIMAL BRAIN RESEARCH**

Research involving the use of living non-human vertebrates and living cephalopods (‘protected animals’) is regulated by the Animals (Scientific Procedures) Act 1986 (ASPA). Regulated procedures under ASPA are those which fall outside clinical veterinary practice; may have the effect of causing the animal pain, suffering, distress or lasting harm (equal to or beyond that caused by the insertion of a needle); and are undertaken for experimental, other scientific or educational purposes. Researchers must apply for a licence under ASPA to be able to undertake regulated procedures. Once an application has been reviewed, the decision as to whether or not to grant the licence is made by the Home Office.

### **GUIDANCE RELEVANT TO NON-HUMAN ANIMAL BRAIN RESEARCH**

Guidance on research with non-human animals containing human material has been provided by the Academy of Medical Sciences in the UK. According to their guidance, research involving “substantial modification of a non-human animal’s brain that might make the brain function potentially more human-like” as well as “experiments that could be expected to significantly alter the aspect and behaviour of non-human animals” should require additional ethical scrutiny. They state that, in some cases, adopting an incremental approach may also be appropriate. Finally, the guidance recommends to assess proposed studies of this nature on a case-by-case basis “at least until experience allows the formulation of guidelines”.<sup>42</sup> The guidance also lists a number of factors that should be considered to minimise the risk that an animal would develop human-like cognitive capacities. These include, for example, the proportion of human neural cells, the animal host species, and brain size and the stage of neurodevelopment.<sup>43</sup>

It should be highlighted that this guidance was published in 2011, prior to the development of neural organoids. As research in this area progresses, an important question to answer will be whether transplanting human neural organoids into non-human animals, as opposed to disorganised human neural stem cells, could increase the chances of significantly alter the behaviour and cognitive abilities of the animal host.

## GOVERNANCE AND RESEARCH ETHICS

Access to human embryonic stem cell lines for the purposes of research is overseen by the UK Stem Cell Bank (UKSCB) via its steering

committee. All UK-created embryonic stem cell lines must be deposited in the UKSCB. Non-embryonic stem cell lines, including iPSCs, can be stored elsewhere including in biobanks, academic laboratories and laboratories of commercial science firms. Research with established stem cell lines, including iPSCs, does not require an HTA licence but may require approval from a Research Ethics Committee (REC) and/or the Health Research Authority (HRA) depending on the nature and scope of the research project. Collections of human tissue or other biological material for potential research purposes (beyond a specific project with ethical approval) do not require HRA approval to be established.<sup>44</sup>

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## ETHICAL CONSIDERATIONS

### ETHICAL CONSIDERATIONS LINKED TO THE BENEFIT OF NEURAL ORGANOID RESEARCH FOR HUMANS

While we still do not know what to anticipate with regard to their future applications, neural organoids have characteristics and properties that make them promising models for research. If the challenges described in earlier sections are overcome, the contribution of organoids to disease modelling, pharmacology, toxicology, and regenerative medicine could be significant, with important implications for relieving suffering caused by neurological and mental health conditions. In particular, neural organoids may help overcome some of the limits posed by the use of non-human animals and other models used in research. There are many reports, for example, of drugs tested on non-human animals which have failed to demonstrate their potential efficacy in humans, particularly in brain and mental health research.<sup>45</sup> This may be because the brains of human and non-human animals commonly used in research (such as those of domestic mice) differ in important ways. For example, the way in which they respond to certain conditions, making the application of lessons from such models to humans difficult.<sup>46</sup> Advancing neural organoid research could therefore make an important contribution to preventing harm and acting to benefit those in need.<sup>47</sup> Some of the characteristics that make them promising, however, raise other important ethical considerations highlighted in later sections.

### IMPLICATIONS OF NEURAL ORGANOID RESEARCH FOR NON-HUMAN ANIMALS

The potential widespread use of neural organoids in brain modelling and drug testing has ethical implications for non-human animals. Regardless of views on the moral acceptability of non-human animal testing, it is widely recognised that the procedures and behavioural tests that non-human animals are required to undergo cause them physical and psychological suffering.<sup>48</sup>

Some have welcomed developments in organoid research as a way to replace, or significantly reduce, non-human animal testing, in line with the principles of reduction, refinement and replacement. Known as ‘the three Rs’, these are well-established principles in research involving non-human animals and are embedded in frameworks for the regulation of animal research around the world, including in the UK.<sup>49</sup> Some say that testing drugs on organoids first could help to narrow down a smaller group of compounds to be tested on non-human animals, and therefore reduce the number of non-human animals needed in experiments.

Not all share this view, and some have suggested that recent developments in transplantation might instead lead to an increased overall demand for laboratory animals.<sup>50</sup> Transplanting human neural organoids into non-human animals could make these models better and the drive to produce better models of human brain could lead to an



increase in the number of models generated. An increased use of neural organoids in this way could lead to a reduction in non-human animal models used per experiment, but an increase in the overall number of experiments and, therefore, of non-human animals used.<sup>51</sup>

### **ETHICAL CONSIDERATIONS LINKED TO THE POSSIBILITY OF NEURAL ORGANOIDS OF DEVELOPING SENTIENCE AND CONSCIOUSNESS**

As research progresses, neural organoids might become more complex, mature, and organised. Concerns have been raised that neural organoids might acquire the ability to develop sentience, consciousness, or acquire other characteristics typical of human and a range of non-human animals.<sup>52</sup> Such concerns have been motivated by findings, discussed in previous sections, that indicate organoids' capacity to establish neural networks, initiate spontaneous electrical activity, and respond to sensory stimulation when presented with input and output mechanisms, like an actual brain.<sup>53</sup> Concerns have also been raised due to recent findings of patterns of activity recorded in brain organoids which showed some similarities with those of the brains of premature babies.<sup>54</sup>

There is currently no agreement on the potential for neural organoids to develop consciousness and sentience, nor on how we might be able to determine that they possess such characteristics. Current neural organoids are relatively simplistic models of the developing brain and therefore lack the complexity that would allow them to generate conscious states or the ability to interact with the rest of the human body and their external environment. Current neural organoids also cannot reach the size and or replicate the structure of a fetal brain, which are considered to be important prerequisites to conscious perception.<sup>55</sup> Some authors have therefore argued that at this stage, neural organoids are not able, and might not be able in the foreseeable future, to achieve something akin to a conscious state.<sup>56</sup> Others have pointed out that, with further advances in assembloid and biocomputing technology, we cannot rule out that complex-enough neural organoids will develop consciousness or sentient-like capacities in the future.<sup>57</sup>

The debate over the potential for neural organoids to develop sentience and consciousness is

further complicated by the lack of a consensus on how best to conceptualise and define these terms. Broadly speaking, consciousness involves possessing a sense of self and being able to experience a rich range of mental states, whilst sentience refers to the capacity to experience positive and negative states.<sup>58</sup> In the literature surrounding neural organoids, however, both consciousness and sentience have been used with different meanings and sometimes interchangeably. While this subject has been widely discussed in philosophical and scientific contexts, there is also no widespread agreement over the anatomical or functional 'hallmarks' of the conscious brain which might also be displayed by neural organoids, and therefore used as criteria for the attribution of consciousness.<sup>59</sup>

### **ETHICAL CONSIDERATIONS LINKED TO THE MORAL AND LEGAL STATUS OF ORGANOIDS**

If neural organoids become more complex and acquire characteristics similar to the fetal human brain, some fear that it might become increasingly difficult to identify a point beyond which similarity becomes identity. This view is well conveyed by Henry T. Greely's quote: "If it looks like a human brain and acts like a human brain, at what point do we have to treat it like a human brain?"<sup>60</sup> Such uncertainties would make it difficult to ethically and legally distinguish between organoids that are models of brains and those that should be regarded as brains. These considerations are important because they influence our idea of what would be morally acceptable to do with neural organoids. While different perspectives exist on what role consciousness should play in attributing moral status, it is generally agreed that beings that have interests (for example in pursuing pleasure and avoiding pain) have a moral status and there should therefore be rules governing what we can do with them.<sup>61</sup> The recognition that a range of non-human animals are sentient has led to the development of frameworks to guide how they should be treated in scientific research. Because of the uncertainties surrounding the future capabilities of neural organoids, some authors have advocated for precautionary measures under the assumption that neural organoids might develop sentience or consciousness in the future. If we cannot rule out this possibility, then precautions aimed at reducing the risk of causing them suffering may be proportionate.<sup>62</sup>

There have been a number of suggestions from ethicists, social scientists, and legal scholars on what appropriate precautionary measures might look like for neural organoids. Some argue that, in determining how they should be treated, our approach to neural organoid research should be consistent with our approach to animal research, and suggest that a proportionate measure would be to bring organoids displaying neurological warning signs of sentience within the scope of ASPA.<sup>63</sup> Others argue that, because humans are generally thought to develop sentience between 20 and 30 weeks of gestation, neural organoids that reach a level of development comparable to that of a 20 week-old fetus should be treated as if they have some level of consciousness and are deserving of a moral status.<sup>64</sup> Discussions of what it means for neural organoids to be sentient or conscious, and how we might be able to recognise these capacities in them as technology advances, will be central in determining what rights, if any, should come with the attribution of a moral status. These discussions, as some legal scholars have argued, should be addressed before their use become more widespread if we are to avoid replicating the same moral concerns arising from animal testing with a new class of subjects that we may conclude in the future also deserve a moral status.<sup>65</sup>

### **ETHICAL ISSUES LINKED TO THE TRANSPLANTATION OF HUMAN NEURAL ORGANOIDS INTO NON-HUMAN ANIMALS**

Transplantation of human neural organoids into non-human animals may be seen as more problematic than transplantation of groups of disorganised human neural cells.<sup>66</sup> While such experiments have only been performed in rodents so far, transplantation of human neural organoids using larger mammals, with a brain size and developmental timings similar to those of humans, could increase the chances of the human tissue integrating with that of the host brain and significantly grow in size. There are concerns linked to the possibility of large human neural organoids grown in an animal host to hybridise cognitively in ways that are difficult to predict, possibly leading to the generation of hybrids that do not belong completely to either species and with a moral status that would be difficult to define.<sup>67</sup>

If such hybrid animals developed human-like cognitive and emotional capacities in a morally

significant way (for example, augmented capacity to suffer or experience pleasure) they may have different welfare needs to animals who have not had human neural organoids transplanted into their brains.<sup>68</sup> Ethical questions have been raised in relation to the concept of ‘unnaturalness’ and the crossing of boundaries between species.<sup>69</sup> There is a tendency to associate our brain with our humanity and individuality. This is because of a range of cognitive and emotional capacities that some believe to be exclusively human, such as exhibiting altruistic and empathetic behaviour, are dependent on characteristics of the human brain.<sup>70</sup> The idea of blurring the distinction between species in such a way that might confer some human-like skills and characteristics to non-human animals can raise discomfort and disgust, sometimes described as a ‘yuck’ response.<sup>71</sup> This is, as social scientists, ethicists, and philosophers have noted, a common response to novel, hybrid biotechnologies which appear to cross boundaries between different categories in ways that appear unnatural, monstrous, or dangerous. Such technologies can be perceived to “pose a threat to shared meanings, values and rules of conduct that make communal social living and organisation possible”.<sup>72</sup> Engaging with publics to understand what generates unease and discomfort and the kind of measures needed to make sure that organoid development and use benefits society may be an important step as technology moves forward, as previously suggested for other biotechnologies such as genome editing.<sup>73</sup>

### **COMMERCIALISATION AND PATENTING OF NEURAL ORGANOIDS**

From precision medicine to pharmaceutical development and biocomputing devices, future applications of neural organoid research are likely to raise commercial interests. In this context, a relevant ethical question is: who will benefit and profit from the use of organoids? Those who donate tissue used to generate organoids, without receiving any benefits themselves, might find it unfair – or exploitative – for commercial parties to profit from organoids that share their genetic identity and that they may perceive are part of them. A recent study exploring patients’ perspectives on the derivation and use of different types of organoids suggests that some patients may feel more of a connection with neural organoids than to those of other organs

because they believe they contain “more of their individual essence”.<sup>74</sup>

It has also been suggested that making profit from organoids developed from patient donor cells could be regarded as more ethically contentious than if using cells derived from healthy volunteers. This is because such patients are, de facto, dependent on the development of drugs by commercial parties. Some have suggested that, in such cases, commercial parties should take proactive measures to ensure equity and fairness in commercialising patient-derived organoids, for example by ensuring fair prices and early access to any innovative therapy that might improve the patient donor’s health.<sup>75</sup> The idea of neural organoids as commodities to own and sell may also be seen as ethically problematic by some, conflicting with their sense of human dignity. The traditional distinction between subjects with rights and objects to own cannot readily be applied to neural organoids, assembloids, and organoid-related technologies because they represent models of an individual’s brain and are made of human-like tissue.<sup>76</sup> Because of their nature, organoids could be considered to belong to a grey area, potentially being subjects and objects at the same time.

### **ETHICAL ISSUES LINKED TO INFORMED CONSENT**

Important ethical considerations arise in the context of appropriate informed consent processes for those donating samples that will be used in neural organoid research. Truly informed consent in organoid research is practically and ethically challenging for a number of reasons. The pace of scientific and technological progress makes it difficult, if not impossible, to predict and describe to potential donors the future applications of neural organoids in both the clinical and non-clinical space. Current applications of neural organoids in biocomputing and microfluidics, for example, might have been difficult to anticipate five years ago.<sup>77</sup> Most biobanks do not include the potential for the derivation of brain organoids in the consenting process. In this context, some have asked whether or not, for example, it is safe to assume that a person who has donated their cells would feel comfortable with the idea of those cells being developed into a neural organoid or assembloid.<sup>78</sup> Unlike broad and blanket forms of consent, dynamic and tiered consent could

allow for continuous interactions between biobanks and donors and allow them to consent to specific uses of their cells and tissue; at the same time, recontacting patients requires time and resources and might risk impeding important research.<sup>79</sup> Moreover, some donors might prefer not to be recontacted. Indeed, findings from a public dialogue carried out in 2017 on behalf of the HTA and HRA show that some donors do not want to consent to specific uses of their cells and tissue. Some donors, for example, think that this would lead to an overload of information or fear that it could hinder important research that their donation was meant to support.<sup>80</sup>

Biobanks and RECs are actively engaging in discussions around appropriate forms of consent for neural organoid research. The difficult task ahead for the research community is to find a balance between facilitating the development of new therapeutics in an efficient and timely way and respecting cell donors’ preferences.<sup>81</sup> More research exploring views and perspectives of donors could help guide biobanks and research institutions in developing appropriate forms of consent.

### **DATA PROTECTION AND PRIVACY CONCERNS WITH PERSON-DERIVED CULTURES**

Organoids originate from the body of a living person with whom they share their DNA. The genetic analysis of organoids raises concerns over health data protection, in particular genetic data, which must be taken into account at the consent stage. In this context, an important question to answer is: what features do organoids exhibit of their cell donors? A common approach is to de-identify the samples and protect the privacy of tissue donors. Many experts, however, agree that the complete anonymisation of organoids is not truly possible. Even if achievable, complete anonymisation of samples may be problematic, as it may make the organoid less useful in a clinical context – if the cell donor cannot be identified, their organoids cannot be used for precision medicine purposes. In cases where a dynamic form of consent is in place, de-identification would make it impossible to re-contact the donor, offer the possibility to control future uses of their samples and also to share benefits from neural organoids derived from their tissues, including sharing findings with potential clinical benefit.<sup>82</sup> In this context,

questions of whether and in what circumstances to report incidental findings about clinically relevant information also arise.

### **ETHICAL ISSUES LINKED TO THE REGULATION AND GOVERNANCE OF NEURAL ORGANOID RESEARCH**

There are calls for ethical guidance to assist researchers, funders, RECs, and biobanks in making decisions about neural organoid research, for example, when reviewing a research study. As research rapidly progresses, there may be a need for a framework on which to base appropriate boundaries and decisions, for example on whether or not to grant permission to use stem cell lines for a study and appropriate forms of consent needed.<sup>83</sup> Developing such a framework should include considerations of what the different stakeholder groups involved, including publics, are comfortable with and find acceptable. This is important to ensure that we all benefit from neural organoid research and future advances.

If feasible, for example, would transplanting a mature and fully formed neural organoid into the

brain of a mouse be viewed as acceptable? Would doing the same with a pig also be viewed as acceptable? RECs, biobanks and steering committees might not always feel qualified to make such decisions, which are likely to become more complex and challenging as research progresses.

Even when projects might seem intuitively problematic, there may not be clear legal or regulatory grounds on which to base the decision to approve or reject them. Even if ethical and regulatory measures may not be immediately necessary, it is possible that current ethical and regulatory frameworks may become inadequate as research progresses and neural organoids become larger, more complex and are connected in assembloids, implanted in non-human animal brains, or combined with computer systems.<sup>84</sup>

Given the potential benefits of neural organoid research for human and non-human animals, it may be important to develop ethical guidance that is future-proof and can account for the many uncertainties surrounding neural organoids and their future capabilities, while ensuring that important health research is not unnecessarily obstructed.

### **BOX2: SUGGESTED ISSUES FOR WHICH GUIDANCE MAY BE NEEDED ACCORDING TO THE STAKEHOLDERS INTERVIEWED**

As highlighted in the introduction, in developing this briefing note, we sought the input of expert stakeholders who attended short interviews and/or commented on earlier versions of this document.

In this box, we list the ethical aspects of neural organoid research that might benefit from guidance, as emerged from our engagement with expert stakeholders. This is an initial list, but we hope that it will be helpful as a starting point on which to base future conversations – for example, on which aspects of neural organoid research might require further ethical discussion.

- Projects where neural organoids are transplanted into large mammals during early stages of development.
- Projects where there is no specified limit to how long the neural organoids will be maintained.

- Projects where neural organoids are linked to other types of tissue, such as muscles or sensory organoids.
- Projects where neural organoids are linked to algorithms and digital systems with the potential to converge in brain-computer interfaces (BCIs).
- Projects where organoids could be used for commercial purposes.
- Projects where organoids (or other types of neural cultures) will be composed of a very large number of connected, functioning brain cells.
- Appropriate forms of informed consent in neural organoid research.

## REPRESENTATION AND PUBLIC PERCEPTION OF NEURAL ORGANOID RESEARCH

Representation of neural organoids has sometimes been misleading, for example, by exaggerating their capability to develop consciousness and their similarities with the actual human brain, or their potential to have a range of medical applications in the near future.<sup>85</sup> Whether positive or negative, these exaggerations risk leaving individuals with a strong sense of threat or hope.<sup>86</sup> They could undermine public trust in and support for important research, and, at the same time, create false hopes and unrealistic expectations in those who are affected by serious conditions and are in a position of vulnerability as a consequence. For example, it is

important to clearly discuss the current limitations of neural organoids that attempt to model late onset and neurodegenerative conditions.<sup>87</sup>

The use of metaphors and intuitive terms to describe neural organoids, such as ‘brain and intelligence in a dish’ and ‘mini-brain’ can be useful in conveying new, complex scientific ideas but they might also contribute to misperceptions developing and giving publics the impression of a fully grown, miniaturised human brain in a dish.<sup>88</sup> Language should therefore be used cautiously and neural organoids should be accurately described. There is a need to maintain a balance between communicating the potential applications of these models, while also clearly describing any limitations of their efficacy and future possibilities.

## CONCLUSIONS

- Neural organoids are promising research tools that could have important applications in the future, improving our understanding of a range of brain conditions and treatment options.
- Neural organoid research is, however, still in its infancy and its potential is yet to be fully explored. There are still uncertainties around future possibilities, research directions, likelihood of success and the extent to which neural organoids currently resemble, and will be able to resemble, the human brain.
- Research is moving at pace, and it is difficult to predict when significant developments will take place. It is important, therefore, for policy makers to work with scientists, ethicists, and publics to ensure that the ethical and regulatory questions are fully explored, in order to ensure that appropriate guidance and regulations will be in place to facilitate innovation and address ethical considerations.
- Relevant ethical considerations in neural organoid research include:
  - whether or not more tailored ethical guidance and oversight is needed;
  - what might be appropriate consent procedures and processes for tissue donors;
  - the potential for neural organoid research to benefit human and non-human animals;
  - the importance of a balanced and accurate communication of neural organoids’ current and potential future capabilities; and
  - the possibility of neural organoids developing capacities increasingly similar to the developing human brain, such as sentience and consciousness, if indeed they ever do.
- Areas where further ethical guidance, policy and regulatory decisions are needed include:
  - appropriate consent processes that can account for the fast-paced developments in this area of research and unpredictability of research directions;
  - what appropriate, future-looking and proportionate regulation for these models might look like – if needed – considering developments in assembloids, neural organoid transplantation and other, more advanced technologies; and
  - what anatomical or functional ‘hallmarks’ displayed by neural organoids might be used as criteria to attribute consciousness to them and what the consequences for their moral significance might be as a result.

Further exploration of the themes identified in this note is needed to better understand potential ethical issues raised by neural organoid research and possible future advances.

The NCOB intends to facilitate future discussions around these important issues, which should involve scientists, ethicists, potential regulators, publics and all those involved in making decisions around neural organoid research.

Clear, accurate communication, as well as meaningful engagement with publics, will be important to ensure that we all benefit from neural organoid research and future advances.

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