Introduction: what is consciousness?

Organoids

The assumption that organoids grown in a reactor, outside a body, will show forms of consciousness of any kind, now or in the near future, is in my opinion highly unlikely to be correct.

Here is how I see it:

1. A brain-organoid is not a brain. It lacks the subcortical regions that are necessary for a global state of consciousness to exist. By that I mean what is called “creature consciousness” being awake (not deeply asleep or in a deep coma) and *being able* to be conscious of specific things such as seeing a red flower. The sub-cortical regions seem to be necessary in the constitutive sense: they seem to be **building blocks** of consciousness. Comparative studies of animals suggest that a neocortex is not necessary for consciousness, although it is necessary for sophisticated forms of consciousness such as that of mammals including humans. There is a growing consensus that basic consciousness exists in most vertebrates including fish. Evolutionary continuity suggests that the consciousness-affording parts of the brain of fish and reptiles are still involved in generating consciousness in the brains of mammals and humans, which did not delegate the whole thing to the neo-cortex.

2. It is questionable whether we can grow an organoid brain with **all** the necessary parts without providing it with inputs from the developing non-neural parts of the body. Evolutionarily, the nervous systems evolved to coordinate motor actions with sensory inputs in large moving multicellular animals, and consciousness evolved on these foundations. The inputs from the developing and changing body are therefore crucial—there are reciprocal interactions between the non-neural parts and the brain. For example, there are bi-directional Interactions with the hormonal and immune systems and with non-neural bioelectric fields in the developing embryo. However amazing autonomous self-organization may be, there is a need for this developmental “dialogue”.

The organoid-in-the vat idea is an extension of the brain-in-the vat thought experiment. The original thought experiment raises many problems, but the organoid-brain raises even more. While in the brain-in-the-vat thought experiment, the brain is a mature brain of an enbrained ex-living bodily being with all its experiences, memories, beliefs etc., here we are dealing with an organoid-brain-in-a-vat, with no such representations, which first needs to develop into something like a human brain that can support conscious states. Even if we have complex assembloids with complex brain activity, this complexity is may be necessary for consciousness, without an ongoing developmental "dialogue" it will not be sufficient.

We will need to worry about organoid consciousness only if we simulate a virtual developing body (including subcortical areas) in a relevant virtual reality. It is up to us **not** to make rich body and world simulations, even if we are ever able to do so.

Of course, we need to stimulate the brain-organoid in various controlled ways to do meaningful research, and I think we should do this, without worrying.

3. If what interests us is human awareness, then we have to give the organoid further developmental inputs. The newborn human is extremely immature, and a crucial part of its brain development occurs in an external environment which is rich is stimuli. Some post-natal stimuli are simple but essential. For example, children (and monkeys) who are not touched during the first 6 weeks of their life become irreversibly catatonic; they do not have what we would call "human awareness". Many post-natal inputs are necessary for the normal development of a brain we shall consider to have human awareness.

In conclusion, I do not think that we need to worry that creating brain organoids and that stimulating them for current research purposes will render them conscious.

On this basis, my answers to the questions you asked with regard to organoid are:

- What types of brain tissue are appropriate for use as neural organoids?

Any brain tissue depending on the purpose of the research.

- How large or complex would the ex vivo brain organoids need to be to attain enhanced or human awareness?

However large the brain-organoid is, it will not be spontaneously conscious. It is not (mainly) a matter of size but of organization. African Gray parrots have tiny brains but great cognitive capacities. As to complexity, what measure of complexity could we use? Patterns of activity similar to those of a conscious human brain? at what stage of development? More generally, it is unlikely that human awareness will develop in the absence of the developmental embryonic and post embryonic inputs necessary for the maturation and learning of the brain.

- Should patients give explicit consent for their cells to be used to create neural organoids?

No more and no less than for other tissue-specific cell lines.

Chimeras

Chimeras are animals, and the kind of chimeras being considered are mammals, which are generally considered to be conscious, albeit not in the human reflective manner. Since non-human mammals are subjectively experiencing beings, they are moral patients (like preverbal babies and people with serious mental handicaps). Since chimeras are animals whose cognition has not been studied, they may have mental capacities and handicaps of which we are unaware. This raises welfare concerns.

If human cells populate the brain of the host animal, or if human brain organoids are transplanted to an animal, they may change the way the whole brain functions and the way the chimera experiences the world.

There are five possibilities: pathological effects; no change; neutral changes; enhancement which is not human-specific; human awareness (something we need to characterize).

First, rather than enhance the host's capacity they could lead to pathological brain activity that would lead to suffering, if the animals are allowed to come to term. This might be because the interactions between human and animal cells lead to stress-induced transposition, or activation of retroviral elements from both tissue types. This a general concern not specific to brain tissue, which I am sure the committee discusses with the relevant experts. A concern that is more specific to brain tissue is the formation of abnormal connections that may lead to behavioral and mental problems.

The literature does not provide much information about the effects on cognition and behavior. The number of behavioral/cognitive experiments of Human-Animal chimeras is very very small. A 2019 review that looked at 150 studies in which human cells were introduced into animals at various stages of development suggested that the cyto-architecture of the host brain in most cases did not change. Behavioral studies were rare. One study deserves special attention. Human glial precursor cells were transplanted into neonatal immune-deficient mice. Human glial cells were found throughout the entire brain within 12–20 months, and the brain was organized in a laminar structure previously found only in humans and nonhuman primates. The human astrocytes maintained a human astrocyte morphology (i.e., larger nuclei, long projections) within the mouse brain. Functionally, human astrocytes propagated calcium waves significantly faster than mouse astrocytes. Behaviorally, relative to wild type mice, chimeric mice displayed more rapid acquisition of an auditory fear conditioning response, reduced latency to escape the Barnes maze, and an increased ability to remember the locations of objects in the object-location memory task. The altered ability of these human/mouse chimeras to learn strongly suggest that learning needs to be thoroughly studied in any chimera.

Macaque-human chimeras have been made. We do not know how the brain of such animals will develop -- size seems not be the most important issue, since there is a mechanical size constraint imposed by

the host (also seen in hybrids), but size it not the only consideration. Anatole France, the Nobel prize winning French writer had a brain 2/3 the size of the normal brain (less than *Homo erectus* 1MYA), and there are people that live a rich human life with a single hemisphere. African gray parrots with an absolute brain size of a few grams but display cognitive sophistication, that in some domains is comparable to that of a child of 4. The **organization** of the chimera brain needs to be studied, for example, the relative size of different areas such as the prefrontal cortex.

As to consciousness and enhancement more generally: there is no linear scale of more or less consciousness. As some people have already suggested we should look at different dimensions of consciousness. Human may have high scores on some but not all dimensions.

Birch and his colleagues identify five dimensions: perceptual richness; evaluative richness (ability to make choices between stimuli differing in value); the richness of a unified multimodal image as shown by episodic memory); the ability to integrate over time (working memory and trace conditioning; the ability to infer what came after what); consciousness of self (as shown by theory of mind test). There are ways of testing all these dimensions.

It is very very unlikely that a chimera will have “human awareness”, because such awareness is the outcome of human social and cultural inputs, which the animal will presumably not get. However, the chimera may have capacities and needs that differ from those of a normal macaque.

So here are my thoughts about the chimera questions:

- **How would researchers define or identify enhanced or human awareness in a chimeric animal?**

We first need to decide what are the hallmark properties of humans; of course they have clear precursors in apes and possibly other animals. But they are very very prominent in humans):

Theory of mind; tendency to share information; self-consciousness, well developed episodic memory; fine motor control of face, hands and gestures; good emotional and executive control. Language is probably the only aspect of cognition which is very very different from the precursors we find in apes.

Behavioral testing of **cognitive and affective capacities**: e.g. pointing for sharing information (not just imperative pointing); theory of mind experiments (experiment like those of Kano et al 2019); mirror test (which is only informative when there is a positive result); extended episodic memory; emotional control (e.g., the ability to delay gratification); expression of social emotions like shame or embarrassment. The capacity to comprehend symbolic language and to use symbols for communication should also be investigated (we know great apes have these capacities to a somewhat limited degree; so do African Gray parrots).

Motor capacities: fine motor control of face, gesture and hands (tool making, gesturing).

Perception: What kind of perception will chimeras have? Will they be synesthetic? Will they have altered connections between brain regions controlling different sensory modalities in the brain? Or more connections to higher level associative areas?

Compared to other primates, humans have larger neocortices, temporal lobe volume, and estimated prefrontal white matter volume, as well as greater gyrification in prefrontal cortex and more gyral white matter in the frontal and temporal lobes. They have relatively smaller primary sensory and motor areas. If the relative proportions in the chimera brain show similarity to human proportions we might expect more similarity to human-like capacities.

- **Do research animals with enhanced capabilities require different treatment compared to typical animal models? What are appropriate disposal mechanisms for such models?**

If (for example) a chimeric macaque shows capacities that are typical of a chimpanzee, we should consider whether it has some chimpanzee-like needs. For example, it may need a longer period of maternal care if the rate of its brain maturation is longer than that of a typical macaque. Welfare decisions are based on what we know about the animals' needs and capacities. So obviously, if chimeras will have different capacities and needs, we should adjust our practices accordingly. They should be taken to a sanctuary taken care of and gently studied. It is irresponsible and arrogant to assume that we know what their capacities and needs are without thorough study of their learning capacities and other aspects of their cognition.

- **What kind of "humanized" brain, in size and structures, would be acceptable in a research animal?**

As long as we don't know what the effects of the human cells are, we cannot proceed with these experiments. The problem is not just enhancement, it is also potential handicapping of the animals. If we don't understand the outcome of what we are doing from the animal's perspective, we cannot make welfare decisions.

In my opinion, measures should be taken to ensure that human cells <u>do not</u> populate the host brain. If they do, the animals should not be allowed to come to term.

If chimeras are formed in order to transplant human brain tissue to sick humans, the tissues should be taken from embryos (chimeras should not come to term).

If non-human animals with human neural tissues are brought to term for whatever reason, it must be recognized that they <u>may</u> have altered cognition and affect. They should be taken to sanctuaries, observed and studied (gently). We cannot care for these chimeras' welfare if we know nothing about their needs, capacities and handicaps. Animal scientists must be involved in such research, if it is allowed to go ahead.