CASE STUDIES

GLOBAL NEUROETHICS SUMMIT 2017

Deep Brain Stimulation (Australia Brain Initiative)

CASE STUDY

Jerry is a 65-year old man who was diagnosed with Parkinson's disease in 2008. He initially responded well to the medication but his motor symptoms gradually worsened despite large increases in drug doses that caused significant side effects. His neurologist suggested that he undergo deep brain stimulation to control his freezing and tremor. Surgery in 2012 significantly reduced his motor symptoms and Jerry was able to return to all the activities that he did before the onset of Parkinson's, such as bowling with friends, bushwalking with his wife, Shirley, and socialising at parties. Jerry was energetic and highly sociable; Shirley had never known Jerry to be so gregarious and full of life. Their sex life was reignited too, after being largely celibate prior to the surgery, although Shirley found his demands for sex were sometimes a bit too much.

In 2013, Jerry was charged with a having sexual intercourse with a minor. At trial, it became apparent that he had developed hypersexuality and had used prostitutes on over 500 occasions in the 18 months after surgery, including male and transgender prostitutes. He claims that he had not previously engaged in homosexual behaviour.

His neurologist believed that the deep brain stimulation had caused his hypersexuality, arguing that around 1 in 5 people who receive this treatment develop a compulsive behaviour (e.g. shopping, gambling). His stimulator was turned off: his compulsive sexual behaviours ceased but his severe motor symptoms returned, worse than before. He became bed ridden and needed to be cared for by his daughter because his wife left him.

For further discussion:
A subsequent scan of Jerry's computer reveals a single photo of child pornography in his files that predates his Parkinson's disease.

Identity and authenticity:

- Were these behaviours an authentic expression of who Jerry was? Was he responsible for them?
- Did the stimulation create new desires, thereby altering his sense of self, or did it simply unmask a latent tendency in Jerry?

Moral responsibility and agency:

- Should Jerry be held responsible for the criminal sexual act?
- Should Jerry have noticed increased sexual desires and sought help?
- Is he responsible for not getting help?
- Does the fact a scan of Jerry's computer reveals a single photo of child pornography in his files that predates his PD make us more willing to attribute responsibility to Jerry?

Consent and coercion:

- How should the clinician treat his Parkinson's disease?
- Can the state force Jerry to have the stimulator turned off if he refuses?

Preclinical Detection (China Brain Project)

CASE STUDY

(A) New tests (cognitive-behavioral, neuroimaging, eye tracking) are in development as early diagnostics for Alzheimer's Disease (AD). As part of their development, a large group of people has been enrolled in a longitudinal study of their effectiveness. The results of the study show that some participants have significantly higher risk for AD. However, there is currently no effective therapy for patients with AD, even if it is diagnosed before the onset of symptoms. Jingqiong participated in the study, and has emailed the study coordinator to find out her results.

- Should the study coordinator inform Jingqiong of her results?
- Should the study have been designed so that individual results would not be identifiable?
- Does Jingqiong's reason for requesting her results matter? For example, she may have a grandmother with AD and just be anxious to know her status, or she might want to enroll in a clinical trial of treatment for persons susceptible to AD.
- If Jingqiong is informed of her results, must all participants be contacted and offered disclosure of their results?
- Is it ethical to conduct a study to diagnose diseases early, when no effective treatment for the disease yet exists?

(B) The study coordinator decides to inform Jingqiong of her results – she is indeed at higher risk for developing AD. The next day the director of the department in which the study was conducted receives an angry phone call from Jingqiong's mother. "How could you tell my daughter that she will develop Alzheimer's?" she asks. "Now she has broken off her engagement and says that she will never have a child. How could you do this to our family?"

- Was the study coordinator wrong to inform Jingqiong of her results?
- Is it unethical to inform participants of diagnoses for which there is no effective treatment?
- Is a higher risk of developing AD relevant to individuals alone, or this information that whole families ought to know?

Finding the right balance? (EU Human Brain Project)

CASE STUDY

Dr X is the PI for a research project that studies the neural mechanisms of behavioural and cognitive processes and brain states. Her project is part of a large scale European initiative that aims to achieve a fuller understanding of the human brain, better diagnoses and treatment of brain disorders, and the development of new brain-like technologies.

Dr X's task requires data on brain dynamics during the performance of a number of specific cognitive and behavioural tasks, from simple skills found in non human species to higher cognitive functions only found in primates. Dr X and her team do not carry out experiments themselves. However, their work requires data mining of existing human and non human animal studies in order to develop models of the neurocognitive architectures of higher cognitive functions.

Dr X and her lab are facing a challenge. When they use and analyze data produced inside the EU such data has been collected through animal research regulated by European legislation and, due to the principle of subsidiarity, is assumed to be compliant with Directive 2010/63/EU. However, the subsidiarity principle cannot be applied to data from countries outside the EU. So how to handle the issue of data coming from research that cannot automatically be assumed to match European requirements? In particular, Dr. X is working in a data integration project that has the explicit goal to make data available to all, within and without the project. While one possible option is to rule out such data in general, Dr. X is trying to find a balance.

In particular, she is concerned with non-human primate (NHP) data. European legislation is stringent regarding research with NHPs: while the relevant Directive allows for NHP research, it also states that "the use of non human primates should be permitted only in those biomedical areas essential for the benefit of human beings for which no other alternative replacement methods are yet available." Most of her colleagues and Dr X herself agree with such legislation. They share the moral intuition that research with animals in general needs strict regulation and that NHP in particular deserve special protections. At the same time, she knows that important research on NHP is carried out abroad. She is also aware that some results of this research are highly valuable, perhaps even indispensable in helping to solve the scientific questions of her own project. She wonders, will she be able to advance her research on the human brain without using such data? She is not just concerned about her specific line of research: she wonders whether a data integration project can be successful if it cannot make NHP derived data available to its users. Even further, will the project she is part of be able to engage the relevant scientific communities? How to find the right balance?

Questions:

- Is it morally acceptable to reject NHP derived data from non EU countries because it does not comply with existing European regulations?
- When is a biomedical research "essential for the benefit of human beings"? From a moral perspective if Dr X's research requires data that non-EU repositories offer, should she use it even if not collected in accordance with EU regulations?
- Is this a case in which moral considerations trump legal considerations? Considering that specific moral ideas underlie EU legislation and regulation, how to move forward?
- Considering the difference in regulatory frameworks and moral intuitions regarding issues such as NHP research (or dual use) how can international collaboration be implemented in practice in the context of brain research?

Neurofeedback (Japan Brain/MINDS)

BACKGROUND

Neurofeedback technology is being explored to treat various disorders including depression, developmental disorders, schizophrenia, and chronic pain. Recent neurofeedback, such as decoded neurofeedback (DECNEF) is characterized by intervention in human capacities using fMRI (fMRI was originally developed for observation of brain activity, not for intervention). With DECNEF, neural activation patterns are recorded. Then an individual is "trained" to match these patterns. DECNEF participants are asked to--without explicit instruction about what precisely they should do or think and without the stimulus--to induce a specific activation pattern in their brains, one that matches the "blueprint" or "template."

For example, in an experiment by Shibata et al, 2011, a template of brain activation created by individuals who had viewed a visual stimulus with a specific orientation of gratings. They describe how then, "With an online-feedback method that uses decoded fMRI signals, we induced activity patterns only in early visual cortex corresponding to an orientation without stimulus presentation or participants' awareness of what was to be learned". (Shibata et al. 2011, 1413).

DECNEF is a technique that aims to modify the state of a participant's neural network through real-time feedback with fMRI (rtfMRI) generated by machine learning (versus conscious learning on the part of the participant) of pattern analysis of voxel space of fMRI.

From Nakazawa et al, 2016, "Their study showed that neurofeedback using rtfMRI has two main advantages. First, it allowed the modification of brain activity without any pharmacological interventions in the body or brain. Thus, this novel treatment could be performed in a drug-free manner. The second advantage is that the repetition of visual stimuli was not necessary for learning. This suggests that using simple visual feedback may promote and allow better recovery of cognitive functions, such as memory retention and emotional control, or better treatment of visual disorders.

Furthermore, this technique may have further applications, such as the treatment of mental illnesses and the enhancement of human faculties. For instance, if we compare the differences in the default mode network (DMN) activity between healthy individuals and patients with mental disorders, it may become possible to adjust the DMN activity of patients with mental disorders using neurofeedback (cf. Ministry of Education 2011). This is also true of enhancement of human faculties." (Nakazawa et al, 2016, 111).

The project is supported by Strategic Research Program for Brain Sciences (SRPBS), which--like as Brain/MINDS--is under the umbrella of the Japan Agency for Medical Research and Development (AMED)-supported grants. Although the underlying mechanisms that allow the improvement or modification of an individual's cognitive (and perhaps even moral) capacities have not been elucidated, this technology has a wide range of potential applications (including learning, memory, and motor rehabilitation) and these applications may impact the society. However, it is difficult to assess the safety and efficacy of

neurofeedback-based interventions in clinical trials because of a shortage of reliable preclinical data.

CASE STUDY

Professor A's group at the hospital affiliated with B university school of medicine, has decided to start a Decoded Neurofeedback study that aims at enhancing interpersonal communication abilities for individuals with autism spectrum disorders (ASD). Ten participants are scheduled to participate in this study. Were this study to demonstrate the safety and efficacy of DECNEF to improving interpersonal communication, it may suggest obtainment of a new tool to control interpersonal communication ability in the future.

Questions

- How do one evaluate the invasiveness (and associated risks) of decoded neurofeedback technology?
- What measures are required to ensure the safety of neurofeedback technology?
- Is it ethically acceptable to use neurofeedback technology for applications beyond therapy, such as for enhancement?
- Patients with autism spectrum disorders questions what is the "typical" pattern of brain development from the perspective of diversity. How will the thresholds for typically developed versus ASD brain be determined for the purposed of neurofeedback?
- Trained machine learning algorithms become difficult to understand with regard to why particular responses occur to a set of data inputs. What considerations should be taken to ensure transparency and accountability of the "black box" these algorithms create?

REFERENCES

Amano K, Shibata K, Kawato M, Sasaki Y, Watanabe T: Learning to associate orientation with color in early visual areas by associative decoded fMRI neurofeedback. Curr Biol. 2016 Jul 25;26(14):1861-6.

Eisuke Nakazawa, Keiichiro Yamamoto, Koji Tachibana, Soichiro Toda, Yoshiyuki Takimoto, Akira Akabayashi. Ethics of decoded neurofeedback in clinical research, treatment, and moral enhancement. American Journal of Bioethics Neuroscience 7(2): 110-117.

Shibata K, Watanabe T, Sasaki Y, Kawato M. Perceptual learning incepted by decoded fMRI neurofeedback without stimulus presentation. Science. 2011 Dec 9;334(6061):1413-5.

Establishing Brain Banks (Korea Brain Initiative)

CASE STUDY

Due to its geographical location, Korea has a long-standing tradition of East Asian culture based on Confucianism, Buddhism, and Taoism, while having gone through rapid industrialization and modernization. Under the influence of Confucianism, dissection of a human body was strictly forbidden in premodern era. Today Koreans have very conservative views on the brain autopsy and demonstrate reluctance about removing the brain from the body. Opening and exploring the inside of the cranium is hardly conducted in Korea. Donating brains for research is unfamiliar to the general public, moreover, it faces vague rejection. A public consensus on related issues is lacking, and relevant laws are not sufficient to address these issues. In contrast, there are increased demands from the researchers and clinicians for using brain tissues obtained from autopsies, which demonstrates the need for legal reform and a shift in the general consensus.
So far, some major hospitals in Korea have been autonomously collecting brain tissue. Researchers had been urging the government to set up a brain repository, for the researches on brain-related diseases in Korea. The brain bank in Korea was recently launched and has collected donated brains from patients who died from the neurological disorders such as Parkinson's disease, Alzheimer's, epilepsy, autism.

- All human material including brain (optionally spinal code) are obtained on the basis of written informed consent. According to the Korean Organ Donation Act, if a brain -dead donor does not indicate the intention of organ donation in advance, organ don ation is permitted only with the consent of the bereaved family of the brain-dead per son is obtained. Is the consent to the bereaved family of the patient is ethically accept able in the case of brain donation too?

- A patient with Alzheimer's disease wanted to let his brain to be used in his physician 's research on Alzheimer's disease. He told his intention to the physician and indicate d his consent of brain donation. After the brain donation, Can the physician transfer a part of the donated brain to another research team beyond the patient's intention? Will be his behavior ethically acceptable?

- What kind of public campaigns or incentives could be launched to encourage brain d onation in ethical and responsible way?

Research with Human Cerebral Organoids (US BRAIN Initiative)

BACKGROUND

The possibility of developing and growing human organoids typically derived from human stem cells, including cerebral organoids, is an emerging area of science that holds great promise for advancing human health and neuroscience (Di Lullo and Kriegstein, 2017; Qian et al. 2017). Researchers have long sought to understand how the human brain functions in health and disease, with much of their work constrained to studies with animal models and post-mortem or pathological human brain tissue. In contrast, human cerebral organoids, grown *in vitro* from pluripotent stem cells, offer the potential for closer approximation of dynamic human brain development and function. At present, that approximation is still fairly limited. On one hand, cerebral organoids can generate diverse cell types, and self-organize into complex structures that resemble parts of the brain. On the other hand, they exhibit heterogeneity in terms of cell types and circuitry, and they don't include all cell types involved in normal brain development (Di Lullo and Kriegstein, 2017). Scientists are still working to understand cerebral organoids and develop this early-stage model system for more widespread use.

Human cerebral organoids also raise important ethical questions. Knowing that cerebral organoids are meant to model human brains and aspects of brain development or disease, but cannot develop into full persons, what are the relevant ethical considerations? Presumably these would be related to the development of human features, rather than the creation of human life. For instance, what morally concerning features might cerebral organoids develop, such as sensory perception, sentience, pain, or cognition (Munsie et al. 2017)? What biological indictors would reveal the development of those features? How can we think about a prospective framework for mitigating ethical risks while not inadvertently stifling promising areas of research inquiry?

CASE STUDY

Scientists in the Temple Lab are growing human cerebral organoids (generated from skin fibroblast-derived induced pluripotent stem cells) to study the effects of prenatal exposure to viruses on neurodevelopment. This research cannot ethically be performed *in vivo* on human embryos or fetuses. The research could provide valuable insights into the effects and prevention of neurodevelopmental insults. Identifying critical developmental periods of exposure could require maintaining the organoids *in vitro* for extended periods of time. Abby donated skin cells for this research. She hopes that the researchers will learn something that will help babies with microcephaly, but she is concerned about 'her' cerebral organoid. How much does it resemble her brain? Does it sense or think? Since it has no way to communicate, how would anyone know if it does?

Questions:

- What features/functions would warrant concern in cerebral organoids?
- Given that, unlike a brain, a cerebral organoid exists in a disembodied state, how would researchers know if/when these features are present?
    - What are the implications of having (or not having) the ability to detect these features/functions?
- What is the moral significance of neurodevelopmental milestones for cerebral organoids?
- Does the provenance of the cerebral organoids (cell lines, fetal tissue, donated embryos) matter in terms of potential concerns?
- What are the existing ethical and regulatory frameworks for cerebral organoids used in research?
    - How should we think about consent for research with cerebral organoids?
    - Should there be limits on allowable development of cerebral organoids?
    - If limits should exist, should the limits be defined by time or by identifiable features/functions?

REFERENCES

Di Lullo, E., & Kriegstein, A.R. (2017). The use of brain organoids to investigate neural development and disease. *Nat Review Neurosci*, doi:10.1038/nrn.2017.107.

Munsie, M., Hyun, I., & Sugarman, J. (2017). Ethical issues in human organoid and gastruloid research. *Development, 144*(6), 942-945. doi:10.1242/dev.140111

Qian, X., Nguyen, H. N., Jacob, F., Song, H., & Ming, G.l. (2017). Using brain organoids to understand Zika virus-induced microcephaly. *Development, 144*(6), 952-957. doi:10.1242/dev.140707