Stem Cells and Epilepsy:
Modelling the Brain with Organoids

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13. February 2024

Abstract

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1 Introduction

Epilepsy, a neurological disorder afflicting around 50 million individuals worldwide (World Health Organization, 2019), manifests through recurrent, unprovoked seizures, which can lead to symptoms such as convulsions (i.e. uncontrolled shaking), loss of consciousness, and unusual sensations or behaviours. The development of seizures in epilepsy is mainly due to a complex interaction between the excitatory and inhibitory activities of neurons in the brain. When there is an imbalance that leads to more excitation than inhibition, it can cause sudden and abnormal electrical activity in localised or entire regions of the brain (Robinson et al., 1997). The dysregulation seems to originate from GABAergic interneurons, whose pivotal role in maintaining neural circuit equilibrium is often compromised in epilepsy, illustrating a critical aspect of the disorder's neuropathology (CITE).

Temporal lobe epilepsy is the most common form (CITE), yet it is the drug-resistant epilepsies, especially those without an identifiable epileptogenic zone, that present the most significant treatment challenges (CITE?). Current interventions, such as neuromodulation, offer some hope, but their effectiveness is variable and can be marred by severe side effects, highlighting the urgent need for novel research directions.

The impact of epilepsy extends far beyond its physiological symptoms, affecting every facet of an individual's life. A large number of people who are diagnosed suffer from uncontrollable seizures, rendering them incapable of performing routine tasks, securing employment, or even driving—a prohibition enforced in many countries due to safety concerns (CITE). This pervasive uncertainty cultivates a lifestyle fraught with limitations, emphasising the disease's profound societal and personal toll.

To fully grasp the essence of epilepsy, one must consider not only its physical manifestations but also the profound psychological toll it exacts on sufferers. The unpredictability of seizures can instil a persistent fear and sense of helplessness, significantly affecting mental health. The origins of epilepsy are diverse, encompassing genetic predispositions (genotype) and observable characteristics (phenotype), including brain injuries and infections, underscoring the complexity of its etiology. The dichotomy between normal and epileptic brain function is starkly illustrated in EEG recordings, as exemplarily shown in **??**. These visual representations not only highlight the aberrant electrical activity characteristic of seizures but also underscore the critical need for a deeper understanding of the underlying mechanisms of epilepsy. Such insights are essential for paving the way toward more targeted and efficacious treatments, addressing the disease's genotype and phenotype.

1.1 Traditional Models for Epilepsy Research

TODO: Briefly mention the traditional models for epilepsy research, such as animal models and in silico models and their limitations.

Personal note: Animal models are not always a good representation of human brain activity (also introduce which animal models are usually used for epilepsy research and why they have a high translational value) and in silico models are not always accurate due to the complexity of the human brain, as a model is only as good as the data it is based on (criticism of in silico and large brain simulation needed, mention

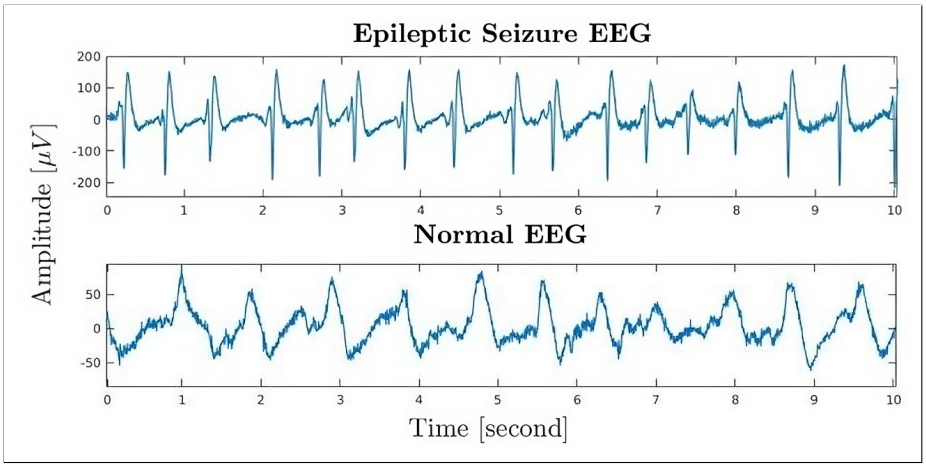

Figure 1.1: Comparative display of EEG waveforms showing brain electrical activity over a 10-second period. The top graph represents EEG data during an epileptic seizure, characterized by high amplitude and frequent spikes, indicative of abnormal neuronal activity. The bottom graph illustrates a normal EEG with regular wave patterns and lower amplitude, reflecting typical brain function. The x-axis measures time in seconds, and the y-axis measures the amplitude of brain waves in microvolts (μV). Image taken from Espinosa et al. (2020).
fig:seizure-eeg

Markram and Blue Brain Project and the energy-need for these simulations). there are ideas to e.g. run personalised virtual brains, but this is still hypothetical as e.g. the Human Brain Project has proposed (however, they failed and stopped working on this in 2023). This is why stem-cell-derived models are so important, as they provide a closer approximation of human neurodevelopmental processes in a controlled environment, which is unique and very valuable for epilepsy research. Not only do they provide a closer approximation of human neurodevelopmental processes, but they also enable detailed studies of epilepsy's pathophysiology, which is crucial for understanding the disease and finding new treatments (explain this in more detail). Mention that most likely we will always need a combination of different models to understand the human brain and its diseases, but that stem-cell-derived models are a very important part of this combination and a very new and promising field of research, not only for studying but also for treating epilepsy (referencing future chapter). it is also very hard to source post-mortem brain tissue for epilepsy research, as it is not always available and not always in a good condition, which is why stem-cell-derived models are so important for epilepsy research. also: explain why using post-mortem brain tissue rather than neuroimaging due to the fact that neuroimaging is not always accurate and can't with a high resolution show the pathophysiology.

1.2 Stem-Cell-Derived Models for the new Era

TODO: Introducing stem-cell-derived models (e.g., hiPSCs, brain organoids (also sometimes called spheroids), etc.) and their relevance in studying neurodevelopmental disor-

ders like epilepsy. Explain how stem cells are reprogrammed to model epilepsy in vitro and how this is a new and promising field of research. Mention how the research wasn't possible if we didn't have the technology to reprogram stem cells and how we used to rely on cells from embryonic tissue, which is not only unethical but also not as effective as using stem cells. This opened up a new field of research and made it possible to study epilepsy in a way that wasn't possible before. Explain how incubating works, and the process of creating neural stem cells from stem cells. How we use model version of healthy and epileptic brain tissue to study the differences and how we can use this to find new treatments for epilepsy as we can apply drugs to the tissue and see how it reacts. Not only this, but also interfacing with it via electrodes and other techniques.

1.3 Current State of the Art

TODO: Discussing the current state of research in this field, referencing Nieto-Estévez and Hsieh (2020) and Wang (2018) for recent advancements in modelling developmental epilepsies and neurological diseases using brain organoids.

Personal note: Mostly brain tissue is studied in a 2D environment, but with stem-cell-derived models, we can study brain tissue in a 3D environment, which is much closer to the real human brain and its activity, so-called brain organoids or cerebral organoids. This is a new and promising field of research, as it allows us to study the human brain in a way that wasn't possible before. We can grow or even 3D print brain tissue around electrodes, or on 3D electrode matrices in order to stimulate and measure the brain organoids. Other techniques include also genetically modifying brain organoids to fine-grain control neuronal firing via a method called optogenetics (just quickly explain it). Say that e.g. when growing brain organoids in a 3D structure (also explain how this works e.g. via a shaker) that they can develop epileptic activity, which is very interesting for epilepsy research. Also, mention that we can use brain organoids to study the development of GABAergic interneurons and how they are affected in epilepsy, as they are crucial for the balance between excitatory and inhibitory neurons in the brain.

2 Discussion

TODO: Short introduction to the discussion section.

2.1 Stem-Cell-Derived Models for Epilepsy

TODO: - Discussing reprogramming stem cells to model epilepsy in vitro, using Parent and Anderson (2015) and Tidball and Parent (2015) as references. - Highlighting recent findings in the field, such as Thodeson, Brulet, and Hsieh's (2017) work on neural stem cells and epilepsy and how these models have enhanced our understanding of epilepsy. - Evaluating the effectiveness and limitations of using stem-cell-derived models, possibly drawing on the comparative analysis provided by Kandemir et al. (2022) between different epilepsy models.

2.2 Case Studies and Practical Applications

TODO: - Presenting specific case studies from the references, like the work by Samarasinghe et al. (2021) on identifying neural oscillations in brain organoids and their implications for understanding epilepsy. - KEY PART OF THE ESSAY: Discussing practical applications of these models in understanding and treating epilepsy, referencing Steinberg et al. (2020) and their modelling of genetic epileptic encephalopathies.

Personal note: Main key takeaway from this section is that studying neural tissue in as-close-to-the-real-thing as possible is key. There are more and more methods to really try to get the tissue structure right in order to be able to study the brain in a very controlled environment without ethical issues or lots of efforts compared to finding in vivo tissue. Not only will this research benefit studying it by modelling it, but also by studying it directly via applying medication onto brain organoids and seeing how they react. Other approaches might be creating individualised brain organoids from patients with epilepsy (also called patient-derived induced pluripotent stem cells) and studying their brain tissue in order to find individualised treatments for epilepsy with their specific case. Also, going beyond just studying, one can go one further and then start to treat epilepsy with brain organoids, e.g. by implanting them into the brain of a patient with epilepsy in order to produce GABAergic interneurons in the parts of the brain where they are needed – generally just genetically modifying the implants for the specific patient's disease (referencing upcoming chapter).

2.3 Other Approaches and Advancements

TODO: - Exploring the transplantation of hiPSCs/brain organoids into living beings, referencing Hunt and Baraban (2015) for their work on interneuron transplantation and others. Also mention the work of NRTX-1001 and how they implanted stem cells into the brain of a patient with epilepsy in order to produce GABAergic interneurons in the parts of the brain where they are needed. - Discuss the role and potential of neuroprosthetics in epilepsy treatment and research, drawing on insights from current studies or reviews. - Discuss how multiple brain organoids can be fused into an assembloid to study e.g. neuronal migration from e.g. GABAergic and glutamatergic neurons and how this can be used to study epilepsy and other neurological diseases.

Personal note: Generally the field of neuroprosthetics with synthetic biological neural tissue is quite interesting and also a personal interest of the author. Not only does it go into the field of personalised treatment (also sometimes called precision medicine) and medicine but also into the field of synthetic biology and bioengineering. Cite text from "Augmenting Cognition" book from Markram, where Mijail Demian Serruya writes: "3.9 Expanding the neural substrate Instead of using pairs of recording and stimulating arrays to reconnect one cortical area to another within a patient's brain, one could consider routing the signals through an artificial model of the cortex. If this were possible, one could provide patients with additional neural substrate.Just as regions of the brain may be become unusable due to stroke, injury or degenerative conditions, so too there might be the possibility to add new virtual or ectopic cortex to compensate for lost tissue. Recordings of units throughout the brain could be fed into a software model, or into actual ectopic neural tissue, and then activity from this

model or neural tissue could be used to trigger stimulation back into the patient's brain (Fig. 3.3c). Initially, such additional cortex could exist as computational models in software programs bidirectionally linked to a patient through wireless connections. Eventually, software models could be rendered in hardware as an encapsulated silicon chip, e.g., neuromorphic very-large-scale-integrated (VLSI) microchips, that in turn could be implanted in the body."

2.4 Ethical Considerations

TODO: - Discussing ethical issues surrounding stem cell research and brain organoid models, citing Farahany et al. (2018) for a comprehensive view of the ethics of experimenting with human brain tissue. - Address specific ethical questions, such as the consciousness of brain organoids and the moral implications of in vitro experimentation.

Personal note: Generally focus on the aspect of scaling brain organoids. Currently limited by the blood supply (still, ongoing research and most likely being solved in the coming years) and the issues that we don't know how to accurately model the tissue structure of an actual human brain, which is most likely necessary to create a consciousness human brain. However, as mentioned before, both of these issues are being worked on as their promises are huge. Therefore the issue of creating sentient/conscious brain organoids in the labs is a topic of ongoing debate and research. Also mention the company FinalSpark in Switzerland, that e.g. uses brain organoids for running AI algorithms and how this is a very promising field of research and how it is important to keep an eye on the ethical implications of this research, as we don't want to create sentient beings in the lab without knowing it and as slaves for AI algorithms (e.g. creating a sentient being that is constantly in pain and suffering, as it is used for running a specific AI algorithm).

3 Conclusion

TODO: - Summarising the key points, emphasising the impact of stem-cell-derived models compared to other models, especially e.g. in silico or animal testing. - Discussing future prospects of stem-cell-derived models in neuroscience, considering technological advancements and potential breakthroughs. - Addressing remaining challenges, including technical, ethical, and funding-related issues, to give a balanced view of the field's future.

Personal note: Basically conclude and have a key focus on that this field needs to get more funding, as brain organoids coupled with personalised medicine (also sometimes called precision medicine) and gene-editing is a very promising field of research and has the potential to cure epilepsy and other neurological diseases. Also, mention somehow neuroprosthetics again the the whole point from Mijail Demian Serruya's part of the "Augmenting Cognition" book from Markram.

References

Espinosa, N., Amorim, A., & Huebner, R. (2020). *Feedforward Neural Network with Backpropagation for Epilepsy Seizure Detection*.

Robinson, P., Rennie, C., & Wright, J. (1997). Propagation and stability of waves of electrical activity in the cerebral cortex. *Phys. Rev. E*, *56*.

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