Computationally Modeling Spreading Depolarizations' Impact on Intrinsic Patterns of Brain Activity

Sex and Racial Discrepancies on Prognosis of Subarachnoid Hemorrhages and Traumatic Brain Injury

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On my honor as a University student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments.

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Introduction

Spreading Depolarizations (SDs) are propagating waves of depolarization that travel across the brain at roughly 2-5 mm/min. SDs typically occur as part of the pathophysiology of several neurological diseases and injuries such as migraines, subarachnoid hemorrhages (SAH), and acute traumatic brain injuries (TBI) (Leao, 1947; Taş et al., 2019). These propagating waves trigger a silencing of neuronal input due to the over exhaustion of Ca^{+2}, Cl^{-}, and Na^{+} usage. This disruption of ionic homeostasis directly contributes to the increase in metabolic rate without sufficient blood flow to meet this demand, which leads to cerebral ischemia (Piilgaard & Lauritzen, 2009).

The project revolves around the relationship between cerebral ischemia and SDs. This relationship will be computationally modeled using data from electrocorticography (ECoG) that record the location of SDs and the severity of ischemic risk, respectively. ECoG is an invasive monitoring method that involves a craniotomy or burr holes in the skull of the patient. Thus, this model will be trained on data from the University of Virginia (UVA) Intensive Care Unit (ICU). The purpose of this project is to enable an novel way to study and interpret SDs and their impact on cerebral ischemia and subsequently neuronal dysfunction.

SDs can easily go unnoticed when the patient doesn't present severe symptoms from their brain injury. These patients can be told that they have a severe headache or a minor concussion with no further tests conducted, allowing for possible cerebral ischemia or undocumented negative long term effects such as neuronal dysfunction. There is a large disparity between both identification and prognosis of migraines, SAH, and TBI across race and sex (Rossi et al., 2022; Schupper et al., 2023). This is due to a lack of research into the presentation of symptoms in these groups as well as the systemic bias that continue to be ingrained into the education system (Cota et al., 2019). Even when these groups are diagnosed, there is often continuous misdiagnosis or delay in proper diagnosis as well as poorer prognosis (Han et al., 2024; Kowalski et al., 2004).

As the computational model is trained on human data, there is room for bias in the model. There is limited confidence that every patient that ever experienced SD waves was monitored due to the invasiveness of ECoG. Additionally, the demographics of the data used can not be fully representative of the world population as Charlottesville, Virginia is uniquely diverse both due to the local college population, as well as the specialty medicine in which UVA Health specializes, that unproportionately draws in advanced cases of care. With this, there must be special consideration of these factors to ensure that this project does not further exacerbate the bias and disparity in race and sex.

Computational Model of Ischemic Processes During Spreading Depolarizations

There is a gap in research regarding SDs and ischemia. Many studies discuss the ischemic brain damage that occurs because of SDs, but not much discussion is done on the precursor events of ischemia. It is known that cerebral ischemia can be predicted using alpha-delta ratios (ADR) and cross-frequency coupling (CFC) (Finnigan et al., 2016; Rosenthal et al., 2018). Despite this knowledge, there has been lacking effort to determine the effect SDs have on these factors. It is not unlikely that SDs modulate these factors and can escalate the ischemic risk of a patient. Due to this, further research needs to be done to understand if these factors can continue to be used as predictive markers of ischemia, even in SD patients. Additionally, it must be found if there is a unique relationship between ischemia, ADR, and CFC when SDs are present.

This project targets this issue by developing a computational model to depict the relationship between SDs, ADR, CFC, and subsequently ischemia. To do this, ECoG data from the UVA ICU will be deidentified and processed, where most of this data comes from patients with SAH. SDs will be identified by locating a negative DC shift in electrical activity at one electrode while there is a depression or shift of DC activity at one neighboring electrodes, evidence of a propagating wave. Once the SD is identified, the data will be filtered using a high-pass filter (0.01 Hz), a bandpass filter

(0.5 Hz – 100 Hz), and a notch or bandstop filter (60 Hz). The high-pass and notch filter will remove low frequency and high frequency noise, respectively, to help identify the negative DC shift. The bandpass filter will be used to verify the period of brain activity suppression.

Using bandpass filtered EEG data, the ADR and CFC will be determined. Ensuring that the data time-segments are the same time segments sampled from the ECoG data, the following will be calculated. A specific type of CFC called phase-amplitude coupling (PAC) will be used as it is highly implicated in ischemia, more so than other forms of CFC. PAC will be determined by calculating the composite signal and surrogate composite signal from the amplitude of the high frequency wave and the phase of the low frequency wave. The PAC will be calculated by subtracting the mean of the original composite signal from the surrogate composite signal and dividing by the standard deviation of the surrogate composite signal. ADR will be found by applying a fast Fourier Transform (FFT) to the data. The absolute power will be found from the power spectra and the alpha (7.81 Hz and 12.21 Hz) waves and the delta (0.98 Hz and 3.91 Hz) waves will be identified. ADR will be calculated by dividing the absolute power of the alpha waves by the absolute power of the delta waves.

These data will be time-linked, allowing for analysis of change over time to occur. A regression model will be made to define the relationship between SDs and CFC and ADR. To determine if the model is accurate, the fit of the data will be analyzed and the output (CFC, ADR after SD propagation) will be compared with literature values. Additionally, new deidentified data can be fed to the model to ensure the model is accurate.

Sex and Racial Discrepancies in Prognosis of Subarachnoid Hemorrhages

The aim of the computational model is to allow easier identification of SDs as well as expand the knowledge base surrounding cerebral ischemia. Consideration of the bias that may arise from this model needs to be acknowledged. As the computational model is trained on data from the UVA ICU,

there is a high likelihood of bias towards the extreme cases as well as the local demographic. The purpose of the sociotechnical research is to acknowledge and propose amends to the bias created by this model.

There are a fair number of papers that discuss these discrepancies specifically in SAH patients. These studies, however, do not discuss cerebral ischemia nor SDs. Delayed cerebral ischemia (DCI) is prominently in the anterior circulation than the posterior for both sexes. However, within the anterior circulation, there are differences in frequency of onset in specific locations. For women, DCI occurs in the middle cerebral artery 58% of the time, whereas for men it occurs 40% of the time (Han et al., 2024). It has also been found that DCI in this area typically occurs in infarction and worse prognosis overall (Wong et al., 2015). Women have a higher mortality rate following aortic aneurysm rupture. Previously, it was believed that men had both higher incidence rate and prevalence to DCI, but recent studies are beginning to contradict this idea (Schupper et al., 2023). In a retrospective study focusing on patients undergoing treatment for unruptured aneurysms between the years 2001 and 2009, it was found that women, White, and insured patients had a higher likelihood of being treated. Black, Hispanic, and Asian patients were more likely to experience a SAH (Brinjikji et al., 2012). However, other studies suggest that there are no racial differences in outcome of SAH (Eden et al., 2007; Rosen et al., 2005).

Due to the many contradictions in the field, it is important to acknowledge and attempt to reconcile these differences. Most of the racial differences are of outcomes, not of DCI onset. This suggests that the issue are due to systemic racism and class differences. Most of the sex differences are of location and intensity of DCI. Overall, there is lacking research that can corroborate the discrepancies seen across studies.

To this end, focus will be on SAH and TBI patients that experience SDs. Demographic data will be analyzed such as race, sex, median income for the zip code, number of days in the hospital,

hospital bill, severity, discharge status (home, secondary care) and readmittance. Comparison of these factors will reveal if there are any existing differences between race and sex and outcome. To properly define prognosis, severity of the disease, number of days in the hospital, and readmittance will be considered. 'Bad' prognosis will be defined as high severity and >14 days in the ICU, or discharged to secondary care or >0 times readmitted for recurring condition. Neutral prognosis will be defined as high to low severity, 4-13 days in the ICU, discharged home, and 0 times readmitted. Good prognosis will be defined as medium to low severity, 0-3 days in the ICU, discharged home, and 0 times readmitted. Analysis of these factors will be done using $\chi 2$ for qualitative analysis and a t-test or ANOVA for quantitative analysis. Analysis of risk ratios, independent effect of race and sex on patient incomes, and multiple testing corrections will be adapted from Schupper *et al.*

Conclusion

The common theme of this paper is lack of research and investigation. To better understand and expand the knowledge base on how SDs affect the human brain, especially its impact on ischemia, a computational model will be made. Investigation of discrepancies in prognosis for the different sexes and races will be done through analyzing the retrospective data set used to create the computational model. This will reveal any patterns of bias and allow for changes to be made to ensure the model is as unbiased and as accurate as possible. If this model can be fully representative of the general population or account for factors that cause the discrepancies in prognosis that we see, then perhaps this model can begin to standardize diagnosis, treatment, and improve prognosis for everyone.

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