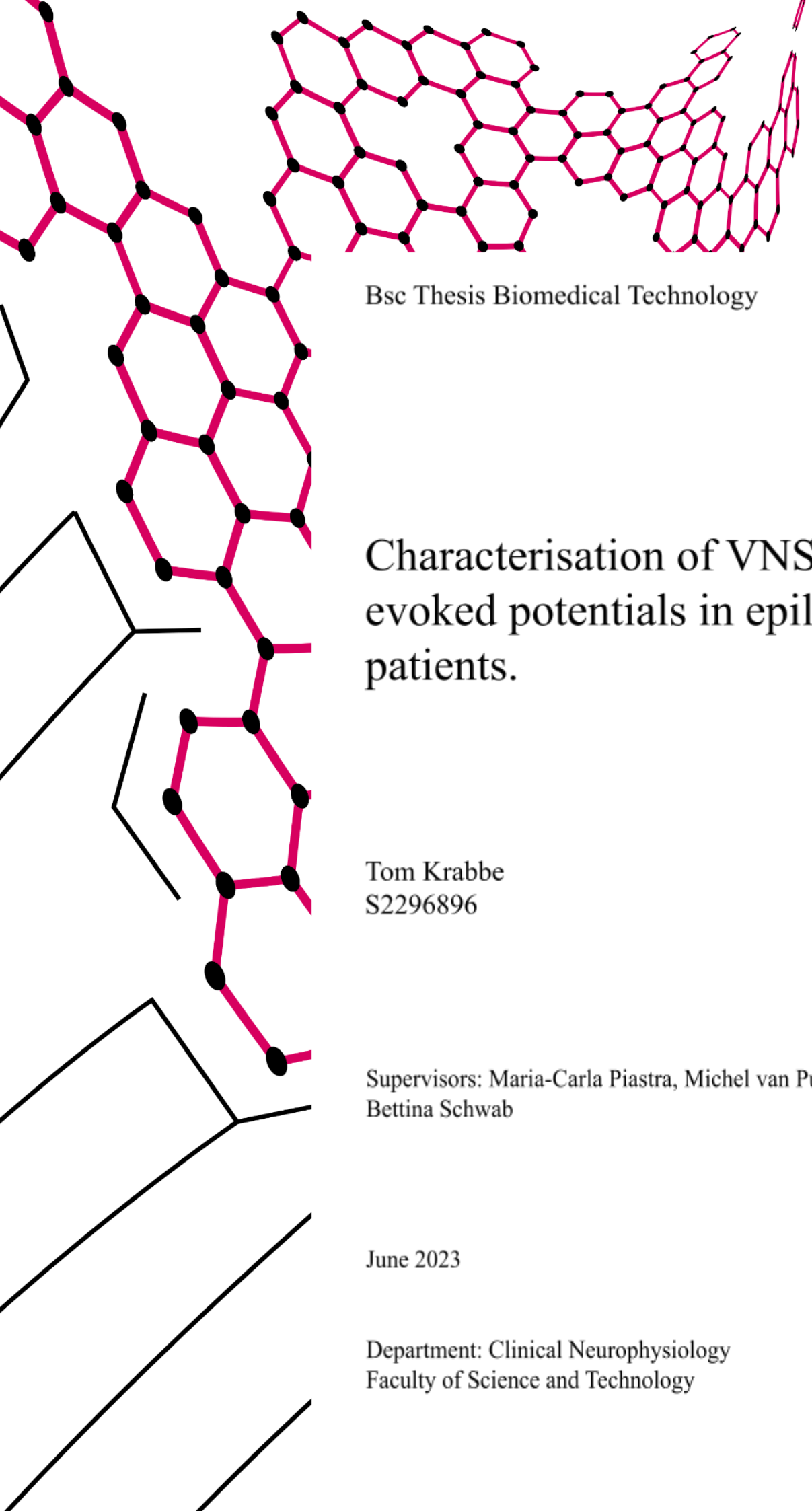

Bsc Thesis Biomedical Technology

Characterisation of VNS-induced evoked potentials in epilepsy patients.

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Abstract

Background: For drug resistant epilepsy, alternative treatments are necessary. Vagus Nerve Stimulation (VNS) is one such safe, palliative treatment, however, a lack of understanding in both its inner workings and regarding the optimal stimulation parameters lead the treatment to being prolonged and often ineffective. EEG can help in this analysis.
Objective: The goal is to analyse evoked potentials induced by VNS to build upon previous research and further characterise the short latency components common in VNS.
Method: 30 minute VNS EEG-data from 5 patients was segmented into 30 ms trials, after which evoked potentials were plotted and characterised according to VNS input parameters. Topographical plots were also made, which depicted the electrical potential in the scalp directly after VNS.
Results: A 10 ms peak was visible in all patients, with a new 5 ms peak appearing in 2 patients, which also seemed to affect spatial reactions in the topographical plots. Input parameters did not seem to have a significant effect on peak-amplitude across these patients.
Conclusions: This study provides valuable insights into VNS-induced evoked potentials in epilepsy patients, uncovering an unexpected peak at approximately 5 ms in specific datasets. Further research is needed to explore these findings, refine analysis methods, and enhance understanding of the impact of VNS on brain dynamics.

Keywords: Epilepsy, Vagus nerve stimulation, Evoked potential

1. Introduction

Epilepsy affects an estimated 50 million people worldwide [1], with approximately one-third of patients not responding adequately to anti-seizure drug therapy [2], which makes the need for alternative approaches necessary to improve the quality of life for these individuals. Epilepsy, characterised by abnormal bursts of electrical activity in the brain, poses substantial challenges for those affected [1]. Consequently, the exploration of alternative treatments becomes crucial.

Vagus Nerve Stimulation (VNS) is one such treatment that involves the placement of an electrode that delivers electrical pulses through the Vagus Nerve to the brain, thereby reducing seizures [3]. The electrode is placed around the vagus nerve and connected to a subcutaneously implanted impulse generator in the upper chest. Notably, VNS is particularly effective in certain types of epilepsy, primarily focal seizures, which have a prevalence of 36% [3,4]. However, there remains a lack of understanding regarding the optimal stimulation parameters for VNS therapy in epilepsy patients, leading to extended periods of parameter titration (4-8 months) to achieve optimal therapy efficacy [5,6].

Parameter titration in VNS has been extensively explored for various neurological disorders [7], however, the lack of a complete understanding of how VNS works has left us searching for the ideal stimulation parameters tailored to each epilepsy patient. Unfortunately, this knowledge gap means that patients often have to endure a long period of trial and error before discovering the optimal settings for effective therapy [5,8]. These settings include pulse-width (ranging from 130 to 500 μs), frequency (20-50 Hz), on/off time ratios (7-120 s on/18 s-60 min off), treatment duration (30 s - 24 months), and current intensity (0.25-3.75 mA) [5]. The wide range of parameters highlights the unique needs of each patient when it comes to reducing seizures. While conservative parameter titration is the norm in current clinical practices, there's growing interest in exploring faster and more aggressive titration approaches, especially for younger individuals (21 years and below) [9].

Evoked potentials (EPs) are an established tool in neuroscience research, enabling the investigation of neural activity and cognitive processes with high temporal resolution [10]. Evoked potentials refer to the electrical responses generated in the brain in response to specific sensory, cognitive, or motor stimuli. Over the years, researchers have made significant progress exploring diverse applications of EPs, such as the application as reliable biomarkers for neurological diseases such as Parkinson’s disease, Alzheimer’s disease and multiple sclerosis [10]. The raw data recorded during an EP experiment is usually obtained through electroencephalography (EEG), subsequently pre-processed and segmented into trials, after which the EPs can be analysed.

One way in which VNS parameter titration can be examined is through these evoked potentials. EPs can be caused directly by electrical stimuli, such as VNS. Different parameters for VNS will give different EPs as a result [11]. A study by Usami et al [11] studied VNS-induced evoked potentials and concluded that studying these EPs may document the cause of treatment failure in some patients. The findings in this paper paved the groundwork for this research and their results will be compared to our results. Usami et al. [11] recognised a few common structures within their research results. For one, they noticed that small currents of 0.25 mA did not yield any evoked potentials. As the current increased, up to 1.0 mA, two biphasic peaks became visible. One very small peak following 3 ms after the large stimulation artefact, and a large peak at 10 ms. With the peaks named

P1 and P2 and the troughs named N1 and N2 respectively. Identifying whether our datasets have similar structures or significant differences will be valuable for future research.

In this study, we aim to investigate VNS-induced evoked potentials in epileptic patients in a way that expands on the research done by Usami et al. [11], further characterising EPs and possibly finding causal relations between input parameters and EP results. First, we evaluate the shapes and distinct features of EPs in different datasets recorded through EEG. Then we compare the input parameters (Current, Frequency and Pulse-width) with EP peak times and amplitudes, which could reveal trends in the data. Last, a topographic plot is made to show the polarity in the brain at key time steps.

2. Materials and methods

In this section, we describe how to characterise VNS-induced evoked potentials. The main steps are schematically visualised in Figure 1.

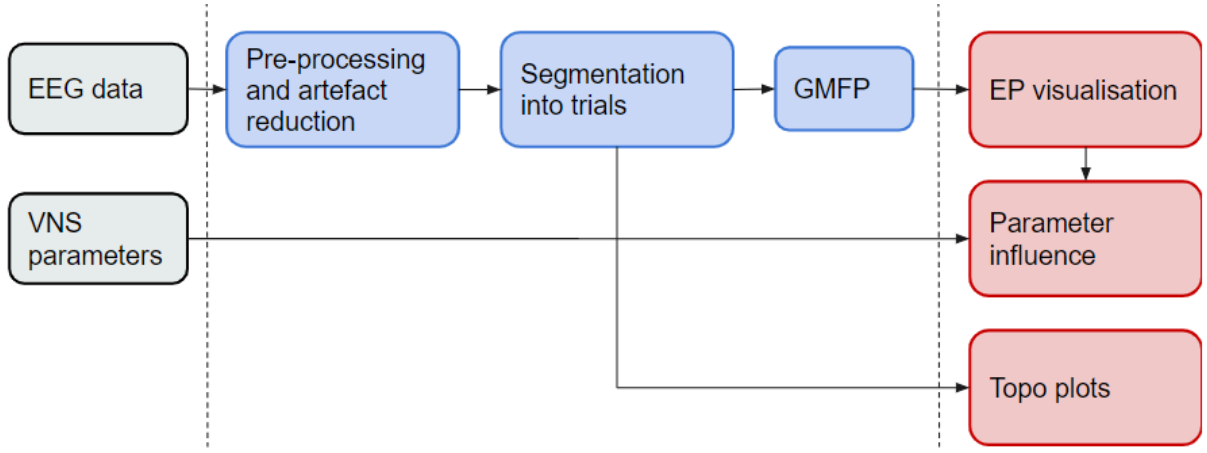

Figure 1: A schematic view of the method used during this research. Grey is the input, which encompasses the obtained EEG data and its VNS input parameters. Blue is the signal processing, which encompasses pre-processing, segmentation and Global Mean Field Power computations. Red is the output, which encompasses the evoked potential visualisation, the parameter influence graphs and the topographical plots.

Dataset acquisition and selection

Data from the PREDYct study, conducted by SEIN (Stichting Epilepsie Instellingen Nederland) and MST (Medisch Spectrum Twente), included the analysis of five (5) distinct subjects, demographics can be seen in Table 1. The EEG-data, in the form of .edf files, pertained to epilepsy patients who underwent an evaluation of the long-term effects of VNS and epilepsy. Before VNS device implantation, these patients were equipped with a single subcutaneous electrode positioned above the ear for two months. Subsequently, the patients continued to undergo EEG monitoring through this electrode for an additional 13 months post-implantation. During the initial and final visits, the patients were also fitted with a 64-electrode EEG cap. These supplementary EEG recordings spanning 30 minutes, were obtained at a sampling frequency of 4000 Hz. The primary objective of these datasets was to comprehensively assess the effects of VNS across the entire scalp in epilepsy patients. These datasets were used for the analyses in this paper. It should be noted that device parameters varied among subjects, and the corresponding input parameters for each subject are presented in Table 2 within the results section, indicated in grey.

Table 1: Patient demographics of the 5 patients. Included is subject ID, sex, age, type of seizure, etiology classification [12] and duration since start of epilepsy.

Subject ID	Sex	Age (y)	Type of seizure	Etiology	Duration (y)
1	F	20	Generalised and focal	Genetic	4
2	F	20	Generalised	Genetic	4
3	M	40	Generalised and focal	Unknown	17
4	M	50	Generalised and focal	Genetic	38
5	F	27	Generalised and focal	Infectious	3

Signal Processing

First, the data was loaded into MATLAB, re-labeled for ease of use and pre-processed through the FieldTrip [13] function ‘ft_preprocessing’. Important to note that for the reference an average was used, instead of Cz. We used the signal in channel M2 to identify the VNS artefacts, since this channel is close to the Vagus Nerve and the peaks it produces are large spikes in the EEG signal. For the rest of this paper, these individual VNS-induced peaks will be named VNS-peaks.

Subsequently, artefact rejection was applied using the FieldTrip function ‘ft_rejectvisual’. This made it possible to select specific channels to exclude. Channels that were excluded differed per dataset but were selected based on variance which made them unfit for further analysis.

For datasets 1 and 3, additional artefact reduction was required. Dataset 1 had a particularly noisy section in the data which made it more difficult for analysis. Dataset 3 had a lot of peaks that weren’t coming from VNS because they were outside VNS on-times, but which were of high enough amplitude to be just as large as the VNS-peaks, which is problematic for a future step. For both datasets, the problematic sections of data were identified and subsequently removed by changing the signal to 0, as seen in Figure 2. No additional filtering was performed on the signal.

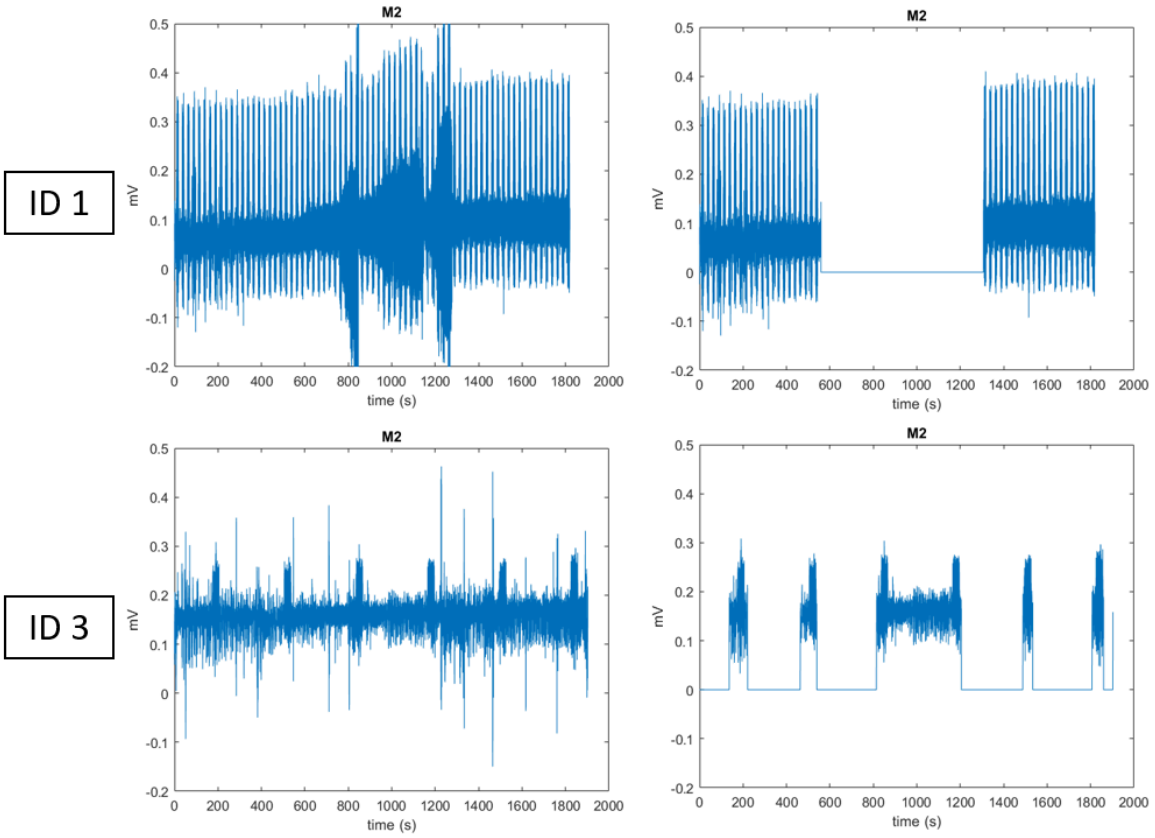

Figure 2: On the left is the EEG signal from channel M2 with large artefacts, on the right, they are removed by setting their value to 0.

Using the signal from M2, we segment the signal into trials. Since the VNS-peaks were of higher amplitude than the baseline EEG brain signal, a MATLAB function called 'findpeaks' was used to identify peak locations. Setting a minimum peak amplitude was crucial for defining the trials. This value varied per dataset ranging from 0.000 - 0.036 mV and had to be manually entered. We fixed the trails to be 7 ms before a VNS-peak and ending 30 ms after a VNS-peak for all datasets for ease of viewing. Baseline correction can then be applied and the evoked potential directly after stimulation becomes visible, while the segment cuts off before the next VNS-peak.

Then, the trials were used in a process called timelock analysis. This is a process where the trials were defined as having the large VNS-peaks at t = 0ms and baseline correction is applied from -6 ms to -2 ms in every trial. The FieldTrip function 'ft_timelockanalysis' can subsequently be used to show all trials on top of each other in a graph. For each channel, all trials were averaged.

Lastly, a global mean field power (GMFP) calculation represents the overall amplitude of the brain activity across time. The GMFP was calculated using a method introduced by Esser et al. [14]. This is the formula used to calculate the global mean field power by squaring and averaging the activity across all channels:

$$GMFP(t) = \sqrt{\frac{\sum_i^k (V_i(t) - V_{mean}(t))^2}{K}}$$

where t is time in seconds, V_i is the voltage at channel i, V_{mean} is the mean of the voltages in all channels and K is the number of channels.

Output

The GMFP was plotted to visualise the EP directly after VNS-peaks. As mentioned in the introduction, two peaks should become visible: one at 3 ms and one at 10 ms. These peaks are biphasic, meaning they have positive (P1 and P2) and negative peaks (N1 and N2). Due to the way GMFP is calculated, the negative peaks will be positive as well, however, they should still be identifiable. Subsequent characterisation is done through the following steps:

- At what times do EP-peaks show up?
- What is the amplitude of the EP-peaks?
- Are there any other things of note?

The EP-peak times and amplitudes across all datasets are plotted according to VNS input parameters to analyse parameter influence. We will look at the influence of input-current, frequency and pulse-width on EP-peak amplitude. This is done by taking the input current multiplied by pulse-width and input current times pulse width divided by frequency. A linear regression model fit is then made using the MATLAB function ‘fitlm’, which also gives the p-values of the graphs. Finding the p-values allows us to determine whether there are any trends in the data that are of significance.

Topographical plots were also made for t = 0ms, t = 5ms, t = 10ms and t = 15ms (all ±2ms), to show the response in the brain spatially. This is a type of plot where the amplitudes of the EEG-channels are plotted on a model of the EEG-cap layout, from which the positive electrical polarity in the brain can be inferred. We used the FieldTrip function ‘ft_topoplotER’ to plot the topography of brain activity which takes the EEG-cap layout and all channels as input and plots their respective amplitudes at specific times.

3. Results

Evoked potential visualisation

The evoked response of subject ID 1, as seen in Figure 3, shows two clear peaks in the GMFP. These peaks are at 5.00 and 9.50 ms, with respective amplitudes of 3.20 and 2.47 µV. P1 and N1 can not be identified in Figure 3, however, we suspect that the peak at 9.50 ms lines up with P2. This evoked potential is peculiar, as it has a peak at 5.00 ms that most other subjects do not have.

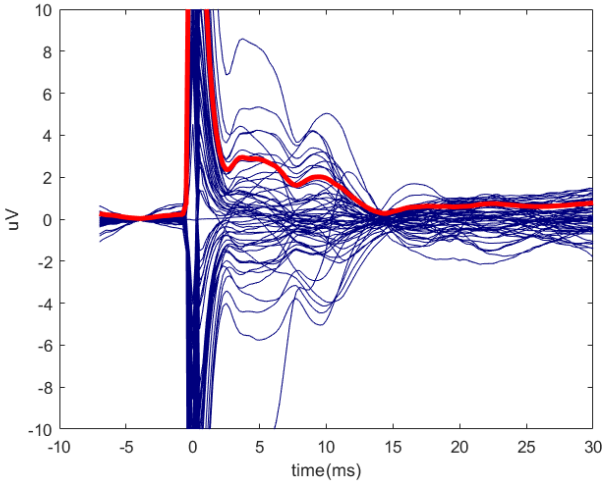

Figure 3: The VNS-induced evoked potential response in subject ID 1 from -7 to 30 ms. The blue lines represent the averaged trials from all included EEG channels, while the red line is the GMFP. Only the red line is considered for analysis. The large peak at 0 ms is the VNS-peak, which was used for timelock analysis.

The evoked response of subject ID 2, as seen in Figure 4, shows one clear peak and one smaller peak in the GMFP. These peaks are at 9.75 and 14.25 ms, with respective amplitudes of 2.18 and 0.73 µV. We surmise these peaks to be P2 and N2. This EP looks similar to those of subject ID 3 and ID 4.

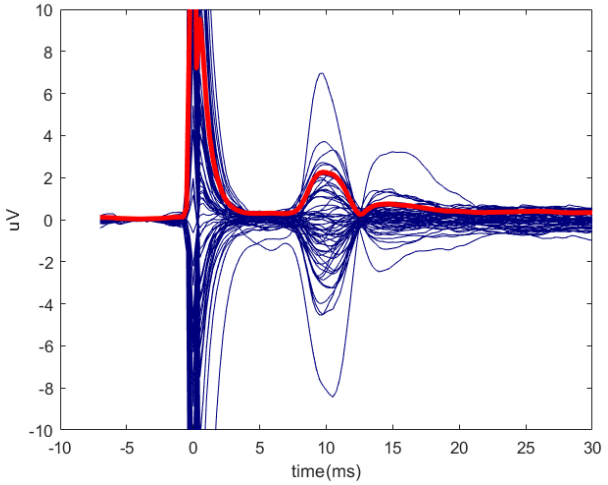

Figure 4: The VNS-induced evoked potential response in subject ID 2 from -7 to 30 ms. The blue lines represent the averaged trials from all included EEG channels, while the red line is the GMFP. Only the red line is considered for analysis. The large peak at 0 ms is the VNS-peak, which was used for timelock analysis.

The evoked response of subject ID 3, as seen in Figure 5, shows one relatively clear peak and one more challenging to discern. These peaks are at 10.00 and 13.75 ms, with respective amplitudes of 1.32 and 0.80 µV. We speculate these peaks line up with P2 and N2. Given the higher amount of noise, it's more difficult to accurately determine the peaks.

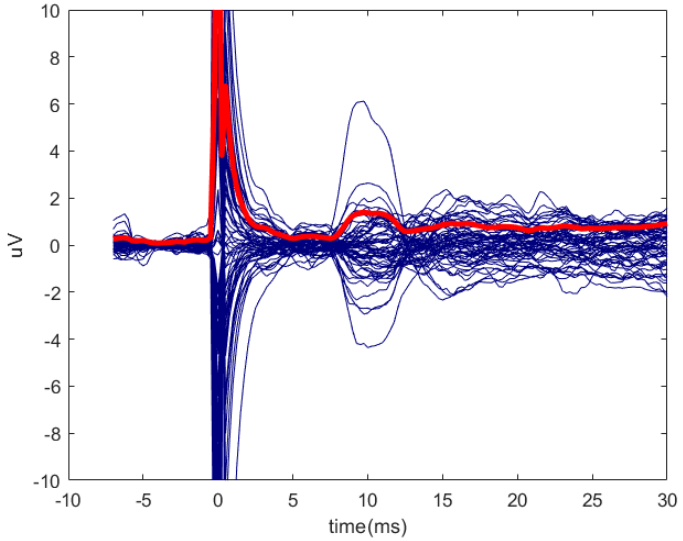

Figure 5: The VNS-induced evoked potential response in subject ID 3 from -7 to 30 ms. The blue lines represent the averaged trials from all included EEG channels, while the red line is the GMFP. Only the red line is considered for analysis. The large peak at 0 ms is the VNS-peak, which was used for timelock analysis.

The evoked response of subject ID 3, as seen in Figure 6, shows two clear peaks. These peaks are at 11.00 and 15.00 ms, with respective amplitudes of 2.60 and 1.72 µV. They seem to line up with P2 and N2, though P1 and N1 are also not visible in this EP.

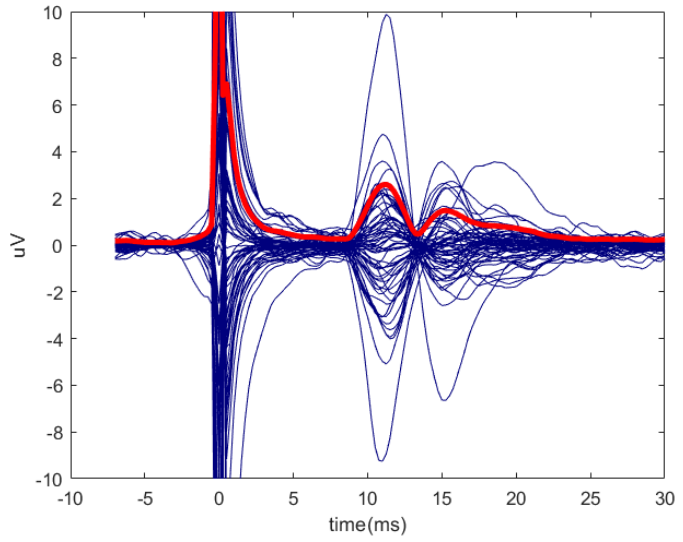

Figure 6: The VNS-induced evoked potential response in subject ID 4 from -7 to 30 ms. The blue lines represent the averaged trials from all included EEG channels, while the red line is the GMFP. Only the red line is considered for analysis. The large peak at 0 ms is the VNS-peak, which was used for timelock analysis.

The evoked response of subject ID 5, as seen in Figure 7, shows three peaks in total: 5.50, 8.75 and 15.50 ms, with respective amplitudes of 3.83, 2.34 and 1.35 µV. Much like subject ID 1, this EP shows a large peak at around 5 ms. Furthermore, we suspect the second and third peaks line up with P2 and N2, though there's a notable time gap between P2 and N2. This time gap is larger than in the other subjects: 6.75 ms compared to 4.13±0.33 ms.

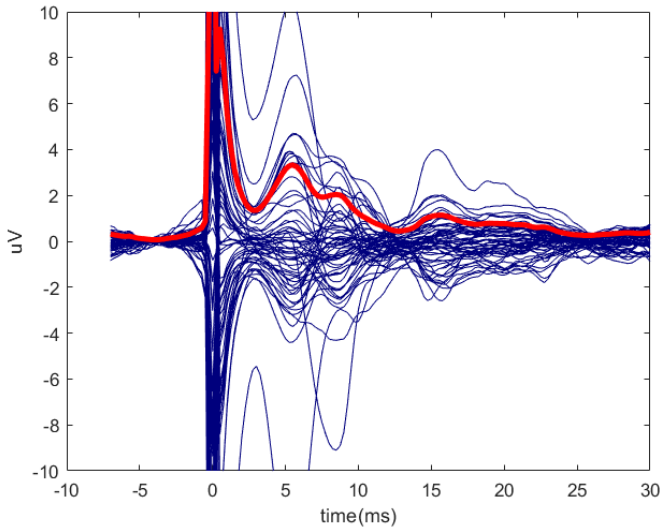

Figure 7: The VNS-induced evoked potential response in subject ID 5 from -7 to 30 ms. The blue lines represent the averaged trials from all included EEG channels, while the red line is the GMFP. Only the red line is considered for analysis. The large peak at 0 ms is the VNS-peak, which was used for timelock analysis.

The first thing to notice among all datasets is that they have a peak, identified as P2, around 10.00±1.25 ms with an amplitude of 1.96±0.0.64 µV and all but one datasets (ID 1) have a smaller peak, identified as N2 at 14.63±0.83 ms with an amplitude of 1.22±0.49 µV. Two of the datasets (ID 1 and ID 5) have an additional large peak at 5.25±0.25 ms, of which the amplitude is 3.51±0.31 µV. This data can be viewed in Table 2. Important to note is that P1 and N1 could not be recognised in any of the datasets.

Parameter influence

We examined the influence of the input current x pulse width to the peak amplitude, see figure 8. From Figure 8, we can see there's trends in the data, however these are not significant. In Figure 9, input current x pulse width / frequency was examined with respect to peak amplitude. Much like in Figure 8, these trends do not seem to be significant. Further quantifiable data has been put in Table 2 and graphs of these direct input parameters compared to output variables are shown in Appendix A. From these figures, it becomes clear that any trend lines made with the first degree fit are not significant, as all p-values exceed 0.05.

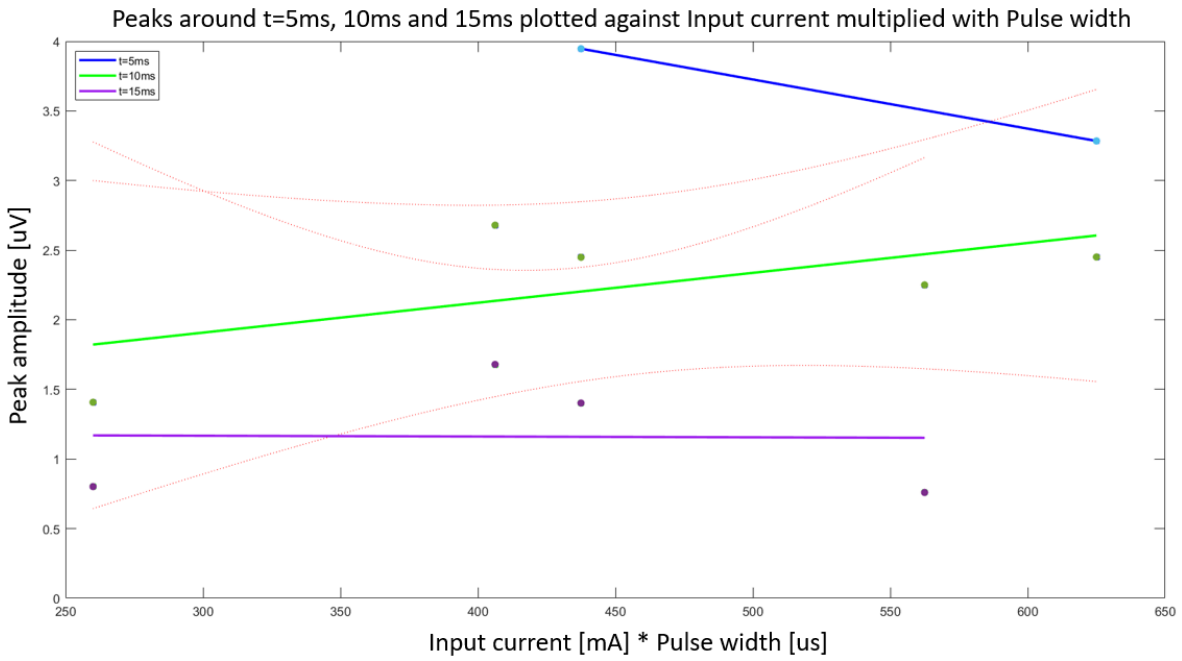

Figure 8: A graph of the evoked potential peak points corresponding to all datasets at times 5, 10 and 15 ms when compared to input current times pulse width. Blue points, which are at the top, show the peak amplitude at 5 ms. Green points, in the middle, show the peak amplitudes at 10 ms and purple points show the peak amplitudes at 15 ms. Corresponding lines have been plotted as well, which show a first-degree fit. Alongside the coloured lines, red dotted lines show the 95% confidence bounds. 5 ms (Blue) slope: -3,5*10^-3, pVal = NaN. 10 ms (Green) slope: 2.1*10^-3, pVal = 0.27. 15 ms (Purple) slope: 0.00, pVal = 0.98.

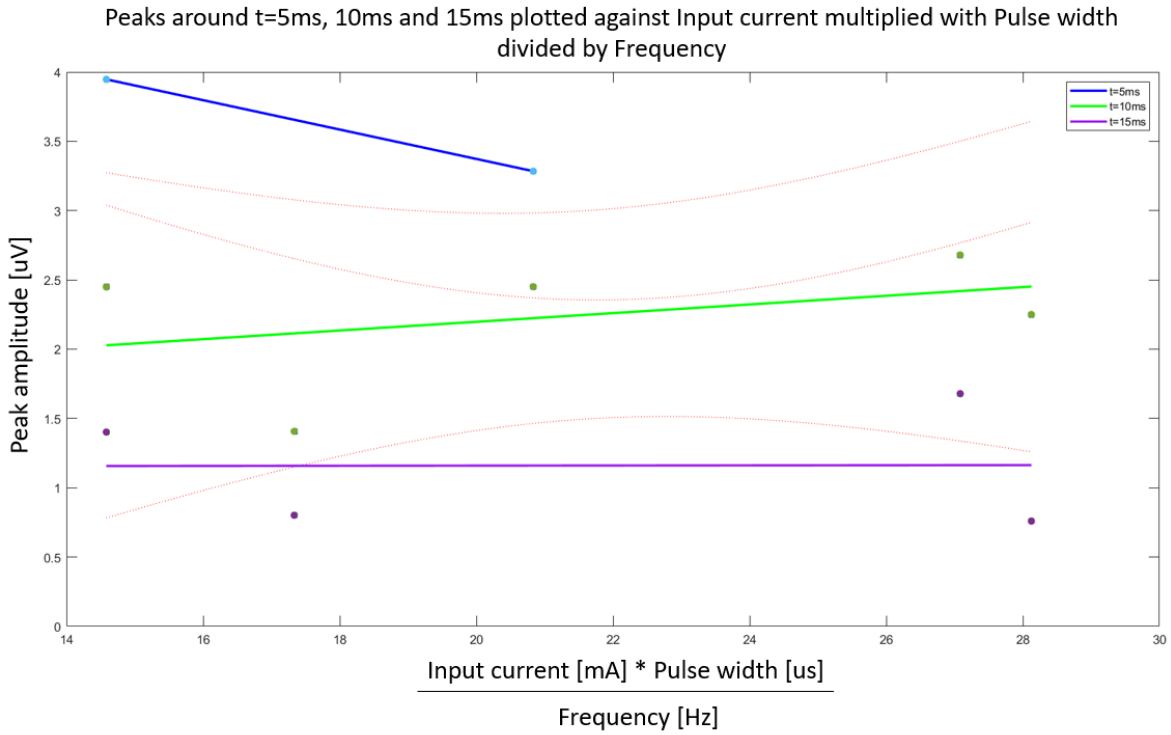

Figure 9: A graph of the evoked potential peak points corresponding to all datasets at times 5, 10 and 15 ms when compared to input current times pulse width divided by frequency. Blue points, which are at the top, show the peak amplitude at 5 ms. Green points, in the middle, show the peak amplitudes at 10 ms and purple points show the peak amplitudes at 15 ms. Corresponding lines have been plotted as well, which show a first-degree fit. Alongside the coloured lines, red dotted lines show the 95% confidence bounds. 5 ms (Blue) slope: -0.11, pVal = NaN. 10 ms (Green) slope: 0.03, pVal = 0.53. 15 ms (Purple) slope: 0.00, pVal = 0.99.

Table 2: VNS input parameters in grey and EP-peak data in red for each subject.

Subject ID	Input-current [mA]	Frequency [Hz]	Pulse-width [µs]	Peak-time [ms]	Peak-amplitude [µV]
1	2.5	30	250	5.00, 9.50	3.199, 2.465
2	2.25	20	250	9.75, 14.25	2.183, 0.728
3	2	15	130	10.00, 13.75	1.320, 0.802
4	1.625	15	250	11.00, 15.00	2.597, 1.715
5	1.75	30	250	5.50, 8.75, 15.50	3.826, 2.343, 1.353

Topographical plots

Furthermore, it may be insightful to look at the topographical plot during an evoked potential response. In this section, we present some noteworthy findings. Important to note is that when the polarity is mentioned, positive electrical polarity is meant.

There are two types of patterns found in the topographical plots. Three of the five subjects showed a consistent EP response, which also resulted in similar topographical plots. As seen in Figure 10, the polarity in the brain seems to flip every 5 ms. The polarity at 5 ms is of very low amplitude but seems to be pointing in a left-forward direction. At 10 ms, the polarity is pointing directly to the right at a high amplitude. Then, at 15 ms, a lower amplitude polarity is pointing to the left. Important to note is that the direction of polarity at the VNS-peak (0 ms) is consistent in all topographical plots.

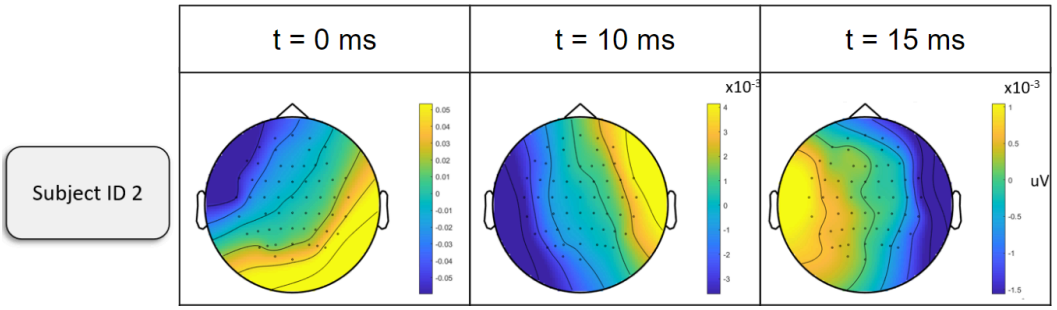

Figure 10: The topographical plots of subject ID 2 serve as a representative illustration of two other subjects: ID 3 and ID 4. The plot displays the polarity distribution at time intervals 0, 10 and 15 ms. The colour scale ranges from yellow, indicating the highest values observed within the plot, to dark blue, indicating the lowest values.

Two of the five subjects showed a different EP response, both containing a large peak at 5 ms. In the topographical plots, see Figure 11, this seems to manifest in a few ways. First, the amplitude of the polarity at 5 ms is quite large and points to the left frontal region of the scalp. Second, the plot at 10 ms now shows the polarity pointing in a purely frontal direction, as opposed to the right as seen in the other three subjects. Lastly, the polarity at 15 ms is pointing downward, the opposite of the polarity at 10 ms.

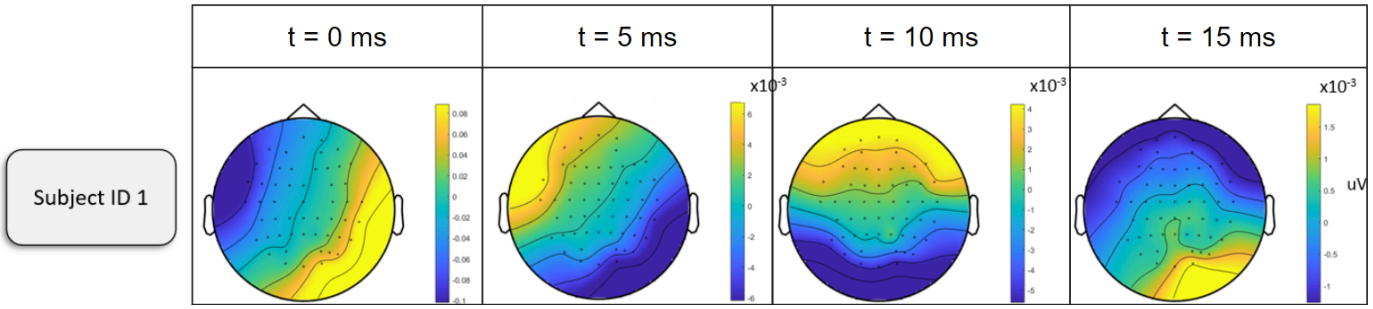

Figure 11: The topographical plots of subject ID 5 are representative of subject ID 1 as well. The top row of the plot displays the polarity distribution at time intervals 0, 5, 10, and 15 ms. The colour scale ranges from yellow, indicating the highest values observed within the plot, to dark blue, indicating the lowest values. On the other hand, the bottom row depicts the polarity at times 5, 10, and 15 ms, with

the amplitudes normalised across all subjects in the dataset. Additional results can be found in Appendix B.

4. Discussion

In this study, we attempted to contribute to the current understanding of VNS-induced evoked potentials. To achieve this goal, we utilised 30-minute EEG data from five epilepsy patients who had undergone VNS-device implantation. The evoked potentials were visualised through the segmentation of the signal into trials, followed by the calculation of a Global Mean Field Power (GMFP). This GMFP served as a valuable metric to determine the amplitude and time signatures of EP-peaks, which were plotted to VNS input parameters. In addition, topographical plots were constructed to provide an overview of the electrical dynamics across the brain during such an evoked potential, which could facilitate better insight into the spatial distribution of VNS-induced evoked potentials.

This research is based on findings in Usami et al. [11], which makes it peculiar that some but not all of their findings line up. Their stimulation parameters were comparable to our parameters, with a few key differences. Their frequency was at 30Hz for all tests, their pulse-width ranged from 130 to 750 μs and their input current ranged from 0.25 to 2.00 mA. For example, our pulse-width primarily was 250 μs and our input current range started at 1.625 mA. In general, it can be said that our research expands on their parameter ranges, especially considering the input current is higher and the frequency ranges from 15 to 30 Hz.

It has to be mentioned that our research contained 5 datasets each from a different patient, meaning that differences in results can also be attributed to differences in (neuro-)morphology. Comparing these different datasets might therefore not deepen understanding of the relation between input parameters and EP output. However, it does shine a light on how EPs look like in different patients in different circumstances.

In none of our results the biphasic peak at 3 ms mentioned in their research shows up, but in two of the datasets a peak at around 5 ms, larger than the peak at 10 ms, seems to show up. This peak can't be the 3 ms peak shown in Usami et al. [11], because that biphasic peak was a lot smaller than the 'main' peak at 10 ms and had clear P1 and N1 components. We do not currently understand why this 5 ms peak shows up in only these two datasets, as the input parameters don't deviate from the other datasets. The only differentiating factor these two datasets share is that they have a frequency of 30 Hz, but if that was the only important factor, Usami et al. [11] would've noticed them too. A possible way to find out where this peak comes from is through source reconstruction. The biphasic peak at around 10 ms does show up in all datasets as expected [11,15] . It is worth noting that Usami et al. [11] utilised a muscle relaxant in their research, after which the biphasic peak at 10 ms did not show up anymore. They posed that this peak is highly likely to be caused by laryngopharyngeal muscles, instead of the brain itself [15]. We weren't able to test this theory, as we had no control over the method by which our data was gathered, and thus could not administer muscle relaxants.

It is likely that we fell in the same pitfalls as previous researchers [12,16] as we focused more on longer-latency (10+ ms) components, as opposed to trying to find the 3 ms component. This early and small component was likely hidden in the initial stimulation peak, likely due to a combination of higher input current, higher pulse width and inadequate exponential correction of the signal [11]. In future research, principal subtraction analysis or template subtraction methods, like used in Deep Brain Stimulation (DBS) artefact reduction, could be utilised to remove or reduce the large stimulation peak that contains the 3 ms component [17,18,19].

The 5 ms peak in two of the datasets is worth researching further. Especially since it has never been documented before. These datasets subsequently also had very similar topographical plots, meaning that whatever caused the peak at 5 ms had a consistent outcome. It is possible that this peak is a direct result of the large initial stimulation peak rebounding back after recovery. Further research could consist of source reconstruction to get a comprehensive understanding where this component comes from.

As mentioned in the results, the trendlines in the correlation between input parameters and EP amplitude can mostly be deemed insignificant, as there is not enough data and too much variability. However, it is worth noting that this new data builds upon the data gathered by Usami et al. [11] and that there is very little overlap between these studies.

Stimulated fibers at the Vagus Nerve consist of three types of fibers: Aβ, Aγ and C fibers [20]. A fibers have high conduction velocity and low action potential threshold while C fibers have low conduction velocity and high action potential threshold. Evidence has been found that there's a correlation between neural conduction of A fibers and antiepileptic effects [20]. According to Usami et al. [11] "The early component was regarded as directly resulting from ascending neural conduction of A fibers of the VN, probably originating around the jugular foramen." The 5ms component we found may also be attributed to the A fiber.

The methods used for processing and analysing the results were valid but could use more refining, such as better filtering techniques or utilising a different reference frame. We chose to utilise the average across all channels as a reference, as this reduces the most amount of noise, but we do realise that other papers made use of the Cz electrode as a reference for scalp recordings [11,15].

Exploring the evoked potential on an extended time scale could prove interesting, as it may offer a more comprehensive understanding of the effects of VNS. The longer time scale would encompass time signatures of 100+ milliseconds, particularly since evoked potential peaks around this range have proven clinically relevant in the diagnosis of various other disorders [10]. Tougas et al. [16] have previously looked at these later evoked potential responses, however, they did not compare input parameters. Currently, attempting to make such visualisations and analysis with our data requires the selection of the final trial at the end of a VNS cycle, which would result in very few trials. The utilisation of a grand average across all patients [21] might be a viable approach to visualise these long-term evoked potentials, but then input parameters couldn't be compared. Possible future experiments could be constructed wherein the input frequency is reduced to see the full evoked potential of a singular VNS pulse, however, this experiment needs to be carefully considered, as patients with epilepsy might need a high VNS frequency to prevent or lessen seizures.

5. Conclusions

In conclusion, this study investigated VNS-induced evoked potentials in epilepsy patients using EEG data. The analysis focused on the amplitude and time signatures of EP-peaks utilising the Global Mean Field Power (GMFP). Additionally, topographical plots were generated to visualise the spatial distribution of VNS-induced evoked potentials on the scalp.

The research expanded on previous findings by exploring a wider range of stimulation parameters, including higher input currents and a frequency range of 15 to 30 Hz. Although some differences were observed compared to a related study by Usami et al. [11], the findings provided valuable insights into the characteristics of VNS-induced evoked potentials in these patients.

The results indicated a consistent biphasic peak at around 10 ms in all datasets, suggesting that VNS-induced evoked potentials are characterised by this specific feature. However, an unexpected peak at approximately 5 ms was observed in two datasets, which merits further investigation. These datasets exhibited similar topographical patterns, indicating a consistent outcome related to the 5 ms peak.

The relation between input parameters and EP amplitude showed a lack of significance due to limited data and variability. Nevertheless, the study built upon the existing literature and offered new insights with minimal overlap with previous research.

In summary, this study contributes to the current understanding of VNS-induced evoked potentials in epilepsy patients. The findings highlight the presence of consistent biphasic peaks at around 10 ms and the emergence of a novel peak at approximately 5 ms in certain datasets. Further research is warranted to explore these findings, refine the analysis methods, and deepen our understanding of the effects of VNS on brain dynamics.

6. References

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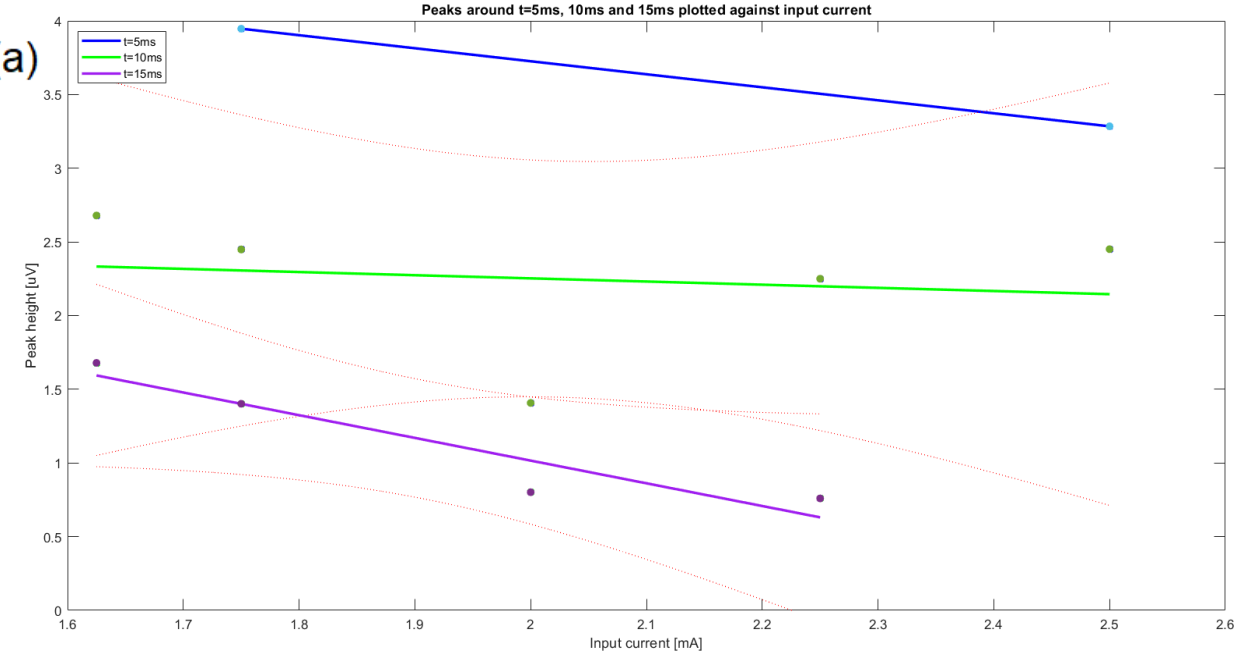
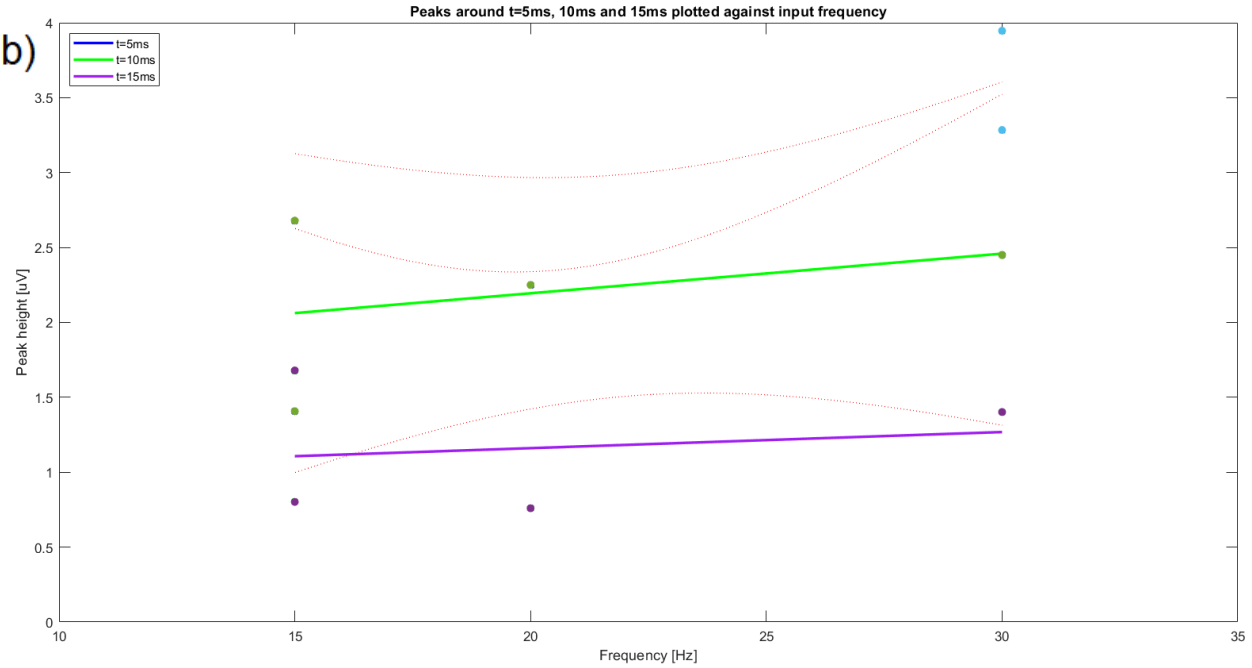
7. Appendices

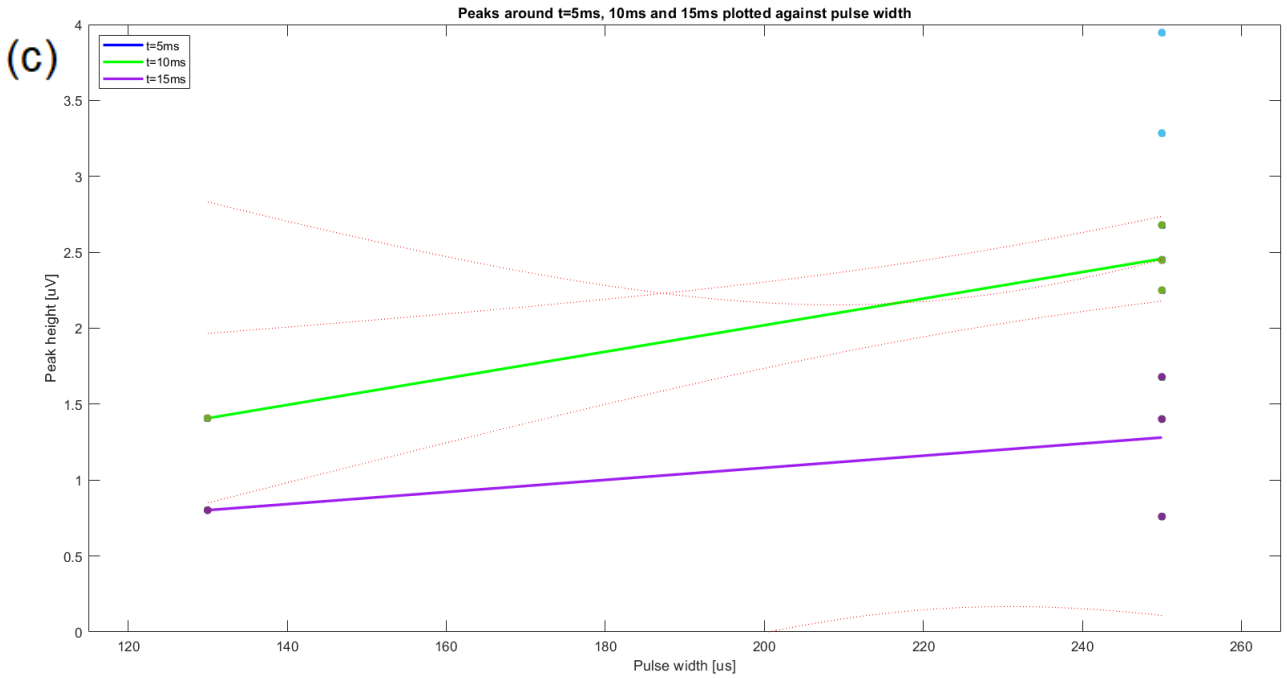
Appendix A

(a)



(b)





Figures 12: Showing (a) Current in mA, (b) Frequency in Hz and (c) Pulse-width in µs plotted against EP-peak amplitude over different times of interest. Red are the data points at 5 ms, purple are the data points at 10 ms (P2) and light blue are the data points at 15 ms (N2). Corresponding P-values can be seen in Table 3.

Table 2: The P-values of trends compared to input parameters. In red are non-significant results, while green is significant.

	t = 5 ms	t = 10 ms	t = 15 ms
Input Current	NaN	0.805	0.058
Frequency	NaN	0.497	0.832
Pulse width	NaN	0.013	0.472
Input current times Pulse width	NaN	0.265	0.984
Input current times Pulse width/Frequency	NaN	0.533	0.993

Appendix B

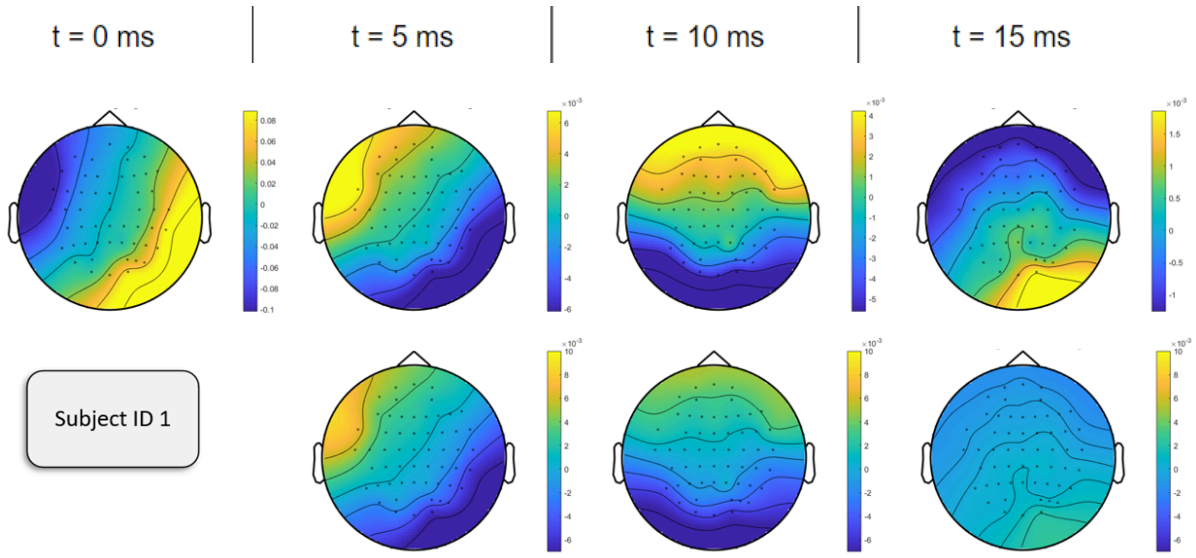


Figure 13: Topographical plots of subject ID 1. The top row displays the positive electrical polarity distribution at time intervals 0, 5, 10, and 15 ms. On the other hand, the bottom row depicts the polarity at times 5, 10, and 15 ms, with the amplitudes normalised across all subjects in the dataset. The colour scale ranges from yellow, indicating the highest values observed within the plot, to dark blue, indicating the lowest values.

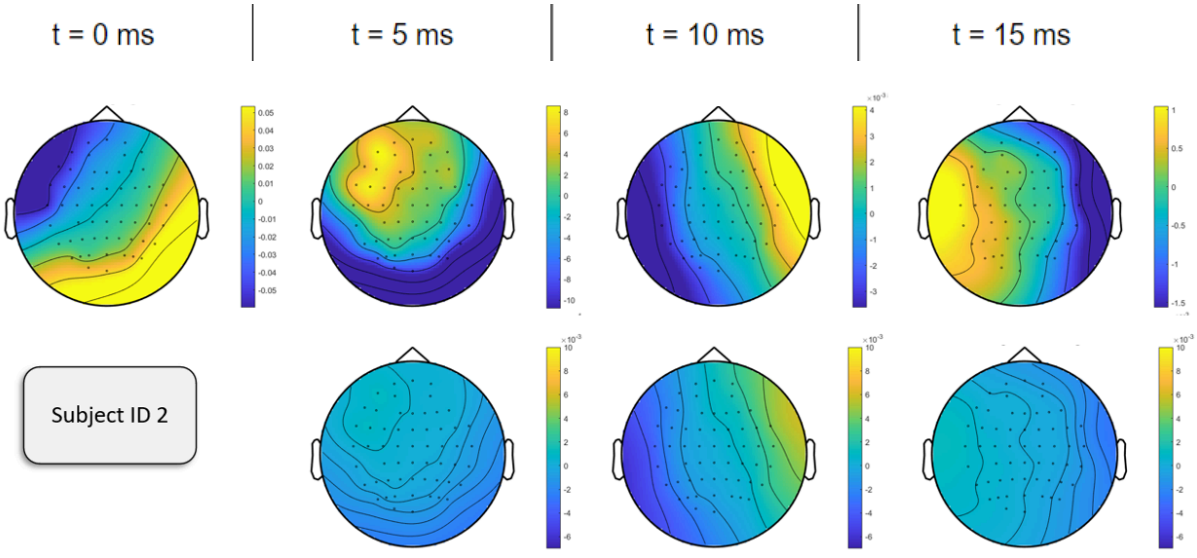


Figure 14: Topographical plots of subject ID 2. The top row displays the positive electrical polarity distribution at time intervals 0, 5, 10, and 15 ms. On the other hand, the bottom row depicts the polarity at times 5, 10, and 15 ms, with the amplitudes normalised across all subjects in the dataset. The colour scale ranges from yellow, indicating the highest values observed within the plot, to dark blue, indicating the lowest values.

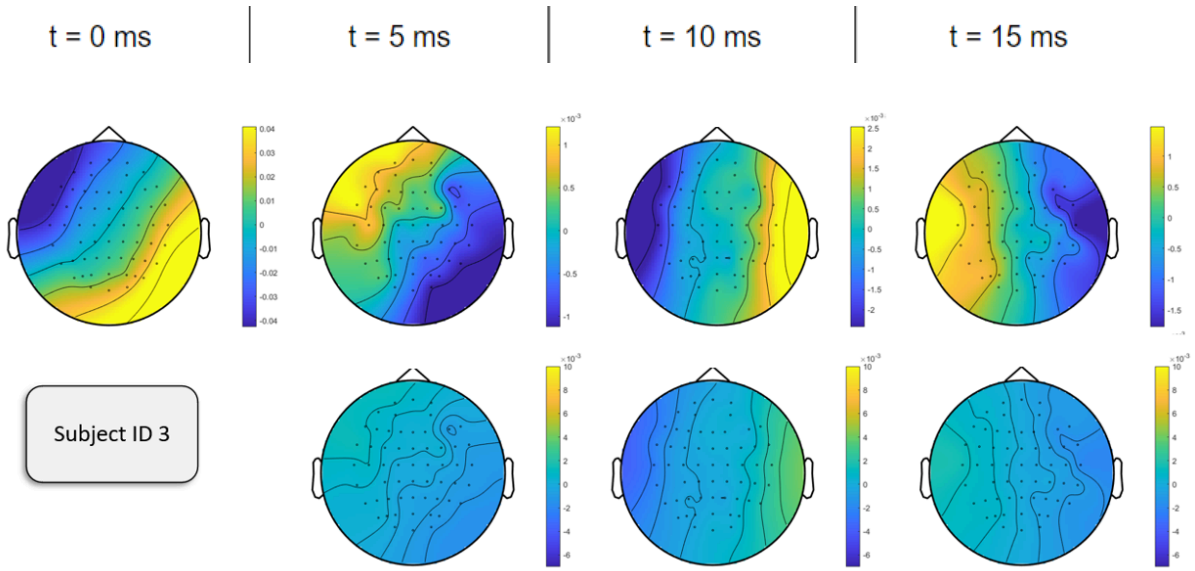


Figure 15: Topographical plots of subject ID 3. The top row displays the positive electrical polarity distribution at time intervals 0, 5, 10, and 15 ms. On the other hand, the bottom row depicts the polarity at times 5, 10, and 15 ms, with the amplitudes normalised across all subjects in the dataset. The colour scale ranges from yellow, indicating the highest values observed within the plot, to dark blue, indicating the lowest values.

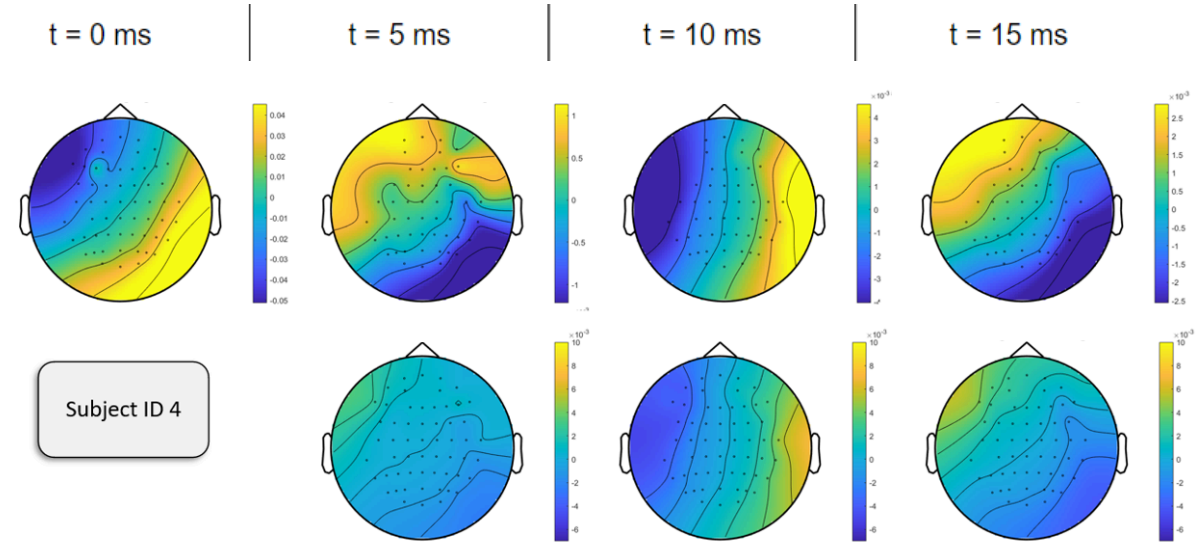


Figure 16: Topographical plots of subject ID 4. The top row displays the positive electrical polarity distribution at time intervals 0, 5, 10, and 15 ms. On the other hand, the bottom row depicts the polarity at times 5, 10, and 15 ms, with the amplitudes normalised across all subjects in the dataset. The colour scale ranges from yellow, indicating the highest values observed within the plot, to dark blue, indicating the lowest values.

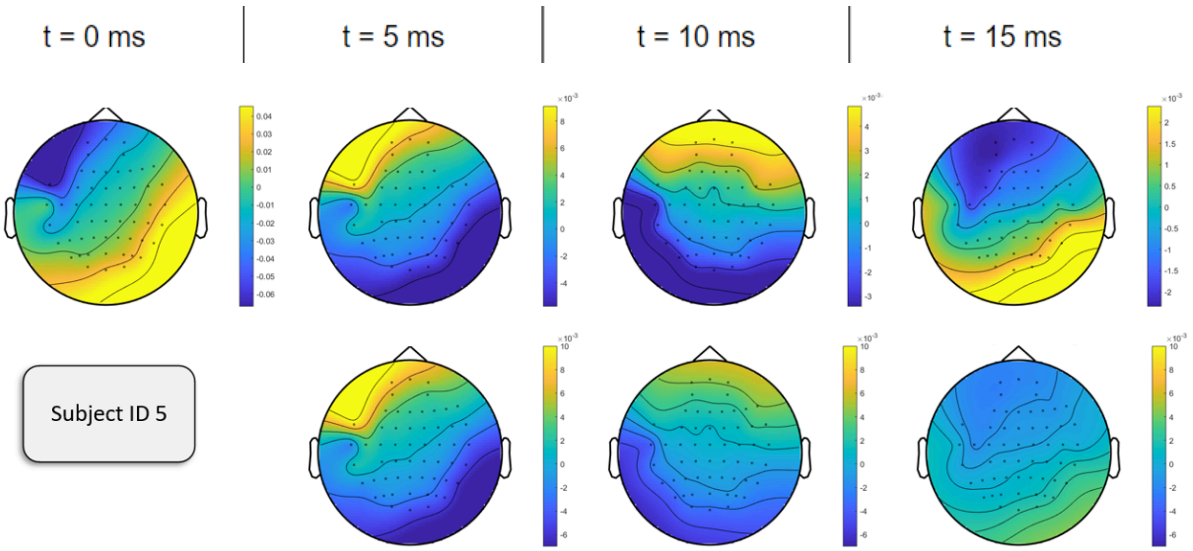


Figure 17: Topographical plots of subject ID 5. The top row displays the positive electrical polarity distribution at time intervals 0, 5, 10, and 15 ms. On the other hand, the bottom row depicts the polarity at times 5, 10, and 15 ms, with the amplitudes normalised across all subjects in the dataset. The colour scale ranges from yellow, indicating the highest values observed within the plot, to dark blue, indicating the lowest values.

Appendix C

Table 4: Questionnaire results of patients before and after VNS implantation. At the bottom is a table that shows improvement or decline in patient health.

ID	QOLIE-31-P Baseline (0-100)	QOLIE-31-P PostVNS (0-100)	GAD-7 Baseline (0-21)	GAD-7 PostVNS (0-21)	BDI-II Baseline (0-63)	BDI-II PostVNS (0-63)	PHQ-9 Baseline (0-27)	PHQ-9 PostVNS (0-27)
1	78.4	76.2	3	1	1	0	4	6
2	61.3	59.9	6	12	9	11	9	11
3	55.9	46.8	11	18	10.5	22	3	14
4	57.2	51.7	19	17	6	18	5	13
5	45.6	30.2	10	5	25	16	15	9

Subject ID	QOLIE-31-P	GAD-7	BDI-II	PHQ-9	Result
1	-2.2%	+9.5%	+1.6%	-7.4%	+1.5%
2	-1.4%	-28.6%	-3.2%	-7.4%	-40.6%
3	-9.1%	-33.3%	-18.3%	-40.8%	-101.5%
4	-5.5%	+9.5%	-19.0%	-29.6%	-44.6%
5	-15.4%	+23.8%	+14.3%	+22.2%	+44.9