POLITECNICO
MILANO 1863

SCUOLA DI INGEGNERIA INDUSTRIALE
E DELL'INFORMAZIONE

Executive Summary of the Thesis

Glymphometer device validation through EEG and fNIRS signals acquisition and processing for functional brain analysis

Laurea Magistrale in Ingegneria Biomedica
Biomedical Engineering - Technologies for electronics

Author: Francesca Mannini

Advisor: PhD Stefania Coelli

Co-advisor: Prof. Teemu Myllylä

Academic year: 2022-2023

1. Introduction

Over recent decades, global improvements in the quality of life have led to an increase in the aging population [1], with a notable rise in age-related neurodegenerative diseases (NDDs). Among them, dementia, characterized by chronic cognitive disorders, represents a significant challenge [2]. Early diagnosis of dementia remains elusive due to its subtle onset and sporadic clinical assessments [3]. At the state of art, between all the most prominent diagnostic methods [4], electroencephalography (EEG) and functional near-infrared spectroscopy (fNIRS) result to prove invaluable in developing therapeutic strategies for NDDs [5], thanks to their common attributes such as minimal invasiveness, safety, ease of use, and repeatability. EEG is an already strongly validated non-invasive and cost-effective technique able to measure the brain electrical activity with a high temporal resolution, but a relatively low spatial one. It is also sensitive to environmental noise and artifacts, making it less reliable when used alone [6]. On the other hand, fNIRS is a relative new optical technique, able to measure hemodynamic changes with advantages like portability, low cost, and minimal constraints on subjects, boasting a higher spatial resolution but a lower temporal one [7]. In particular, about brain state monitoring in clinical settings, the integration of different diagnostic techniques, such as EEG and fNIRS, appears to be a much sought-after goal to date. Since both EEG and fNIRS possess attributes such as minimal invasiveness, safety, ease of use, and repeatability, they prove invaluable in developing therapeutic strategies for NDDs [5].

2. 'The Glymphometer', Research to Business project, University of Oulu

The primary goal of this work has been to further explore and validate a hybrid device, called Glymphometer, able to simultaneously acquire and to real-time monitor EEG and fNIRS signals, with the aim of commercializing it and making it suitable for future studies, especially about NDDs investigation. Currently under development at the University of Oulu by Professor Teemu Myllylä's and his research team [8], the Glymphometer is a user-friendly wearable medical device designed for brain

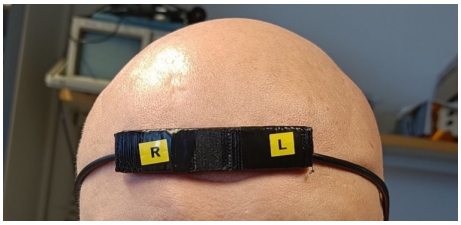
monitoring. The primary advantage of this device lies in its compact size and non-invasive nature, allowing for continuous brain monitoring during both wakefulness and sleep phases. It facilitates the easy measurement of various brain health parameters and the activity of the brain's cleansing system, which is closely linked to the glymphatic system's functionality. This device is intended for use both at home and in hospital settings, with the ultimate goal of advancing early diagnostic methods and promoting brain well-being.

In order to validate this brand new device - especially for future developments in the field of NDDs - two acquisition protocols have been defined from sketch. One concerns the acquisition of the Baseline signal, while the other one the acquisition of the Memory Activation signal. In particular, the last one is based on a previous study [9] where it was demonstrated that resting fNIRS signals recorded from the prefrontal cortex can provide a promising methodology for detecting NDDs, resulting in a relatively lower hemodynamic activity.

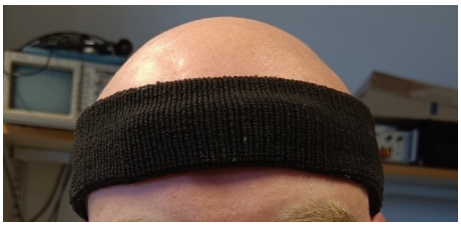
3. Methods and Materials

Glymphometer Device - For this work, the Glymphometer prototype used consists of a main unit box connected to a headcap unit that incorporates the fNIRS system - equipped with two photodiodes (PDs) and two LEDs - positioned in the middle of the forehead, a few centimeters above the eyebrows.

(a) Main unit box



(b) fNIRS setup: PDs and LEDs



(c) Headband

Figure 1: Glymphometer Device.

Initially, the idea was to use the EEG system integrated into the Glymphometer device but, after some attempts, it resulted that using both EEG and fNIRS systems caused a very high battery consumption. Therefore, for this pilot study, it has been decided to use an external EEG acquisition system, the Bittium NeurOne™ Tesla cap [10]. Since the fNIRS signal was acquired from the forehead, also the EEG signal was acquired from the same place, so just the two electrodes (Fp1 and Fp2) at the frontal cortex were considered. They are placed in the middle of the forehead, a few centimeters above the eyebrows and around 0.5 centimeters above the fNIRS system, while the ground electrode is located behind the right earlobe and the reference electrode (Cz) in the middle of the head.

GlYmphometer Software - About the acquisition software, the "GlYmphometer" Software is an advanced and comprehensive platform, totally developed by the Glymphometer research team at the University of Oulu. It has been designed for the simultaneous acquisition and real-time visualization of both EEG and fNIRS signals - even if, for this work, it was just involved for the fNIRS signal acquisition: for the EEG acquisition it was used the NeurOne™ Software, developed by Bittium [11].

Participants - A sample of nine healthy controls affiliated with the University of Oulu - including both Erasmus students and employees of different gender (2 males and 7 females), nationality and age (between 21 and 47) - has been analyzed.

Place - Data collection took place in Kieppi Lab, located in the Kontinkangas campus of the University of Oulu, between March and May 2023.

Acquisition Protocols - Two distinct protocols have been created from sketch specifically for the main aim of this work: the Baseline Acquisition Protocol and the Memory Activation Protocol. For the Baseline Acquisition Protocol, subjects were asked to sit in a relaxed position, with eyes closed, trying to minimize their thinking. A 5-minute signal was recorded under these conditions. On the other side, the Memory Activation Protocol consisted of two segments: a 1.5-minute open-eyed rest phase and a memory activation task. The task itself includes three phases: visualization, memorization and recall. In the visualization phase, subjects were presented 10 images of common objects, each one displayed for 2 seconds, and were instructed to name aloud these objects in English. After the presentation, they closed their eyes for 15 seconds (memorization), thinking about the images they had just seen. At the end, subjects opened their eyes and verbally recalled as many images as they could remember (recall).

3.1. Signal Analysis

After data collection, a detailed analysis of both fNIRS and EEG signals has been entirely conducted in MATLAB®.

fNIRS Signal Analysis - The fNIRS signal analysis involved several key steps. The raw fNIRS data were first downsampled from 250 Hz to 10 Hz. Then, a forward and backward moving average filter - window size (N) = 100 - has been applied in order to improve the signal-to-noise ratio (SNR) and smooth the data. From the filtered signals, optical density (OD) was calculated using the Modified Beer-Lambert's Law

$$OD = log\frac{I_o}{I} = \epsilon(\lambda) \cdot C \cdot l \qquad (1)$$

where I_o is the incident light intensity, I is the transmitted light intensity, ϵ is the molar absorption coefficient of the medium at a certain wavelength λ, C is the molar concentration of the analyzed molecule and l is the optical path length. From the OD, Hb_{0_2} and Hb_R concentrations have been calculated and then shown through plots representing their temporal evolution. Additionally, for each subject and for each side sensor, a Variation of Concentration Index (VCI) representing the percentage mean variation of Hb_{0_2} concentration - during each task phase, relatively to the baseline - has been calculated. Positive VCIs indicates hemodynamics activation, while negative VCIs indicates hemodynamics inhibition.

EEG Signal Analysis - On the other side, also the EEG signal analysis involved several key steps. In this case, the raw EEG data were pre-processed using the EEGLAB® Toolbox. They were first downsampled from 1000 Hz to 250 Hz, and then a digital FIR bandpass filter between 0.5 Hz and 45 Hz has been applied to remove noise and unwanted frequency components. Additionally, blink artifacts were removed from the EEG signals by dividing the signal into 2-seconds non-overlapping epochs, and then by discarding all the epochs with a maximum absolute amplitude above a defined threshold (50 μV in this case). From the pre-processed EEG signals, PSDs were calculated using the Welch method, allowing for the analysis of power distribution across different frequency bands - in particular θ (3-8 Hz), α (8-13 Hz), and β (13-30 Hz). Then, the dominant frequency within each band was determined, and the power was averaged within $\pm$2 Hz of it. For each electrode (Fp1 and Fp2) and during each task phase, PSD plots have been finally displayed. Baseline PSD has been also displayed, as a reference. Additionally, for each subject and for each side electrode, an Attention Index (AI) was calculated as the ratio of α power to β power, in order to provide an estimation of the subject's attention level. An AI higher than 1 indicates lower attention, while an AI lower than 1 indicates higher attention compared to the baseline.

Statistical Analysis - For what concerns the statistical analysis, aimed to investigate data distribution and to identify potential correlations, the Shapiro-Wilk Test was first used to assess whether the data of both the AI and the VCI follow a normal distribution across the six different classes - corresponding to the three cognitive task phases on the left and right forehead sides. Due to the small sample size - just 8 subjects were considered for further analysis, one has been discarded because extremely noisy - two non-parametric tests were then applied regardless: the Wilcoxon Signed Rank Test and the Friedman's Test. In order to visualize both AI and VCI distributions across different conditions, boxplots were generated and both medians and interquartile ranges were calculated for each class considered. Additionally, a combined analysis between AI and VCI was led in order to try to find potential correlations between EEG and fNIRS signals. Scatterplots and linear regression lines were used to visually explore this relationship. Additionally, the Pearson Coefficient (PC) was calculated in order to quantitatively measure the correlation between AI and VCI.

4. Results

Given the small sample size, the combination of these statistical tests and visualization techniques should be interpreted with caution.

fNIRS Analysis

	median	iqr
left	0.8708	41.9142
right	2.0327	21.8243

Table 1: The table shows both medians and interquartile ranges (iqr) of the VCI divided into the two sides.

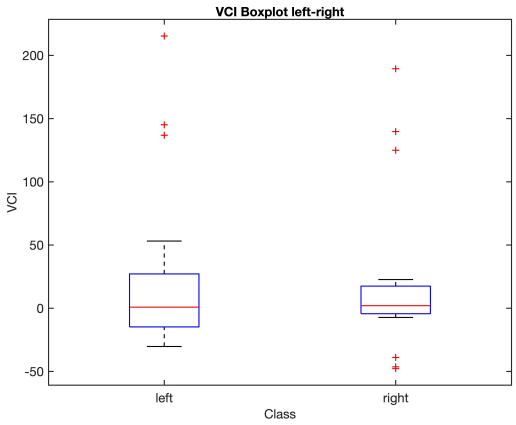


Figure 2: The boxplot shows the comparison between VCI from different sides.

The visual comparison of VCI between the two sides suggests that the left one has a wider distribution range, so greater data variability, even if medians in both groups are similar, suggesting similar data distribution. Additionally, longer whiskers in the left group indicate higher data dispersion and, even if outliers are present in both groups. In general, the VCI analysis shows an increased Hb_{O_2} concentration during cognitive tasks with respect of the baseline.

EEG Analysis

	median	iqr
Fp1	0.3142	0.2067
Fp2	0.3346	0.2108

Table 2: The table shows the medians and interquartile ranges (iqr) of the AI divided into the two sides.

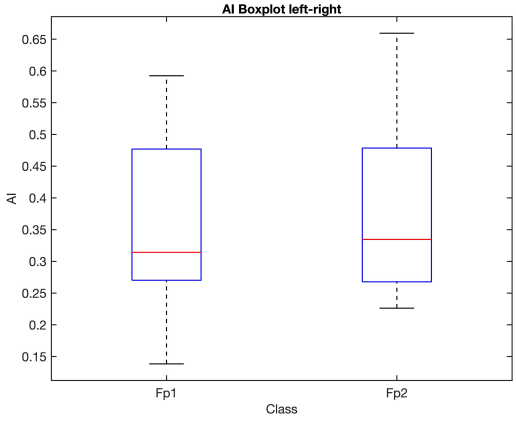
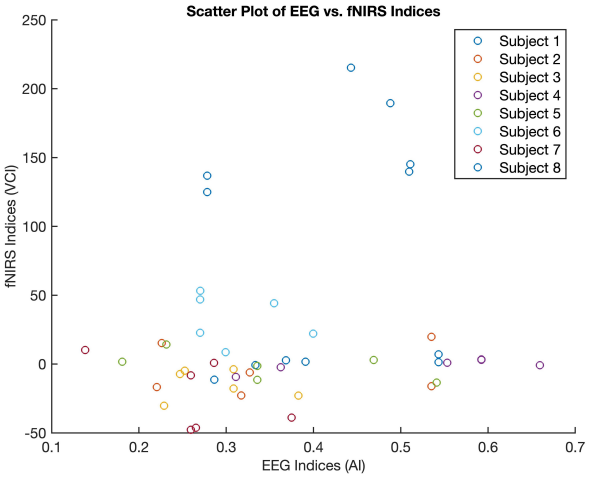


Figure 3: The boxplot shows the comparison between AI from different sides.

The visual comparison of AI between Fp1 and Fp2 suggests that Fp1 has slightly higher variability, while Fp2 has a slightly higher median, indicating higher AI on the right side (Fp2) of the prefrontal cortex. In general, the AI analysis during different task phases shows that it is higher during the visualization phase, decreases during recall, and is lowest during memorization on both sides.

fNIRS-EEG Combined Analysis



(a) AI

Figure 4: Scatterplot between AI and VCI, divided into the 8 subjects.

Starting from the general scatterplot, representing the AI-VCI relation divided into the 8 subjects, it has been noticed that Subject 6 and Subject 8 visually resulted as outliers, so they both have been removed for further analysis.

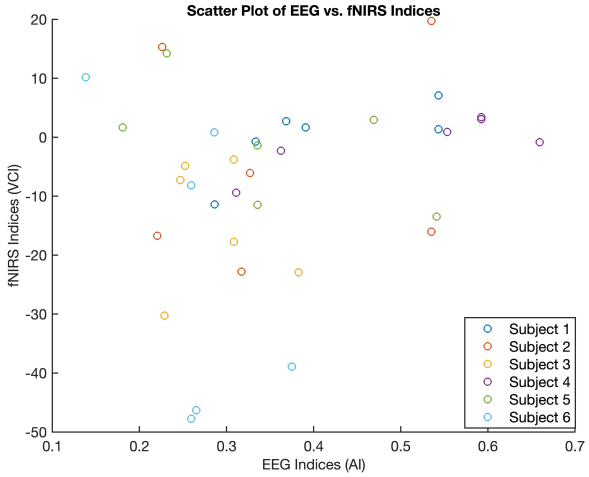


Figure 5: Scatterplot between AI and VCI, divided into the remaining 6 subjects.

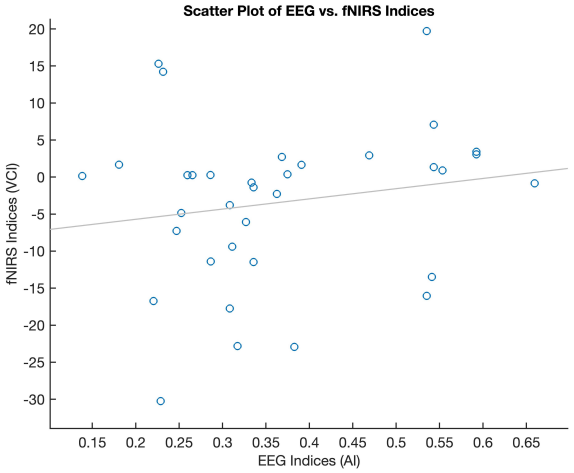


Figure 6: Scatterplot between AI and VCI, with the linear regression line.

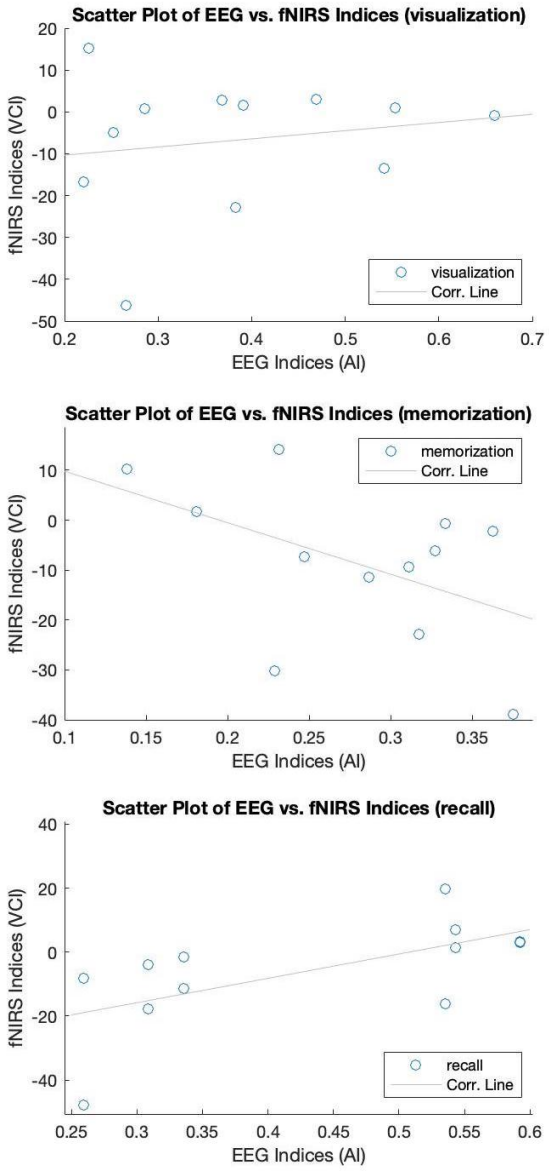


Figure 7: The pictures show the scatterplots between AI and VCI, divided into the three task phases - visualization, memorization and recall - with the linear regression line.

Scatterplot analysis suggests, in general, some correlation between AI and VCI. During the memorization phase, there is a medium-strength negative correlation (PC = -0.4842), suggesting that higher mental relaxation corresponds to lower oxygen supply to the frontal brain region. On the other side, there is a positive correlation in both memorization (PC = 0.1746) and recall phases (PC = 0.6504), suggesting that higher concentrations require less oxygen supply to the frontal brain region.

5. Discussions

Despite the small sample size, these results provide some interesting insights and trends.

fNIRS Analysis

Visualizing changes in Hb_{O_2} and Hb_R concentrations over time provides valuable insights into neural hemodynamic activity in the brain. In a resting state, elevated Hb_{O_2} levels and reduced Hb_R levels are commonly observed, signifying increased blood flow and metabolic activity in specific brain regions due to ongoing neural processes related to introspection and maintenance of baseline brain functions [12]. During cognitive tasks, the behavior of Hb_{O_2} and Hb_R reflects the brain's adaptive responses to cognitive demands: positive Hb_{O_2} levels typically accompany heightened neural activity, while elevated Hb_R concentrations suggest increased oxygen consumption due to neural firing. Additionally, also VCI behavior results consistent with expectations [13], with positive values during the memory activation task phases, indicating brain activation during cognitive tasks.

EEG Analysis

The Power Spectral Density (PSD) plot of an EEG signal is a valuable tool for understanding how the brain adapts and responds to cognitive tasks. The PSD plot during the close-eyed rest condition shows a dominant α rhythm, indicating a relaxed state of open-eyed wakefulness. In contrast, during the performance of the cognitive task, there is a shift with decreasing α power and increasing β power, highlighting brain's cognitive engagement. Also in this case, the importance of the outcomes obtained lies mainly in their scientific consistency [14–16]. Consistently [17], during baseline condition, the AI tends to get value higher than 1, reflecting a dominance of α power associated with relaxation. In contrast, during the open-eyed cognitive task, the AI tends to get values lower than 1, indicating both lower α power and greater β power associated with focused attention.

Combined Analysis

As already mentioned, it is essential to approach all these statistical outcomes with caution, since

it results challenging to drawn robust conclusions about the significance of the data when the sample size is limited. However, the combined fNIRS-EEG statistical analysis revealed a positive correlation trend between AI and VCI, indicating that as mental effort increased - AI increases - hemodynamic activation tended to increase as well - VCI increases. Analyzing the correlation by task phase, a negative correlation during memorization suggests that higher mental relaxation - higher AI - corresponds to lower oxygen supply - lower VCI - in the frontal brain region. On the contrary, during both visualization and recall, a positive correlation indicates that lower mental relaxation is associated with lower oxygen supply, which might seem counterintuitive physiologically. This behavior could be justified as an adaptive response, where increased α activity modulates cognitive effort during open-eyed tasks, as a compensation for the higher oxygen demand.

6. Conclusions and Future Developments

In this study, the validation of the Glymphometer device marks a significant beginning of a path toward the field of neurodegenerative disease diagnosis. Through rigorous signals collection, analysis, and then validation, it has been demonstrated that the device works as intended, providing coherent and consistent results that align with expectations based on empirical reality and scientific researches. Furthermore, the device's correlation with established benchmarks from scientific literature searches adds to its credibility. However, while the Glymphometer represents a significant advancement, there is room for further exploration and refinement. Overall, this study establishes the technical credibility of the Glymphometer and paves the way for proactive and personalized neurological care.

References

[1] U.s. census bureau international programs: An aging world: 2020, https://mtgis-portal.geo.census.gov/arcgis/apps/mapseries/index.html?appid=3d832796999042daae7982ff36835e2e.

[2] World Health Organization. World health organization (who): 'global status report on the public health response to dementia', https://apps.who.int/iris/bitstream/handle/10665/344701/9789240033245-eng.pdf.

[3] Nol Swaddiwudhipong, David J Whiteside, Frank H Hezemans, Duncan Street, James B Rowe, and Timothy Rittman. Prediagnostic cognitive and functional impairment in multiple sporadic neurodegenerative diseases. *Alzheimer's & Dementia*, 2022.

[4] Elham Rostami, Henrik Engquist, and Per Enblad. Imaging of cerebral blood flow in patients with severe traumatic brain injury in the neurointensive care. *Frontiers in neurology*, 5:114, 2014.

[5] Laura Dubreuil-Vall, Peggy Chau, Giulio Ruffini, Alik S Widge, and Joan A Camprodon. tdcs to the left dlpfc modulates cognitive and physiological correlates of executive function in a state-dependent manner. *Brain stimulation*, 12(6):1456–1463, 2019.

[6] Pedro MR Reis, Felix Hebenstreit, Florian Gabsteiger, Vinzenz von Tscharner, and Matthias Lochmann. Methodological aspects of eeg and body dynamics measurements during motion. *Frontiers in human neuroscience*, 8:156, 2014.

[7] Gary Strangman, Maria Angela Franceschini, and David A Boas. Factors affecting the accuracy of near-infrared spectroscopy concentration calculations for focal changes in oxygenation parameters. *Neuroimage*, 18 (4):865–879, 2003.

[8] Glymphometer - project description by 'research.fi', https://www.research.fi/en/results/funding/33395.

[9] Hasan Onur Keleş, Ece Zeynep Karakulak, Lütfü Hanoğlu, and Ahmet Omurtag. Screening for alzheimer's disease using prefrontal resting-state functional near-infrared spectroscopy. *Frontiers in Human Neuroscience*, 2022.

[10] Bittium neurone™ tesla eeg system, https://www.bittium.com/medical/bittium-neurone.

[11] 'bittium neurone software', https://www.jalimedical.com/bittium-neurone-tesla-eeg.php.

[12] Zhen Yuan and JongChul Ye. Fusion of fnirs and fmri data: identifying when and where hemodynamic signals are changing in human brains. *Frontiers in human neuroscience*, 7:676, 2013.

[13] Sahar Jahani, Antoniu L Fantana, David Harper, James M Ellison, David A Boas, Brent P Forester, and Meryem A Yücel. fnirs can robustly measure brain activity during memory encoding and retrieval in healthy subjects. *Scientific reports*, 7(1): 9533, 2017.

[14] Yolande AL Pijnenburg, Y Vd Made, AM Van Cappellen Van Walsum, DL Knol, Ph Scheltens, and Cornelis Jan Stam. Eeg synchronization likelihood in mild cognitive impairment and alzheimer's disease during a working memory task. *Clinical neurophysiology*, 115(6):1332–1339, 2004.

[15] Cornelis Jan Stam, Y Van Der Made, Yolande AL Pijnenburg, and PH Scheltens. Eeg synchronization in mild cognitive impairment and alzheimer's disease. *Acta neurologica scandinavica*, 108(2):90–96, 2003.

[16] LS Prichep, ER John, Steven H Ferris, B Reisberg, M Almas, K Alper, and R Cancro. Quantitative eeg correlates of cognitive deterioration in the elderly. *Neurobiology of Aging*, 15(1):85–90, 1994.

[17] Karin van der Hiele, Robert HAM Reijntjes, Alla A Vein, Rudi GJ Westendorp, Mark A van Buchem, Eduard LEM Bollen, Huub AM Middelkoop, and J Gert van Dijk. Electromyographic activity in the eeg in alzheimer's disease: noise or signal? *International Journal of Alzheimer's Disease*, 2011, 2011.