



Cognitive Measurement in Vascular Dementia Patients with Prefrontal Cortex Activation Analysis

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Abstract. Stroke is one of the world's second leading causes of death, with a prevalence of 10.9% in 2018. In Indonesia, strokes have increased over the last five years. Epidemiology suggests that small strokes in the prefrontal cortex (PFC) can cause cognitive impairment, leading to vascular dementia. The prefrontal cortex is a structure in the brain that is located in the frontal lobe. Accurate detection or diagnosis becomes important for therapeutic management because, it is difficult to identify at an early stage. Therefore, in this study, an analysis of differences in brain activation in healthy elderly (non-stroke) and post-stroke patients with vascular dementia was conducted when performing memory recall work. This study involved seven elderly non-stroke and seven stroke patients with vascular dementia. Brain activity was recorded using a 19-channel clinical electroencephalogram (EEG). The study compared prefrontal cortex activity during an attention test. Standardized low-resolution brain electromagnetic tomography (sLORETA) was used to analyze active brain areas. Then the analysis of differences in prefrontal cortex activity between non-stroke patients and those with vascular dementia used a paired T-test. The results of the paired T-test (with $p < 0.05$) showed that elderly non-strokes produced significant differences in activity when repeating numbers correctly (remember the numbers) and incorrectly (forget the numbers), while in stroke patients with vascular dementia, there was no significant difference when repeating numbers correctly and incorrectly. Another implication is that there is a decrease in the prefrontal cortex activity in stroke patients with dementia compared to elderly non-stroke patients. This study is expected to support the early detection of vascular dementia, especially in post-stroke patients.

Keywords: EEG; Prefrontal Cortex; sLORETA; Stroke; Vascular Dementia

1. Introduction

A stroke is a medical emergency because brain cells can die in a few minutes. An ischemic stroke is caused by a blockage along the path of an artery leading to the brain. One type of ischemic stroke is an atherothrombotic stroke. An atherothrombotic stroke occurs due to the blockage of blood vessels by plaque in the walls of the arteries (Alway et al., 2009). Epidemiologists show that small strokes in the PFC can result in cognitive impairment (Zhou, 2016). Research on prefrontal cortex activity has been carried out on the human brains of stroke patients, including (Hermand et al., 2019; Mori et al., 2018; Takeuchi et al., 2016; Al-Yahya et al., 2016).

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doi: [10.14716/ijtech.v13i8.6142](https://doi.org/10.14716/ijtech.v13i8.6142)

Several studies have reported that dual tasks activate the prefrontal cortex, which plays an important role in executive functions such as attention and multi-tasking (Miller & Cohen, 2001). Dual tasks, in this case, employ both cognitive and physical treatment. PFC activity in older subjects was lower than in younger individuals, which emphasizes the association between lower PFC activity and an increased risk of falls in the elderly. Therefore, changes in PFC activity may affect the risk of falls in stroke patients. However, the difference in PFC activation during dual tasks between stroke patients and healthy subjects is still unclear (Takeuchi et al., 2016). A study conducted by (Mori et al., 2018) found that the effect of PFC activation on dual tasks was different between young and old subjects. However, no studies have investigated the relationship between dual-task and PFC activation in stroke patients. The correlation between PFC activity and the decrease in the dual tasks was carried out by the Analysis of Variance (ANOVA) test. This can be useful for determining the risk of falling in stroke patients.

Several studies have used sLORETA to analyze problems related to brain damage. In the study of Cao et al. (2009), the functional connectivity properties of 29 student-athletes were compared under resting conditions and after sport-related mild traumatic brain injury (MTBI). The method used Independent Component Analysis (ICA) to remove noise and then applied the source reconstruction algorithm (sLORETA) to identify the cortical region of interest (Cao et al., 2009). sLORETA analysis revealed that patients with psychosis had decreased scores in the alpha band and patients with apathy had higher scores, especially in the right frontal and temporal regions (Shim & Shin, 2020).

In contrast to previous studies, this study used a single-task treatment, cognitive. Then, selected non-stroke patients and vascular dementia stroke patients were to perform Electroencephalography (EEG) recording for 20 minutes with the Montreal Cognitive test (MoCA) and hyperventilation tests. Furthermore, to determine the active brain areas in vascular dementia stroke patients by performing the inverse problem using sLORETA, then to find out whether or not there is a difference in prefrontal cortex activity between non-stroke and vascular dementia stroke patients when repeating numbers correctly and incorrectly, the paired T-test was used statistically.

2. Methods

As part of the design of this system, a signal analysis was performed to compare the activation of the prefrontal cortex between non-stroke and stroke patients. The signal analysis scheme is illustrated in Figure 1. The first step is EEG recording. The next step is data grouping. The authors collected data from non-stroke patients and stroke patients with vascular dementia. Then, researcher labels the data when the patient receives treatment and at the time of memory recall. Independent Component Analysis (ICA) was used to eliminate noise and artifacts. After obtaining a clean signal, data segmentation was carried out, followed by converting the EEG signal into a source signal using the inverse problem and identifying the cortical region of interest using the sLORETA method. Lastly, a significance test analysis was performed using the paired T-test. Stages of data processing and statistical tests using Brainstorm.

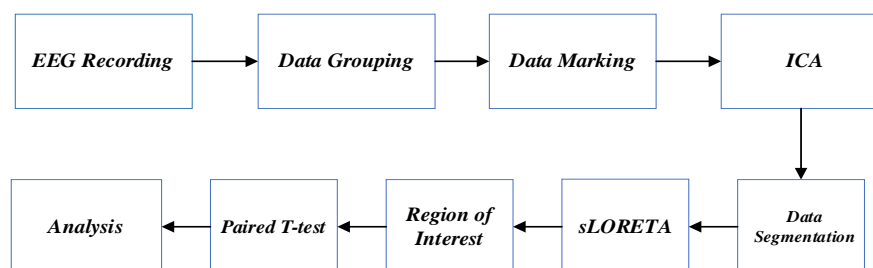


Figure 1 Scheme of signal analysis

2.1. Data Retrieval

EEG recording experiments in this study were carried out for 20 minutes at Hasan Sadikin Hospital, with details as shown in Table 1. This study has received ethical approval from the ethics committee of the Hasan Sadikin hospital with number LB.02.01/X.6.5/272/2019. All subjects agreed to participate in this study by filling out informed consent forms. Subjects will be given two types of tests, the MoCA test and the hyperventilation test. Furthermore, this study focuses on the attentional MoCA test, specifically when testing the forward and backward digits.

Table 1 Experimental design of EEG data recording

No	Description of recording	Recording Duration
1	Resting condition with eyes closed	5 minutes
2	Resting condition with eyes open	3 minutes
3	Montreal Cognitive Test (MoCA)	5 minutes
4	Resting condition with eyes closed	5 minutes
5	Hyperventilation Test	2 minutes
	Total recording time	20 minutes

The MoCA test aims to determine the presence of Mild Cognitive Impairment (MCI) (Julayanont & Nasreddine, 2017). MCI is a clinical condition intermediate between normal cognitive aging and dementia; in many cases, MCI can lead to dementia in the future (Nasreddine, 2005).

Husein et al. (2010) have tested the validity and reliability of the Indonesian version of the MoCA instrument, which aims to adapt the application of the test to the Indonesian people. The validity test of the MoCA-Indo test was carried out using the Transcultural World Health Organization (WHO) method, and the reliability test was carried out using the K statistic (Kappa).

The Indonesian version of MoCA consists of 30 points that will be tested by assessing several cognitive domains:

- Executive function can be defined as a person's complex process of solving a new problem or problems. Executive function was assessed by trail-making B (1 point), the phonemic fluency test (1 point), and two-item verbal abstraction (1 point).
- Visuospatial is a constructional ability such as drawing or imitating various kinds of images and also arranging blocks. Visuospatial was assessed by a clock drawing test (3 points) and by depicting a three-dimensional cube (1 point).
- Language is assessed by mentioning three animal names (lion, camel, rhino; 3 points), repeating two sentences (2 points), and language fluency (1 point).
- A delayed recall is assessed by mentioning five words (5 points) and mentioning them back after 5 minutes (5 points).
- Attention by assessing alertness (1 point), subtracting sequentially (3 points), forward and backward digits (1 point each).
- Abstraction assesses the similarity of an object (2 points).

g. Orientation is assessed by mentioning the date, month, year, day, place, and city (1 point each).

2.2. Independent Component Analysis

It is implicit that the electrical signals measured on the scalp are a combination of brain activity as well as different artifacts. An EEG signal is an electrical impulse that propagates through all layers of the cortex, skull, and tissues, and is ultimately present at every location of the scalp. This ICA is the stage for removing noise and artifacts from the recording (Michel et al., 2019).

2.3. Data Segmentation

The next stage is data segmentation. This study was divided into two categories, non-stroke and stroke patients. Seven non-stroke and seven vascular dementia stroke patients were selected to obtain attentional MoCA data. Short-term memory can store seven items of information in 15 to 30 seconds. The memory retrieval process requires a search of short-term memory, with each item checked individually. This serial short-term memory search works at a speed of 35 to 40 milliseconds per item, which is too fast for humans to realize (Vergauwe, 2014). The segmentation process takes 0.75 seconds before the forward and backward digit recall, until 1.25 seconds after.

During the attention test, the patient is given verbal instructions. The time delay between the patient being given instructions and when the patient recalls them is approximately 12 seconds. During the time delay, the patient is resting. The author chooses only 2 seconds of data by throwing away the first and last 5 seconds of recording on the resting state data.

Based on the results of the EEG recording, it was found that not all patients recalled numbers correctly, but there were also patients who recall numbers incorrectly. Some patients recall the forward and backward numbers correctly, and some patients only repeat one of the numbers correctly. Therefore, the data is divided into two categories, repeating true numbers and repeating wrong numbers. The results of the data segmentation process were obtained in as many as 42 parts, with 11 data for non-stroke patients and 10 data for stroke vascular dementia patients, respectively, on MoCA attention and resting state. In non-stroke patients, 7 patients recall numbers correctly, and 4 patients recall numbers incorrectly. In contrast, fewer stroke patients correctly recalled the numbers; 5 patients recalled the correct numbers and 5 patients recalled the incorrect numbers.

2.4. sLORETA

Standardized Low-Resolution Electromagnetic Tomography (sLORETA) is the most effective solution for the inverse EEG/MEG problem in three-dimensional head shape modelling (Shim & Shin, 2020). The inference of the current source position from the electrode potential is known as the “inverse EEG problem”, An illustration of the inverse problem can be seen in Figure 2. This method converts the EEG signal (electrode potential) into a source signal.

sLORETA produces a linear imaging method with precise zero-error localization under ideal conditions, as shown (Tong, 2009).

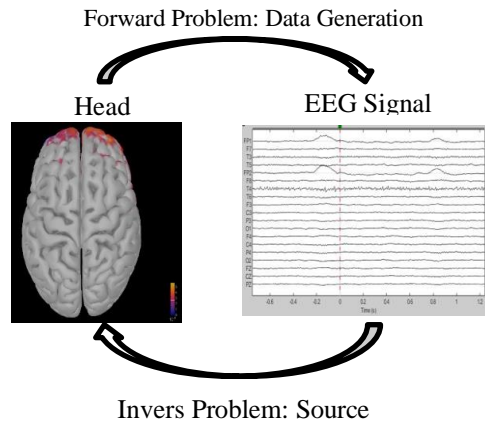


Figure 2 Illustration of forwarding problem and inverse problem

$$S_{\emptyset} = KS_JK^T + S_{\emptyset}^{Noise} \tag{1}$$

where S_{\emptyset}^{Noise} is related to noise in the measurement, and S_J to the biological source of variability, i.e., covariance for current density. When S_J is set to the identity matrix, it is equivalent to allowing equal contributions from all cortical neurons to biological noise. Usually, the noise covariance in the measurement S_{\emptyset}^{Noise} is considered to be proportional to the identity matrix. Under these conditions, the current density covariance is given by

$$S_J = TS_{\emptyset}T^T = T(KS_JK^T + S_{\emptyset}^{Noise})T^T = T(KK^T + \alpha H)T^T = K^T(KK^T + \alpha H)K \tag{2}$$

The linier imaging sLORETA method is

$$\sigma_v = [S_J]_v^{-\frac{1}{2}} \hat{j}_v \tag{3}$$

Where $[S_J]_v \in R^{3 \times 3}$ shows the 3x3 diagonal matrix block in S_J , and $[S_J]_v^{-\frac{1}{2}}$ is the inverse of the symmetry square root.

2.5. Region of Interest (RoI)

Using the sLORETA method, identify the cortical region of interest, Region of Interest (ROI) (Cao et al., 2009). The analysis in this study is based on short-term memory. The most active part of the brain during short-term memory activity is the prefrontal cortex (Daniel et al., 2018). Therefore, sLORETA is needed to indicate the position of the active brain region. The RoI of the prefrontal cortex is shown in Figure 3.

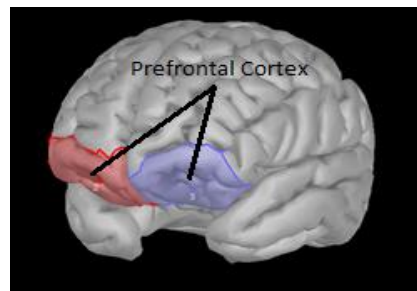


Figure 3 Region of interest (prefrontal cortex)

2.6. Statistical Paired T-test

The last stage in this research is the significance test. The significance test was used to determine whether or not there was an average difference between non-stroke and stroke patients in the prefrontal cortex in memory recall activity. The statistical test used is the

paired t-test. The Paired t-test is a parametric test that can be used on two paired data sets (Widiyanto, 2013). The purpose of this test is to see if there is a difference in the mean between two paired or related samples. Because it is a pair, the data from both samples must have the same amount or come from the same source. For example, if the two samples are not related or do not have the same data, then the independent sample *t-test* can be used. Data criteria for paired t-test: 1) the data is normally distributed or Gaussian; 2) the same number of samples; 3) the variance values may or may not be the same; 4) The scale requires an interval or ratio.

In this test, several stages must be completed, including (Santoso, 2010):

- a. Determining the null hypothesis (Ho) and alternative hypothesis (Ha), whose principle is to test the characteristics of the population based on the information received from a sample. Example: Ho = Both population means are identical ($\mu_1 = \mu_2$ or $\mu_1 - \mu_2 = 0$); Ha = Both population means are not identical ($\mu_1 \neq \mu_2$ or $\mu_1 - \mu_2 \neq 0$).
- b. Determine the level of significance (α), which is the probability of an error rejecting the hypothesis that turns out to be true. If it says 5%, it means that the risk of making a wrong decision is 5%. The smaller the level of significance, the lower the risk of error.

c. Paired T-Test Formula:

$$t = \frac{\bar{D}}{\left(\frac{SD}{\sqrt{N}}\right)} \quad (4)$$

where: *t* is T-value; \bar{D} is Average sample measurements 1 and 2; *SD* is Standard deviation of sample measurements 1 and 2 and *N* is Number of samples

- d. Define table statistics and test statistics. In this test, the T-table and T-value will be searched. For conditions of unequal standard deviation ($\sigma_1 \neq \sigma_2$) get the T-value and calculate the formula used as follows (Sudjana, 2005).

$$t = \frac{\bar{x}_1 - \bar{x}_2}{\sqrt{\left(\frac{s_1^2}{n_1} + \frac{s_2^2}{n_2}\right)}} \quad (5)$$

$$s^2 = \frac{n \sum x_i^2 - (\sum x_i)^2}{n(n-1)} \quad (6)$$

Where, S^2 represents the sample variance, *n* is the number of samples, x_1 is sample data 1, and x_2 is sample data 2. As for the T-table, the formula used is (Štolc, 2003):

$$t \text{ tabel} = t_{(1-1/2\alpha)}, (n - 1) \quad (7)$$

- e. Draw conclusions based on the results of T-tables and T-value. Accept Ho if T-value is less than T-table and reject Ho if T-value is greater than T-table (Widarjono, 2015).

3. Results and Analysis

This chapter is organized as follows: First, we discuss the results of sLORETA, a particular technique we use to find ROI. Then we will discuss paired t-test results, a particular technique we use to compare the prefrontal cortex of non-stroke and those with vascular dementia stroke patients.

3.1. sLORETA Result

sLORETA can be used to determine which brain regions are active during treatment (Pascual-Marqui, 2002). Analyzing the activation of not only single voxels but all regions associated with certain brain functions (Pascual-Marqui, 1999). The current density map as defined in the system was normalized to the estimated covariance of the data, which was derived as the sum of the noise covariance and brain signal covariance models. The

sLORETA transformation is shown in Figure 4. The sLORETA process is carried out in three stages; anatomical modeling, head modeling, and noise covariance. As for the test using the Brainstorm software.

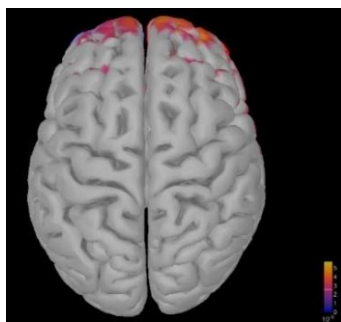


Figure 4 Transformation of sLORETA

3.1.1. Anatomical modeling

Anatomical modeling followed the ICBM152 template with 15002 vertices and 29984 faces (Do et al., 2021). The appearance of the cortex can be seen in Figure 5.

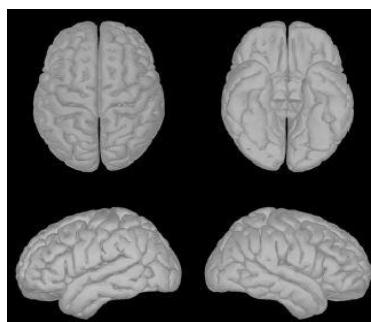


Figure 5 Anatomical model

3.1.2. Head modeling

In this research, the head model chosen is OpenMEEG BEM. This forward model uses Symmetric Boundary Element Method (Symmetric BEM) and was developed by the French public research institute INRIA. This model uses three layers; scalp, inner skull, and outer skull, with details of 1082 vertices on the scalp and 642 vertices (inner skull and outer skull).

3.1.3. Noise covariance

Minimum Norm Estimate (MNE) and dipole modeling are best with an accurate noise covariance model, generally calculated from experimental data. As such, these estimates are prone to errors arising from relatively few data points, weak sensors, and data that can cause the eigen spectra of the covariance matrix to become unconditioned (i.e. a large spread of eigenvalues or matrix condition numbers). To “stabilize” or “adjust” the noise covariance matrix, the L2 matrix norm is defined as the largest eigenvalue of its eigen spectrum. This adds a diagonal matrix whose entries are fractional norms of the matrix to the covariance matrix. The norm value of the matrix is used at 0.1, so the covariance matrix is stabilized by adding it to the identity matrix which is scaled to 10% of the largest eigenvalues.

3.2. Paired T-test Result

The non-zero values show a significant difference between the two conditions. This analysis focuses on when the patient will repeat numbers or recall memories, precisely before the zero point in the prefrontal cortex. There are four paired T-test statistical tests;

- Non-stroke patients were compared when they correctly repeated numbers and when resting.
- Non-stroke patients were compared when they repeated numbers incorrectly and were in their resting state.
- Compared to stroke patients when repeating numbers correctly and at rest
- Compared to stroke patients when repeating numbers incorrectly and at rest

3.2.1. Paired t-test results for non-stroke patients

The following is a graph of the paired T-test statistical test in non-stroke patients when memory recall. Figure 6 shows that there are non-zero values before the zero point, indicating that there was a difference in prefrontal cortex activity between non-stroke patients' memory recall and their resting condition. There was a significant difference between correctly and incorrectly repeating numbers.

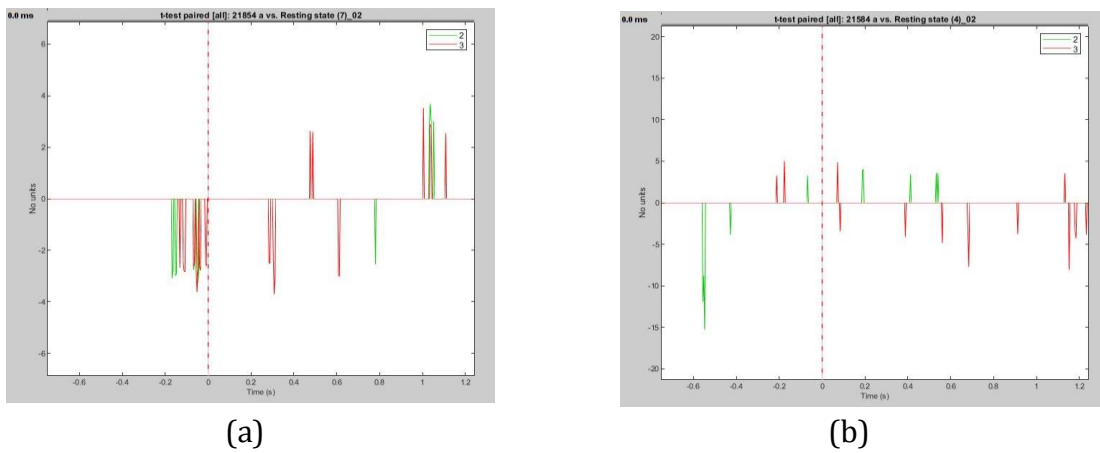


Figure 6 (a) Non-stroke patients who correctly repeat numbers, (b) Non-stroke patients who incorrectly repeat numbers

3.2.2. Paired t-test results for vascular dementia stroke patients

Based on the graph of the statistical test results of the paired T-test in Figure 7, it can be seen that before the zero point there are non-zero values. It can be concluded that there is a different brain activity in the prefrontal cortex when vascular dementia stroke patients memory recall and resting condition, but there was no significant difference when correctly compared to repeating numbers incorrectly.

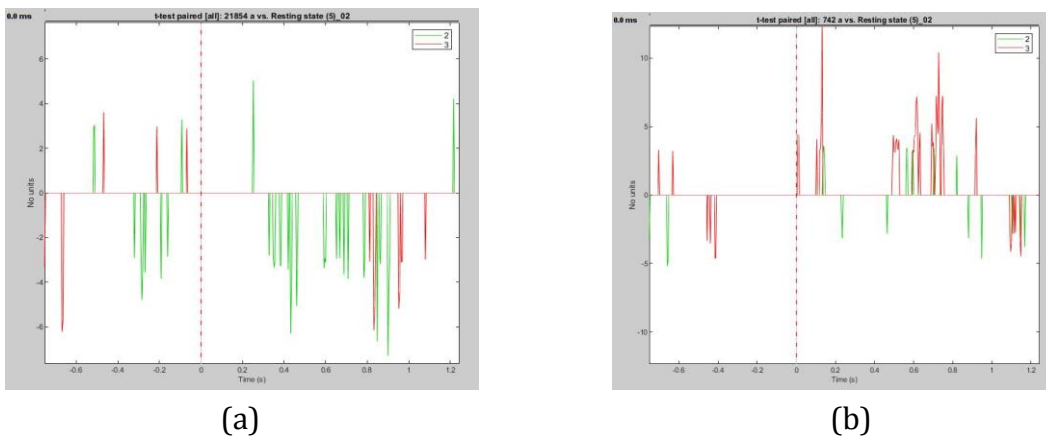


Figure 7 (a) Stroke patients when repeating numbers correctly, (b) Stroke patients when repeating numbers incorrectly

3.3. Analysis

In the attention MoCA experiment, two conditions were applied, non-stroke and vascular dementia stroke patients during memory recall. As explained in the previous chapter, for the MoCA attention test, the patients were asked to repeat two different sequences of numbers, one sequence of numbers was ordered from the front, and one sequence of numbers was ordered from the back.

Looking at the results of the EEG recording, the authors want to see if there is a significant difference in the prefrontal cortex between non-stroke and vascular dementia stroke patients. As well as observing the effect of activation in non-stroke patients and vascular dementia stroke patients on the success of memory recall.

- In assessing the different cognitive domains, i.e., attention, executive functions, memory, language, visuospatial skills, conceptual thinking, calculation, and orientation, with a total score of 30 points; 26 or above is considered normal. Subjects with a MoCA-Ina score less than 26 (<26) indicate impaired cognitive functions. The result of the MoCA score is shown in Table 2.

Table 2 MoCA score in non-stroke and vascular dementia stroke patients

Subject	Class	MoCA Score	Subject	Class	MoCA Score
1	Non-stroke	27	8	Stroke	19
2	Non-stroke	27	9	Stroke	24
3	Non-stroke	26	10	Stroke	22
4	Non-stroke	28	11	Stroke	24
5	Non-stroke	26	12	Stroke	20
6	Non-stroke	26	13	Stroke	24
7	Non-stroke	27	14	Stroke	25

3.3.1. Analysis of activation in non-stroke and vascular dementia stroke patients

The following will explain the meaning of brain activation as seen from non-zero values. If the non-zero values are further away from the zero point, both positive and negative, and there are more non-zero values before memory recall (dotted vertical line), it means that the brain shows a high activation condition.

The condition of brain activation in non-stroke patients can be seen in the patterns in Figures 6 and 7. So some descriptions of the analysis can be taken as follows:

- There is a significant difference between the conditions of the brain during recalled memory activity with resting state conditions in non-stroke patients.
- There is a difference, but not significant, between the condition of the brain during memory recall activity and the resting state in stroke patients.
- When it comes to repeating numbers correctly versus incorrectly, non-stroke patients have significantly higher activation.
- When stroke patients correctly repeat numbers, their brains are more activated than when they incorrectly repeat numbers, but the difference is not statistically significant.

3.3.2. Analysis of prefrontal cortex activity in non-stroke and vascular dementia stroke patients

The distinct prefrontal areas have extensive interconnections with the dorsomedial nucleus of the thalamus. Playing an important role in the work of this cortical area, lesions of the dorsomedial nucleus have effects that are in some ways similar to prefrontal damage. Areas exposed to the lateral convexity (dorsolateral prefrontal cortex) have massive interconnections with the parietal multimodal cortex and somatosensory, visual, and

auditory association areas. Patients with damage to this prefrontal area have problems with planning, problem-solving, and maintaining attention (Vanderah, 2018).

It is seen that in non-stroke patients, there is a significant difference between repeating numbers correctly and incorrectly. In contrast, in vascular dementia stroke patients, there is no significant difference when repeating numbers correctly and incorrectly. This means a decrease in activity in the prefrontal cortex in vascular dementia and stroke patients.

4. Conclusions

This study analyzes brain activation when doing memory work in elderly non-stroke and post-stroke vascular dementia patients. The aim is to determine whether there are changes in brain activation in post-stroke dementia patients so that they can be used as biomarkers in the diagnosis of vascular dementia. This study used the sLORETA tool to observe brain activation based on recorded EEG signals. The results of the paired T-test showed a decrease in the activity of the prefrontal cortex in stroke patients with vascular dementia. In non-stroke patients, there is a significant difference between repeating numbers correctly and incorrectly, while in stroke patients with vascular dementia, there is no significant difference between repeating numbers correctly and incorrectly. The results of the activation of the prefrontal cortex have relevance to the MoCA score. The results showed that stroke patients with vascular dementia had risk factors for cognitive decline. This study is expected to be a supporting analysis in the detection of post-stroke vascular dementia. Future research needs to be validated in a larger population.

Acknowledgments

We acknowledge the support received from Hasan Sadikin hospital. In addition, the author wants to thank, in particular, the patience, care, and support of the laboratory assistant.

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