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EFFECTS OF STROKE ON EEG ORIGINATING FROM CHANGES ON BRAIN TISSUE ELECTRIC ACTIVITY AND GEOMETRY

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ABSTRACT

Aleksi Siro: Effects of stroke on EEG originating from changes on brain tissue electrical activity and geometry
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Stroke is the second leading cause of death in the world. Therefore, new and improved diagnosis or treatment methods need to be developed. Nowadays, diagnosis of the stroke is made by using magnetic resonance imaging or computed topography scan. Both methods have an excellent localization and recognition ability, but they are not 100% accurate. In some cases, these imaging methods are able to detect the brain defect within hours or days, based on how bad the injury is. Also, they cannot provide in-line follow up of the patient condition.

In this thesis, effects of stroke on electroencephalography (EEG) is evaluated by searching subject related articles from several databases such as Google Scholar and Andor. Background from brain electrical activity, EEG, stroke and its subtypes are given. There are several clinical researches considering on changes on EEG during stroke. However, in most of the cases there were only few patients involved in the study. Therefore, more research must be done, so that the relationship between EEG changes and stroke could be fully understood. Several studies suggest that EEG would add crucial value to the early diagnosis of stroke in the future.

PREFACE

Acknowledgements to my director Jari Hyttinen and his assistant Antti Paldanius for their guidance and suggestions during bachelor's thesis. Also, I would like to thank University of Tampere for their wide Andor database. Thanks to Andor, subject related information was easy to find.

Tampere, 6 June 2019

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LIST OF SYMBOLS AND ABBREVIATIONS

3D	Three dimensional
ACA	Anterior cerebral artery
ATP	Adenosine triphosphate
AVM	Arteriovenous malformation
CBF	Cerebral blood flow
$CMRO_2$	Cerebral metabolic rate of oxygen
CNS	Central nervous system
CT	Computed tomography
CSF	Cerebrospinal fluid
DMS	Differential-mode signal
EEG	Electroencephalography
EPSP	Excitatory postsynaptic potential
GABA	Gamma-Aminobutyric acid
ICA	Internal carotid arteries
ICH	Intracerebral haemorrhage
IPSP	Inhibitory postsynaptic potential
MCA	Middle cerebral artery
MFEIT	Multi-frequency electrical impedance tomography
MLS	Midline shift
MRF	Modifiable risk factors
MRI	Magnetic resonance imaging
NMRF	Nonmodifiable risk factors
Non-REM	Non rapid eye movement
PCA	Posterior cerebral artery
PNS	Peripheral nervous system
PSP	Post synaptic potential
SA	Saccular aneurysm
SAH	Subarachnoid haemorrhage
tPA	Tissue plasminogen activator
VA	Vertebral arteries

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1. INTRODUCTION

In 2016, stroke was the second leading cause of death in the world after the ischemic heart disease [1]. It has been estimated that the number of the stroke patients will increase in the following years due to an aging population. There are several modifiable and non-modifiable risk factors of stroke and these risk factors are more common with the aged people. Even though, the aged people are more likely to have a stroke, everyone might have a stroke despite the age.

Stroke is a disease where the cerebral blood flow is disturbed due to a blockage or a rupture in the cerebral artery or in the cerebral vein. Stroke is divided into the two subtypes; ischemic stroke and haemorrhagic stroke. In the ischemic stroke, the blood flow is reduced due to a thrombosis, an embolus or an atherosclerosis. In the haemorrhagic stroke, the blood vessel ruptures and blood leaks into the brain parenchyma or into the cerebrospinal fluid. [2] Separation between ischemic and haemorrhagic mechanism is crucial so that the patient receives the right treatment. For example, if the patient with the haemorrhagic stroke is treated with tissue plasminogen activator, the patient will die quickly because blood can no longer coagulate. Nowadays these two disease mechanisms are separated from each other with the magnetic resonance imaging (MRI) or the computed tomography (CT).

Electroencephalography (EEG) is a non-invasive recording method, which is used to measure electrical activity of the brain [3]. EEG system can detect changes within milliseconds, making it fast and real time measuring system. Multiple electrodes are attached on the scalp, where electrodes collect data of the potential changes. For standard measurements, 10-20 electrode placement system is preferred but it can be extended into various systems for example, into the 10-10 system or the 10-5 system. When using different placing systems, more electrodes can be attached on the scalp. [4]

When patient has a stroke, the brain tissue undergoes functional, electrical and geometrical changes. This causes several changes in the EEG, such as increased amount of epileptic activity and delta wave activity. The purpose of this thesis is to search literature on how stroke changes the EEG and evaluate the utility of EEG in stroke management. The results could be applied to future research and the development of optional diagnosis methods of stroke. In this thesis, basics of the brain’s electrical activity, EEG system and stroke are covered. At the end of the thesis effects of stroke on EEG is discussed.

2. ELECTRICAL ACTIVITY OF THE BRAIN

Electrical activity of the brain is generated by neurons, which are the functional units in the central nervous system (CNS) and peripheral nervous system (PNS). On the daily basis, the brain receives a lot of information from our environment. Sounds, smells, light sensed by the retina, pressure on our skin etc. is turned into electrical form and the specific stimuli activates specific region in the brain. Our brain then interprets these electrical pulses, and that is why we see different colours or saliva is secreted as result of smelling food.

Brain's electrical activity is a complex set of specific activations and responses that are not fully understood nowadays. It has been estimated that there are 100 billion neurons in the human brain [5] and they are able to create complex neural pathways involving millions or billions neurons. Neurons cause action potentials, and action potentials cause postsynaptic potentials. Especially potential changes caused by postsynaptic potentials can be observed with EEG [3].

2.1 Lobes of the brain

The brain is commonly divided into four lobes, which are called frontal lobe, parietal lobe, occipital lobe and temporal lobe. Different lobes are presented in Figure 1. It is well known that different brain lobes are associated with certain functions [6]. For example, right and left temporal lobes are involved in processing of memories and occipital lobe is involved in visual processing. [7] So, when we are solving a problem or hear music, different lobes in our brain are activated. Activation increases amount of the postsynaptic potentials, which can be observed with the EEG.

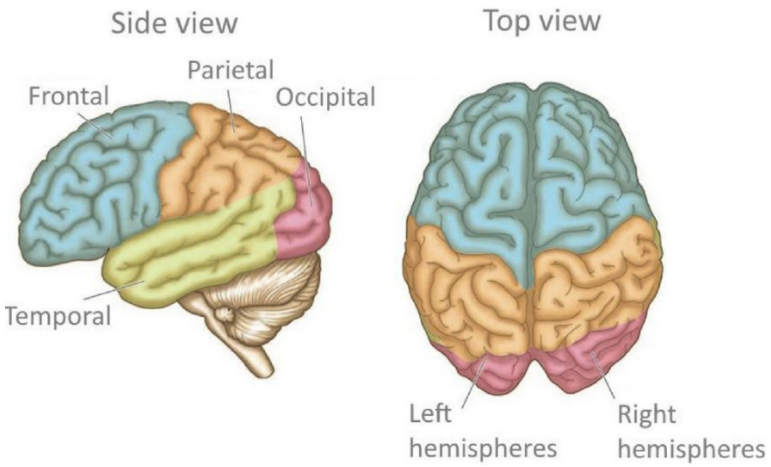

Figure 1: *Different lobes of the human brain* [7]

Brain is able to deal with huge amount of information within milliseconds and the changes in brain's electrical activity occur in the same time scale. Because EEG has high temporal resolution it can detect electrical activity at the same time as the brain processes electrical information. EEG is therefore, capable to detect abnormal electrical activity in real time. [3] Because of trauma or disease such as stroke, brain undergoes changes in minutes that affect its electrical activity. This is why EEG could be potentially used in stroke diagnosis.

2.2 Nerve cell

Neurons are the functional unit of CNS and PNS and they are communicating to each other via neurotransmitters. Typical neuron cell consists of a cell body, an axon, multiple axon terminals and multiple dendrites. Cells receives electrical information from other neurons via dendrites and passes information via axon. [8]

There are different types neuron cells in our body. Differences mainly consist of different number of dendrites and axon terminals in the neurons. For example, motor neuron axon is covered with myelin so that signals can move even faster between the brain and the muscle or in the nervous systems, neuron cells have a high number of dendrites so they could get the maximum amount of information from another neuron cells. [8] Especially activity of the large cortical pyramidal neurons can be detected with the EEG and the illustration of it is presented in Figure 2.

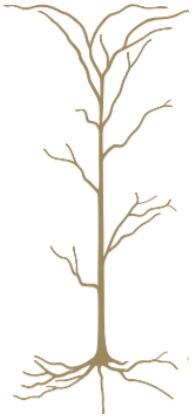

Figure 2: *Illustration of the cortical pyramidal neuron cell* [9].

2.3 Action potential and postsynaptic potential

Action potentials are all-or-none phenomena, which consists of three phases: depolarization, repolarization and hyperpolarization [4]. Different phases are presented in Figure 3. In a resting state, membrane potential is around -70 mV. Due to a stimulus, sodium

ions start to accumulate inside of the neuron, causing an increase in the membrane potential. [4] If the membrane potential reaches -55 mV, which is a threshold potential, all sodium voltage gates are opened. Rapid accumulation of sodium ions is called depolarization. [10]

In the repolarization Na^+ voltage gates close and at the same time, K^+ voltage gates are opened, allowing K^+ to flow to the extracellular matrix. This phase lasts as long as membrane is more negatively charged than in resting state. In the final phase called hyperpolarization, Na^+ ions are transported out of the cell and K^+ back to inside aiming to bring membrane potential a bit lower than its resting potential. During hyperpolarization neuron cannot be depolarized, this is called latency period. [4] [10]

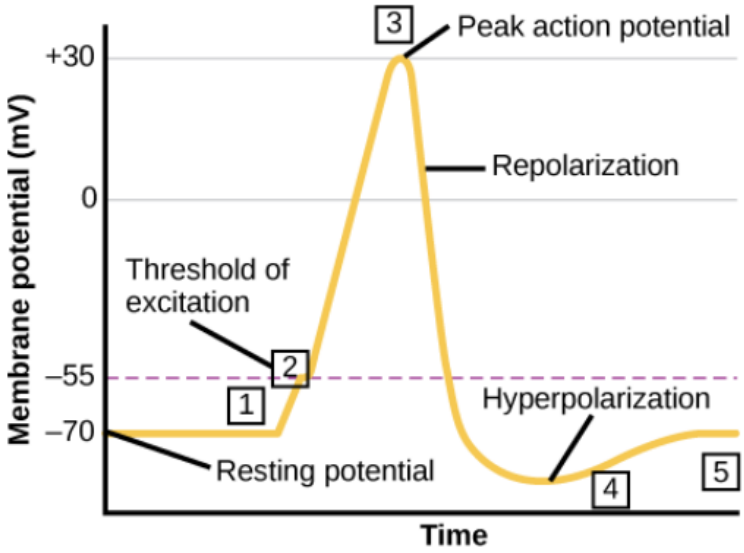

Figure 3: *Illustration of how depolarization, repolarization and hyperpolarization effect on the membrane potential* [11].

When threshold potential has been surpassed, action potential will occur. Eventually, signal reaches axon terminal. As a result of action potential, membrane comes more permeable to calcium ions (Ca^{2+}). [10] [12] Sudden influx of the Ca^{2+} triggers various complex chemical reactions which lead to exocytosis of the vesicles. Vesicles release neurotransmitters to extracellular space called a synapse. In the synapse, neurotransmitters bind to the postsynaptic receptor [12], as shown in Figure 4.

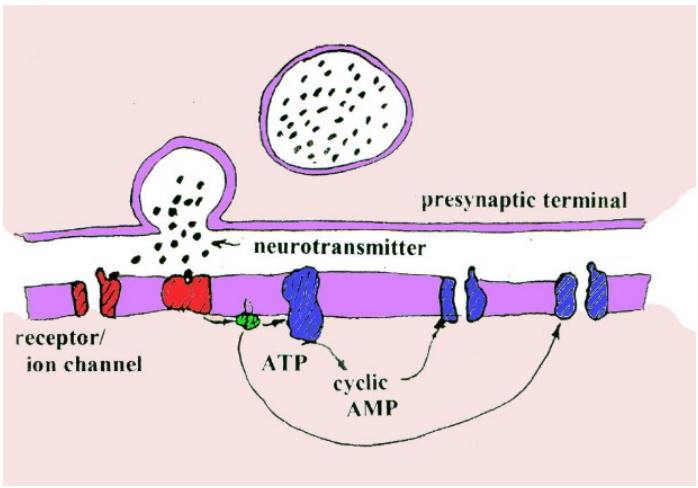

Figure 4: *Binding of the neurotransmitter to the postsynaptic receptor.* [13].

Postsynaptic potential is a change in the membrane potential of the postsynaptic neuron, caused by binding of the neurotransmitters. Binding of the neurotransmitter can either cause excitatory (EPSP) or inhibitory postsynaptic potentials (IPSP). Type of a postsynaptic potential is based on used neurotransmitter. Multiple EPSPs increases the chance of an action potential in the postsynaptic neuron, while multiple IPSPs have an opposite reaction [12], as shown in Figure 5.

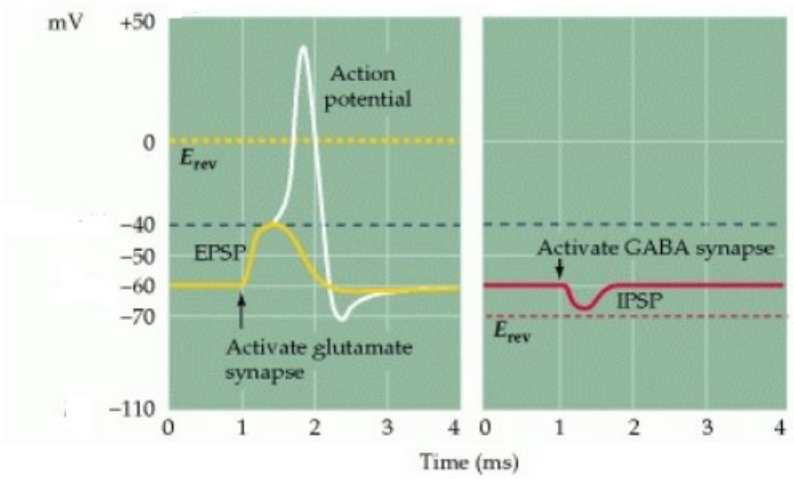

Figure 5: *Effects of ESPs and IPSPs on membrane potential* [14].

EEG is able to measure summed postsynaptic potentials from the surface of the scalp [3]. Large cortical pyramidal neurons are the most important source of postsynaptic potentials that can be seen on EEG. Postsynaptic potentials can last for 10 ms or even more while action potentials last for 1 ms. Because postsynaptic potentials last longer, they can sum up sufficiently, causing detectable potential changes on EEG. [15]

3. ELECTROENCEPHALOGRAPHY

In 1875, British physician Richard Caton exposed cerebral hemispheres of rabbits, monkeys and cats. He successfully gathered information of brain's electrical properties with galvanometer. These studies constructed the base for the future of the EEG. Many scientists followed Catons work and successfully measured electrical potentials of the brain with animals. First human EEG was recorded by German neuropsychiatrist called Hans Berger in 1925. [4]

EEG is non-invasive recording method for brain's electrical activity. Measurements are made with multiple electrodes, which are placed on the scalp. Majority of the voltage changes that can be seen in the EEG is caused by postsynaptic potentials (PSPs) of the apical dendrites of pyramidal neuron cells. Single postsynaptic potential is way too small to be measured, but the sum of approximately 50 million PSPs rises into scale of microvolts and this summation can be measured with the EEG. Recorded data is modified with filters and amplified with amplifiers before display. [3]

EEG is capable of reacting to changes in the electrical activity of the brain within milliseconds, because the neuronal activity occurs in the same time scale [4]. Therefore, it could be a valuable tool in the detection of the stroke. First line methods MRI and CT scan reveal information about the structure of the brain. It might take hours before stroke patient is imaged and even after that MRI and CT cannot always detect abnormalities in the images [16]. If the abnormalities are not seen in the first pictures, patient is imaged again after some time and images are compared with each other. Therefore, in some cases it takes a lot of time before stroke is identified with MRI and CT scan.

Compared to MRI and CT scan, EEG provides information of the brain a lot faster. Also, the EEG system is transportable because it basically consists of electrode mask and computer software. [3] So, when patient is having a stroke, patient's state could be monitored with EEG already in the ambulance before admission for example. This could make the diagnosis process faster. Like any other methods, also EEG has its pitfalls. A major limitation of the EEG is its poor spatial resolution [4].

3.1 EEG measurement system

EEG system measures summed PSPs from the scalp. This can be done by using multiple electrodes, jackbox and computer software. In clinical use, electrodes are placed on the scalp with international 10-20 system or 10-10 system. For a sufficient measurement, electrode contact impedance must be as low as possible. Natural insulators like oil and

keratin are found on scalp and they increase a contact impedance so, their effects must be reduced by alcoholic wipes, conductive gels or ionic solutions. [4]

In Figure 6, traditional EEG jackbox is shown. Jackbox is one of the main parts of EEG measuring system. Different number of electrodes are attached into jackbox via lead wires based on the used placement system. Standard input number in clinical use is 21 plus ground electrode. There are also jackboxes, which allow input of 300 electrodes. Larger number of inputs are beneficial in events that require more comprehensive sampling such as in epilepsy monitoring [4] or possibly in a stroke monitoring in the future.

Figure 6: *10-20 EEG jackbox with standard electrode input* [17].

Before signals can be displayed, they must be amplified, filtered and transformed into a digital form with the analog-to-digital converters. Amplifying of the signal is made with single differential amplifier or multiple consecutive differential amplifiers. EEG signals are easily interfered with noise and other bioelectrical signals. For example, blink of an eye or muscle movement disturb the measurement. Therefore, these unwanted signals must be eliminated with filters. In the EEG, sets of low pass filters and high pass filters are used so noise and other unwanted signals would not mix into essential information and deform it. The low pass filter allows frequencies with lower amplitude pass through and its bandpass is usually set to 70 – 100 Hz. The high pass filter passes frequencies with higher amplitude and its set to 0.1 Hz. This is because waveforms created by the brain's

electrical activity is in range from 0.1 to 100 Hz. Also notch filter is used to prevent noise caused by mains current. [4]

3.2 Electrode lead systems

Electrode placement is standardized so that the results are comparable, and the measurement covers hemisphere lobes. In clinical measurements, 10-20 system is often used and it allows a usage of 21 electrodes. Number of electrodes in the scalp can be extended by changing placement system for example, into 10-10 system which allows usage of 74 electrodes or 10-5 system where over 300 of electrodes can be attached. However, there are various choices for the placement system. Higher number of electrodes usually provides more accurate information, which is useful for example in localization of abnormalities in the electrical activity or in researches. [18] [19] Higher number of electrodes may however create conductive shunting layer on the scalp, which can disturb measurement [20].

Names for the electrodes are given based on the underlaying anatomical structure of the brain. So, F stands for frontal regions, P for parietal regions, T for temporal regions, O for occipital regions. In addition, A is for ears and C is for central regions. Specific numbers are also given to electrodes. All the electrodes with odd number are placed on left side of the head and electrodes with even numbers are placed on right side of the head like shown in Figure 7. Higher number indicates greater distance from the middle line. [19] These guidelines make reading of the EEG data easier and it can be estimated where the abnormal activity occurs.

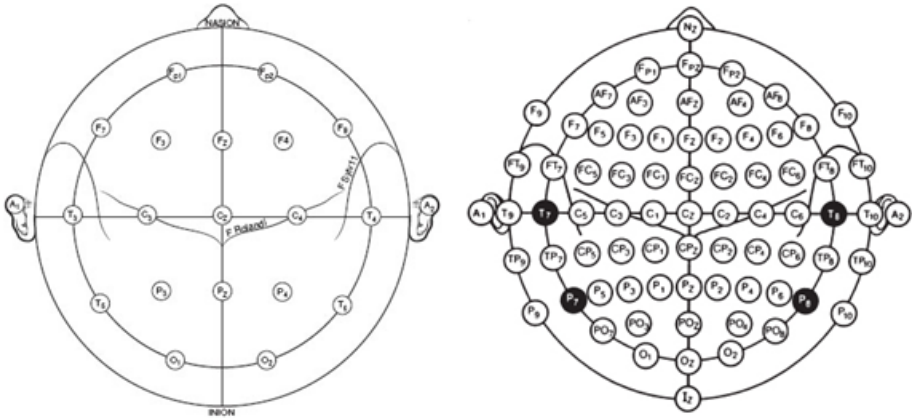

Figure 7: *Comparing 10-20 system and 10-10 system. On the left side electrode placement of 10-20 system is shown and on the right side 10-10 system is shown.* [19]

Placing 19 electrodes individually is rather a slow process, not to mention placing over 100 electrodes. Therefore, electrode placement is often speeded up by making EEG caps. EEG cap is a sort of hat made from flexible material and places for the electrodes [4]. In case of stroke, EEG cap could be attached fast to the patient for example in the ambulance so that as much as possible information could be gathered from the electrical activity of the patient's brain before admission.

3.3 EEG waves

When neurons are communicating and working together, they produce PSPs that can be measured with the EEG. Based on our activities different brain lobes and neural pathways are activated. Over the centuries, researchers have examined EEG data and they have found that certain patterns occur in specific actions. So, basically the EEG data examination is recognising normal and abnormal brain wave patterns in specific action. [4] [19]

Researchers have named five different waveforms; alpha, beta, delta, gamma and theta wave. For example, alpha wave is the dominant wave pattern during relaxation and delta wave occurs during deep non rapid eye movement (non-REM) sleep. Frequency ranges of different waveforms and function where they are most likely seen are collected in Table 1. It should be noticed that frequency ranges vary a bit between adults, elderly and children. [3] [19]

Table 1: *Names of the different waveforms, frequency ranges and action where the waveform is dominant with adults.* [4]

Name of the waveform	Frequency range (Hz)	Function where found normally
Alpha	8-13	Relaxation with eyes closed
Beta	14-30	Planning, voluntary muscle movement and focused attention
Delta	0,2-3,5	Deep non-REM sleep
Gamma	30-90	Information processing and learning.
Theta	4-7,5	Mental processing and work memory

4. STROKE

Stroke is the second leading cause of death in the world and a major cause of disability. Due to the aging population, the number of stroke deaths is expected to double by the year 2030 in industrial countries. [2] [21] Even though the patient receives high quality treatment, two out of three die or become disabled [22] [23]. Therefore, it's crucial to develop more accurate diagnostic and more efficient treatment methods so, that as many patients as possible could be able to continue normal life after a stroke.

Like any other organ the brain needs glucose, oxygen and other essential nutrients to maintain its normal functions. The brain is responsible for almost ¼ of the body's oxygen and glucose consumption [21]. Blood is supplied into the cerebral blood circulation by two artery pairs, left and right internal carotid arteries (ICA) and vertebral arteries (VA) in both sides of the neck [24], as shown in Figure 7. The stroke is a vascular CNS disease, where cerebral blood supply is interrupted either by blockade or rupture in the cerebral blood vessel and its symptoms last over 24 hours [22]. There are two main subtypes of the stroke, which are ischemic stroke and haemorrhagic stroke. When blood supply is interrupted, the brain tissue starts to die within minutes. The size of the lesion depends how long tissue undergoes hypoxia and on how severe the circulatory disorder is. Distinction between ischemic stroke and haemorrhagic stroke is crucial in stroke treatment because the management of these sub-types differ. Nowadays, distinction is made with CT or MRI [2].

4.1 Symptoms and risk factors

Each lobe is responsible for specific functions in the brain, as explained in the Chapter 2. Therefore, symptoms vary on each patient and the location of the blocked or ruptured artery can be predicted based on the symptoms of the patient. For example, if the patient has trouble with vision, the blockage or rupture is more likely in posterior part of the brain, due occipital lobe being responsible for visual processing [7] Most common symptoms of the stroke are sudden numbness in either side of the body, difficulties understanding speech, and speaking, trouble with vision and sudden dizziness.

If any of the previous symptoms is observed, a simple test should be done immediately by using F.A.S.T aide-memoire, which is presented in Table 2. [25]

Table 2: *With following aide-memoire, a person can be tested if he or she is having a stroke. F stands for face, A stands for arms, S stands for speech and T stands for time.* [25]

F.A.S.T	
Face	Stroke patient usually have hard time to smile or either side of the face is drooping
Arms	Arm feels heavy and patient does not have full control of it.
Speech	Speaking and understanding of the speech is hard for the patient.
Time	If any of the previous symptoms have occurred, call local emergency number.

Both subtypes of stroke share the same risk factors and they can be divided into two categories, modifiable risk factors (MRF) and nonmodifiable risk factors (NMRF) [26]. List of the most common modifiable risk factors and nonmodifiable risk factors are presented in Table 3.

Table 3: *Common modifiable and nonmodifiable risk factors of stroke* [27]

MRFs	NMRFs
High blood pressure (hypertension)	Age
Cardio vascular disease	Gender
Atrial fibrillation	Genes
Physical inactivity	Ethnicity
Hyperlipidaemia	Family history
Diabetes mellitus	

4.2 Normal blood supply of the brain

Cerebral blood flow (CBF) is a heterogenous function, meaning that blood flow isn't equal in the brain but rather changes locally based on the activity of the brain. On a healthy adult, cerebral blood flow is around 800 ml/min which is 15% of total cardiac output. [21] VAs arise from both sides of the subclavian arteries and before entering into the brain, VAs are combined to form a larger artery called basilar artery (BA). BA then branches into the right and left posterior cerebral arteries (PCAs) which are responsible for the posterior blood circulation of the brain. Some branches of PCAs supply blood into the

middle of the brain but the main responsibility of the middle cerebral blood supply is at middle cerebral arteries. [28] [14]

Common carotid arteries are located on both sides of the neck. Left ICA, left VA and basilar artery are shown in Figure 8. Carotid artery is divided into two branches, these two branches are called external- and internal carotid arteries. The ICAs carry oxygenated blood into the brain and the external carotid arteries carry oxygen rich blood into facial area. In the brain, the internal carotid arteries are divided into anterior- (ACA) and middle cerebral arteries (MCA) which are responsible for anterior and middle cerebral blood supply. [28] [14]

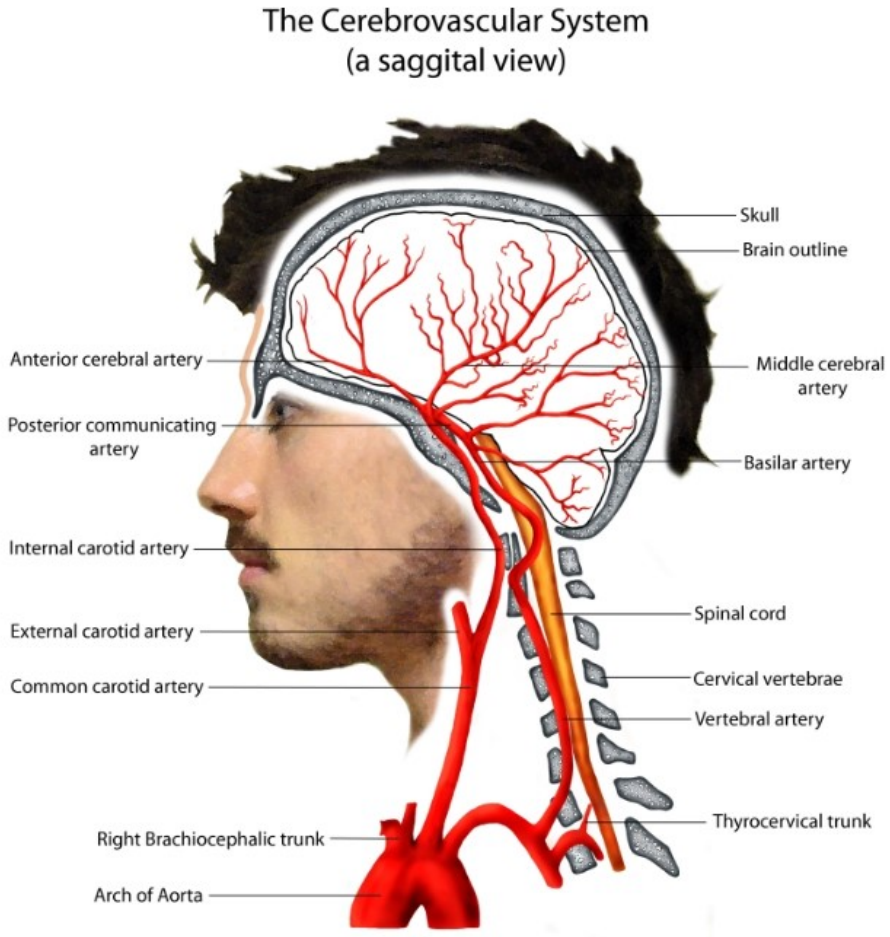

Figure 8: *A saggital view of arteries that are involved in the CBF* [29].

ICAs are connected to each other via anterior communicating artery. ICAs are also connected to posterior cerebral arteries via posterior communicating arteries. All these structures combined form the circle of Willis [24]. Illustration of the circle of Wills is presented in Figure 9. Communicating arteries ensure that blood can flow into both halves of the brain even if the blood flow is reduced or totally blocked in one of the cerebral arteries [28].

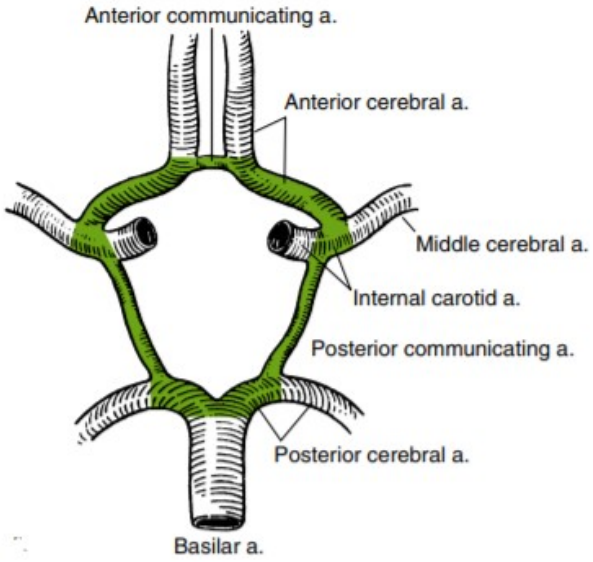

Figure 9: *Circle of Willis' anatomy is highlighted with green* [28].

Overall, cerebral blood supply is a complex system. Therefore, it is vulnerable to different vascular diseases [28].

4.2 Ischemic stroke

Ischemic stroke occurs when the blood supply is reduced or completely blocked by a blockage in the cerebral arteries. Almost 80% of all stroke cases are caused by ischemic stroke. Reduced blood flow is either caused by thrombosis, atherosclerosis or embolism and these conditions are presented later. Normal blood supply of the brain varies from 50 ml/(100g min) to 70 ml/(100g min) on a healthy adult [30].

When the normal CBF is disturbed, the brain tissue will undergo an event called ischemic cascade. Once the brain tissue does not get oxygen, the tissue starts to produce adenosine triphosphate (ATP) molecules trough anaerobic pathway. This method has two major pitfalls. [21] Firstly, with the anaerobic ATP production, enough ATP molecules cannot be produced so that the brain tissue would function normally and secondly, it

produces lactic acids as a side product. High amount of lactic acids disturbs the normal acidic-base relation and the tissue will get damaged. [31]

Lack of ATP affects the functions of potassium, sodium and calcium ion pumps. Because of this, sodium, potassium and calcium ions accumulate inside of the neurons and water flows inside of the cell to dilute the ion concentrations, leading to swelling of the neuron. At the same time, accumulation of the calcium ions in the neuron cell causes mitochondria to release apoptotic factors into cytoplasm leading to controlled cell death called apoptosis. All the factors mentioned above are involved in the tissue death during the ischemic stroke. [21] In reality, the ischemic cascade is a more complex series of chemical reactions and the more complex version of ischemic cascade is presented in Figure 10.

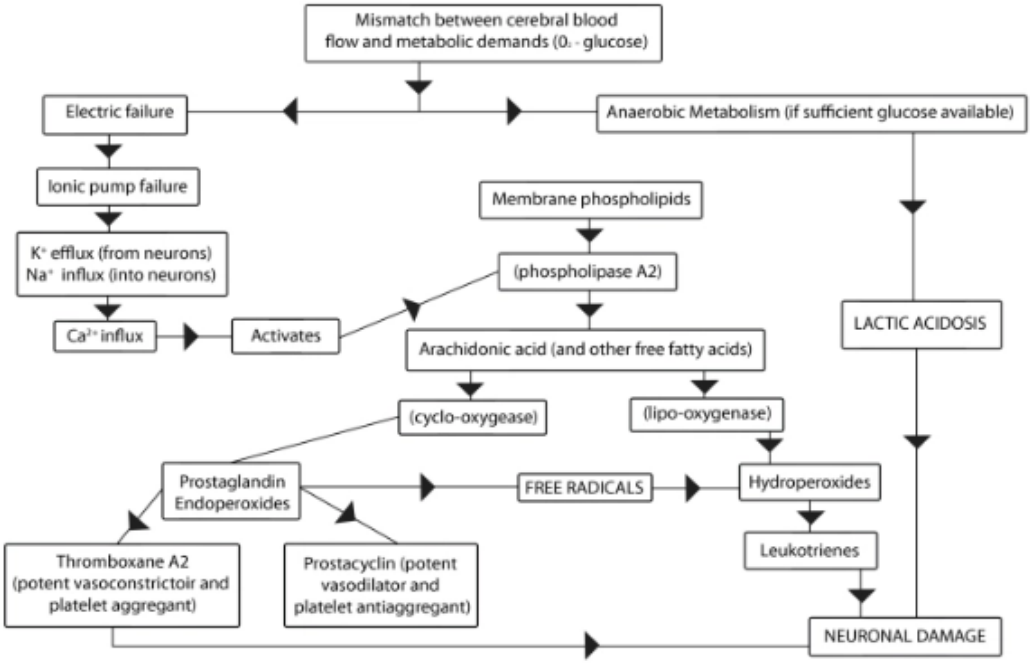

Figure 10: *More detailed description of ischemic cascade* [29].

The first line method of ischemic stroke treatment is to give to the patient tissue plasminogen activator (tPA). In tPA treatment, tPA is given intravenously and it dissolves blood clot, thus improving the CBF. Treatment should be given within 4 hours from the onset. After that, tPA treatment is not efficient [32].

4.3 Causes of ischemic stroke

Atherosclerosis is a vascular disease where plaque starts to accumulate in a subendothelial layer of blood vessel due to inflammatory reaction [33]. Plaque formation is a time-

consuming and complex process where multiple molecules are involved. Over time, growing plaque formation narrows vessels and therefore reduces the blood flow. [34]

When a blood vessel is damaged due to hypertension, atherosclerosis e.g., tissue factors and collagen are exposed to blood. Tissue factors and collagen induce platelets and fibrinogen into the damaged site, which can lead to thrombus formation. In the normal wound healing process, fibrinogen is transformed into fibrin, and fibrin molecules creates fishnet like network to prevent further bleeding. Function of platelets is to adhere to each other in order to block the wound. Because of fibrin and platelets, blood starts to coagulate and coagulated blood forms a thrombus. [35]

Embolus is a thrombus which is formed elsewhere in the body. Part of it or the whole thrombus is loosened and emanated via bloodstream to another blood vessel for example to blood vessels in the brain. It is estimated that with one-third of stroke patients, the embolus originates from the heart due to atrial fibrillation. [35]

4.4 Haemorrhagic stroke

Haemorrhagic stroke is another subtype of a stroke and it accounts for 15% - 25% of all stroke cases. With 40% of 1-month stroke mortality, haemorrhagic stroke is a lot more dangerous compared to ischemic stroke. [36] Haemorrhagic stroke is divided into two subtypes. The more common one is called intracerebral haemorrhage (ICH), in which bleeding occurs directly into the brain parenchyma. The other one is called subarachnoid haemorrhage (SAH), in which the blood bleeds into cerebrospinal fluid (CSF). [37] The separation between ICH and SAH is crucial, so that the best treatment can be chosen for the patient. Bleeding into the CSF causes hematoma formation. Increasing hematoma size of the ICH patient is shown in Figure 11.

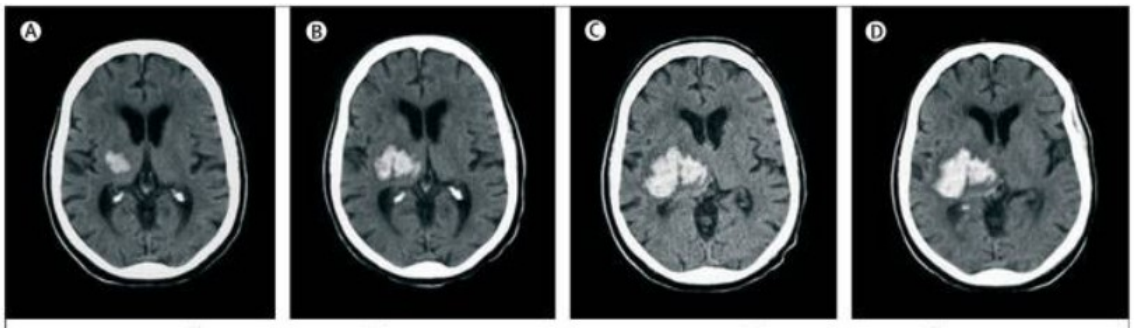

Figure 11: *Size of the ICH hematoma increases as time passes. Images were taken with CT imaging machine.* [38]

Major task in haemorrhagic stroke treatment is to prevent further bleeding. It can be done by surgery or by placing a mechanical agent into the bleeding site [39]. Bleeding to the brain parenchyma and CSF can occur in multiple mechanisms and most common ones are presented in the chapter below.

4.4.1 Causes of haemorrhagic stroke

There are several causes concerning haemorrhagic stroke, but the major ones are intracranial aneurysm and arteriovenous malformation (AVM). Intracranial aneurysm is a vascular disease where the artery walls are weakened. Weakening of the artery wall is caused by hypertension, lack of collagen, elastin and connective tissue in the structure of the artery. Weakening can cause widening or ballooning of the artery. Most common type of aneurysm is a saccular aneurysm (SA) and it accounts for 90% of all the cases. In the SA, weakening of the artery wall often causes berry-like shape in the blood vessel. [40] SA alone does not cause any harm, but it highly increases the risk of haemorrhagic stroke, especially SAH. SAs are most likely found in the proximity of the circle of Willis [41].

In normal blood circulation system arteries and veins are connected to each other by capillary bed. AVM is a vascular disease where arteries are connected to veins without capillary bed. Normally, the capillary bed would decrease the blood pressure, but when it is missing, veins and arteries are under greater pressure than normally. This strains vessels and the stress is more likely to develop into other diseases such as SA. [42]

4.4.2 Intracerebral and subarachnoid haemorrhage

ICH is one subtype of the haemorrhagic stroke, in which bleeding occurs in brain tissue (parenchyma). In ICH, most often the small intracranial vessels branched from basilar artery, posterior, middle and anterior arteries are ruptured due to chronic hypertension or other vascular diseases. [38] When the blood vessel is ruptured, blood leak into the parenchyma and starts forming a hematoma (blood clot). At the same time, the pressure starts to increase. Increased intracranial pressure decreases the CBF causing decreased metabolic rate of the neurons and eventually leading to necrosis [43]. Similar effects can be seen in cerebral oedema [44]. Expanding hematoma pushes parenchyma against the skull, causing damage to the surrounding tissue by mechanical force [45]. Mechanical pressure causes similar reactions as in ischemic cascade. In addition to cell necrosis, released molecules induce breakdown of the blood-brain-barrier, so harmful

molecules can enter to the parenchyma and cause further damage. [38] Causes of the hematoma to the brain tissue is presented in Figure 12.

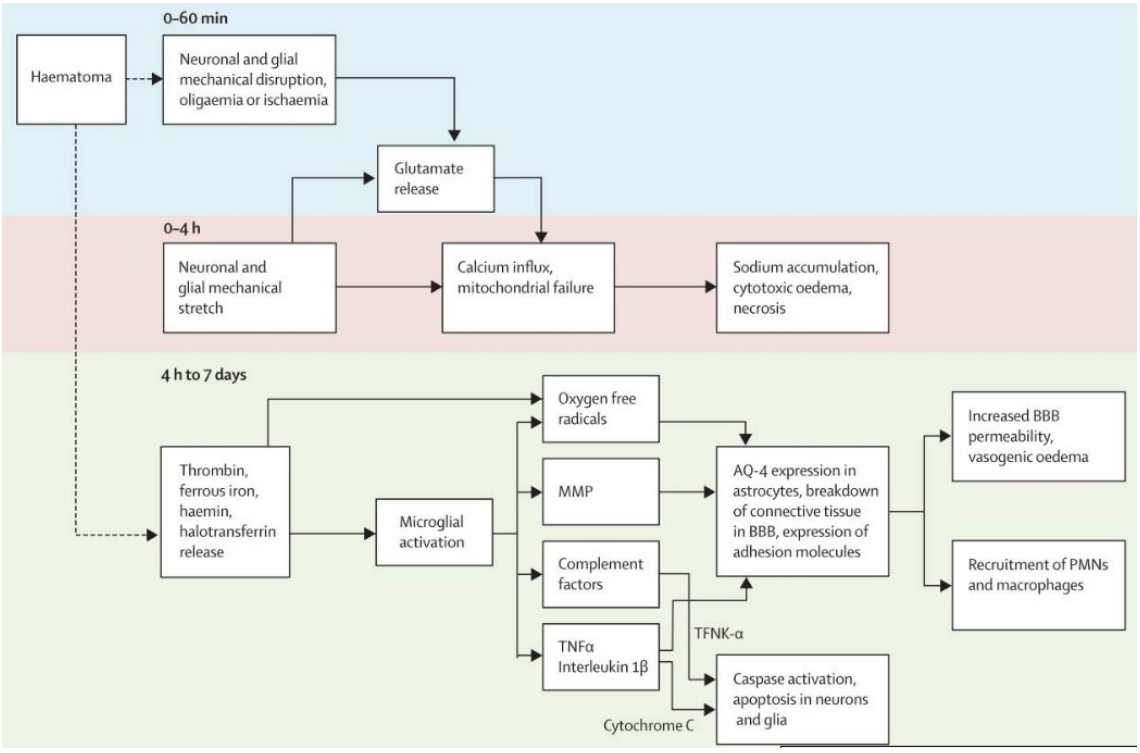

Figure 12: *Pathway to neural injury in ICH.* [38]

SAH is another subtype of haemorrhagic stroke, where blood leaks to CSF. Just like in ICH, SAH has high mortality rate. In 85% of the SAH cases, SAH is caused by the saccular aneurysm. [46] Just like in ICH, pressure inside of the skull starts to increase and cumulative blood can cause brain shifts. Blood in the interspace starts to break down to blood products. When the blood products are in touch with the blood vessels, blood vessels narrow a bit and decrease the CBF. [40]

5. EEG CHANGE DUE TO STROKE

When the patient is having a stroke, the brain tissue starts to undergo changes due to the absence of oxygen or rupture in a blood vessel. For example, hematoma and oedema create greater intracranial pressure, which forces the brain tissue to undergo geometrical changes and most likely the CBF is reduced in some regions of the brain. As mentioned in chapter 3, EEG measures electrical changes of the brain within milliseconds, making it fast, real-time measuring system [3]. This is why EEG is capable of detecting brain wave patterns fast, which suggest that the parenchyma is undergoing serious changes and patient can get quicker treatment [47].

Even though there are various reports stating that EEG would offer clinical utility in the early diagnosis and management of stroke, CT and MRI remain as the first line method of the stroke diagnosis. Despite the multiple advantages of CT and MRI, they are not 100% accurate methods. Research made by Chalela JA et al. showed that MRI was able to detect stroke from 83% of the patients (181 out of 217) and CT-scan had sensitivity of 26% (56 out of 217) to any stroke type [16]. It may take hours or even days before for changes to occur in the CT and MR images and by then the brain tissue has suffered irreversible damage [48]. EEG on the other hand may detect changes within minutes due to the fact that the neuronal activity decelerates within couple of minutes if the normal CBF is not restored [49].

In several studies, quantitative or continuous EEG monitoring is used to detect abnormalities that could be associated to stroke [47] [48] [49] [50] [51] [52]. In the quantitative EEG, data is processed with fast Fourier transform in way that in the x-axis is frequency and in the y-axis, power is presented. [4] In case of stroke, usually alpha frequencies are compared to delta frequencies. High delta/alpha or (delta + theta)/(alpha + beta) ratio is associated with the stroke [53]. In continuous EEG, data is collected from minutes to several hours. Data is presented as function of time. [4] In continuous EEG, effects of stroke can be often seen as an increased delta activity [50].

5.1 Geometrical and electrical property changes in the brain tissue

Due to focal ischemia, capillaries found in the blood brain barrier do not function correctly. This leads to efflux of water, Na^+ and blood into the extracellular matrix, causing swelling of the brain called an oedema. Overtime, swelling of the brain can potentially block the cerebral blood circulation. [54] It is well known that due to both subtypes of stroke, passive and active electrical properties are changed [55].

In a study made by Kin Fong Lei et al. made an *in vitro* test with microfluidic chip. When they forced the blood to coagulate, they noticed that impedance magnitude of the blood increased from 10^4 Ω to 10^6 Ω. [56] De Zanet et al. also found out that the coagulated blood has increased impedance [57].

Seonae et al. measured changes in the parenchyma under hypoxia with pigs. They noticed that the resistance of the brain tissue increased under hypoxia, probably due to cellular oedema. Pigs were also monitored with the EEG. During the test, Seonae et al. noticed rapid loss of the electrical activity. They suggested that this is due to reduced extracellular space [58]. Normally electrical current flows in the extracellular space, so when the extracellular space is reduced, electrical current is not able to flow efficiently [59].

In a normal state, the line between the right and left cerebral hemispheres is straight but the oedema or hematoma can change this alignment, causing a midline shift (MLS). MLS is defined as a horizontal shift seen in brain's midline structures. The MLS over 5 mm is associated with high mortality and it also affects to the cerebral metabolic rate negatively. [60] The MLS is also associated with electrical seizures [61] [62].

5.2 Changes on EEG due to stroke

When the CBF is reduced, the parenchyma starts to undergo an event called ischemic cascade because of the lack of oxygen and glucose. Pathophysiology of the ischemic cascade is presented in Figure 9. It is well known that the EEG changes are related to changes in the CBF. Pyramidal neurons are highly sensitive to hypoxia and therefore leading into multiple abnormalities, which can be seen on EEG. [47] Animal models and intraoperative EEG monitoring have shown that the changes on EEG during acute cerebral ischemia occurs within minutes [30]. In most of the cases, changes on EEG can be seen in four steps. In the first phase, when CBF drops around to 25 ml/100g/min, faster

frequencies like alpha and beta waves are gradually lost. As the CBF continues decreasing, lower frequencies like theta waves (phase two) and delta waves (phase 3) becomes more dominant. When the CBF drops below 10 ml/100g/min, parenchyma undergoes irreversible changes and EEG goes silent. [63] All the four phases that are associated to changes on EEG due to reduced CBF, are shown in Figure 13. Suppression of all frequencies on the left hemisphere, due to acute ischemic stroke is presented in Figure 14.

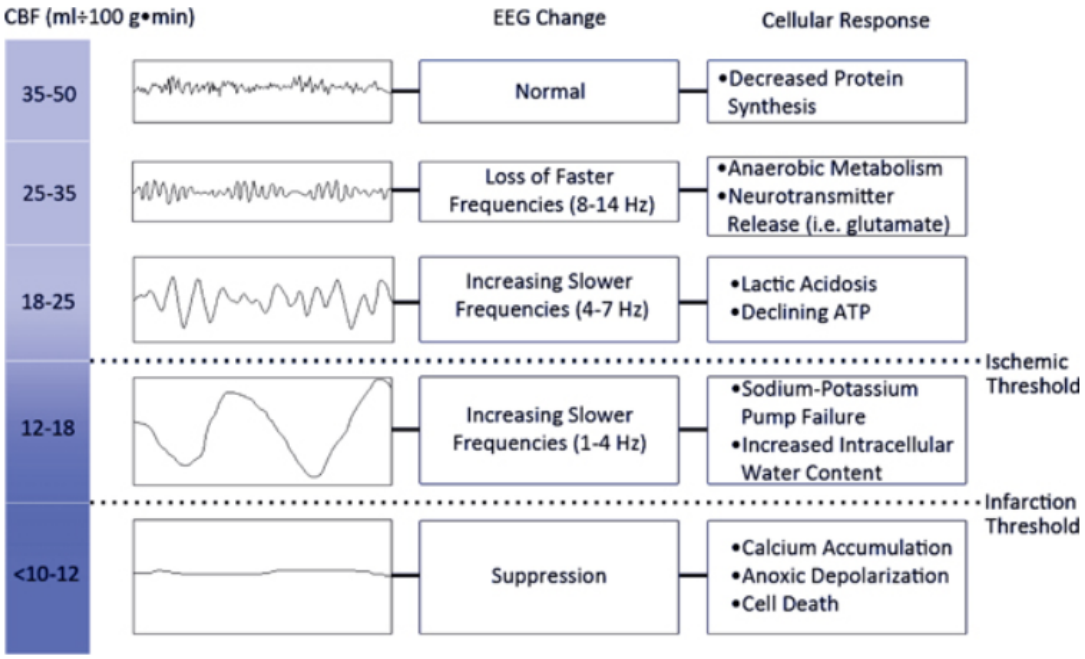

Figure 13: *Relationship between reduced CBF to EEG. Also steps of the ischemic cascade is presented.* [47]

Wu et al. examined 24 patients with the ischemic stroke. Patients were examined with high density EEG (256 electrodes) for 3 minutes. They found out that larger injuries were associated to larger delta power. Yet ischemic events are not always detectable with EEG. [60] MacDonnel et al. found out that infractions deeper than 3 cm may not be able to create abnormalities in the EEG [64]. Also, the seizures do not always create focal changes but rather bilateral changes, making localization of the lesion much harder with EEG alone. [30] [64]

In haemorrhagic events blood leaks into parenchyma or CSF. In both cases blood starts to coagulate and forms a blood clot called hematoma. Overtime, the size of the hematoma increases and pushes the parenchyma, potentially causing MLS. Valadka et al. collected data from 454 patients who had severe head injuries. 329 of the patients did not have MLS and the rest of the patients had MLS. Valadka et al. found out that cerebral metabolic rate of oxygen ($CMRO_2$) was reduced significantly when patients had MLS [60]. Slowed $CMRO_2$ could cause ischemic events that could be seen with the EEG as a

gradual slowing of the brain waves. Ghearing et al. investigated four patients with MLS, caused by lobectomy, SAH, subdural hematoma and traumatic brain haemorrhages. They found out that all four patients had contralateral epileptiform discharges which were most likely caused by MLS. [61] Another study made by Vespa et al. also suggests that the MLS is causing seizures that can be monitored with continuous EEG. Vespa et al. examined 46 patients with ischemic stroke and 63 patients with intraparenchymal haemorrhage. They found out that 28% of patients with intraparenchymal haemorrhage and 6% of patients with ischemic stroke had electrographic seizures within 72 hours from admission. The most common finding was that the patients had focal changes with secondary generalization. A minority of the patients had focal changes without the spread or generalized seizures with focal features. [62]

In a later study made by Rudzinski et al., Rudzinski and her team investigated how subdural hematoma affects EEG with 24 patients. Most common finding was the slowing of the brain waves. Slowing occurred in 92% of the patients, which supports the findings of Valadka et al. Fifteen patient had focal slowing in the EEG on the same side as the hematoma was and two patients had focal changes on the contralateral side. Rudznski et al. also found combinations of slowing, asymmetric epileptiform and periodic lateralized epileptiform discharges in 21 patients. [50]

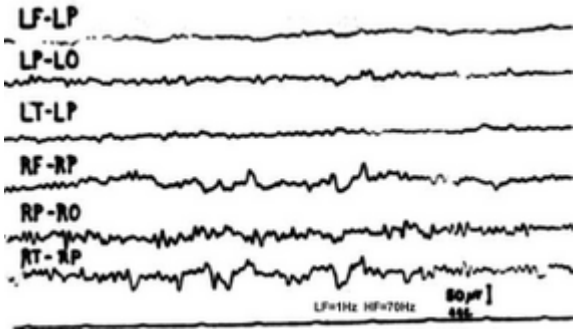

Figure 14: *Suppression of all frequencies on the left hemisphere due to massive acute ischemic stroke* [51].

Tanaka et al. noticed that subdural hematoma caused bilateral slowing in the frontal regions of the brain [52]. Hematoma also increases the distance between electrode and the brain tissue. Due to that signal detection is harder and it possibly can be seen in the EEG as a weakened amplitude [66].

In several cases, focal EEG abnormalities can be detected by using 10-20 system when data is read by an expert. However, with low electrode density, EEG data is usually rather

biased, causing mislocalization of the brain lesion. [67] For more accurate localization, electrode density of 64 electrodes or higher is required. [67] [47]

6. CONCLUSIONS

The stroke is a life-threatening condition, which causes a high number of deaths and disabilities globally. The number of the stroke patients is expected to increase in the following years, so therefore new or enhanced treatment and diagnosis methods need to be invented. EEG would add value in both pro- and post diagnosis of the stroke. Several studies show that abnormal electrical behaviour is shown in EEG within minutes [30], while MRI and CT can detect changes within hours or days based on how bad the injury is [51]. In most of the cases, the parenchyma has already suffered inversible changes before lesion is detected. It is well known that EEG changes are related to the changes in the CBF [47]. In both, ischemic and haemorrhagic events, awake patient's alpha waves are replaced with slower delta waves, which are associated with deep non-REM sleep. Also, with multiple patients, epileptic disorders are also formed.

Data produced by EEG is complicated to read since there are various montage settings and the younger patients have different EEG patterns when compared to older patients. Also, an untrained person might miss some crucial data. Therefore, nowadays EEG data should be interpreted by an expert. This problem could be overcome by developing easy-to-use algorithms which would notice these abnormal EEG changes without continuous monitoring and give approximate diagnosis. For this, more research on the relationship between stroke and EEG must be done so that algorithms have a higher probability to recognize different stroke subtypes. Another pitfall of the EEG is its poor spatial resolution. Localization is important especially in the haemorrhagic event, because further bleeding needs to be stopped fast. In some cases, EEG changes are not shown as a focal change but rather as a bilateral change. Therefore, final confirmation of a stroke needs to be done with MRI or CT.

If the EEG is used in pro diagnosis of stroke, electrodes should be applied fast, in the ambulance, for example. Also, more time can be saved by using electrodes, which can remain on the scalp during MRI or CT scan [4]. Because of the similar outcome of ischemic stroke and haemorrhagic stroke on EEG [52], EEG should be combined with another diagnosis tool so that the subtypes of stroke could be identified better. One possible combination could be EEG and multi-frequency electrical impedance tomography (MFEIT). MFEIT would be able to detect impedance changes which would add value into the localization and EEG would detect electrical changes, which are associated with the stroke.

EEG would be a beneficial tool also in post treatment of stroke. Sometimes seizures occur after days of the symptom onset [68] or ischemic stroke can recurrent within days [69]. In some cases, tPA treatment can cause a haemorrhagic event [70]. Therefore, it is crucial that patients are also monitored continuously with EEG after the stroke.

In most of the studies, there were a limited number of patients. Usually the number of patients varied from 20-60. Therefore, more research must be done so clear correlation between stroke subtypes and EEG changes can be made. In the presented studies, EEG was able to detect electrical changes due to stroke well. Therefore, EEG would add value to stroke diagnosis in the near future.

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