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Investigation of Alzheimer's disease using braingraphs

TDK Thesis
37th OTDK Informatics Section

Supervisor:
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Table of Contents

1	Introduction	3
2	Computation of braingraphs	3
3	Background of working with braingraphs	4
3.1	Difficulties with braingraphs	4
3.2	Some earlier results	4
4	Main properties of the used data and the workspace	5
5	Fundamentals for Alzheimer's disease	5
6	Averaged braingraphs	6
7	Graphs with maximal edges	7
7.1	Graph-theoretical tools	7
7.2	Biological meaning of maximal graphs	9
7.3	Analysing the maximal graphs for the first set of graphs	9
7.3.1	Connectivity properties of the maximal graph	9
7.3.2	Comparison of the global connectivity of the brains of female and male subjects	9
7.3.3	Proving differences between the brains of females and males	10
7.3.4	Comparing the global connectivity properties of demented and healthy subjects	11
7.4	Conclusions from connectivity properties	11
8	Difference between demented and healthy people in the level of communication of specific vertices	11
8.1	The role of hippocampus in dementia	11
8.2	Finding vertices which can have a role in dementia	12
8.3	Connection between Alzheimer's Disease and Attention Deficit Hyperactivity Disorder	13
9	Examining single edge weights and their change	13
9.1	Background for working with SVM-s	13
9.1.1	Separation of 2 classes	14
9.1.2	Some well-known kernel functions	14
9.1.3	Optimization	16
9.2	Data used during the SVM-analysis	16
9.3	Classification by edge weight	17
9.4	Statistical analysis of edge weight differences	19
9.5	Edge weight changes	20
9.6	Biological findings	22
10	Summary	24
	References	25

1 Introduction

The human brain is undoubtedly the most complex organ known to humanity, and its function and structure have captivated mankind for centuries. In this work, we analyse the structure of the human brain using braingraphs. These are mathematical graphs: their vertices represent different brain regions, while the edges characterize their connections. Our primary results involve finding differences between the brains of female and male subjects and noting significant differences connected to brain areas having specific responsibilities, such as short-term memory and attention orientation. We also make a significant conclusion about the scientifically important role of the caudate nucleus in dementia, as we notice a higher connectedness of the caudate nucleus in demented people. This is crucial, as the thoughts about the role of the caudate nucleus are not consistent in the literature, as different authors conclude multiple possibilities on this topic.

2 Computation of braingraphs

Modern technology enables the precise use of MRI scans. Thanks to this, the Oasis Brains Project [1] released MRI and PET data of 1098 individuals. (Diffusional MRI is a type of magnetic resonance imaging that examines water molecules, taking advantage of the fact that they move differently near axons. PET stands for positron emission tomography, which uses radioactive substances to visualize metabolic changes [2].) Subsequently, using the Lausanne2008 atlas [3], the brain (surface) was divided into 1058 brain regions, each approximately 1 cm^2 in size. The vertices of the braingraphs are the aforementioned brain regions, with consistent labels from 1 to 1058 across individuals. Weighted edges are drawn between vertices based on the number of axon bundles (i.e., the thickness of the nerve bundle) connecting two brain regions. Additionally, we will use the length of nerve fibers. It is important to note that the length of an edge does not correspond to the geometric distance between the two vertices, as the geometric locations represent only three coordinates. At the same time, the examined brain regions are not point-like. (Moreover, axonal fibers are geometrically not close to line segments.) The coordinate system determining the coordinates of brain regions has three axes: the x -axis for left-right, the y -axis for front-back, and the z -axis for up-down direction. The larger the coordinate value, the farther the vertex is forward, upward, or to the left in the brain. (The fractional anisotropy of the fibers is also saved in the graphs, but we will not address this in our thesis. Fractional anisotropy is a quality measure of the tractography process, which is not necessary for our purposes here.) We did not create individual graphs: Bálint Varga calculated the graphs before we started our work based on the MRI data. For an example of a braingraph projected onto a cross-section of the brain and the axonal fibers in the brain, see Figure 1. [4] [5] [6] Note that the axonal fibers end at the surface of the brain, where the grey matter is located, which cannot be seen in the image. The fibers connect those grey matter areas.

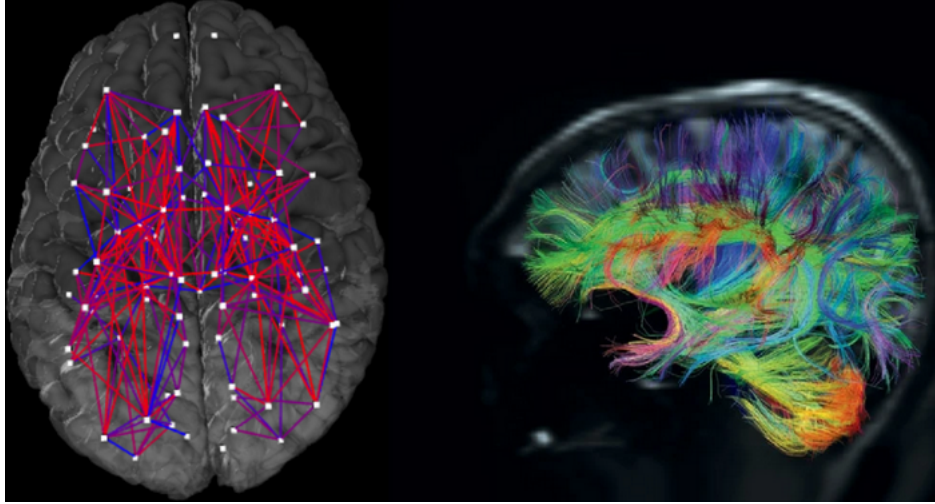


Figure 1. The left side of the figure shows a braingraph projected onto a human brain. White dots indicate the positions of the different brain regions. We connect two brain regions with an edge if we detect axonal fibers between them. The colour of the edge carries information about the thickness. On the red-blue scale, the more red an edge, the thicker it is. On the right side of the figure, the physical location of the axonal fibers can also be observed, with different colours indicating different directions.

3 Background of working with braingraphs

3.1 Difficulties with braingraphs

MRI datasets need to fulfill several quality-related characteristics for braingraph construction. The first one is the aforementioned high and consistent quality of the images. That is not surprising: if we want to work with graphs calculated from MRIs, there are two steps where inaccuracies can happen. In the MRI-making phase and in the graph-calculating phase, roundings occur, implying natural inaccuracies. In the past decade, we have been able to use technologies to make the construction of the braingraph possible. The second problem is that many MRI sets contain few MRIs. That is a big problem, as from a set of 10-20 MRIs, it is hard to have a statistically significant conclusion. Furthermore, two different MRI sets can hardly be compared because of the possibilities of various methods the data acquisition modalities use during the MRI scans, and that different scanners are used in different locations.

3.2 Some earlier results

Because of the above, the method of using braingraphs is new to science. One of the first MRI datasets that is large enough and of good quality was provided by the Human Connectome Project [7]. The primary dataset of young adults contains 1064 people's MRI, for each person one MRI. The subjects are only healthy people, so the dataset can only be used for fundamental research. From this dataset, braingraphs were calculated, described in [8]. From these graphs, the Budapest Reference Connectome Server [4] [5] was produced, which is an online, parametrizable graph-visualization software. The data was used internationally, for example graph convolutional networks were investigated in [9]. The data can be used for finding differences between sexes, as in [10]. The data was already analysed by us in two earlier papers [11] [12]. Through the thesis, the set of

graphs from the Human Connectome Project is called the *first set of graph*, and the set of graphs from the OASIS Project (which includes demented people) is called the *second set of graphs*.

4 Main properties of the used data and the workspace

From the OASIS-3 dataset, braingraphs were calculated by Bálint Varga in five different resolutions. During our research, we only used the lowest and highest resolutions, which have 124 and 1058 vertices respectively. The usage of the different resolutions have different advantages and disadvantages. The benefit of higher resolution is that we can investigate smaller parts of the brain, making it easier to be more specific in our conclusions. The disadvantage is that the new vertices are often obtained from the divisions of vertices in lower resolutions. Furthermore, inaccuracies are much more significant in higher resolutions. Additionally, in lower resolutions the larger brain areas usually correspond to only one or two vertices and can be trusted more. All the graphs are undirected. Loops (self-edges) exist in the original graphs but are used only in Section 9. This is because until that point, we mostly investigate the different vertices' connection with the other vertices and look at connectivity properties. While in the case of SVM analysis, there is no reason to exclude the loops, as self-edges can also be helpful in recognizing dementia.

The entire graph analysis was written by us, in language Python. The codes were written in the IDEs Pycharm and Visual Studio Code. The main libraries that were used are Pandas [13] for dataframes, Scipy [14] for mathematical formulas and statistical investigation, Networkx [15] for graph properties, scikit-learn [16] for support vector machines (SVM-s), Matplotlib [17] for diagrams and Paramiko for the easier usage of the datamine server.

The Oasis Project also published data on the subjects' different basic properties. These include their gender, handedness, age, educational level, race, height, weight, etc. In addition, the results of the psychological examination of the subjects were also published. These include the Clinical Dementia Rating (CDR) [18] and the conclusion about the level of dementia. Some subjects were examined multiple times, and all their results were published. For this reason, we call a subject demented if at least one psychological test concluded dementia. The attributes of the subjects were collected and merged into two easy-to-use Excel tables.

Unfortunately, the published psychological results are incomplete in some cases and therefore, cannot be used. Also, not all the graphs are available in the desired form, so we will only work with the subjects with complete psychological results and a proper graph. During most of the research, we used 1098 subject's MRIs, from which 493 were demented and 605 was healthy. The sex of 1077 subjects were provided, from which 600 were female and 477 were male.

5 Fundamentals for Alzheimer's disease

Alzheimer's disease is a progressive neurodegenerative disorder that primarily affects the brain, leading to a decline in memory, cognitive function, and the ability to perform daily activities. It is the most common cause of dementia among older adults. The hallmark characteristics of Alzheimer's include the formation of abnormal protein deposits called

plaques and tangles in the brain, which disrupt communication between nerve cells and ultimately result in death.

As the disease progresses, individuals may experience memory loss, confusion, difficulties in problem-solving, language impairment, and changes in behavior. Alzheimer’s disease significantly impacts not only the affected individuals but also places a substantial burden on their families and caregivers.

While there is currently no cure for Alzheimer’s disease, various treatments and interventions aim to manage symptoms and improve the quality of life for individuals living with the condition. Ongoing research seeks to understand the underlying causes of Alzheimer’s more and develop potential therapies to slow down or halt its progression. Early detection and timely intervention are crucial in managing the disease and supporting the affected individuals and their families. In 2020, the approximated number of people worldwide affected by Alzheimer’s was around 50 million [19] [20]. Throughout the thesis, dementia and Alzheimer’s will be used for the same disease (although they do not mean exactly the same). This is because science can hardly differentiate patients with only psychological tests used for diagnostics in the OASIS Project. This implies that we can only talk about the diseases of dementia and Alzheimer’s together.

6 Averaged braingraphs

Analysing individual braingraphs from n people to draw general conclusions about the human brain can be challenging. Therefore, instead of analysing individual graphs, we can average them to create a consensus graph. We averaged the graphs in the following way: the position of each vertex is calculated by simple averaging, placing different brain regions in an average-sized brain. (The positions are still given with three coordinates: the origin is in the lower-right corner of the back of the brain.) Averaging the attributes of the edges is more complicated. The first step is to sum all the values obtained from the people. The first non-trivial question is whether the lengths and thicknesses of the edges should be averaged differently. It makes no sense to divide the sum of lengths by n because most edges do not appear in all of the subjects. However, we would lose information in this case, since we would obtain a disproportionately small number for the length. Therefore, in the case of length, we must divide by the number of individuals in which the given edge appears. On the other hand, in the case of thickness, it is informative whether 0 thickness occurs in some people. Therefore, in the case of thickness, we must divide by n . So, using this averaged graph, we do not need to perform calculations on n graphs in every case, it is sufficient to work only with the averaged graph. Through the thesis, some results will use the averaged graphs, and some will not, so in every result, we make it clear whether we analyse the individuals or the averaged graph. (It is essential to consider that every edge in the averaged graph appears in at least one person, as we divide by a positive number in both cases.) Thus, if $\#(i, j)$ denotes the number of occurrences of edge (i, j) , and $s_{i,j,k}$ and $h_{i,j,k}$ are the weight and length of edge (i, j) in the k -th person, then the equations for the edges of the averaged graph are as follows.

$$s_{i,j} = \frac{\sum_{k=1}^n s_{i,j,k}}{n} \quad (1)$$

$$h_{i,j} = \frac{\sum_{k=1}^n h_{i,j,k}}{\#(i, j)} \quad (2)$$

An averaged graph can be calculated separately for the sick subjects and healthy subjects, giving us two different graphs. The main differences between these two graphs suggest tendencies of differences between the brains of healthy subjects and sick subjects.

7 Graphs with maximal edges

7.1 Graph-theoretical tools

We want to examine the structure of the brain not only as a whole but also by looking at the structure of only the thickest edges. This way, we can only investigate the most crucial connections. It should be mentioned that the motivation is not to filter out the distorting thin edges, as for that goal, looking at only the thickest $p\%$ would be more efficient, with some well-chosen p . Actually, p could depend on the data, as we do not know anything about the distribution of the thickness of the edges in advance.

Definition 7.1. Consider any weighted simple graph with pairwise distinct edge-weights. Call the associated *maximal graph* the graph whose vertices are the vertices of the original graph, and its edges are exactly those edges that are the maximal weighted edge of at least one of their endpoints. Call the *extended maximal graph* the one whose edges consist of exactly the two largest weighted edges for each vertex.

In the case of the brain with n vertices, we selected n edges considering multiplicities in the maximal graph, but there may be edges that we chose twice. First, let us state and prove a general graph-theoretical lemma connected to this.

Lemma 7.1. Consider any simple graph with weighted edges and suppose that all the edge weights are different. We state that the corresponding maximal graph is acyclic, i.e., it does not contain any cycle of length at least three. Graphs of this type are called forest graphs, as all their components are tree graphs.

Proof. Let us assume indirectly that the graph has a cycle and let its length be $k \leq n$. Enumerate the vertices of the cycle in order with the numbers $1, 2, \dots, k$.

We know that any edge has two endpoints, so any selected edge has the largest weight for one of its endpoints. Since both endpoints of each edge in the cycle are contained in the cycle, it must have been selected because of one of the vertices in the cycle. We know that exactly one edge has been selected for each vertex, so there is a bijection between vertices and edges in the cycle based on for which vertex we selected which edge.

Since the edge $(1, 2)$ was selected, without the loss of generality, we can assume that it was selected for vertex 1. However, as the vertex 2 has two edges in the cycle and one of its edges already has a bijection pair found, the edge $(2, 3)$ must have been selected for vertex 2. This means that the weight of the edge $(2, 3)$ is greater than the weight of the edge $(1, 2)$ because otherwise the edge $(2, 3)$ would not have been selected for vertex 2. Proceeding along the cycle with the previous reasoning, we get that the weight of each new edge is greater than the previous one. But then, denoting the weight of the edge (i, j) by $w(i, j)$, we obtained that $w(1, 2) < w(2, 3) < \dots < w(k-1, k) < w(k, 1) < w(1, 2)$. This is a contradiction as $w(1, 2) < w(1, 2)$ cannot hold. $\square$

Remark 7.1. The previous proof can also be said by starting from the largest weighted edge in the cycle. We can assume without the loss of generality that this is the edge $(1, 2)$, and it is selected for vertex 1. However, due to the selection at vertex 2, the edge

$(2, 3)$ must have a higher weight, which is a contradiction. Another alternative proof is that no edge could be the minimal weighted edge in the cycle. That is because, for both endpoints of this edge, the other edge from the endpoint has greater weight, meaning that the least-weighted edge could not have been paired for either of its endpoints in the bijection.

Remark 7.2. It is worth noting that during the proof, we only used the fact that no two edges sharing an endpoint have the same weight. So, the condition that every weight is different can be replaced by the more general one, only needing the different weights for the vertices locally.

For each component of the maximal graph, we can select the most important vertex. The importance criterion for the vertices is the sum of weights of their edges (equality does not hold in this ordering either).

Definition 7.2. The *center* of a graph (V, E) is the set of v vertices, for which $\max_{u \in V} d(u, v)$ is minimal, where the function d denotes the graph-theoretical distance for unweighted graphs. (The definition makes sense as the distance is unique for any pair of vertices.)

Lemma 7.2. For tree graphs, the center consists of at most two vertices.

Proof. Let us assume indirectly, that the graph has three vertices in the center. Then, as the graph is acyclic, there must be two of them that are not neighbours, let them be u and v . Then, there must be a vertex $s \neq u, v$ on the unique path uv . As u and v are both in the centers, the vertex having the largest distance to v is in the direction of u from v and vice versa. This implies that s also must be in the center, as otherwise, moving u towards v and v towards u would decrease the maximal distance of u and v , so they would not be in the center. However, this means that in the path uv , which is not empty, the maximal distance of s is smaller than the maximal distance for u and for v . This is because the vertex with maximal distance for u and for v must be in the direction of s . This is a contradiction, as s would have a smaller maximal distance than the vertices in the center. $\square$

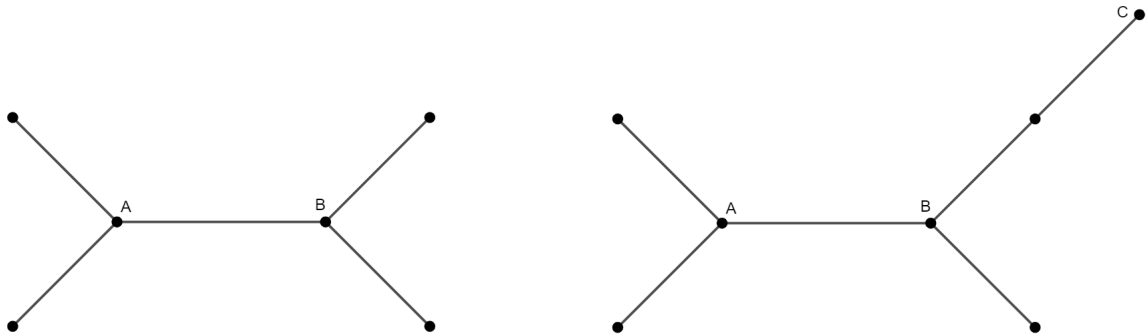


Figure 2. On the left part of the figure, we can see a tree with two vertices in the center, namely A and B . This is because the maximal distance for them is 2, but for all the other vertices, the maximal distance is 3. On the right part of the figure, we added the vertex C . This changed the center to the set $\{B\}$, as now only B has maximal distance 2.

7.2 Biological meaning of maximal graphs

The question arises: What biological role do connectivity properties play in the brain? Let us consider why it is essential for the brain to have strong edges connected cohesively. Connectivity means that any two vertices can communicate with each other through the specified, fast nerve fibers. It is important to note, that unmyelinated axons can conduct at the speed from about 0.5 to 10 m/s, while myelinated axons can conduct at the speed of even up to 150 m/s [21]. Compared to this, the 2-4 ms synaptic delays in chemical synapses are significant losses of time [22]. The mentioned property is fulfilled when the most important edges form a network encompassing the entire brain, allowing any two vertices to communicate.

Biconnectivity (nonseparability) means that even in the case of failure or weakening of any vertex, we can still reach any other vertex from any vertex. This is a crucial brain property, because the ability to bypass certain vertices' functions is important due to diseases or aging. Some vertices can take over the role of others to some extent, this phenomenon is called neuroplasticity.

Furthermore, it is biologically advantageous when the most important vertices are central in each component, because this places the most vertices as close as possible to the most important vertex (with the given physical characteristics).

7.3 Analysing the maximal graphs for the first set of graphs

7.3.1 Connectivity properties of the maximal graph

First, we describe the results using the above tools for the graphs that were calculated from MRIs of the Human Connectome Project. These graphs have 1015 vertices, and fortunately, in our averaged braingraph, every edge has a different weight, so Lemma 7.1 can be applied to it. From this, we know that in the brain, this graph is a forest graph (containing only tree graphs as components). In the case of the averaged braingraph, its maximal graph has 27 components. The components are not of the same size: there are three components with a vertex count above 200. Interestingly, one covers most of the right hemisphere, the other covers most of the left hemisphere, and the third is symmetrically present in both.

In the view of Lemma 7.2, we found that from the 27 components, 19 has the most important vertex in the center. This implies a really strong correlation, because for a graph with n vertices, the probability for this is at most $\frac{2}{n}$. (It is worth noting, that out of the remaining 8 components, 6 has a central neighbour for the most important vertex, so it is also relatively close to the center of the component.)

7.3.2 Comparison of the global connectivity of the brains of female and male subjects

The neuroscience of sex differences delves into the intricate study of characteristics that distinguish the female and male brains, exploring the interplay of genes, hormones, and social learning in shaping brain development over the lifespan. The debate surrounding male and female brain anatomy persists, with controversies arising from brain size, structure, neurotransmitters, and function differences. While some argue for significant sex differences, others challenge these claims, citing potential biases and methodological flaws. For example, recent research has scrutinized structural disparities, with a 2021 meta-synthesis revealing that sex accounts for approximately 1% of the brain's structure

or laterality, mainly manifesting in total brain volume differences [23]. However, conflicting findings persist, as subsequent studies emphasize regional sex differences even after adjusting for global brain size [24].

Historically, by 1854, German anatomist Emil Huschke observed a size discrepancy in the frontal lobes, laying the groundwork for intensified research into sexual dimorphisms [25]. As scientific methodologies evolved, studies applying molecular and neuroimaging approaches uncovered a wealth of information about both structural and functional disparities between male and female brains.

Evolutionary explanations propose that sex differences in cognition, such as enhanced information recall in females and higher spatial intelligence quotient in males, may have arisen from adaptive pressures during human evolution. For instance, oxytocin, a hormone associated with uterine contraction and lactation, has been linked to improved spatial memory, potentially aiding mothers in locating distant food sources for nurturing offspring [26].

Structurally, male brains tend to be larger and heavier than female brains, with variations in cortical thickness, surface area, and grey matter. Lateralization, the specialization of brain functions in one hemisphere over the other, is also a topic of discussion, with men often attributed to having a more lateralized brain. Discrepancies in the amygdala, hippocampus, and grey matter distribution contribute to behavioral differences between males and females [27].

Brain networks, combined with precise imaging technology, open a new dimension to the discussion. In the next subsection, we highlight some differences using the connectivity methods described at the beginning of the thesis.

7.3.3 Proving differences between the brains of females and males

As mentioned above, it is biologically advantageous to have a smaller number of components in the maximal graph and to have the extended maximal graph closer to being biconnected. Earlier, from the Human Connectome Project MRI-s with different methods, it was found that the brains of females are better structured than the brains of males [28]. Here, we substantiate these results by looking at the subjects' brains one by one. The average number of components in the case of females is 62.1, while in the case of males, it is 66.2. This is a small but significant difference. Running a Student's t-test [29] on the component numbers gives a p-value less than 10^{-17} . On the other hand, a bigger difference occurs in the case of biconnectivity of the extended maximal graphs. Here, the number of vertices without the extended maximal graph becomes disconnected is 54.6 for females and 74.9 for males. Running a Student's t-test gives a p-value less 0.09. One should note, that this data is highly deformed, because in some subjects, the extended maximal graph is not even connected (this is more likely to happen in males). If we only look at connected extended maximal graphs, we get an average number of cutting vertices of 5.4 in females and 7.0 in males. Running a Student's t-test on the number of cutting vertices, gives a p-value less than 10^{-16} . This observation may relate to the fact that males have a higher mortality rate than females with strokes [30].

The above calculations were also done for the second set of graphs. The exact numbers of the two sets of graphs cannot be compared, as a slightly different parcellation of the brain was used, and the technology was not the same either. However, the tendency was the same: women had a slight advantage when looking at the number of components in the maximal graph. In comparison, there was a massive difference in the level of how close the extended maximal graph is to be biconnected.

7.3.4 Comparing the global connectivity properties of demented and healthy subjects

One could expect that demented people should have less connected brains. On the other hand, the difference between the demented and healthy people is really small also in the case of the averaged graph and also in the case of looking at the individuals one by one. Both in the case of maximal graphs and extended maximal graphs, the difference is less than 1%. Running a Student's t-test gives a p-value of 0.49. A trivial idea could be to check whether the sum of all weights differs. The answer is no: the exact numbers for demented and healthy people are 676881.5 and 695905.7 respectively, so the difference between demented and healthy people's sum is less than 3%. Running a Student's t-test gives a p-value of 0.04.

It is really important to consider the fact, that until now, we have only looked at the average of the people's properties, and the averaged graph has not been examined. It is not automatic that we should get similar results in any of the above questions for the averaged graph. So, the averaged graphs are tested too: we make an averaged graph for females, males, demented people and healthy people. In fact, we get that the averaged graph of females has better connectivity than the averaged graph of males. Furthermore, there is no significant difference in the case of demented and healthy people. On the other hand, maybe surprisingly, the averaged graphs have better connectivity than the individuals one by one. In fact, in every attribute of connectivity mentioned above, the averaged graph of all subjects is significantly better, even than the subject with the best connectivity.

7.4 Conclusions from connectivity properties

To summarize the results above, we can state that these connectivity attributes have biological meanings matching earlier theories. These include the fact that the brains of females are better connected than the males'. On the other hand, in the case of dementia, no general differences can be concluded between healthy and demented people with this method.

8 Difference between demented and healthy people in the level of communication of specific vertices

In the previous section, we saw that it is likely that the difference in demented people's brains is much more local than global. This leads to the idea of investigating the vertices one by one in the averaged braingraph.

8.1 The role of hippocampus in dementia

The main idea comes from the fact that people with Alzheimer's usually lose short-term memory first [31]. This means that memories from the early past are usually forgotten easier for people with dementia. The brain area hippocampus is scientifically accepted to greatly impact short-term memory. Because of this, if people with dementia had a worse-connected hippocampus, that could be a reason. (Actually, it is difficult to tell which is the reason and which is the result. It is not known whether the dementia comes from the not well-connected hippocampus or backwards.) It is really important to state

that in the earlier sections, we saw that there is no significant difference when looking at the sum of all weights. This does not imply that there is no significant difference for some vertices. In fact, because of the Law of large numbers [32], the existence of vertices having more weight-sum in healthy people is likely, but the number of these vertices is expected to be the same as the number of vertices having more weight-sum in demented people. (This was not a precise formulation of the Law of large numbers, but here, the intuition is enough to show that we need to have significant differences.)

After the calculations, the average fiber counts of the hippocampus for sick and healthy people are respectively 5097.22 and 5630.74, which is a significant difference of more than 10%. Running a Student's t-test gives a p-value less than 0.01. This means that the area hippocampus is connected worse and degenerated in the case of demented people compared to healthy people.

So, what we got here is that the hippocampal region in demented subjects is degenerated compared to the healthy subjects. One thing can surely be stated: the short-term memory loss symptom really is a direct implication of hippocampal deficits. On the other hand, at this phase, it cannot be decided whether the hippocampal damages implied the dementia or backwards.

8.2 Finding vertices which can have a role in dementia

The one-by-one sum of weights for all the 124 vertices were calculated for the demented subjects and for the healthy subjects too. A threshold ratio of 10% was chosen, which we will use as a threshold for significance. If a vertex has difference of at least 10% between healthy and demented weight-sum, then we say this vertex does have a role in dementia. Running Student's t-tests gives p-values less than 0.01.

Now we give the list of brain areas that have significantly less weight-sum in demented people than in healthy people: caudal middle frontal, entorhinal, posterior-medial pulvinar and hippocampus.

Now we give the list of brain areas that have significantly less weight-sum in healthy people than in demented people: caudate nucleus and medulla oblongata.

The average weight-sum of brain areas for demented and healthy subjects

Brain areas	Hippocampus	Middle frontal	Entorhinal	Medial pulvinar	Caudate	Medulla oblongata
Demented	5097.22	8492.34	1662.19	1857.75	10620.16	872.6
Healthy	5630.74	9434.9	1856.96	2118.83	9509.07	755.28

Table 1. We can see the six brain regions with a difference of at least 10% between the weight-sum in demented and healthy people. The first row lists the brain areas, the second row lists the weight-sum in demented people, and the third row lists the weight-sum in healthy people.

Now we go through all the listed brain areas and give reasons, using results from literature and symptoms of dementia, why they really have a role in dementia. We already mentioned the hippocampus and its role in short-term memory.

The (caudal) middle frontal is thought to have a role in attention control and attention orientation [33] [34].

The entorhinal cortex is proven to have a serious role in memory formation and memory navigation [35]. This makes the statement stronger that memory loss is caused by the lack or dying of neurons around brain areas responsible for memory.

The medial pulvinar nucleus is famous for its role in eye movement [36] and attention regulation [37]. It is also proven that it has a role in attention deficit disorders [38].

The caudate nucleus is most famous for its role in motor processes and in Parkinson’s disease [39]. On the other hand, it has an impact on procedural learning and associative learning [40]. As Parkinson’s also includes dementia in many cases, it is not surprising that the caudate nucleus is also in the list. On the other hand, the role of the caudate nucleus in dementia is controversial. Some in the literature conclude that the volumetric reduction correlates with dementia [41], and some conclude the opposite [42]. As we saw above, our thesis concludes that the overconnectedness of the caudate nucleus correlates with dementia. So, this thesis is important in this controversy, as we only looked at the axonal fibers connected to the caudate nucleus, not its volume. Hence, the results listed in this paper show that the level of communication of the caudate nucleus is higher in demented people.

The medulla oblongata is located in the lower part of the brainstem. Its main responsibilities are involuntary functions. On the other hand, it is already thought to have an impact on dementia and aging [43] [44]. The higher sum of edge-weight in demented people can be because of the severe axonopathy and tauopathy in this brain area, and these could distort the MRIs and braingraph-calculating codes. One could notice that plaques similar to this also exist in the hippocampus, and reduction was still explored in the weight-sum of the hippocampus. A reason for this anomaly could be the original lack of axons from the hippocampus causing dementia, while tauopathy is just a symptom of dementia. Also, the structures of plaques in the hippocampus and in the medulla are not exactly the same. In the case of the caudate nucleus, the plaques are not a possible reason, as no plaques were found in the region of the caudate nucleus.

8.3 Connection between Alzheimer’s Disease and Attention Deficit Hyperactivity Disorder

New research papers found connection between ADHD and Alzheimer’s using psychiatric methods [45] [46]. Our work also proves the connection, as the areas (caudal) middle frontal and medial pulvinar have a serious role in attention orientation. Actually, our work only proves that demented people tend to have attention deficits too, the backwards does not imply automatically. It is a possibility that people with ADHD do not tend to also have Alzheimer’s. This cannot be investigated in this situation, as the examined subjects are only diagnosed with the existence of dementia and nothing else.

9 Examining single edge weights and their change

In this section, our main goal is to find single edges whose weight decides with high precision whether an individual is healthy or not. We also investigate the change of weights as the subjects age.

9.1 Background for working with SVM-s

Support vector machines were one of the earliest well-performing machine-learning tools. They are used for classification problems. The general idea is to separate the classes with hyperplanes. We take a hyperplane defined by its normal vector n , take the vector to the point from the origin v and check whether the scalar product $n \cdot v$ is smaller or greater than some constant value c . There are strategies to separate more than two classes but I will not describe them because we worked with only two classes in our research.

9.1.1 Separation of 2 classes

Lemma 9.1. Let us formally define what a separation by a hyperplane means. We take the normal vector n and constant w and points belong to one of the classes in case $nx + w < 0$ and belong to the other otherwise. We can say that $n + 1$ points in general position are always separable in n dimensions regardless of how they form the two classes. General position means that $k + 2$ points always span a $k + 1$ dimensional affine plane, which is equivalent to the statement that no $n - 1$ dimensional hyperplane contains more than n points.

Proof. Proof by weak induction. In the case of $n = 0$ and $n = 1$, the statement is trivial. Let us assume that we already proved the lemma for $n = k$ and now we would like to prove it for $k + 1$. Now we can look at the first $k + 1$ points and transform the space in such a way, that the last coordinate of those $k + 1$ points are 0. After that, separate them in k dimensions. Now without impacting the scalar product of the first $k + 1$ points with the normal vector of the hyperplane, we can add any last coordinate. Therefore, we can choose it in such a way that the scalar product of it and the last point have the required relation with the constant w . This finishes the proof. $\square$

Now we know that even though our data might not be perfectly separable - each point is on the required side of the hyperplane - in our current dimension, in high enough dimension the data will almost surely be perfectly separable. Therefore the approach we would like to take is to map our data points into higher dimensions and optimize the separation process there. After that, we can take the intersection of the separating hyperplane with the image of the original plane. This is not necessarily a line since our mapping was not necessarily a linear mapping. For example, if we map our two-dimensional data to three dimensions using $f(x, y) = (x, y, x^2 + y^2)$ function, then the (x, y) plane transforms into a cone in the (x, y, z) space. This means that our decision boundary will be the intersection of a plane and a cone, thus a hyperbola, parabola, or ellipse.

As we can see from this example, the method's advantage is that we can recognize nonlinear connections between the points of the classes using a nonlinear mapping. On the counterpart, it requires a lot of computational power to calculate the position of our original plane in the higher dimension, find the separating hyperplane and then take the inverse of its intersection with the original planes image. Fortunately, we do not need the exact position of the points, only their scalar product, which makes the computation much quicker.

Definition 9.1. The kernel function is a $\kappa : \chi^2 \rightarrow \nu$ function, which satisfies the following conditions:

- Symmetric: $\kappa(x, y) = \kappa(y, x)$
- For any $m \in \mathbb{N} \forall x_1, \dots, x_m \in \chi$ its corresponding kernel matrix $K(i, j) = \kappa(x_i, x_j), \forall i, j \in \{1, 2, \dots, m\}$ is positive semi-definite $\Leftrightarrow K(c, c) = c^T K c \geq 0 \quad \forall c \in \mathbb{R}^m$.

We know that for every kernel there exists a mapping $\Phi : \chi \rightarrow \nu$, where ν equipped with an inner product, where $\chi(x, y) = \langle x, y \rangle_\nu$ [47]. And we also have alternative criteria to check whether a function is a valid kernel or not [48].

Therefore, it is possible to reduce the number of required calculations by only defining the kernel function and not caring about the position of the mapped points. This is called the kernel trick or kernel method.

9.1.2 Some well-known kernel functions

- Linear kernel: $\chi(x, y) = x^T y$. In this case, the decision boundary remains an $n - 1$ dimensional hyperplane if our data is n dimensional.

- Polynomial kernel: $\chi(x, y) = (\gamma x^T y + c)^d, \gamma > 0$. A valid γ, c value pair is $\frac{1}{d}, 1$ if our original data was d dimensional. Here, the decision boundary is a degree d polynomial in our original plane.
- RBF kernel: $\chi(x, y) = \exp\left(\frac{|x-y|_2^2}{\sigma^2}\right)$, where σ is the variance of the kernel. A proper value for it, is for example $\frac{1}{d}$, where the data was d dimensional.
- Sigmoid kernel: $\chi(x, y) = \tanh(\gamma x^T y + c), \gamma > 0$, with an example proper parameter of $\gamma = \frac{1}{d}, c = 1$ in the case of the d dimensional dataset.

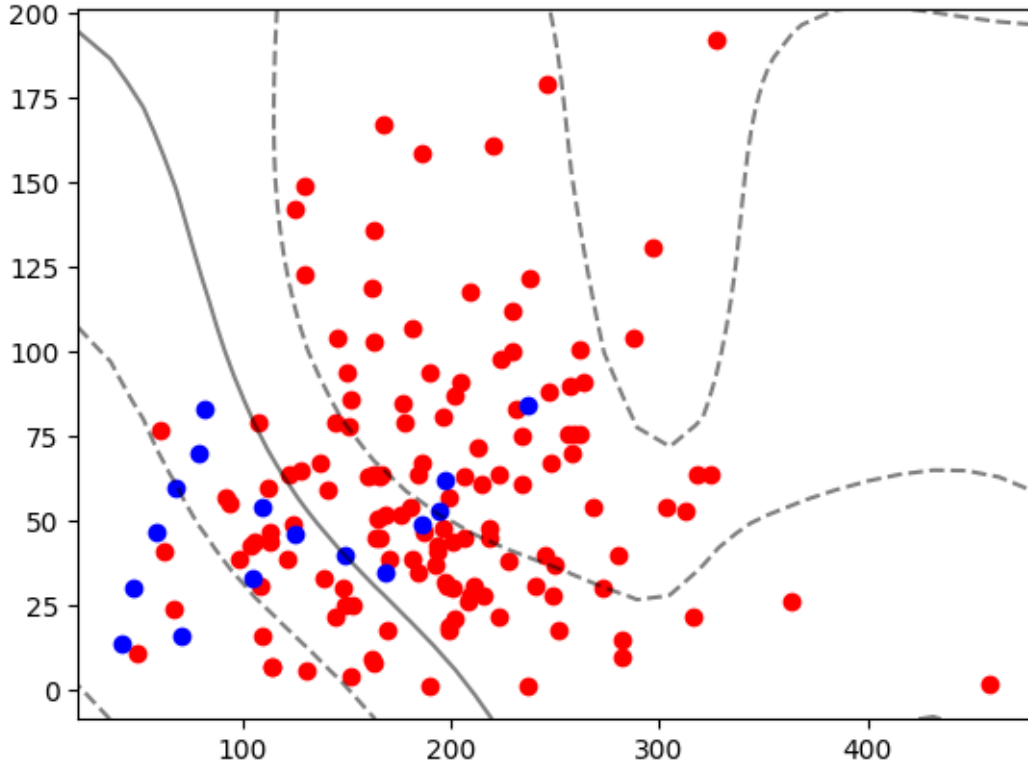


Figure 3. Decision boundary of a support vector machine with RBF kernel visualized. The blue dots represent demented individuals, whereas the reds represent healthy ones. The stripped curves represent its margin

Decision boundaries of sigmoid kernel in SVC

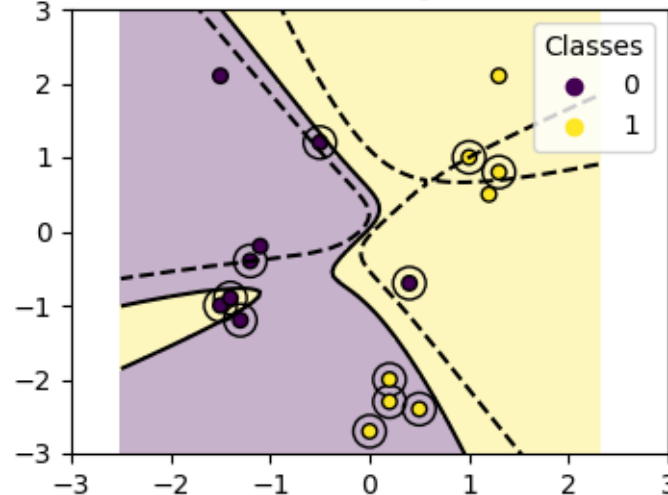


Figure 4. Decision boundary of a support vector machine with sigmoid kernel visualized. The stripped curves represent its margin. The picture is from the Scikit-learn website [49]

9.1.3 Optimization

The optimization part works just as in the case of other machine-learning tools. First of all, we normalize the input data - map all coordinates into $[0, 1]$ - to avoid being influenced too much by coordinates, which has significantly larger values than others. We initialize some function that maps our input data to a guess (in this case, that is a $wx + b = 0$ plane, and our guess is the value of $wx_i + b$ for input data x_i). Our goal is to find the optimal parameters. Furthermore, we define a softmax function. We use it for the output of our prediction, and it maps it into probabilities, i.e., our prediction vector $p \in \mathbb{R}^n$ if we have n categories and we map it to a vector such that the sum of its coordinates is one and none of them is negative. A common function for that is $f(p_i) = \frac{e^{p_i}}{\sum e^{p_j}}$, where our prediction vector was $p = (p_1, p_2, \dots, p_n)$. If we have two categories, our output vector is only one dimensional, representing the likelihood of the input being in category 1 and is usually mapped into $[0, 1]$ using the softmax function $f(p) = \frac{1}{1+e^{-p}}$. After that, we define some loss functions in such a way that the smaller our loss, the better our separation. Therefore, we would like to minimize the loss function (or maximize the dual problem). For that reason, we calculate its derivative in our weight and bias parameters (if our separating hyperplane is $wx + b = 0$, then w is the weight and b is the bias) and upgrade those parameters using the fact that the greatest increase is to the direction of the gradient, and greatest decrease is to the opposite direction (we make a small step with our parameters into that direction). After some steps, we should find a local minimum, (which is likely not a global minimum) and we can consider our optimization done. We might want to start from multiple initial guesses so we increase the chance of not finding a local minimum with unusually high loss value [50] [51] [52].

As in the case of most AI-s, the issue of overfitting exist here as well. It can be avoided by techniques such as introducing a penalty term which makes the SVM prioritize a higher even if it comes with a few more misclassification, choosing only the most important features and cross-validating (having a training and testing group).

9.2 Data used during the SVM-analysis

From the OASIS-3 dataset we had multiple clinical diagnoses - such as AD demented, healthy, and uncertain - across several years for each person participating in the study. The diagnoses were also marked with the day they were made on. It also contained their MRI scans Bálint Varga used for calculating the braingraphs, marked with the day they were made on as well. In order to have a better training group for the SVM, at this part of the research we used a stricter classification method for the patients. At first, we only classified those who had more than one clinical diagnosis whose results were consistent - had the same healthy, uncertain or demented diagnosis - over time. Even though we could only classify 721 - 616 healthy, 99 demented, and 6 uncertain - braingraphs from the original 974, we had enough graphs from both classes to start training the SVM.

For the later part of the research which will be specified later, we classified the rest with the following method. Checked the day their MRI scan was performed and compared it with the neighboring clinical results. if those matched, the braingraph was classified as that class. If not, we marked it as uncertain. In addition to that, we said that if any of the later clinical results were healthy, the graph should be classified as healthy. It was done because it is impossible to recover from dementia. Furthermore, we assumed that it is less likely that a demented individual is diagnosed as healthy than its counterpart.

It is important to mention that 3 subjects were excluded from the study, because they had only one clinical test (on day 1), therefore it would have been impossible to accurately predict the class of their brain graph.

For the complete information about which brain area is coded by which id, see Table 2.

Node id - name pairs

node id	node name
106	Left Amygdala
107	Left Hippocampus
46	Right Amygdala
47	Right Hippocampus
87	LH Entorhinal Cortex
29	RH Inferiortemporal Cortex
27	RH Entorhinal Cortex
44	Right Pallidum
99	Left Central Lateral Posterior Medial Pulvinar
89	LH Inferiortemporal cortex
116	Left Hippocampus Fimbria
104	Left Pallidum
56	Right Hippocampus Fimbria

Table 2. Id - name pairs of the brain areas presented in our paper. RH denotes right hemisphere and LH denotes left hemisphere

9.3 Classification by edge weight

To decide which kernel function should be used, we searched for edges where the difference of mean weights between the two classes was substantial to make it more probable that there is an accurate separation using that edge. After that we tested the efficiency of different kernel types using these edge weights by averaging the results of the classification process - randomly selecting a 0.8 part of the edge weights as training group, training the SVM on it and test it on the test group - 1000 times. We did the averaging to ensure that the results were not due to some unlucky or lucky selection of the test group. Due to the huge sample difference between the two classes, we used the SVM with a balanced class weight setting throughout the research. Therefore, it penalized the misclassification of demented people more to simulate a scenario where the two groups are of the same size. That way we avoided results with no significance, such as classifying everyone as healthy. The results in the case of one edge can be found in Table 3. Efficiency represents the success rate of the separations.

Kernel functions and their efficiencies

Kernel function	efficiency demented	efficiency healthy	efficiency overall
linear	0.740000	0.721500	0.723400
polynomial	0.814375	0.609900	0.631000
rbf	0.691900	0.768900	0.760770
sigmoid	0.686900	0.772000	0.761200

Table 3. Performance of the different kernel types in our dataset in two-dimensional separation. Performance can be seen in both classes, and an overall success rate is calculated as well.

As we could see the linear kernel performed well in both classes and had a great overall efficiency as well. This implies the presence of a very simple relationship between edge weights and dementia. Due to its other advantages we decided to continue our research using linear kernel. Furthermore, we only included edges found in at least 500 of the healthy braingraphs and 80 of the demented ones to ensure that our findings are extensive in the population. This criterion was satisfied by 2098 edges. Then, we randomly selected 80% of each group to train our SVM on that data and tested the decision function on the rest. That was done to avoid the phenomenon of overfitting. We also averaged the results of 10 iterations this time. The edges with at least 0.7 overall efficiency can be seen in Table 4.

Separation by a single edge weight

source id	target id	success rate demented	success rate healthy	success rate overall
106	107	0.715	0.828	0.812
46	47	0.68	0.798	0.781
87	106	0.68	0.759	0.748
47	47	0.785	0.732	0.740
29	47	0.715	0.738	0.735
27	46	0.75	0.724	0.727
107	107	0.815	0.711	0.726
44	47	0.74	0.717	0.720
99	107	0.765	0.701	0.710
89	107	0.655	0.714	0.706
107	116	0.632	0.715	0.703
104	107	0.715	0.698	0.700
47	56	0.69	0.702	0.700

Table 4. Performance of the edge in the classification of the individual based on its edge weight. Decision function in this case is checking whether the value is greater or smaller then the learned optimal separation point. Performance can be seen in both classes and an overall success rate is calculated as well.

After that we selected the 72 edges which had an efficiency rate of at least 0.6 or 60% in both classes. This was made to test the most promising two dimensional sub-spaces in a two-dimensional SVM classification process. During that we tested each pair of those edges. The three best performing edge pairs are listed in Table 5.

Best pairs when separating in two dimensions

source 1	target 1	source 2	target 2	Success rate
L.C. L. P. M. Pulvinar	L. Hip. Fimbria	R. Amygdala	R. Hippocampus	0.838
R. Amygdala	R. Hippocampus	L. Entorhinal Cortex	L. Amygdala	0.827
R. Amygdala	R. Hippocampus	R. Amygdala	R. Hippocampus	0.824

Table 5. Best performing edge pairs in the decision of whether the individual is demented or healthy based on these two weights. In the used version of the braingraphs multiple smaller regions were united to a larger region, therefore there are self-edges (loops) in the graphs.

We would like to mention the fact that even though it was a bit lower on the list, the left amygdala - left amygdala, right hippocampus - right hippocampus performed best in the

demented category with a success rate of 0.825 and achieved a combined success rate of 0.813. For this reason, this edge was selected for the following step.

These rates showed that the addition of more dimensions can increase accuracy. It means that even though there is some dependency between the decrease of different edge-weights in healthy people - since $1 - A_{e_1, e_2}$ accuracy of edges e_1, e_2 in two dimension does not equal to $(1 - A_{e_1}) \cdot (1 - A_{e_2})$, where A_{edges} is the accuracy of the SVM in those dimension-, the correlation in the demented brains is higher. To further strengthen this claim, we classified the brain graphs of the group whose clinical test results were not consistent.

During the SVM classification we trained the SVM 10 different times on a randomly selected part of the original group, then predicted the individuals class and if 8 out of 10 times it gave the same result we accepted it and otherwise we diagnosed the person as uncertain.

After that, we compared it to the results of the method described in the diagnoses part. The seen outcome was mixed. Out of the 116 patients whom the SVM classified as healthy, only 11 was classified as demented when the other was used. This matched up with the expectations. But out of the 126 patients classified as demented by the SVM, 81 was classified as healthy by the method that used clinical test results. From this comparison, those who were classified as uncertain were excluded due to their diagnosis being uncertain. This discrepancy could be explained by several factors. First of all, the individuals had to have only one late healthy diagnoses to classify their brain graphs as healthy using the second method and during classification if the previous result was healthy and the following is uncertain we considered them healthy. These facts could have resulted in a huge amount of false healthy classifications. (There were several patients who had been diagnosed as demented or uncertain at one point and then got healthy. Maybe taking the demented result as stronger would have been a better approach.) Furthermore, it is hard to catch by clinical test the point of them becoming demented as it does not even have a clear boundary (remember that all of these persons got diagnosed as demented at one point by the clinical tests). We looked for but did not find a correlation between the misdiagnosed persons and whether their dementia was caused by Alzheimer's disease or not.

9.4 Statistical analysis of edge weight differences

It was known before this research that some brain areas increase in size in the event of dementia [53]. This phenomenon was also observed during our research. Therefore a two-tailed p-value calculation and t-test is necessary. It was also observed in our data that not only do the healthy and demented edge weights follow a normal distribution (which is predicted), but they have a very similar standard deviation. Some data regarding that fact about the 9 best performing edges during the separation are listed in Table 6.

Differences of distribution between healthy and demented edge weights

source id	target id	number h	mean h	std h	number d	mean d	std d	significance (p)
106	107	613	168.731	45.772	98	100.500	52.112	$< 10^{-14}$
46	47	613	158.922	40.509	98	100.469	44.804	$< 10^{-14}$
87	106	609	220.179	62.814	98	150.500	62.116	$< 10^{-14}$
47	47	616	652.503	129.481	99	492.768	131.267	$< 10^{-14}$
29	47	615	212.745	72.756	97	143.639	70.853	$< 10^{-14}$
27	46	609	227.117	58.187	98	158.561	66.327	$< 10^{-14}$
107	107	615	646.829	126.411	98	500.980	113.209	$< 10^{-14}$
44	47	615	110.649	42.313	98	69.061	36.826	$< 10^{-14}$
99	107	615	85.333	31.683	99	54.212	29.387	$< 10^{-14}$

Table 6. We performed a two-tailed paired t-test under the null hypothesis that the edge weight does not change in the case of dementia. With $\alpha = 0.001$ and using the Holm-Bonferroni [54] method, we got the result that we can reject the null-hypothesis in all of these cases.

We calculated the p-values for all of the 2098 edges with the null-hypotheses of the mean edge weights not changing. That was made by using two-tailed, equal variance t-test. After that, we performed the Benjamini-Hochberg [55] procedure on their respective p-values with $\alpha = 0.001$. The result was, that we can accept the hypothesis of the mean edge weight being different in the case of demented individuals and healthy individuals in the case of 447 edges. Using Holm-Bonferroni, we could accept the alternative hypothesis in 196 cases.

9.5 Edge weight changes

Another method of our research was to look at how brain graphs evolve over time. We only focused on the 9 best-performing edges from the 1 dimensional separation problem. In the ideal case we would have been able to study those people’s braingraphs whose diagnoses changed from healthy to demented over time. Unfortunately, this group contained only 6 people. In the following tables, std diff means the standard deviation of the elements in the difference vector. Statistics about these 6 people and the edges are listed in Table 7.

Edge weight changes, different diagnosis - sample size 6

source id	target id	mean h	std h	mean d	std d	std diff	significance (p)
44	47	63.667	16.207	54.833	24.653	22.302	0.377
27	46	220.667	76.146	169.833	57.513	42.428	0.032
46	47	129.167	21.028	112.833	34.452	19.356	0.094
29	47	148.333	49.682	172.500	72.351	51.113	0.299
99	107	52.833	17.747	49.333	23.338	24.089	0.736
106	107	129.333	49.625	104.667	41.491	20.733	0.033
107	107	524.167	121.901	455.500	105.521	65.717	0.051
87	106	156.667	50.571	161.667	62.012	30.509	0.705

Table 7. We performed a two-tailed paired t-test under the null hypothesis that the edge weight does not change in the case of dementia. The std diff value represents the standard deviation of the values in the difference vector, i.e. for each patient we calculate the difference of the edge weights at time 1 and time 2, and calculate the standard deviation of these values. H represents the healthy result, d represents the demented result.

We also calculated the same for people who had multiple braingraphs, but had the same diagnosis each time. These can be seen in Table 8. and Table 9.

Edge weight changes, demented diagnosis twice - sample size 10

source id	target id	mean m1	std m1	mean m2	std m2	std diff	significance (p)
44	47	55.600	20.678	49.200	26.832	20.748	0.355
27	46	148.900	39.416	169.500	69.524	41.794	0.153
46	47	84.700	26.086	62.100	16.495	16.534	0.002
29	47	101.700	29.766	102.300	47.917	53.146	0.972
99	107	57.300	25.241	58.200	33.373	19.779	0.889
106	107	78.800	35.739	59.600	29.342	39.578	0.159
107	107	464.900	100.732	410.500	71.951	55.909	0.013
87	106	158.000	58.543	150.300	67.697	38.586	0.544

Table 8. We performed a two-tailed paired t-test under the null hypothesis that the edge weight does not change in the case of dementia. The std diff value represents the standard deviation of the values in the difference vector, i.e. for each patient we calculate the difference of the edge weights at time 1 and time 2, and calculate the standard deviation of these values. M1 and m2 represent the calculated edge weights from the first MRI scan and second MRI scan respectively.

Edge weight changes, healthy diagnosis twice- sample size ~ 190

source id	target id	mean m1	std m1	mean m2	std m2	std diff	significance (p)
44	47	104.401	44.416	110.859	44.147	38.924	0.023
29	47	212.479	74.809	210.974	77.609	67.234	0.757
46	47	156.411	37.003	153.167	44.333	37.237	0.229
27	46	221.237	67.014	221.653	58.580	59.552	0.924
87	106	213.505	61.576	216.147	59.326	59.999	0.545
106	107	163.677	47.354	164.255	49.546	40.355	0.842
99	107	81.573	30.540	82.339	31.880	27.505	0.700
107	107	650.625	116.661	631.589	121.133	83.132	0.002

Table 9. We performed a two-tailed paired t-test under the null hypothesis that the edge weight does not change in the case of dementia. The std diff value represents the standard deviation of the values in the difference vector, i.e. for each patient we calculate the difference of the edge weights at time 1 and time 2, and calculate the standard deviation of these values. M1 and m2 represent the calculated edge weights from the first MRI scan and second MRI scan respectively.

Using the Benjamini-Hochberg method, we got the result that we can not reject the null hypothesis of these edge weights that do not change over time in the individual’s brain even with a higher than the previous $\alpha = 0.01$ value. However, in the case of the first two tests, it might be due to the small sample size.

We were also interested in how these numbers compare to each other in the case of interhemispheric and same hemispheric connections. Since tractography, may be less accurate in the case of interhemispheric connections, we did a verification by summing up all interhemispheric and same hemispheric connections in healthy and demented individuals and made the same t-test as above.

Edge weight changes, same and different hemisphere

edges	mean h	std h	mean d	std d	significance (p)
in the same hemisphere	396411.484	19857.142	389677.434	29644.329	0.00395
interhemispheric	6842.836	1497.570	5393.354	1413.936	$2.122 \cdot 10^{-18}$

Table 10. We performed a two-tailed paired t-test under the null hypothesis that the edge weight does not change in the case of dementia.

As the table shows, there is a much more drastic difference in the case of interhemispheric connections. In the case of edges connecting vertices in the same hemisphere, there is only a loss of 1.7% of the total edge weights, whereas there is a 21.2% decrease in the case of interhemispheric connections. Furthermore, we performed a SVM separation for these summed up values and got a total accuracy of 66.7% using only the interhemispheric edges and 56.7% using only the edges connecting vertices in the same hemisphere.

9.6 Biological findings

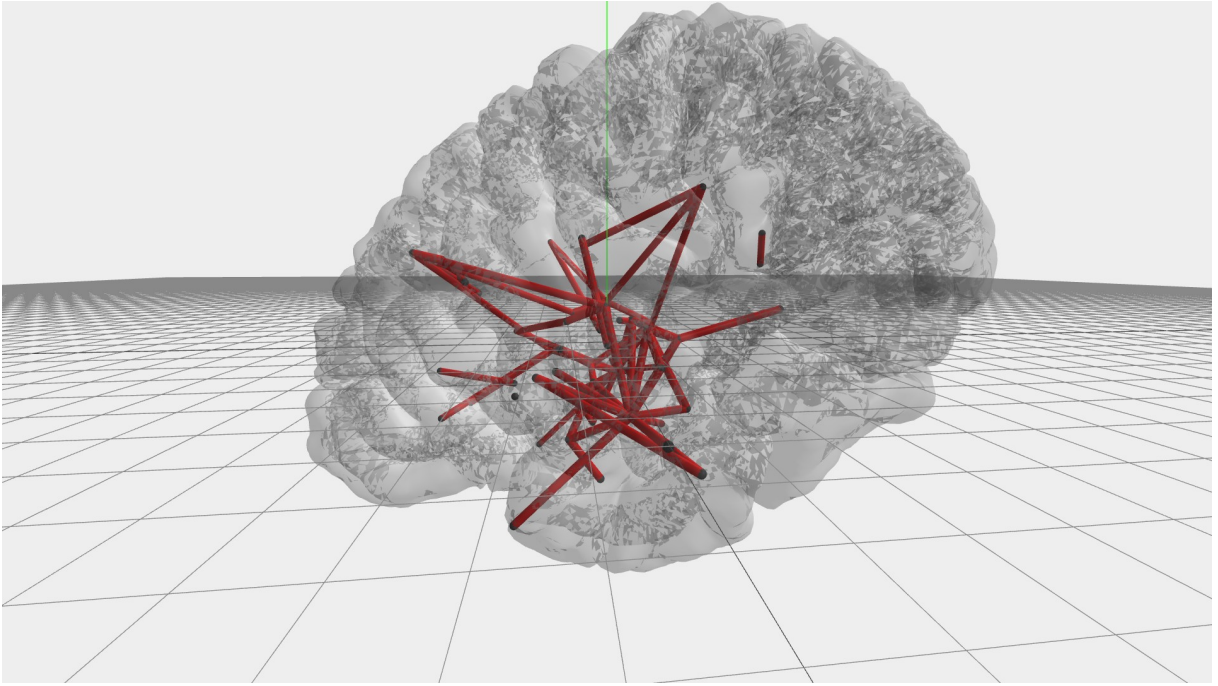


Figure 5. Edges in which case the SVM separation had efficiency 0.6 in both categories. The edge standing a little bit alone is the edge between the cuneus, and calcarine sulcus.

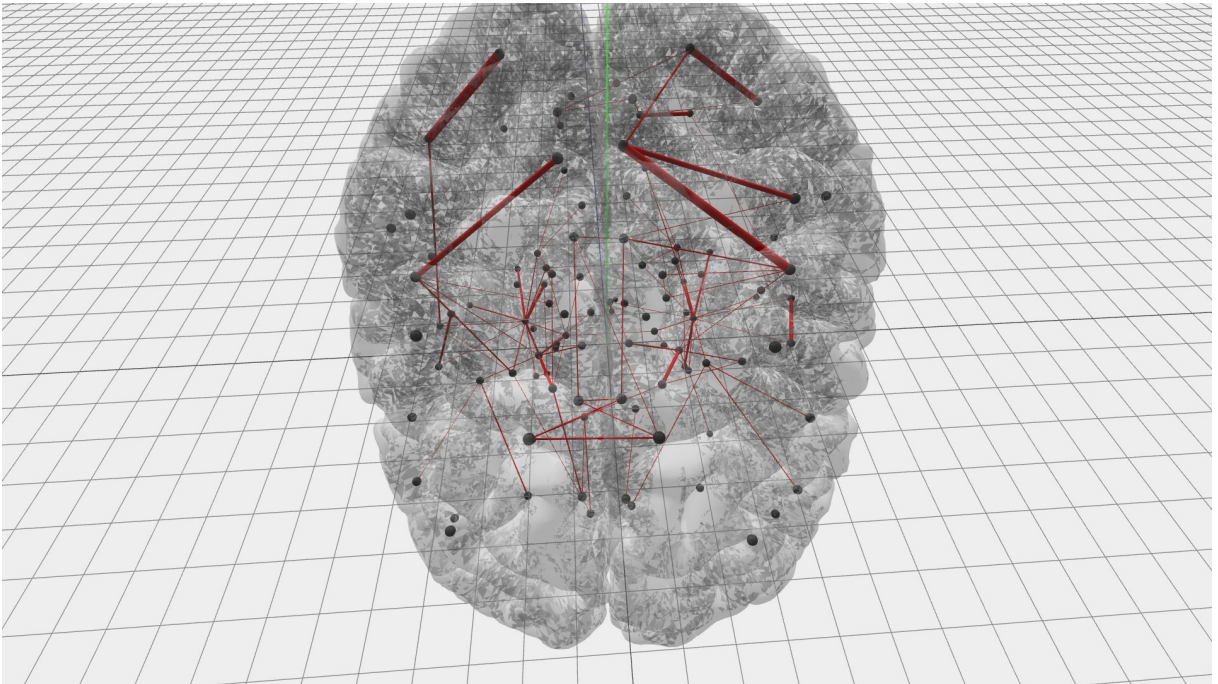


Figure 6. These edges' weight differed significantly between the healthy and demented group with significance value of 0.01 (after performing the Benjamini-Hochberg correction)

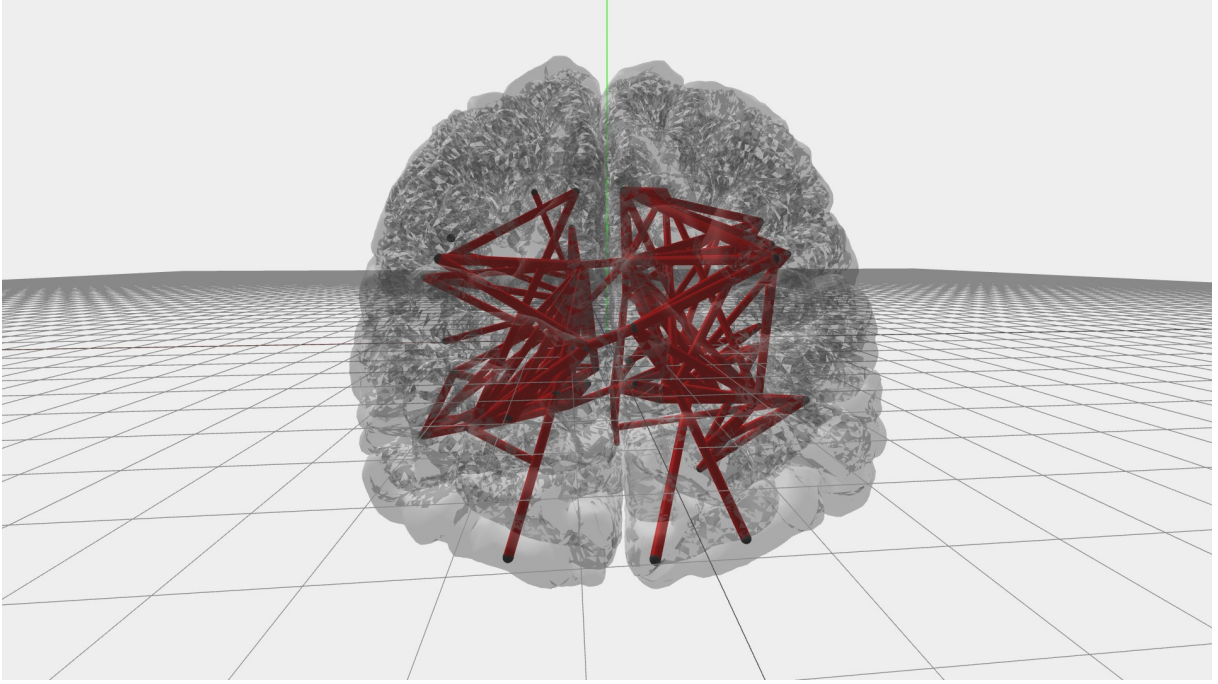


Figure 7. These are the edges whose weight differed significantly between the healthy and demented group with significance value of 0.01 (after the Benjamini-Hochberg correction) and also had an increase of their mean edge weight. This means that the edges shown here usually had a higher weight in the demented than in the healthy ones.

We can notice a few phenomena on Figures 5-7. Unsurprisingly, they show an extensive amount of spatial symmetry between the two hemispheres. Furthermore, it is the most dense around the hippocampus region which is consistent with current knowledge about dementia[56], but there are also a lot of edges in the frontal-lobe and cerebral cortex which are memory related regions as well and finally a few in visual areas such as the cuneus and calcarine sulcus. These later areas are rather interesting, since there can be found an edge between those, which weight is significantly larger in the demented individuals and it performs well - over 0.6 efficiency in both classes - during SVM classification (when we use the weights of this edge). This means that increased connection between these areas related to image processing characterizes dementia with great accuracy.

With significance level of 0.001 we have identified 445 edges - 21,2% of all the edges found in most of the brains - with a significant change in their mean weight - after the Benjamini-Hochberg correction - 76 or 17.1% - of which had increased. During the one-dimensional separation, there were 72 edges with at least 0.6 efficiency in both classes, two of which had an increase in their mean edge weight. This shows the presence of neuroplasticity in all brain areas during dementia. That is further reinforced by the fact, that the increased strength of connection is present in areas where we found a huge amount of weakened connection as well.

Our data suggests that most of the critical connections do not get weakened over time in healthy people. The only suspect to it are the inner connections of the hippocampus. However, due to the small sample size, we can not derive any kind of similar conclusion regarding the change of connections in demented individuals as they age.

Another conclusion we can derive from our data is that during dementia, not complete brain areas lose their connections, rather there are specific connections which become weaker. And for some areas, it means that an extensive amount of their connections become weaker, but on the other hand, they are going to experience more strengthened connections as well (thanks to neuroplasticity).

However, from the data in table 9 we can derive, that the effect of neuroplasticity might be

negligible in the case of interhemispheric connections of the brain. We can also conclude that dementia generally affects interhemispheric connections much more severely, than those in the same hemisphere.

Furthermore, the large increase of accuracy in the two-dimensional separation compared to the one-dimensional one, implies that with the selection of just a few edges and their weights, we can identify demented individuals.

10 Summary

During our research, we worked with braingraphs of individuals and averaged braingraphs. First, we concluded some general results about differences between females and males. For these results, we noticed, proved and used some mathematical attributes of graphs with only the maximal edges. After that, we investigated general properties of the brain, trying to find differences between demented and healthy people. We concluded that there are no significant differences in the investigated general connectivity properties. However, we showed a significant difference between the roles of interhemispherical connections and connections in the same hemisphere in the event of dementia. After that, we tried to find significant differences for specific brain areas, which was successful. We compared our results with the literature and concluded that these anatomical results confirm the psychological results. It was also shown, that at least 20% of all of our connections in the brain change significantly during dementia. We also conclude a significant result in a controversy around the role of the caudate nucleus in dementia, as higher weighted edges were found in demented people than in healthy people. One of our most important result is the conclusion, that Alzheimer's and ADHD do have a strong connection. Furthermore, our results strongly imply that there are a couple of brain areas whose connections characterize dementia.

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