

Aalto University
School of Science
Degree programme in Engineering Physics and Mathematics

Anatomical connectivity networks of the human brain

Bachelor's thesis

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Title of thesis Anatomical connectivity networks of the human brain		
Degree programme Engineering physics and mathematics		
Major System research		Code of major F3010
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Date 17.09.2015	Number of pages 14	Language English

Abstract

The human brain consist of billions of brain cells and quadrillions of connection between them. This complexity means that studying brain at cell level is often both impossible and unnecessary. The brain can be roughly divided to cerebral cortex which has neural cell bodies and the interior which has the connections between the cells. When doing brain research the cerebral cortex is usually divided to areas and connections between these areas are studied.

Different kind of Magnetic Resonance Imaging (MRI) based methods are often used in brain research. Their benefit is that the brain can be scanned in vivo. In this theses datasets collected with two different kind of MRI methods are used. With Diffusion Tensor Imaging (DTI) it is possible to study diffusion in the interior of brain and thus find how different areas of brain cortex are connected. Functional MRI (fMRI) can detect which brain areas are activated at each moment.

For both DTI and fMRI data it is possible to form graphs where the nodes are brain areas and edges are connections between them. In DTI-graphs an edge is strong if there are a lot of physical connections between the areas and in fMRI-graphs when the areas often activate at the same time. Networks can be created with different algorithms and using different parameters.

DTI- and fMRI-networks can be studied computationally with complex networks tools. There are plenty of tools that can be used to get simple measures which help comparing different graphs or datasets of graphs. In this theses two datasets were used. The first dataset includes DTI and fMRI data for same patients. The second dataset includes only DTI data, but the data is considered to be of really good quality.

First the DTI networks from the first datasets was analysed and compares to properties found in other studies. The results were similar. Then the both DTI datasets were compared. In the second dataset the graphs were much denser and similar to each other than in the first one. Finally the DTI and fMRI networks in the first dataset were compared. There was only a little correspondence in graphs gotten with different imaging methods. There might be many reasons for the differences both inside and between the datasets. Data is collected with different devices, there are many ways to create the graphs from imaging data and choosing parameters isn't straightforward. More analysis using different options should be done to find the reasons for these differences.

Keywords Diffusion Tensor Imaging, Functional MRI, complex networks,

Contents

1	Introduction	1
2	Methods	2
2.1	Magnetic Resonance Imaging	2
2.2	Diffusion tensor imaging	2
2.2.1	Brain anatomy and diffusion	2
2.2.2	Measuring diffusion	3
2.2.3	Tractography	3
2.3	Functional MRI	4
2.4	Networks	4
2.4.1	Atlases	4
2.4.2	DTI network construction	4
2.4.3	fMRI network construction	5
2.4.4	Network analysis	5
3	Used datasets	7
3.1	Atlas	7
3.2	Emotions project	7
3.2.1	DTI networks	7
3.2.2	fMRI networks	7
3.3	Alexander Leemans DTI networks	7
4	Results	10
4.1	Properties of Emotions DTI dataset	10
4.2	Cross validation between DTI datasets	10
4.3	fMRI data	11
4.4	Comparison between DTI and fMRI	11
5	Conclusions	14
A	Terminology	16

1 Introduction

The human brain is an extremely complex system that consists of billions of neurons and quadrillions of connections between them. The cell level network is both impossible to obtain with existing technologies and contains information which is irrelevant when considering the global organization of the brain. By grouping thousands or millions of neurons to a node and searching the connections between those areas the global properties of the brain can be examined with graph analysis. [6]

The structure of the human brain has been studied a lot since the development of diffusion MRI techniques. Diffusion based MRI methods enable studying of the structural connectivity networks of the brain in vivo. An interesting area in the field of brain research is to compare the structural and functional networks of the brain.[6]

In this thesis a dataset of structural brain networks is studied. First the data is validated inside the dataset and set against the results found in literature. Then the data is compared to structural networks found in another study. Finally structural and functional networks of the same subjects are compared.

2 Methods

The data used in this study was collected by using two kinds of Magnetic Resonance Imaging (MRI) methods, Diffusion Tensor Imaging (DTI) and functional MRI (fMRI). Diffusion tensor imaging is used to find structural connections in the brain whereas fMRI is used to study how different brain areas are activated. From imaging data it is possible to create networks that represent connections between different brain areas. In this section brief introductions to brain anatomy, DTI, fMRI, graph creation and relevant graph analysis tools are given.

2.1 Magnetic Resonance Imaging

When using Magnetic Resonance Imaging (MRI) the tissue is held in a strong magnetic field B_0 which aligns the magnetic moments of the protons. In the human body this mostly means hydrogen nuclei in water molecules. When a radio magnetic (RM) pulse is applied to the tissue at the right frequency the protons absorb energy and create a faint signal that can be detected by coils in the MRI system. RM pulses can be added with different directions and timings, and by mathematically manipulating the detected signals an MRI image can be produced. [10]

2.2 Diffusion tensor imaging

Diffusion tensor imaging (DTI) is an MRI technique which was introduced in the mid 1990's and has been studied a lot since. With DTI it is possible to detect an internal fibrous structure of the human brain in vivo by measuring the diffusion of water. [8]

2.2.1 Brain anatomy and diffusion

The human brain can be divided into two main components, gray and white matter. Gray matter is formed from cell bodies of neurons whereas white matter is composed of the myelinated axons and glial cells. For example the cerebellar cortex consists of gray matter and white matter connects the different parts of the cortex. In white matter axons often form bundles.

There is a lot of water in the brain and due to thermal motion the water diffuses. If the matter is homogenous, diffusion is isotropic which means it is similar in all directions. In white matter diffusion is anisotropic because water can move more easily along the axonal bundles. [8]

2.2.2 Measuring diffusion

In the beginning of a DTI study all water molecules are in the same phase and have the same frequency because the magnetic field B_0 is homogenous. When measuring diffusion with MRI linear gradient pulses are applied to the B_0 field. This has an effect on the frequency of the MR signal, ω because the magnetic field and frequency have a relation:

$$\omega = \mu B_0, \quad (1)$$

where μ is called the gyromagnetic ratio.

When the first (dephasing) gradient is applied the frequency of the water molecules changes. After the gradient pulse ends water molecules again have the same frequency but the phase is different depending on the location of the molecule along the gradient axis.

The second (rephasing) gradient has the same length and strength as the first pulse but its orientation is the opposite. If rephasing is perfect the phases of all water molecules are the same after the second pulse ends. However, because of the diffusion of water rephasing is imperfect. This leads to lower signal intensity.

With this method diffusion is detected along the applied gradient. To find out in which orientation diffusion is the highest gradients are applied from multiple directions. The measurements are then fitted to a 3D ellipsoid, which represents average diffusion distance in different orientations. The longest eigenvector of the ellipsoid is interpreted as the direction of strongest diffusion. [8]

2.2.3 Tractography

Tractography is a set of methods used to determine how white matter tracks are orientated in the brain based on diffusion ellipsoid data. In this thesis an algorithm called fiber assignment by continuous tracking (FACT) was used. The algorithm initializes tracts from many seedpoints and then propagates these tracks along the longest eigenvector of the diffusion ellipsoid.

Information of diffusion ellipsoids can be reduced to the longest eigenvector v_1 which can be assumed to be the local fiber orientation. When using the FACT algorithm streamlines are propagated from multiple seed voxels. At the edge of a voxel the new orientation is decided based on the v_1 in the new voxel. Streamlines are terminated if the turning angle is too high or diffusion is too isotropic. [9]

2.3 Functional MRI

Blood flow in a brain area increases in activation to bring more oxygen and glucose to the activated area. Deoxygenated hemoglobin (dHb) is more magnetic (paramagnetic) than oxygenated hemoglobin (Hb), which is virtually nonmagnetic (diamagnetic). This change in the level of oxygen can be detected because it increases MR signal. [5]

To make it most relevant to compare fMRI with DTI data, resting state fMRI data was used. This means that fMRI images were taken without any specific external stimulus.

2.4 Networks

For both DTI and fMRI, network analysis has three steps. First the cortex is divided into Regions Of Interests (ROI) based on some atlas. ROIs become nodes of the resulting graph. Then connections between these nodes are defined from imaging data. Finally graphs are analyzed using complex networks tools.

2.4.1 Atlases

Brain atlases are standardized mappings of the brain where different brain areas and structures are put to the coordinate system. Atlases can be used to divide the cortex to regions of interest.

2.4.2 DTI network construction

Graphs can be created from tractography data. The nodes of a graph are the ROIs of the used atlas. The weight of an edge between two regions can

be extracted from tractography data by calculating how many tracts connect the two regions.

2.4.3 fMRI network construction

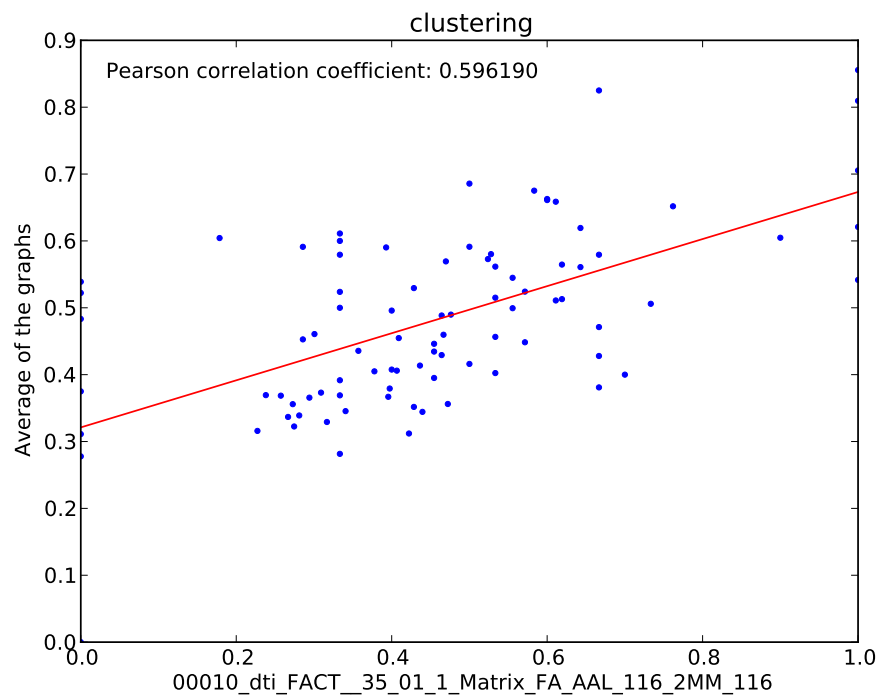
In fMRI graphs the nodes are also ROIs of the used atlas. The edges of fMRI networks are created by calculating correlations between different areas from the fMRI timeseries. If some areas activate often at the same time, they have high correlation which is then interpreted as an edge with high weight in the graph. Because all the areas have some kind of correlation a threshold must be defined to decide which of the connections to use in the graphs. There is no exact threshold but it can be varied.

2.4.4 Network analysis

The graphs can be analyzed with different kinds of complex networks tools, only some of which were used in this thesis. For each data set edges that were common to all graphs were defined and for each graph a percentage of those was calculated. For the complete graphs the number of nodes and edges, the clustering coefficient, transitivity and shortest path lengths were calculated.

For each node some properties, like degree and clustering coefficient were calculated. Also averages over the graphs were calculated. These properties were plotted so that for each node x-axis included property for the specific graph and y-axis the average value. For those plots Pearson correlation coefficients were calculated. One example of a this kind of graph can be found from figure 2.4.4. If the coefficients are high (close to one) the node properties of a single graph correspond to the average properties. This is one way to find out how similar different graphs are on the node level.

Figure 1: Clustering coefficient plotted for each node. Value for a subject is at x-axis and the average over the graphs is at y-axis. If all the graphs were the same the Pearson correlation coefficient would be one



3 Used datasets

3.1 Atlas

The used brain cortex atlas was made with Automated Anatomical Labeling (AAL) [11]. It includes 116 regions.

3.2 Emotions project

The data set used for DTI and fMRI networks was collected for the Decoding Emotions project of Aalto University's Brain and Mind laboratory. The experiments were performed in the Advanced Magnetic Imaging -center on a 3 T MAGNETOM Skyra whole-body scanner (Siemens Healthcare, Erlangen, Germany), using a standard 20-channel head-neck coil.

3.2.1 DTI networks

DTI networks were made from dicom files with FSL and the Matlab based toolbox Pipeline for Analysing braiN Diffusion imAges (PANDA). Networks were made using the FACT algorithm.

At first the graphs were made using the AAL atlas which had 116 ROIs. After this a new set of graphs was made by removing the nodes which don't belong also to the atlas used in Leemans dataset to make comparison between datasets possible.

3.2.2 fMRI networks

fMRI networks were created from nifti-files with a matlab script written by Hanna Halme.

3.3 Alexander Leemans DTI networks

Some ready-made DTI networks were received from Alexander Leemans (Associate Professor Image Sciences Institute, University Medical Center Utrecht, The Netherlands). The networks were made of 56 subjects, both male and female, ages 22-57.

Leemans' networks were also made with AAL atlas but the atlas included only 90 nodes because cerebellar hemispheres and cerebellar vermis were excluded [2]. From these graphs a subset of eight graphs was randomly selected to make the number of graphs match with the set of DTI graphs from the Emotions project.

Table 1: Some average graph properties for different datasets

Dataset	Nodes	Edges	Common edges (%)	Clustering coefficient	Transitivity	Shortest Path length	Shortest Path length unweighted
Emotions DTI, 90 ROIs	86	375.62	44	0.489	0.419	0.820	2.786
Random graphs	86	376	0	0.104			2.261
AL 8 DTI graphs, 90 ROIs	90	2011.38	53.4	0.657	0.627	0.493	1.525
Emotions DTI, 116 ROIs	111.23	523.25	43	0.491	0.412	0.809	2.891
Random graphs	111	523	0	0.085			2.330
Emotions fMRI, 116 ROIs	116	523.25	21	0.486	0.5315	2.65	3.17

Table 2: Average Pearson correlation coefficients calculated for some properties in different data sets

Dataset	Degree	Clustering coefficient	Betweenness centrality	Eigenvector centrality	Closeness centrality
Emotions DTI, 90 ROIs	0.894	0.671	0.832	0.874	0.890
AL	0.893	0.784	0.847	0.903	0.890
Emotions fMRI	0.811	0.529	0.666	0.723	0.756
Emotions fMRI vs DTI	0.39	0.05	0.03	0.26	0.25

4 Results

4.1 Properties of Emotions DTI dataset

The first analysis was carried through with networks done with an atlas that had 116 ROIs. There are 225 edges in common in all the networks. On average 43 percent of the edges of one graph belong also to all the other graphs. Then analysis was done with an atlas that had 90 ROIs. There are 165 edges common in all the networks. On average 44 percent of the edges of one graph belong also to all the other graphs. Some calculated average properties for the graphs can be found in table 1.

To check if the networks are similar to each other node properties were plotted with the value from one network in x-axis and the average value in the y-axis. If the networks were really similar the Pearson correlation coefficients calculated from the plots would be close to one. The results can be found in table 2.

According to [3] brain networks are a small world. This means that they have comparable average shortest path length but much higher clustering coefficient than random networks. To analyze this, one hundred random graphs were created with same number of nodes and edges as the original DTI dataset had on average. Average node properties were calculated and they can be found in table 1. From the results can be seen that indeed the unweighted average shortest path length is of the same magnitude but the clustering coefficient is much smaller in the random networks. This is some evidence that graphs created from the Emotions DTI dataset are similar to graphs found in other studies.

4.2 Cross validation between DTI datasets

In the subset of the eight Leemans' graphs there are 1072 edges common in all the graphs and on average 53.4 % of the edges of one graph belong also to all the other graphs. This proportion is higher than in the Emotions dataset. Leemans graphs also have a lot more edges because the average number of edges in Leemans dataset is over five times as high as in the Emotions dataset.

Some calculated average properties for the graphs can be found in table 1. It can be seen that Leemans' graphs have much more edges, higher clustering and transitivity and shorter path lengths. A lot of this is due to the higher number of edges.

Pearson correlation coefficient calculated for node properties can be found in table 2. For Leemans' networks correlation coefficients are higher than for Emotions networks. This means that Leemans networks are more similar to each other than the networks in the other dataset. Anyhow, the difference is relatively small.

4.3 fMRI data

Original fMRI networks had edges between every node. To do the analysis a weight threshold was chosen to filter edges so that only those with highest weights were taken into account. There is no exact threshold to be chosen and networks were constructed with different thresholds. For further analysis a threshold was chosen so that fMRI networks had as many edges as corresponding DTI networks.

There are 109 edges common in all the graphs. On average 21 percent of the edges of one graph belong also to all the other graphs. Results are in table 1. None of the fMRI graphs are connected but they consist of multiple subgraphs. Average shortest path lengths given in the table are the results for the largest connected components of the graphs.

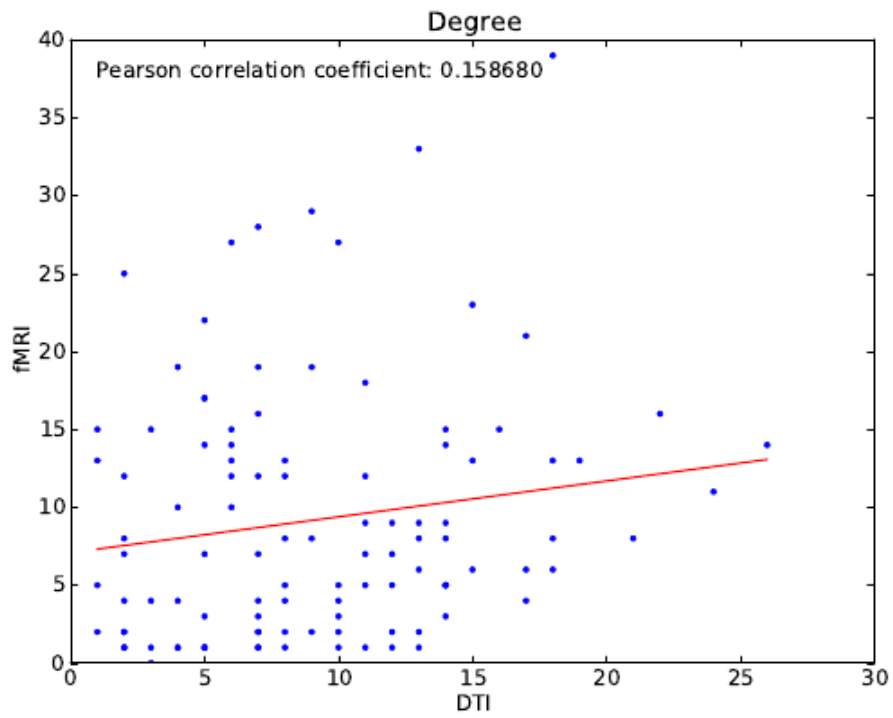
Pearson correlation coefficients calculated for node properties can be found in table 2. Coefficients are lower than the coefficients for DTI networks so the fMRI networks aren't as similar to each other as DTI networks are. There is, however, some correlation so the networks are similar to some extent to each other when considering node properties.

4.4 Comparison between DTI and fMRI

fMRI graphs were made with an atlas that has 116 ROIs so the comparison between functional and structural networks is done with DTI networks of 116 ROIs. As there is no connection between the weight in DTI and fMRI networks analysis was done for unweighted graphs.

As DTI and fMRI networks are from the same subject with the same atlas different nodes should represent the same areas of the brain. Some node properties were calculated for all of the nodes and then plotted to graphs so that the value gotten from DTI network was at x-axis and value gotten from fMRI network was at y-axis. One example can be found from figure 4.4.

Figure 2: Comparing DTI- and fMRI graphs for one subject. For each node the degree in the DTI network is at x-axis and in the fMRI network is at y-axis



Average Pearson correlation coefficients calculated for different properties can be found from table 2. If fMRI and DTI networks were similar, correlation should be close to one because then for example nodes which had a high degree in the DTI network would have a high degree also in the fMRI network. In this case only one property (degree) has relatively high correlation, all the others being almost uncorrelated. According to [6] functional and structural networks from same subjects should be similar. In this study fMRI networks seem to be different to the DTI networks.

5 Conclusions

There are multiple options as to how to create networks from DTI and fMRI data. Different software and parameters probably give out different kinds of networks. When comparing different datasets, the differences in graph creation should also be taken into account. It seems that DTI networks of the Emotions project are small world as literature suggests. Different networks are somewhat similar to each other, but less so than in Leemans data.

Networks from different datasets differ both on the global and node level. There might be many reasons for this. The number of subjects is quite low, which might cause random effects to change the results. Data is probably collected with different hardware or imaging parameters, which might have an effect on the data. The graphs might also be created with different algorithms or parameters, which of course has an effect on the created graphs.

More research would be needed to find out the cause for the differences. It would be easiest to find out the technical details Leemans used and compare them with the Emotions project. In addition more results from different ways to create graphs could be tried to find out what is the effect of the algorithms and parameters used. Leemans' networks could also be reduced to have the same number of edges as the networks from the Emotions project to check how big an effect the difference in the number of edges has on the results.

Creating networks from fMRI data is not straightforward. It is difficult to know the correct threshold for edge weights, and changing the threshold even slightly has a huge effect on the results. In this study only a slight correspondence was found between DTI and fMRI networks. More research should be done on the topic and different ways to create fMRI networks should especially be tried.

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A Terminology

A **cluster** is formed if the nearest neighbors of a node are also connected to each other. [4] **Clustering coefficient** for weighted graphs is calculated by taking the geometric average of edge weight for the subgraph. [1]

The **degree** of a node tells how many connections there are that link the node to other nodes in the graph. **Degree distribution** includes degrees from all the nodes in a graph. [4]

A **graph** is a set of **nodes** connected by **edges**. [4]

A **neuron** is a brain cell which consists of a cell body and axons which connect the cell to other neurons. [8]

In **random networks** each pair of nodes has equal probability to be connected. Random networks are often used in graph theory as a reference to check if some networks properties are higher or lower than in random networks.

The degree distribution of a **scale-free network** is in the form of power-law. [4]

Shortest path length is the shortest distant between two nodes. [4]

Graphs that are **small-world** have two main properties compared to random graphs that have the same number of edges and nodes. They have much greater clustering coefficient and comparable average shortest path length. [7] This means that though small-world graphs have quite a low degree and they are mostly connected within cliques, the average shortest path length is low. Many networks from in nature are small-world [4].

Transitivity is the fraction of triangles present in the graph [1].

In **unweighted graphs** all edges have a weight of 1.

Voxel is a pixel in 3D.

Tekijä Milja Asikainen		
Työn nimi Anatomical connectivity networks of the human brain		
Koulutusohjelma Teknillinen fysiikka ja matematiikka		
Pääaine Systemitieteet	Pääaineen koodi F3010	
Vastuopettaja Harri Ehtamo		
Työn ohjaaja(t) Raj Kumar Pan, Jari Saramäki		
Päivämäärä 20.09.2015	Sivumäärä 14+1	Kieli Suomi

Suomenkielinen yhteenveto

Ihmisaivot on äärimmäisen monimutkainen kokonaisuus, joka koostuu miljardeista aivosoluista ja vielä useammasta yhteydestä niiden välillä. Karkeasti aivot voidaan jakaa kuorikerroksen harmaaseen sekä sisäosien valkeaan aineeseen. Harmaa aine sisältää aivosolujen solukeskuksia kun taas valkea aine koostuu aivosolujen välisistä haaraisista yhteyksistä. Valkeassa aineessa yksittäiset hermosäikeet usein niputtuvat suuremmiksi, aivoalueelta toiselle kulkeviksi kimpuiksi. Ihmisaivojen laajuisten verkkojen havainnointi solutasolla olisi mahdotonta sekä useimmissa tapauksissa myös tarpeettoman yksityiskohtaista. Ryhmittelemällä kuorikerroksen aivosoluja suuremmiksi kokonaisuuksiksi on mahdollista tutkia eri aivoalueiden välisiä yhteyksiä.

Eläviä aivoja voidaan tutkia esimerkiksi erilaisilla magneettikuvausmenetelmillä. Magneettikuvaus perustuu vahvaan magneettikenttään, joka kääntää protonien spinin samansuuntaiseksi. Ihmisaivoissa tämä tarkoittaa etenkin vesimolekyylin protoneita. Kun kudokseen kohdistetaan pulssi sopivalla radio- taajuudella, protonit imevät itseensä energiaa ja lähettävät havaittavissa olevan signaalin. Muuntelemalla pulssien taajuutta, suuntaa ja ajoitusta, voidaan muodostaa kuva aivoista. Tässä työssä on käytetty kahdenlaisilla MRI-menetelmillä saatua aivokuvaa.

Diffuusiotensorikuvantaminen on magneettikuvausmenetelmä, jolla voidaan havaita valkoisen aineen kimppujen suuntia. Se perustuu siihen, että veden lämpöliike on voimakkaampaa kimppujen suuntaisesti kuin kohtisuoraan niitä vastaan. Diffuusiotensorikuvantamisessa kudokseen kohdistetaan kaksi radio- taajuista gradienttipulssia. Näistä ensimmäinen muuttaa protonien taajuutta.

Pulssin jälkeen taajuus palaa entiselleen, mutta vaihe vaihtelee protonin paikan mukaan. Toisen pulssin pituus ja voimakkuus ovat täysin samat kuin ensimmäisellä, mutta sen suunta on vastakkainen. Jos uudelleenvaiheistus onnistuisi täysin, kaikkien vesimolekyylien vaiheet olisivat samat kuin ennen gradienttipulsseja. Veden lämpöliikkeen takia näin ei kuitenkaan tapahdu, mikä voidaan mitata heikompana signaalina.

Diffuusiotensorikuvantamisella voidaan havaita gradienttipulssin suuntaisen lämpöliikkeen voimakkuus. Lähettämällä gradientti useammasta suunnasta ja mittaamalla lämpöliikkeen voimakkuutta mittaustuloksiin voidaan sovittaa kolmiulotteinen ellipsoidi. Ellipsoidi kuvaa keskimääräistä lämpöliikkeen voimakkuutta karteesisessa koordinaatistossa ja sen suurin ominaisvektori tulkitaan voimakkaimman lämpöliikkeen suunnaksi.

Ellipsoideista voidaan määrittää valkoisen aineen kimppujen kulkusuunnat useilla menetelmillä. Tässä työssä käytetyssä FACT-menetelmässä juosteet alustetaan useissa siemenpisteissä. Aina kolmiulotteisen kuvapisteen rajalla juosteen kulma käännetään ellipsoidin suurimman ominaisvektorin mukaiseksi. Juosteen pituutta kasvatetaan, kunnes käännöksen kulma olisi liian suuri tai päädytään kuvapisteeseen, jossa lämpöliike on satunnaista.

Toinen työssä käytetty magneettikuvausmenetelmä on toiminallinen magneettikuvaus. Aivoalueen aktivoitumisen seurauksena veren virtaus kyseisellä alueella voimistuu, mikä kohottaa happipitoisuutta. Tämä suurentaa magneettikuvaus synnyttämää signaalia mitattavasti, joten kullakin hetkellä aktiiviset aivoalueet voidaan havaita.

Mitatuista aivokuvista voidaan tehdä verkkoja jakamalla aivokuori alueisiin, jotka ovat verkkojen solmuja. Diffuusiotensorikuvista muodostettavissa verkoissa solmujen välisten särmien paino määritetään alueiden välillä kulkevista valkoisten aineen kimpuista. Mitä enemmän kimppuja on, sitä painavampi on myös särmä. Toiminnallisista magneettikuvista tehtävissä verkoissa taas särmien painot saadaan laskemalla eri alueiden aktivoitumisen aikakorrelaatio. Särmä on vahva, jos alueet aktivoituvat usein samanaikaisesti.

Tässä työssä käytettiin kahdesta eri lähteestä saatuja aivokuvia tai jo valmiita aivoverkkoja. Ensimmäinen aineisto oli kerätty Aalto-yliopiston Decoding Emotions- projektissa ja se sisälsi diffuusiotensorikuvia sekä toiminnallisia magneettikuvia samoilta koehenkilöiltä. Työssä näistä kuvista muodostettiin verkkoja eri menetelmillä.

Toisena aineistona käytettiin hollantilaisen Alexander Leemansin diffuusionensorikuvista muodostamia verkkoja. Leemansin tutkimusta ja tuloksia pidettiin yleisesti onnistuneina. Eri aineistojen verkkoja analysoitiin ja vertailtiin monilla laskennallisilla analysointimenetelmillä.

Ensimmäisen aineiston diffuusionensorikuvista muodostettuja verkkoja verrattiin satunnaistetusti luotuihin. Diffuusionensorikuvista muodostetuilla oli korkeampi klusteroitumiskerroin, mutta suunnilleen sama keskimääräinen lyhimmän polun pituus. Samanlaisia tuloksia on saatu aiemmissa tutkimuksissa.

Seuraavaksi työssä muodostettuja verkkoja verrattiin toisen aineiston vastaviin. Toisessa aineistossa verkoissa oli paljon enemmän särmiä, lyhyemmät polun pituudet sekä korkeampi klusteroitumiskerroin. Lisäksi toisen aineiston verkot muistuttivat toisiaan huomattavasti enemmän.

Ensimmäisen aineiston diffuusionensorikuvista ja toiminnallisista magneettikuvista muodostettuja verkkoja vertailtiin myös keskenään. Samoilta koehenkilöiltä oli kuvattu aivot kummallakin menetelmällä, joten verkkojen olisi oletettavasti pitänyt muistuttaa toisiaan. Tällaisia tuloksia on saatu myös aiemmissa tutkimuksissa. Työn tutkimuksessa kuitenkin vain yksi tutkituista ominaisuuksista, solmujen aste, korreloi merkitsevästi eri menetelmällä kerättyjen verkkojen välillä. Vaikuttaakin siltä, että rakenteelliset ja toiminnalliset verkot ovat erilaisia.

Sekä aineiston sisäisiin että aineistojen välisiin eroihin voi olla monta syytä. Aivojen kuvaamisessa on saatettu käyttää eri laitteistoja ja erilaisia parametreja. Lisäksi verkkoja voi muodostaa monenlaisilla menetelmillä ja käyttämällä erilaisia parametreja. Aihetta tulisikin tutkia lisää, jotta verkkojen eroavaisuuksien syistä voitaisiin olla varmoja.

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