CORTICAL THICKNESS ANALYSIS – THE METHODS

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Abstract

Over the course of the last century, the cerebral cortex has been of interest for neuroscientists, and the work with mapping and measuring the cortex started in the early 1900s (Brodmann 1909).

The advances in medical imaging over the recent decades has given the opportunity to measure the cortex in vivo, and several algorithms and types of software applications has been developed for this purpose. These software applications can be used to execute complex analysis to determine both cortex thickness and density.

The algorithms and software applications presented in this paper are the ones most utilized to measure cortical thickness today, and include four software applications and two algorithms. The basic principles of these tools will be outlined, as well as their strengths and weaknesses.

Introduction

For the last century, the human cerebral cortex has been of interest for neuroscientists. As early as 1909 Brodmann, with the use of cuts from dissected brains, mapped the cerebral cortex and measured its thickness (Brodmann 1909). The efforts to understand the structure of the cortex continued, and two decades later a more detailed description of the cytoarchitectonics of the cerebral cortex was published (von Economo & Koskinas 1925).

The recent years advances in medical imaging with Computed Tomography (CT), Magnetic Resonance Imaging (MRI), Single Photon Emission Tomography (SPECT) and Positron

Emission Tomography (PET) has changed the way the human body is imaged. This has also changed the way cortical thickness is analyzed, from measuring on cuts from dissected brains; to statistical analysis on preprocessed T1 weighted MRI images. Several algorithms and types of software application has been developed for this purpose.

The most recent algorithms are Cortical Reconstruction Using Implicit Surface Evolution (CRUISE) (Han et.al 2004), and Constrained Laplacian – based Anatomic Segmentation using Proximities (CLASP) (Kim et.al 2005, MacDonald et.al 2000, MacDonald 1997). The software applications used today are Brainvoyager (Goebel 2012), SurfStat (Worsley 2008) and Freesurfer (Fischl 2012, Fischl & Dale 2000), the latter being the one used by most.

There has also been developed a pipeline, or a preprocessing software, called Corticometry Analysis Tools (CIVET) (http://cbrain.mcgill.ca). This pipeline measures the cortical thickness, and the output is in such a format that it can be used for statistical analysis by for example SurfStat (http://cbrain.mcgill.ca).

Together all of these methods have been used to examine the effect of loss of a sense like hearing or smell(Li et.al 2012, Frasnelli et.al 2013), the effect of Alzheimers disease (Li et.al 2012), Parkinsons disease (Wu et.al 2011), and aging (Salat et.al 2004, Van Velsen et.al 2013). It has also been used to see the effect of a premature birth (Nagy, Lagercrantz & Hutton 2011, Kapellou et.al 2006, Martinussen et.al 2005, Nosarti et.al 2014), as well as the effect of psychiatric disorders such as bipolarity (Oertel – Knöchel et.al 2015, Giakoumatos et.al 2015), schizophrenia (Zugman et.al 2015), ADHD (Fernández-Jaén et.al 2015) and autism (Richter et.al 2015).

Cortical thickness analysis gives an excellent opportunity to measure morphometric changes associated with disease, neurophysiological variables or age with good accuracy. This is clinically relevant since it can give a better understanding of the mechanisms behind diseases, how they affect the brain or where in the brain they originate, and potentially help the development for treatments.

The purpose of this paper is to try to summarize how we got to the methods used to measure cortical thickness today, and give an overview of the basic principles of today's software applications and algorithms, as well as their strengths and weaknesses. The software applications and algorithms that are chosen to focus on are the ones aforementioned.

Methods and Materials

There exists several software application packages and algorithms for measuring cortical thickness on the market today. Since all of them can't be explained in this paper, there has been chosen to focus on the software applications/algorithms most widely used today, seeing those as the most relevant to explain further.

A literary search was performed in several databases. See table 1 for the databases, keywords and results. The literary search was ended at august 27th 2015.

The searches was limited to include articles from the last fifteen years (2000), and in the database Science Direct, one search (Cortical thickness AND Surfstat), was also limited to review articles, which yielded one result. This was done in order to limit the amount of results (which otherwise was several thousand), and the majority did not discuss SurfStat itself, but it had been used as the statistical tool in the study.

In another search (Cortical thickness AND Freesurfer) additional filters had to be applied. The period was reduced to the last five years, and the filter reviews only was applied in Science Direct. This was done to limit the amount of results, and get results that are more relevant. For the search Cortical thickness AND CLASP additional filters had to applied so the results only referred to brain research on humans. The same applies to the search for Cortical thickness AND brainvoyager in SD, filters had to be applied so the results only referred to cortical thickness analysis.

The articles relevance was at first hand evaluated on account of the articles title and abstract. Full text was read in 14 articles and 12 of these were included. Articles was included based on these criteria: discusses methods used in cortical thickness analysis, discusses cerebral cortex, discusses algorithms that are used to compute cortical thickness, or were the basis for developing such algorithms. Exclusion was based on the criteria: did not discuss the methods of cortical thickness, discussed cortex in bone etcetera, rather than cerebral cortex, discussed algorithms that are not used to compute the cerebral cortex. In addition to this, a review of the references in these articles were included. The relevance of these articles were also evaluated based on the title and the abstract. Full text was read in 13 and 10 were included.

Database	Keywords	Results
Science Direct	Cortical thickness AND Surfstat	73
	Cortical thickness AND Freesurfer	189
	Cortical thickness AND brainvoyager	20
	Cortical thickness AND CRUISE	77
	Cortical thickness AND CLASP	58
Pubmed	Cortical thickness AND Surfstat	1
	Cortical thickness AND Freesurfer	210
	Cortical thickness AND brainvoyager	0
	Cortical thickness AND CRUISE	2
	Cortical thickness AND CLASP	3
Biomed Central	Cortical thickness AND Surfstat	1
	Cortical thickness AND Freesurfer	59
	Cortical thickness AND brainvoyager	14
	Cortical thickness AND CRUISE	0
	Cortical thickness AND CLASP	0
Academic Search Premier	Cortical thickness AND Surfstat	1
	Cortical thickness AND Freesurfer	207
	Cortical thickness AND brainvoyager	0
	Cortical thickness AND CRUISE	1
	Cortical thickness AND CLASP	2

Table 1: Table showing the results for the different combination of keywords in the different databases science direct, pubmed, biomed central and academic search premier, using the filter only showing articles from 2000-2015

Early methods

The early methods used for cortical thickness analysis started developing in the eighties, with an algorithm called Marching Cubes (Lorensen & Cline 1987). This method was a purely bottom – up approach of edge detection, meaning it measures from the bottom border (grey matter (GM) / white matter (WM) border) and finds the edge upwards (GM / cerebrospinal fluid (CSF) border). The strength of using this method is its high resolution, however this method suffered from an inability to interpolate data, and it was also very sensitive towards noise (Lorensen & Cline 1987).

One year later a new method only called Snakes, or active contour models, was published (Kass, Witkin & Terzopo 1988). This method sought to address the problems seen with the marching cubes algorithm, and did this by developing a dynamic algorithm that could change its interpretation of edges and lines with the evidence brought by higher levels of processing. This method had several advantages over the marching cubes algorithm, such as accurate edge detection, as well as motion tracking and stereo matching (Kass, Witkin & Terzopo 1988). This method has also been the foundation of many deformation methods used today.

Through the 1990s the efforts were concentrated on geometrically accurate topology correction, and the accurate detection of edges. This was still challenging, especially in the deep sulci where the banks often lie quite close.

In the early 90's a novel Volumetric Brain Structure Model (VBSM) was published (Collins et.al 1992). This model would automatically segment and classify the brain into different neuro – anatomical components using both multiresolution registration and matching with a novel VBSM. This model separated all the MRI data into two different types of data. Raster data, which consists of the mean MRI volume after a set of individual volumes of healthy volunteers was transformed to stereotaxic space, and geometric data, which consists of polyhedral objects representing anatomy (Collins et.al 1992). The strength this method had was segmentation by iterative registration, which provides strong information about the expected image data. The drawback was that it relied heavily on high accuracy of the registration between the brainatlas and the unsegmented brain, which can be very hard to obtain (Collins et.al 1992, Rudra et.al 2011, Duncan et.al 2004).

In the same period there was developed a method using the information about the white matter to expand a deformable surface from the white matter boundary towards the outer boundary of the gray matter. This method had several advantages, however it does not prevent self-intersecting topologies, and it is difficult to guarantee for the resulting surface being in the shape of a sphere (Dale & Sereno 1993). This makes it difficult to separate close sulci and gyri, and information might be lost.

The 2000s also saw new developments in this field, with more and more sophisticated methods of automatic segmentation of the cortex and calculation of the cortical thickness. At the same time, new coordinate systems were born to better accommodate the anatomic nature of the cortex. Improvement on the ability to differentiate the cortex in areas with tight gyri and sulci were in focus in this period (Lerch & Evans 2005, Yezzi & Prince 2003 & Fischl et.al 2000). The methods developed at the time are the basis for the software applications and algorithms used today.

Freesurfer

Freesurfer was developed with Bruce Fischl as a driving force, and the preliminary version was released in 1999 (Fischl 2012). This is the software application most widely used for cortex analysis today, and it can provide an extensive and automated analysis of key features in the brain. This includes mapping of the thickness of cortical grey matter Fischl et.al 2002;2004, Fischl & Dale 2000).

There are two major steps in the process of cortical thickness analysis in Freesurfer: topology correction and surface deformation and thickness estimation (Fischl 2012).

Earlier methods had focused on topological accuracy by deforming a surface with a known topology to lie at a specified interface in the image data (MacDonald 1997, MacDonald et.al 1994; 2000). This means that the methods tried to drive a spherical model to lie at each point of the cortical surface. The issue with models like these was that it was difficult to generate surfaces that accurately follow the entire boundary of interest, i.e. it was difficult to push the surface through the narrow openings of deep sulci and still end up with a smooth surface (Fischl 2012). The way this was solved was to take a cortical surface and driving it outwards towards the surface of a sphere. This meant that one could localize defects and limit the topological correction to only where the defects were, and focus on geometric accuracy on the rest (Fischl 2012).

Surface – deformation techniques had been utilized in an attempt to generate accurate models of various boundaries from MRI (MacDonald et.al 2000). The issue with using these methods was that it was difficult to directly apply these techniques to construct surface representations. Firstly, the use of isointensity surfaces depends on the MRI intensity for each surface being constant, which it for a number of reasons is not (Fischl 2012). Secondly the surfaces must be constrained as not to self – intersect and maintain their topology. Already existing methods dealt with the first problem easily, but had no easy way to impose topological strains. Freesurfer solved this by modeling the surface by using a quadratic function and implementing fast triangle – triangle intersection (Fischl 2012, Fischl & Dale 2000, Möller 1997). This resulted in a procedure robust to variations in sequence parameters, and that generated models accurate enough to measure cortical thickness reliably, which has been used in an array of different studies (Fischl 2012).

SurfStat

SurfStat is a toolbox for statistical analysis on a wide array of imaging data (univariate/multivariate, surface/volumetric), the only requirement being that they are registered to a common surface (Worsley 2008). This tool was initially developed to utilize a model formula, and avoid the explicit use of design matrices and contrast, which tends to baffle most users not already familiar with this way of working with the data (Chung et.al 2010).

In use and output, this method is quite similar to Freesurfers statistical tool. They both require the user to write commands, and the output produced are similar to each other (Worsley 2008, Kaufman 2015). In function however, SurfStat differs from Freesurfer. Whereas the Freesurfer software application is a package where you can both calculate the cortical thickness and perform statistical analysis on your data, SurfStat is more a specialized statistical tool. The fact you have to preprocess your data in CIVET before you can analyze them in SurfStat can be pointed out as a big weakness compared to Freesurfers package.

The advantages of using SurfStat includes the fact you can analyze a wide array of data (even data from other software applications, like Freesurfer), and that it completely avoids the complexity of

specifying design matrice (Chung et.al 2010). Although it has its weaknesses, and is not as widely used as Freesurfer, this is still a robust, easy to use and accurate tool for the statistical analysis on cortical thickness.

Brainvoyager

In the beginning, Brainvoyager was meant to be a tool for analyzing fMRI – data only, which developed into a multi tool for image analysis (Goebel 2012, http://www.brainvoyager.com). This software application package can be used to measure cortical thickness of the individual hemispheres, compute average thickness maps across subjects as well as statistical group difference maps, and calculate individual and group thickness values in any region of interest.

This software application is, as Freesurfer, a package where you can do segmentation, calculation of the thickness and statistics on T1 weighted MRI images in the same package. The segmentation is done through a segmentation pipeline, which involves several steps. The data will go through a filter enhancing tissue contrast, masking to remove cerebellum and other non – brain tissue, filling of the ventricles and subcortical structures, an histogram analysis to properly separate white and gray matter, morphological operations to smooth the resulting surface and lastly a "bridge removal" tool which corrects any topological errors (http://www.brainvoyager.com).

The alignment of the resulting surface is similar to the one used in both Freesurfer and SurfStat, based on the surface being pushed outwards towards a sphere shape, each vertex on the sphere corresponds to a vertex on the folded cortex surface (http://www.brainvoyager.com).

This tool measures the cortical thickness by using the LaPlacian equation, which is widely used in different sciences (Hawking & Ellis 1973, Stigler 1986, Green 2008)). The advantages of using this equation was that it is a robust equation with good generality. A disadvantage of using this method was that this type of analysis is computationally intensive, the whole analysis taking 24 hours on a PC from the late 90's (Jones et.al 2000).

The limitations of using this method includes signal contrast, image resolution and limitations to computing power. This however will not be as much of a limitation today, with the improvements of computers that have happened since the late 90's / early 2000's (Goebel 2012, http://www.brainvoyager.com, Jones et.al 2000).

CIVET

This is a human brain image – pipeline for fully automated corticometric, morphometric and volumetric analyses of MR – images. It involves several different steps, which starts with a 9 – 12 parameter registration of the images, which are usually T1 weighted MRI images, even though the pipeline can preprocess T2 or proton density weighted images as well. These registered images are then transformed to stereotaxic space before they are corrected for radio – frequency non – uniformities. The next step in the process of preprocessing is to compute a brain mask (http://cbrain.mcgill.ca).

The next step is tissue classification into WM, GM or CSF. The brain is then split into the left and right hemispheres for surface extraction and the surfaces are registered to an available surface model. The cortical thickness is then computed by evaluating the distance between the original WM and GM surfaces transformed back to native space in the MR images. The data output

from this process can then be used in (among others) SurfStat to do statistical analysis (http://cbrain.mcgill.ca).

CRUISE

CRUISE stands for Cortical Reconstruction Using Implicit Surface Evolution. CRUISE uses T1 weighted volumetric MR brain images, and is an almost fully automatic algorithm, with only a brief manual preprocessing procedure (Han et.al 2011).

The preprocessing step is used to remove skin, bone, fat and other noncerebral tissues in the images, as well as removing the cerebellum and the brain stem. When this is done three landmarks are identified manually (Goldzal et.al 1998, Talairach & Tornoux 1988). The rest of the steps are automated and consists of: tissue classification, editing the WM membership function, topology correction of the WM isosurface, anatomically consistent GM enhancement, nested cortical surface reconstruction, the making of a surface model and lastly the reconstruction of the cortex (Han et.al 2011).

CLASP

CLASP stands for Constrained Laplacian – based ASP; a modification of an already existing algorithm called ASP (Kim et.al 2005, MacDonald et.al 2000). Where this method differs from the others is that it uses measured CSF from partial volume classification to preserve the morphology of the boundary between GM and CSF, even in tight sulci, which has been a challenge with other methods (Kim et.al 2005).

As the other methods CLASP also consists of several steps. These steps consists of: Preprocessing by intensity inhomogeneity correction and spatial normalization to stereotaxic space, tissue classification, splitting the brain into its respective hemispheres, and reconstructing the surface. The WM surface is reconstructed first, before the GM surface is initiated from the WM surface and expanded to the boundary between GM and CSF using a Laplacian map (Kim et.al 2005).

This methods advantage is its use of simple geometric constraints that results in surfaces that provide a valuable model for morphological experiments. The disadvantages are also it constraints, which may exclude the thinnest and thickest cortices. (Kim et.al 2005).

Discussion

Since the humble beginnings of the automated extraction, segmentation and measurement of the cortical thickness, we have come a long way. A combination of improvement in computer technology, imaging technology and algorithms has brought us the several software applications we have today.

How can these be clinically relevant however? With new information, there is the possibility to see developments in treatments of different diseases that might help patients earlier in the course of their disease. Cortical thickness analysis has already been used to look at the normal thinning of the cortex with age (Salat et.al 2004), to see the changes in the brain after a sensory loss (Li et.al 2004), or if the brain differs from a control when one of the senses was never there (Frasnelli et.al 2013). It has been used to explore how diseases such as Parkinson's disease (Wu et.al 2011) and Alzheimer's disease (Li et.al 2012) affects the brain, and how an early start at life

may affect the development of gray matter (Nagy, Lagercrantz & Hutton 2011, Kapellou et.al 2006, Martinussen et.al 2005, Nosarti et.al 2014).

Without cortical thickness analysis we might not have the insight we have today on how chronic pain affects the brain (DaSilva et.al 2008, Moayedi et.al 2010), and see there are differences in the brain with different pain sensitivities (Erpelding, Moayedi & Davis 2012).

Cortical thickness analysis have given us a better insight in the mechanisms of psychiatric disorders such as depression (Truong et.al 2013), body dysmorphic disorder (Madsen et.al 2015), depersonalization disorder (Sierra et.al 2014), schizophrenia (Zugman et.al 2015) and even psychosis (Buchy et.al 2015).

As we can see from this, there is a wide range of studies cortical thickness analysis can be used for, and which software application or algorithm that is chosen is based on what the research set at to answer, the availability of the different software applications and to some degree, which software application the researchers feel the most comfortable with.

All the software applications have their strengths and weaknesses; however, the software applications in use today are fundamentally similar. This means that the methods have the same basic applications, the differences lie in that some are packages where you have everything you need in one software(Freesurfer, Brainvoyager), while some of these software applications need to be run through some other software (SurfStat). The algorithms and the preprocessing software will do the extraction, segmentation and evaluation of the cortex but the statistical analysis can't be performed with these tools (CIVET, CRUISE and CLASP).

With that said, Freesurfer is still the software package most widely used. This might be because it is highly available, as it is free to both download and use, it is user friendly in that it is relatively easy to understand and use, and it is an accurate and robust tool. Brainvoyager is also used quite frequently, and is quite well known. This might be because it easy to learn and use, and free to download. To be able to use the full software package you have to pay a licence, which can be quite expensive.

SurfStat has reached popularity in certain communities, even though it is not as widely used as Freesurfer and Brainvoyager. This might be because there are more requirements of having access to other software applications, and you don't have a software package as with Freesurfer and Brainvoyager. SurfStat in itself is a toolbox, which is free to download, and use. To be able to use SurfStat however, MatLab must be available, a software that can be somewhat expensive if not already installed since it is pay per licence. Access to CIVET must also be provided, since SurfStat doesn't do the preprocessing steps itself. This might contribute to fewer researchers choosing this software application.

The least used of all the tools mentioned in this paper are the two algorithms. The reason behind this might be because it feels less user friendly than the software application packages since it requires the user to know where and how to run the algorithm. It might be less available than the software application packages (does not say if it is free download, have to pay, something that needs to be installed in a software application), and they include more manual steps than the software application package, increasing the workload for the users.

As of today, none of previously mentioned the software applications are used as a diagnostic tool, even though the method itself has shown promise for early detection of Alzheimer's disease (Lerch et.al 2008, Querbes et.al 2009).

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This might become one of its future applications, since it may give the opportunity to set a diagnosis earlier than the tools used by health care providers today, for not only Alzheimer's but other conditions as well, neurological or otherwise. This might lead to a higher quality of life for the patients in questions, since the treatments potentially can start as early as before the first onset of symptoms (Querbes et.al 2009). It could also be used to help diagnose focal epilepsy, which is often associated with thickened cortex (Jones et.al 2000)

However, there is a lack of accuracy in analysis on the individual level, making it difficult to use this method as a diagnostic tool (www.brainvoyager.com/). The cerebral cortex will never be completely homogeneous, even in the individual, which can make it difficult to say if the cortex in any given area is thickened or thinned before there has been done a group analysis, preferable a larger group for the most precise results.

If this is a limitation that can be solved, then this could be beneficial as a diagnostic tool for several groups, such as Alzheimer's, several psychiatric diseases, epilepsy, and so forth with that the presence of a certain pattern of thickening of thinning of the cortex would be indicative of a certain diagnosis.

As a summary, there can be said that cortical thickness has been, and still is, extensively used in research, and has great potential in that field Even though it has shown some promise as a diagnostic tool there is unlikely it will be used as such, unless the limitations in accuracy can be overcome.

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