Surfing the Hippocampus Wave

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Chapter 4 and 5 showed that FASTSURF is a promising time-saving method for the segmentation of the hippocampus and deep grey nuclei. However, FASTSURF is limited in a few aspects which need further attention:

- In chapter 4 and 5 FASTSURF was only validated with simulated sparse contours and not with independently created manual sparse contours.
- FASTSURF can only be used for relatively smooth structures, not for delineation of irregular structures such as tumours.
- So far, for FASTSURF only one contour on each slice can be outlined, which might not always be sufficient. However, this is not a fundamental limitation because it is conceptually straightforward to connect a single contour on one slice to two or more contours on the next, by defining an appropriate connecting mesh.
- If a structure contains cavities that should be excluded from the volume, special precautions in the outlining software need to be implemented to account for this.

The harmonized hippocampus outlining protocol (HarP) is the most modern and most widely accepted outlining protocol. Therefore, in the ideal case longitudinal hippocampus segmentation in a scan-rescan MRI setting outlined using HarP would complete a validation for FASTSURF or automatic segmentation methods.

In chapter 6, non-linear registration was performed on 3D T1 weighted MPRAGE MRI scans acquired at various locations from different vendors (GE, Philips and Siemens). Image post-processing procedures such as bias field correction or intensity normalization might improve registration performance and make the registration more robust across images from different vendors. Furthermore, for images acquired with different sequences parameters of non-linear registration methods most probably need to be tuned to those images. However, even without such procedures, the results in chapter 6 are very promising.

As mentioned in the introduction, imaging limitations such as resolution, noise and artefacts affect the investigation of segmentation and hippocampal atrophy. In this thesis, only segmentations of T1-weighted images were investigated. In the future perspective and development section of this chapter it is discussed why high field MRI T2-weighted images might be advantageous.

Clinical workflow

Considering the need for fast and accurate hippocampus segmentation and reliable automatic atrophy measurement methods in clinical neuroradiology and radiotherapy, two possible clinical workflows are presented resulting from the work of this dissertation.

In subjects with neurodegenerative diseases in which hippocampal atrophy is a secondary outcome measure in clinical trials the subject must undergo longitudinal MRI scan sessions with the same MRI protocol. To obtain the hippocampus segmentation of the baseline MRI, a trained operator can delineate approximately five contours of the hippocampus and use FASTSURF to complete the segmentation. Then, with a symmetric non-linear registration method (for instance ANTs, Elastix or NiftyReg) the baseline MRI can be mapped to the follow up MRI and atrophy rates can be determined by either measuring the longitudinal volume change of the baseline and the mapped hippocampus using mesh-based methods or by using Jacobian integration. The same workflow is applicable for clinical trials in which the assessment of radiation induced brain atrophy is of interest.

In subjects that receive HA-PCI, a subject must obtain a brain MRI and CT simulation scan, which is used for HA-PCI treatment planning. The MRI must be mapped to the CT scan prior hippocampus delineation. Using FASTSURF with approximately five input contours left and right hippocampus delineations can be obtained, and hippocampal avoidance region can be generated by expanding hippocampal contours by 5mm. To create the HA-PCI treatment plan, also the whole brain and lenses must be contoured, and the planning CT and accompanying contours must be transferred to a treatment planning system. Finally, a radiotherapy treatment plan can be determined which minimizes the dose to the lenses and the hippocampi.

7.4. Future perspectives and developments

FASTSURF

In the future, FASTSURF might find its role in creating standard reference segmentation sets and, as described in the clinical workflow section, it could be used in clinical trials in which changes of anatomical structures need to be determined. For these applications, the FASTSURF algorithm needs to be implemented in a delineation tool for ease of use. Furthermore, FASTSURF should be validated against fully manual and automatic segmentation methods using independently obtained manual sparse contours. For an even more complete validation, a multiple observer analysis should be performed, in which experienced and inexperienced/untrained observers use FASTSURF with a well-defined segmentation protocol.

FASTSURF should be further improved and developed to increase its performance. A possible improvement of FASTSURF might be the inclusion of drawing sparse contours in multiple directions (coronal/axial/sagittal) to increase segmentation accuracy and ease of use.

T2-weighted MRI and hippocampal subfield analysis

Almost a decade ago, special oblique coronal T2-weighted high field strength (3T-7T) MRI sequences have been developed to increase in-plane resolution of images (~0.5x0.5mm^2) and to provide better intensity contrast in the hippocampal region [38–43]. The slice thickness for those methods is usually thicker (~2.0mm), nevertheless the voxel volume can be reduced [38]. It has been shown that whole hippocampal volumes measured on T1- and T2-weighted MRI did not differ [44], but because T2-weighted images provide better intensity contrast in the hippocampal region and higher in-plane resolution, the study concludes that measurements on T2-weighted images are more sensitive [44]. Furthermore, visual evaluation on T2-weighted images seems to provide a better discrimination power between AD and MCI groups [45]. Finally, on T2-weighted MRI manually segmenting hippocampal subfields is possible [38–43,46,47]. Hippocampal subfield analysis was shown to be more sensitive to disease effects, as for instance in AD related neuronal tangles tend to happen most in the CA1 region of the hippocampus [48–50]. Also, annual atrophy rates in the CA regions and dentate gyrus have been shown to be significantly larger (~1% to 1.5% larger) in MCI than in controls [44]. However, manually segmenting hippocampal subfield is even more labour intensive then measuring whole hippocampal volumes, but atlas-based (semi-)automatic segmentation of these subfields seems to be possible [47,51,52]. These findings suggest that measuring hippocampal (subfield) volumes on high field strength T2

weighted MRI is more sensitive than measuring volume on T1 weighted MRI with lower (1.5T) field strength. But it should be noted that determining 1-3% atrophy rates in smaller regions might be more challenging than measuring whole hippocampus atrophy rates on clinical T1-weighted MRI.

Deep learning algorithms

Due to its popularity in many areas of medical image analysis in the last few years [53], the topic *deep learning* in the field of brain image analysis cannot be overlooked and will be briefly discussed.

Deep learning is a machine learning technique, which computes predictions using imaging features from large image databases. The difference between classical machine learning techniques and deep learning is that features are learned from data and are not designed by human engineers [54]. It is appearing that such self-learned imaging features may be useful for quantitative brain image analysis.

Deep learning consists of neural networks with multiple layers, usually more than five [53]. Neural networks are decision trees with features as inputs and an output prediction. Due to the large quantity of necessary training data, deep learning is computationally very expensive. However, advances in graphics processing units (GPU) massively accelerate deep learning training and makes deep learning algorithms more accessible [54].

Akkus et al. give an excellent overview of deep learning algorithms used for brain segmentation [53] and it is shown that convolutional neural networks (CNNs) are the most commonly used for image classification and segmentation. CNNs are a type of multi-layer models consisting of trainable filters and pooling operations which are alternatingly applied on the input images [55,56]. Akkus et al. also show that CNN-based deep learning approaches achieved high segmentation accuracy results [53]. For instance, dice overlap indices higher than 0.8 for sub-cortical structures were obtained in [57]. Similarly, for the hippocampus, WM, GM and CSF Dice overlap values of 80.45%, 86.15%, 89.46% and 84.25% were obtained with only five training MRIs, respectively [58]. The later article also shows that the dice overlap for the hippocampus increased to 84.91% using 25 training MRIs, concluding that segmentation accuracy can be increased using more training data. In [59] a CNN model was trained with a large dataset of automated FreeSurfer hippocampus segmentation and simulated data. CNN based segmentations correlated well with FreeSurfer segmentations, but less erroneous segmentations were observed, and the trained model was much faster in segmenting one hippocampus (<30s) compared to FSL-FIRST (~10min) or FreeSurfer (~4h).

The segmentation results of deep learning algorithms seem very promising. However, a large amount of training data is necessary for deep neural networks to make them robust for different types of scanners, image inhomogeneities or anatomical variation. FASTSURF could be used for to create such training datasets.

7.5. Conclusions

In this thesis it has been shown that testing and developing methods to analyse anatomical structures is challenging. The following main conclusions can be drawn from the work presented:

- For manual segmentations a well described outlining protocol and good guidelines are important (chapter 3). However, manually segmenting anatomical structures is subjective and segmentations can only be reproduced to some extent (chapter 2 and chapter 6). Furthermore, outlining brain structures on every slice of T1-weighted 1.5T or 3T MRI is very inefficient and a lot of redundant information is provided.
- FASTSURF is a novel segmentation method which reduces segmentation time. It can be used to create standard segmentation reference sets or to outline brain structures to create avoidance treatment plans in radiotherapy (chapter 4 and chapter 5).
- Mesh representations of 3D objects are recommended for accurate segmentation comparison in which segmentations need to be mapped to the same space.
- Non-linear registration methods are recommended to determine hippocampal atrophy rates (chapter 6). FASTSURF could be used to obtain a baseline segmentation for such a registration-based setting.
- Generally, the quality of segmentations should be visually inspected (preferably in 3D) to avoid and correct for segmentation errors.

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Samenvatting

Dit proefschrift heeft als doel om bestaande methodes voor het segmenteren (intekenen) van de hippocampus te analyseren, deze aan te vullen met eigen nieuwe ontwikkelingen en atrofie (volume afname) van de hippocampus te kwantificeren. Dit werk is van belang voor zowel de neurologie, omdat verschillende neurologische aandoeningen gepaard gaan met volume reductie van de hippocampus, als voor de radiotherapie, waarbij men deze volume reductie wil voorkomen bij het toepassen van profylactische bestraling. Verschillende openbaar beschikbare automatische segmentatiealgoritmes zijn nauwgezet geanalyseerd. Hierbij is de hippocampus in verschillende regio's opgedeeld en zijn de prestaties voor elke regio gekwantificeerd. Daarnaast is een semi-automatisch segmentatiealgoritme ontwikkeld, dat volgens een vergelijkbare methodologie werd geanalyseerd voor de hippocampus en andere subcorticale gebieden. Tot slot is er een kwantificatie analyse voor het meten van atrofie van de hippocampus uitgevoerd en methodes met grote "statistische power" voor het meten van deze atrofie zijn geïdentificeerd.

Het eerste deel-onderwerp van dit proefschrift wordt beschreven in hoofdstuk 2. Hier worden systematische verschillen tussen handmatige en automatische hippocampus segmentatie gekwantificeerd en de reproduceerbaarheid van de verschillende methoden vergeleken. Hiertoe zijn MRI scans van gezonde proefpersonen, personen met milde cognitieve beperking en personen met Alzheimer, die vlak na elkaar gemaakt waren ("back-to-back" scans), gesegmenteerd door een daar in getrainde expert en door automatische methodes. De belangrijkste bevinding van hoofdstuk 2 is dat handmatige segmentatie van de hippocampus minder reproduceerbaar is dan één van die automatische methoden, namelijk FSL-FIRST. Daarnaast zijn er ook systematische verschillen tussen de verschillende regio's van de hippocampus waargenomen. Deze verschillen ontstaan deels door de verschillende definities van de anatomische grenzen van de hippocampus structuur die de verschillende methoden hanteren. Een belangrijk aandachtspunt is om de hogere reproduceerbaarheid niet te verwarren met een hogere acuraatheid. Goede reproduceerbaarheid garandeert niet dat de anatomisch juiste gebieden zijn ingetekend en dit hoeft daarom ook niet te leiden tot hogere voorspellende kracht in het constateren van door pathologie geïnduceerde verandering van de hippocampus.

In hoofdstuk 3 wordt voor handmatige hippocampus-segmentatie de overeenkomst tussen meerdere personen besproken. Er wordt een uitlijnings-protocol gebruikt dat dient voor het plannen van hippocampus-sparende radiotherapie. Daar waar de manuele segmentaties van hoofdstuk 2 werden uitgevoerd door een expert vanuit

de radiologie, worden in hoofdstuk 3 alle segmentaties manueel uitgevoerd door professionals met verschillende specialismes, zoals een technicus radiotherapie, een oncoloog en een neuro-radioloog. De intekeningen zijn verricht aan de hand van een inteken-protocol waarmee zij nog niet veel ervaring hadden. Dit is een mogelijke verklaring voor de lagere reproduceerbaarheid in deze studie in vergelijking met voorgaand werk in hoofdstuk 2. De ICCs van 0.56 en 0.69 voor respectievelijk de linker en rechter hippocampus zijn relatief laag vergeleken met segmentatie overlap bekend uit neuro-radiogische studies, welke een ICC groter dan typisch 0.85 hebben. Dit leidt tot de conclusie van hoofdstuk 3 dat de segmentatienauwkeurigheid baat heeft bij een beter segmentatie protocol, en een uitgebreidere training. Desalniettemin had de waargenomen inteken-variatie slechts een geringe invloed op het klinische doel, het terugdringen van gemiddelde stralingsdosis aan de hippocampus, want in nagenoeg alle gevallen bleven de intekenvariaties binnen de dosis randvoorwaarden van het bestralingsplan.

In hoofdstuk 4 wordt een innovatief semi-automatisch segmentatiealgoritme, met de naam FASTSURF, gepresenteerd. In deze “proof-of-concept” studie zijn handmatige hippocampus segmentaties met beperkte uitlijningen gesimuleerd, door slechts in enkele vlakken de contour over te nemen. Deze werden vervolgens gebruikt om een segmentatie met volledige uitlijning te reconstrueren. De resultaten lieten zien dat de volume reconstructie door FASTSURF, aan de hand van een beperkte manuele uitlijning, een betere overeenkomst met de handmatige segmentaties geeft dan beide automatische methodes uit hoofdstuk 2. FASTSURF produceerde zelfs wanneer slechts uitlijningen op zes tot zeven slices voor de reconstructie beschikbaar waren een betere overlap met manuele segmentaties dan deze twee automatische methoden. Een mogelijk bezwaar tegen deze conclusie is dat de segmentatie van FASTSURF gebaseerd is op een “under-sampling” van een originele segmentatie waardoor de analyse van FASTSURF mogelijk bevoordeeld wordt. Dezelfde conclusie werd echter ook bereikt door de FASTURF reconstructie te vergelijken met de “back-to-back” scan segmentaties. Ook hier werd vastgesteld dat FASTSURF zelfs met minimaal vijf input contouren al meer reproduceerbare segmentaties genereerde dan FreeSurfer en FSL-FIRST.

Hoofdstuk 5 beschrijft een studie waarin werd onderzocht of FASTSURF ook geschikt is om op een nauwkeurige en efficiënte manier andere subcorticale structuren dan de hippocampus te segmenteren; namelijk het putamen, de nucleus caudatus en de thalamus. Het segmenteren van deze drie structeren is een belangrijk onderdeel van een nieuw segmentatie protocol voor het genereren van een standaard segmentatie-set, die als referentie kan dienen voor toekomstig onderzoek in het neurowetenschappelijk veld. Net als in hoofdstuk 4 hadden de segmentaties gemaakt met FASTSURF een uitstekende overlap met de volledig

handmatig gemaakte segmentaties, wat tot de conclusie leidt dat FASTSURF inderdaad een tijdbesparend alternatief kan zijn voor volledig handmatig gegenereerde segmentaties.

De mate van atrofie van de hippocampus is een belangrijke “bio-marker” voor klinische geneesmiddelenstudies en het bepalen hiervan is het onderwerp van het laatste hoofdstuk van dit proefschift. In hoofdstuk 6 worden acht verschillende methodes beschreven en vergeleken, om de percentuele volume afname van de hippocampus te bepalen. Hiertoe zijn MRI scans van “baseline” en scans van een jaar later van dezelfde proefpersonen geanalyseerd. Deze scans zijn afkomstig van gezonde controle personen, personen met milde cognitieve beperking en personen met Alzheimer. De resultaten lieten zien dat atrofie bepalingen die gebaseerd zijn op niet-lineaire registratie technieken beter presteerden dan volume verandering bepaald door handmatig gegenereerde segmentaties. Van deze registratie methodes presteerde ANTs het beste, gevolgd door Elastix en daarna NiftyReg.

Een belangrijk tweede aspect van deze studie was het vaststellen of bestaande methoden gevoelig genoeg zijn om stralings-geïnduceerde atrofie van de hippocampus te detecteren. Hiertoe is aan de hand van een literatuurstudie van de relevante radiotherapie literatuur een schatting gemaakt van de verwachte effectgrootte. Aan het einde van hoofdstuk 6 voorspellen wij dat de verwachtte effectgrootte van stralings-geïnduceerde atrofie waarneembaar is in de data, zelfs met een kleine steekproefomvang (N≈20 per groep) wanneer een van de drie hiervoor genoemde registratie technieken wordt gebruikt. Wanneer men volledig handmatig gegenereerde segmentaties wil gebruiken om deze atrofie te bepalen is de benodigde steekproefomvang veel groter (N≈90).

Zusammenfassung

Diese Dissertation hat das Ziel, bestehende Methoden zur Segmentierung des Hippocampus zu analysieren, mit eigenen Entwicklungen zu ergänzen und die Atrophie (Volumenabbau) des Hippocampus zu quantifizieren. Damit ist diese Arbeit sowohl für die Neurologie wichtig, da verschiedene neurologische Erkrankungen, wie zum Beispiel Alzheimer, mit der Volumenreduzierungen des Hippocampus zusammenhängen, als auch für die Radiotherapie, welche die Volumenreduzierung durch Anpassung von prophylaktischer Bestrahlung zu verhindern versucht. Die Hippocampus Segmentierungsqualität wurde von verschiedenen, open-source", automatische Segmentierungsalgorithmen (FSL-FIRST & FreeSurfer) detailliert analysiert. Des Weiteren wurde eine halb-automatische Hippocampus Segmentierungsmethode entwickelt und mit denselben Methoden verglichen. Diese wurde auch zur Segmentierung von subkortikalen Gehirnstrukturen getestet. Schließlich wurde eine Analyse zur Atrophiequantifizierung vom Hippocampus durchgeführt und Methoden mit hoher statistischer Aussagekraft für das Messen dieser Atrophie identifiziert.

Das erste Thema dieser Dissertation wird in Kapitel 2 beschrieben. Systematische Unterschiede zwischen manuellen und automatischen Hippocampusegmentierungen wurden quantifiziert und die Reproduzierbarkeit der unterschiedlichen Methoden verglichen. Hintereinander aufgenommene Magnetresonanztomographie (MRT) Bilder („back-to-back“ scans) des Gehirns von gesunden Testpersonen, Personen mit milder kognitiver Beeinträchtigung und Personen mit Alzheimer wurden durch einen trainierten Segmentierungsexperten und durch automatische Segmentierungsmethoden verarbeitet. Das wichtigste Ergebnis aus Kapitel 2 ist, dass manuelle Hippocampussegmentierungen schlechter reproduzierbar sind, als eine der automatischen Segmentierungsmethoden, nämlich FSL-FIRST. Weiterhin wurden systematische Segmentierungsunterschiede zwischen den unterschiedlichen Regionen des Hippocampus festgestellt. Diese Unterschiede entstehen teilweise durch verschiedene Definitionen der anatomischen Begrenzungen der Hippocampusstruktur in den unterschiedlichen Methoden. Die höhere Reproduzierbarkeit ist nicht mit höherer Segmentierungsgenauigkeit zu verwechseln. Eine gute Reproduzierbarkeit garantiert nicht, dass die anatomischen Gebiete des Hippocampus richtig segmentiert sind, und das führt auch nicht dazu, dass pathologisch induzierte Veränderungen des Hippocampus besser vorausgesagt werden können.

In Kapitel 3 wird die Übereinstimmung von manuellen Hippocampussegmentierungen von mehreren Personen analysiert. Ein Segmentierungsprotokoll wurde verwendet, welches zum Planen von Strahlentherapie bei Hirntumoren dient und der Hippocampus mit geringerer Bestrahlung ausgesetzt wird als der Rest des Gehirns. Im Gegensatz zu in Kapitel 2 durchgeführten Untersuchungen, während derer die

Hippocampi von einem Experten aus der Radiologie segmentiert wurden, wurden in Kapitel 3 alle Hippocampi durch verschiedene Spezialisten aus verwandten Fachgebieten umzeichnet. Dies erfolgte durch zwei technische Radiologen, vier Onkologen und einem Neuroradiologen, welche ein für sie neues Segmentierungsprotokoll verfolgten. Dies könnte, im Vergleich zu den Ergebnissen aus der Studie in Kapitel 2, die niedrigere Reproduzierbarkeit erklären. Die Intra-Klassen-Korrelationen (intra-class-correlation (ICC)) von 0.56 und 0.69 für den jeweiligen linken und rechten Hippocampus sind gering im Vergleich zu neurologischen Segmentierungsstudien, in denen normalerweise ICCs grösser als 0.85 zu finden sind. Als Fazit aus den in Kapitel 3 vorgestellten Ergebnissen lässt sich ziehen, dass die Segmentierungsgenauigkeit durch ein besseres Segmentierungsprotokoll und durch Training gesteigert werden kann. Nichtsdestotrotz haben die Segmentierungsvariationen kaum einen Einfluss auf das klinische Ziel, die Reduzierung der Strahlendosis auf den Hippocampus. In beinahe allen Fällen blieben die Segmentierungsvariationen stets im Rahmen der Randbedingungen des Bestrahlungsplans.

In Kapitel 4 wird ein innovativer, halb-automatischer Segmentierungsalgorithmus mit dem Namen FASTSURF vorgestellt. In dieser „proof-of-concept“ (Machbarkeitsnachweis) Studie wurden manuelle Segmentierungsschichten simuliert. Dies erfolgt, durch Selektion von nur wenigen Schichten einer kompletten Hippocampussegmentierung. Diese Schichten wurden anschließend benutzt, um einen kompletten Hippocampus zu rekonstruieren. Die Ergebnisse zeigten, dass die FASTSURF-Rekonstruktionen genauer mit manuellen Segmentierungen übereinstimmen, als die zwei automatischen Methoden, die in Kapitel 2 vorgestellt wurden. Die bessere Übereinstimmung von FASTSURF-Rekonstruktionen mit manuellen Segmentierungen war selbst mit nur sechs bis sieben simulierten Schichten nachweisbar. Zu beachten ist, dass die Segmentierungen von FASTSURF auf ein „under-sampling“ von den originalen Segmentierungen basiert, was die Analyse von FASTSURF möglicherweise begünstigt. Allerdings konnte das Resultat auch beim Vergleich von FASTSURF-Rekonstruktionen mit Segmentierungen von „back-to-back“ scans erreicht werden. Auch hier generiert FASTSURF mit nur fünf simulierten Segmentierungsschichten besser reproduzierbarere Segmentierungen, als FreeSurfer und FSL-FIRST.

Kapitel 5 beschreibt eine Studie, die untersucht, ob FASTSURF sich auch eignet, andere subkortikale Gehirnstrukturen als den Hippocampus genau und effizient zu segmentieren, In dieser Studie wurden Segmentierungen vom Putamen, Nucleus Caudatus und vom Thalamus untersucht. Das Segmentieren dieser drei Strukturen ist für eine neues Segmentierungsprotokoll zum Generieren eines Standard Segmentierungssets wichtig. Dieses Set soll als Referenz für zukünftige Forschungen im Feld der Neurowissenschaft dienen. Ebenso wie in Kapitel 4 hatten die

FASTSURF generierten Segmentierungen eine hervorragende Übereinstimmung mit den manuellen Segmentierungen. Daher das Fazit, dass FASTSURF tatsächlich eine zeitsparende Alternative gegenüber komplett, manueller Segmentierungen sein kann.

Der Grad der Atrophie des Hippocampus ist ein wichtiger „bio-marker“ für klinische Medikamentenstudien und die Quantifizierung der Atrophie ist das Thema des letzten Kapitels dieser Dissertation. Kapitel 6 beschreibt und vergleicht acht verschiedene Methoden, um die Volumenabnahme des Hippocampus in Prozent zu bestimmen. Hierfür wurden Gehirn MRT Bilder vom Referenzzeitpunkt und ein Jahr später aufgenommene MRT Bilder der gleichen Testperson analysiert. Die MRT Bilder stammen, wie auch in den ersten Untersuchungen, von gesunden Testpersonen, Personen mit milder kognitiver Beeinträchtigung und Personen mit Alzheimer. Die Ergebnisse zeigen, dass Registrierungstechniken, die auf nicht-linearen Methoden basieren, Atrophie exakter quantifizieren, als Methoden, die manuell erzeugte Segmentierungen als Grundlage haben. Von den Registrierungsmethoden schnitt ANTs am besten ab, danach folgten Elastix und NiftyReg.

Ein zweiter wichtiger Aspekt dieser Studie war es festzustellen, ob existierende Methoden sensibel genug sind, um strahlungsinduzierte Atrophie vom Hippocampus zu detektieren. Anhand einer Literaturstudie von Radiotherapieliteratur wurde eine Einschätzung zur Effektgröße gemacht. Aus den Ergebnissen, der in Kapitel 6 vorgestellten Studie, wurde geschlossen, dass die erwartete Effektgröße von strahlungsinduzierter Atrophie in den vorliegenden Daten erkennbar ist. Dies gilt auch bei einem relativ kleinen Stichprobenumfang (N≈20 pro Gruppe), wenn eine der drei vorher genannten Registrierungsmethoden benutzt wird. Manuelle Segmentierungen benötigen einen deutlich größeren Stichprobenumfang (N≈90) zum Bestimmen der Atrophie.

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I often described the PhD life as wave representing periods of success and fun and periods of frustration and dislike. I was able to push through these wave-like periods, not because I thought I was an extraordinarily smart scientist, but because I was always surrounded by intelligent and motivating people. They helped me to navigate the ups and downs and taught me the beauty of science. Here, I would like to thank all the people who took part in my personal development and supported me throughout my research and with this thesis.

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Dr. Jan de Munck, Jan, and **Dr.ir. Hugo Vrenken**, Hugo, you were my day-to-day supervisors and you are the people I must thank the most. Without both of you, I would not have been able to make it through these PhD years, and I probably wouldn't have been close to finishing my thesis.

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Furthermore, I had a wonderful time with the structural brain imaging group (**SBIG**) lead by Hugo Vrenken. **Iman**, **Ronald**, Alexandra, **Houshang**, various **interns** and old members of the group such as **Adriaan**, **Martijn**, **Veronica**, **Yaou**, **Christiane** and **Mara**, thank you so much for the fantastic meetings, lunch breaks and for supporting my research. Also, thanks for letting me be part of your research; in each of our meetings I learned something new which is why I enjoyed the meetings so much.

Unforgettable are my moments with the “**lunch boys**”. **Jim**, **Alex**, **Jacob**, **Omar**, **Hugo** and Martin, I really enjoyed our lunch breaks, discussions about science and utter nonsense. My PhD life was much more enjoyable due to you guys.

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I partially worked at the NKI where I was able to learn more about brain and lung radiotherapy. I was lucky to obtain fantastic supervision from Marcel van Herk, **Dr. Jose Belderbos** and **Dr. Michiel de Ruiter**. Jose, thanks for integrating me in the lung research group and for supporting my research. I loved our talks and meetings because you always had great ideas to accelerate my work and to push me in the right direction. Michiel, thanks for helping me with my research, for organizing data for me and introducing me to your field in cognitive neuroscience. It was fun to work and cooperate with you. Also, I want to thank you both for spending hours reading my papers.

I’m very thankful that I could work at the radiotherapy department (**RT**) and attend the lung research group meetings lead by **Prof. Dr. Jan-Jakob Sonke**. I had great times and always learned something new during those meetings.

For the fabulous book cover you deserve a big praise **Jennifer Alcock**. You gave my title and cover ideas a great artistic and final touch and therefore, the book is an eye-catcher for everyone.

Finally, I would like to thank the people who are closest to me and who have supported me throughout my entire life.

I have a large group of **friends** with different nationalities spread throughout Germany, Netherlands and the United States of America. I will not name any specific names, because it would be far too extensive for this section. My friends are very an important piece of my life and they indirectly contributed to my work, because they gave me the strength to push through any kind of hardship and helped me to forget about science and work in my free time. This was important for me to relax and sort out my brain. Thank you all for being there for me.

Papa und **Mama**, euch habe ich natürlich unheimlich viel zu verdanken. Ihr habt mir meine Laufbahn eigentlich in die Wiege gelegt. Von Papa habe ich die Leidenschaft an Technology und Ingenieurswissenschaften und von Mutter das Interesse an

Medizin geerbt. Vielen Dank, dass ihr mich jeder Zeit während meines Doktors unterstützt und mir mit meinen arbeitsunabhängigen Problemen geholfen habt. Bessere Eltern kann man sich nicht wünschen! Natürlich geht auch ein riesen Dank an meine Geschwister, **Kai**, **Lara** und **Christiane**. Ich weiß, dass es manchmal nicht einfach ist einen Bruder zu haben, der ständig unterwegs ist, viel zu tun hat und wenig Zeit für euch aufbringen kann. Darum bin ich euch für euren Rückhalt und euer Verständnis sehr dankbar.

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Curriculum Vitae

Fabian Bartel was born in 1987, in Haselünne, Germany. After finishing high school in 2006, he joined the Bundeswehr to fulfill his mandatory nine months of service. This time gave him the opportunity to learn that you can always push past your limits and work harder then you thought possible. This important lesson has fueled his academic career and served as the foundation of his achievements.

After completing his service in 2007, Fabian choose to pursue a degree in medical technology at the University of Applied Sciences Bremerhaven in Germany. During his studies, Fabian became interested in imaging methodologies, specifically MRI. This led to an internship in 2010 in Australia at the University of Queensland in the MedTeQ center where he designed and developed MRI coils.

After his diploma, in 2011, Fabian started his master's program in Biomedical Engineering at the University of Applied Sciences Lübeck in Germany. He focused on imaging methodologies and improving his electronics and image processing skills. In 2012, Fabian expanded his experience in MRI through an internship at Queen Elizabeth II Health Science Center, Halifax Canada. The internship focused on implementation of methods to improve efficiency of 3D MRI and implementation of a protocol for an MRI sequence to capture the articular cartilage of the knee.

Due to his developed passion for image processing and with MRI being his favorite imaging methodology, Fabian was inspired to search for PhD programs in this field. He focused his search on programs in Amsterdam and found his PhD position in the field of brain image analysis at VU University Medical Center (VUmc) in 2014. This gave him the opportunity to improve his knowledge in MRI and image processing and to perform research on the most interesting human body part, the brain. During his PhD, Fabian obtained the first prize in the young investigators competition during the European Medical and Biological Engineering Conference (EMBEC) and the Nordic-Baltic Conference on Biomedical Engineering and Medical Physics (NBC) in Tampere, Finland, in June 2017.

After finishing his PhD research in April 2018, Fabian accepted a position working at MR Coils, a Dutch company that designs and develops specialized MRI coils. Fabian is motivated by the opportunity to contribute to the medical world and to continue to develop his management skills.

List of Publications

F. Bartel, H. Vrenken, F. Bijma, F. Barkhof, M.B. van Herk, J.C. de Munck. Regional Analysis of Volumes and Reproducibilities of Automatic and Manual Hippocampal Segmentations. PLoS ONE 12(2): e0166785 (2017)

F. Bartel, M.B. van Herk, H. Vrenken, F. Vandaele, S. Sunaert, K. de Jaeger, N.J. Dollekamp, C. Carbaat, E. Lamers, E.M.T. Dieleman, Y. Lievens, D. de Ruysscher, S.B. Schagen, M.B. de Ruiter, J.C. de Munck, J. Belderbos. Inter-observer variation of hippocampus delineation in hippocampal-avoidance prophylactic cranial irradiation. Clin Transl Oncol (2018). https://doi.org/10.1007/s12094-018-1903-7

F. Bartel, H. Vrenken, M.B. van Herk, M. de Ruiter, J. Belderbos, J. Hulshof, J.C. de Munck. Fast Segmentation Through Surface Fairing (FASTSURF): A novel semi-automatic hippocampus segmentation method. Submitted to PLOS ONE May 2018

A. de Sitter, **F. Bartel**, M. Palotai, J. Burggraaff, Y. Liu, J. Simoes, S. Ruggieri, K. Schregel, A. Morales Pinzon, S. Ropele, M.A. Rocca, C. Gasperini, A. Gallo, M. Schoonheim, M. Amann, M. Yiannakas, M.P. Wattjes, J. Sastre-Garriga, L. Kappos, M. Filippi, C. Enzinger, O. Ciccarelli, J. Frederiksen, F. Barkhof, C.R.G. Guttmann, J.C. de Munck, H. Vrenken. Creating accurate reference segmentations of deep GM structures in MS patients by fast semi-automated outlining. Submitted to Multiple Sclerosis Journal June 2018

F. Bartel, M. Visser, M.B. de Ruiter, J. Belderbos, F. Barkhof, H. Vrenken, J.C. de Munck, M.B. van Herk. Non-linear registration improves statistical power to detect hippocampal atrophy in aging and dementia. Submitted to NeuroImage: Clinical July 2018

Training plan

Courses, Schools and Conferences	Organizer	Completion date
C++ Programming Methods	University of Amsterdam (UvA) – National research institute for mathematics and computer science (CWI)	2015
iQ Winter School 2016 – "Quantitative Analysis of Medical Images"	Institute Quantivision (iQ)	February 2016
Christie Advanced Radiotherapy Summer School	The Christie School of Oncology	July 2016
Basic Medical Statistics	Antoni van Leeuwenhoek hospital (AvL)/Oncology Graduate School Amsterdam (OOA)	November 2016
Scientific Integrity – Biomedical Sciences	VU University Medical Center (VUmc) Academy	May 2017
PCDI course – "Employability outside academia"	Postdoc Career Development Initiative (PCDI)	October 2017
EuSoMII Acadamy – "Game changers in radiology"	European Society of Medical Imaging Informatics (EuSoMII)	November 2017
iQ Winter School 2018 – "Machine Learning Applied to Quantitative Analysis of Medical Images"	iQ	March 2018
5th Dutch Bio-Medical Engineering Conference		January 2015
5th International Cognition and Cancer Task Force Conference (ICCTF)		March 2016
6th Dutch Bio-Medical Engineering Conference		January 2017
1st Institute Quantivision Conference		February 2017
EMBEC and NBC Conference		June 2017
Supervising and teaching		
Two bachelor students and one master student	VUmc	2015 - 2017
Practical part of the Advance Medical Image Processing course (AMIP)	VU University	2015 - 2017