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Chronic traumatic encephalopathy –

Neuroimaging markers and brain function

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List of Abbreviations

AD *Alzheimer's disease*

AFE *Age of first exposure*

APO ε4 *Apolipoprotein-epsilon 4*

BMI *Body mass index*

CBD *Corticobasal degeneration*

CSF *Cerebrospinal fluid*

CSP *Cavum septi pellucidi*

CT *Computed tomography*

CTE *Chronic traumatic encephalopathy*

DETECT *Diagnosing and Evaluating Traumatic Encephalopathy using Clinical Tests*

DTI *Diffusion tensor imaging*

fMRI *functional Magnetic Resonance Imaging*

GGT *Globular glial tauopathy*

MP-RAGE *magnetization prepared rapid gradient-echo*

MRI *Magnetic resonance imaging*

MRT *Magnetresonanztomographie*

NFL *National Football League*

NFTs *Neurofibrillary tangles*

NIA *National Institutes on Aging*

NICHD *National Institute of Child Health and Human Development*

NIH *National Institutes of Health*

NINDS *National Institute of Neurological Disorders and Stroke*

PET *positron-emission tomography*

PSP *Progressive supranuclear palsy*

p-tau *phosphorylated tau protein*

RHI *Repetitive head impacts*

ROI *Region of interest*

TDP-43 *43 kDa TAR DNA binding protein*

TES *Traumatic Encephalopathy Syndrome*

Publication record of the presented work

The presented work is based on the following two papers:

1. Koerte, I. K.*, **Hufschmidt, J***., Muehlmann, M., Tripodis, Y., Stamm, J. M., Pasternak, O., Giwerc, M. Y., Coleman, M. J., Baugh, C. M., Fritts, N. G., Heinen, F., Lin, A., Stern, R. A., & Shenton, M. E. (2016). Cavum Septi Pellucidi in Symptomatic Former Professional Football Players. *Journal of neurotrauma*, *33*(4), 346–353. https://doi.org/10.1089/neu.2015.3880

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2. Lepage, C., Muehlmann, M., Tripodis, Y., **Hufschmidt, J**., Stamm, J., Green, K., Wrobel, P., Schultz, V., Weir, I., Alosco, M. L., Baugh, C. M., Fritts, N. G., Martin, B. M., Chaisson, C., Coleman, M. J., Lin, A. P., Pasternak, O., Makris, N., Stern, R. A., Shenton, M. E., Koerte, I. K. (2019). Limbic system structure volumes and associated neurocognitive functioning in former NFL players. *Brain imaging and behavior*, *13*(3), 725–734. https://doi.org/10.1007/s11682-018-9895-z

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Summary

Chronic Traumatic Encephalopathy (CTE) is a neurodegenerative disease possibly affecting many individuals. It is strongly associated with a history of exposure to repetitive head impacts (RHI), both concussive and subconcussive. Besides the number and strength of head impacts, the genetic variant Apolipoprotein-epsilon 4 allele (APO ε4) is a known risk factor. Individuals who suffer from CTE can experience a variety of symptoms, including headache, depression, aggression, severe cognitive impairments, and ultimately dementia. On neuropathological evaluation, CTE is characterized by an accumulation of hyperphosphorylated tau protein around small vessels at the depths of the cortical sulci. Two other frequent findings in CTE are the presence of a cavum septi pellucidi (CSP) and regional brain atrophy predominantly of the limbic system.
While the diagnosis of CTE requires post-mortem neuropathological examination, in-vivo diagnostic tools would allow early diagnosis and the development of specific treatment. Magnetic resonance imaging (MRI) provides an excellent opportunity to develop such in-vivo diagnostic tools.
Combining efforts and methods, the Diagnosing and Evaluating Traumatic Encephalopathy using Clinical Tests (DETECT) study was initiated. DETECT studied a sample of symptomatic former American football players from the National Football League (NFL) and non-contact sports athlete controls. The former NFL players were deemed at high risk of CTE, given that all exhibited symptoms matching the assumed clinical presentation of CTE.
All participants underwent MRI and extensive neuropsychological testing. Within DETECT, the present work aims at identifying potential in-vivo neuroimaging markers of CTE. More specifically, we investigated the presence of CSP (publication 1) and assessed regional brain volume of limbic system structures (publication 2) and their connection to cognitive and behavioral functioning in individuals at high risk for the development of CTE.

Publication 1

This study examined the occurrence and size of a CSP and its relationship with neurocognitive function. The CSP is a cyst within the anterior septum pellucidum, probably resulting from trauma-induced fluid waves within the lateral ventricles. CSP has been found with a higher likelihood in individuals following traumatic brain injury. Here, CSP and septum length were measured in 72 former NFL players and 14 controls on structural MRI. We compared CSP length, septum length, and their ratio between former NFL players and controls and calculated the relationship between CSP length and neurocognition in NFL players. In former NFL players, the CSP was more frequent (92% vs. 57%, p=0.0006), and larger (7.7mm vs. 4.4mm p=0.03) than in controls. A CSP longer than 2mm discriminates former NFL players from controls with a sensitivity of 87.5% and specificity of 57%. In former NFL players, a CSP length of more than 6mm compared to less than 2mm was also associated with lower scores of letter processing (p=0.0222) and verbal memory (p=0.0448). CSP presence and size might thus be potential neuroimaging markers in the context of RHI exposure and possibly CTE [1].

Publication 2

The second study is based on the analysis of the volumes of the cingulate gyrus, hippocampus, and amygdala and their association with cognitive functions involving the limbic system (i.e., memory, mood, behavior, attention, and psychomotor speed). Structural MRI of 86 former football players and 22 controls were segmented into anatomical regions of interest using automated processing. Next, we compared volumes between former NFL players and controls and correlated them with cognitive functioning and behavior within the NFL group. All studied brain structures were significantly smaller in former NFL players compared to controls (amygdalae: left p=<0.005, right p=0.012; hippocampi: left p=0.024, right p=0.032; cingulate gyri: left p=0.036, right p=0.032). Also, atrophy of the cingulate gyri (attention/psychomotor speed p<0.001) and hippocampus (visual memory p=0.027) was associated with impaired cognitive function. The atrophy and correlation with

impaired function suggests that limbic system volumes may potentially serve as in vivo diagnostic markers for CTE diagnosis [2].

Zusammenfassung

Die Chronisch Traumatische Enzephalopathie (CTE) ist eine neurodegenerative Erkrankung, die in Zusammenhang mit wiederholten Schlägen gegen den Kopf (repetitive head impacts, RHI) womöglich bei vielen Menschen auftritt. Die RHI können sowohl symptomatisch als auch asymptomatisch verlaufen. Zusätzliche individuelle Risikofaktoren sind beispielsweise genetische Varianten, wie Apolipoprotein-epsilon 4 Allele (APO ε4).
Betroffene können unter sehr unterschiedlichen Symptomen leiden, darunter Kopfschmerzen, Depressionen, Aggressivität und schwere kognitive Einschränkungen bis hin zur Demenz. Strukturell kennzeichnet CTE eine perivaskuläre Akkumulation von hyperphosphoryliertem Tau-Protein in der Tiefe der kortikalen Sulci. Daneben finden sich häufig strukturelle Veränderungen wie ein Cavum septi pellucidi (CSP) oder fokale Atrophie, vor allem im limbischen System. Eine CTE Diagnose zu Lebzeiten ist zurzeit nicht möglich, würde allerdings eine frühe Diagnose erlauben und die notwendige Basis für die Entwicklung spezifischer Therapieoptionen bilden. Hierzu bietet sich die Magnetresonanztomographie (MRT) an.
Um Methoden und Möglichkeiten zu bündeln wurde die Diagnosing and Evaluating Traumatic Encephalopathy using Clinical Tests (DETECT) Studie durchgeführt (gefördert u.a. durch die National Institutes of Health der USA). Untersucht wurde eine Gruppe symptomatischer ehemaliger American Football Spieler der National Football League (NFL) mit einem hohen Risiko für CTE, sowie ehemalige Athleten von Nicht-Kontaktsportarten als Kontrollen. Alle Studienteilnehmer wurden umfassend neuropsychologisch und mittels MRT untersucht.
Die Arbeiten, die im Rahmen dieser Dissertation entstanden, zielten auf die Identifikation potentieller in-vivo Bildgebungsmarker für CTE ab. Untersucht wurde das Vorliegen und die Größe des CSP (Publikation 1) und die Volumina der Strukturen des limbischen Systems (Publikation 2), bei Probanden mit einem hohen Risiko für CTE.

Publikation 1
Diese Studie untersuchte die Häufigkeit und Grösse eines CSP und den Zusammenhang mit kognitiven Funktionen. Das CSP ist eine häufig bei CTE beschriebene Zyste im anterioren Septum pellucidum, welche nach RHI-Exposition vermutlich durch traumainduzierte Druckwellen innerhalb der Seitenventrikel auftritt. Die Länge des CSP und Septum pellucidum, sowie ihr Quotient wurden bei 72 ehemaligen NFL Spielern und 14 Kontrollen mittels MRT gemessen, zwischen den Gruppen verglichen und auf Zusammenhänge mit den Ergebnissen der neuropsychologischen Testung hin untersucht. NFL Spieler zeigten signifikant häufiger (92% vs. 57%, p=0.0006), und längere (7.7mm vs. 4.4mm p=0.03) CSP. Ein CSP länger als 2mm unterschied ehemalige NFL-Spieler von Kontrollen mit einer Sensitivität von 87,5% und Spezifität von 57%. Außerdem zeigten NFL Spieler mit einem CSP länger als 6mm, verglichen mit solchen unter 2mm, signifikante Defizite bei Schriftverarbeitung (p=0.0222) und verbalem Gedächtnis (p=0.0448). Das CSP und seine Länge könnten somit mögliche neuroradiologische Marker im Kontext von RHI Exposition und möglicherweise CTE darstellen [1].
Publikation 2
Die zweite Studie untersuchte die Volumina des Gyrus cinguli, des Hippocampus und der Amygdala, sowie ihre Bedeutung für Funktionen des limbischen Systems, wie Gedächtnis, Stimmung, Verhalten, Aufmerksamkeit und psychomotorische Geschwindigkeit. MRT von 86 Football Spielern und 22 Kontrollen wurden mittels computergestützter Bildauswertung in anatomische Regionen unterteilt. Die resultierenden Volumina und Ergebnisse der neuropsychologischen Testung wurden zwischen den Gruppen verglichen. Bei NFL Spielern wurden außerdem Zusammenhänge zwischen den Volumina und kognitiven Funktionen untersucht. Alle untersuchten Hirnregionen waren in der Gruppe der NFL Spieler signifikant kleiner (Amygdalae: links p=<0.005, rechts p=0.012; Hippocampi: links p=0.024, rechts p=0.032; Gyrus cinguli: links p=0.036, rechts p=0.032). Atrophie des Gyrus cinguli

(Aufmerksamkeit/psychomotorische Geschwindigkeit $p<0.001$) und des Hippocampus (visuelles Gedächtnis $p=0.027$) war mit reduzierter kognitiver Funktion assoziiert. Die Atrophie des limbischen Systems und der Zusammenhang mit entsprechenden Funktionen weist auf ihren potentiellen Nutzen als in vivo Marker für CTE hin.

Introduction

1. Chronic Traumatic Encephalopathy

Chronic Traumatic Encephalopathy (CTE) is a neurodegenerative disease associated with repetitive head trauma. First described in boxers as 'punch-drunk syndrome' in 1928 [3], it was later called 'dementia pugilistica' [4], before the term, 'Chronic Traumatic Encephalopathy' was established in 1949 [5]. In recent years, CTE has been identified in a variety of different populations such as contact sport athletes, including American football [6-8], wrestling [9], rugby [6, 10], ice hockey [6], and soccer [11], military personnel with blast exposure [12-14], victims of physical abuse, and individuals with epilepsy or other forms of frequent head trauma [10, 15]. The annual number of sports-related traumatic brain injuries (TBI) in the United States alone has been estimated to range between 1.6 and 3.8 million [16]. However, this does not take into account subconcussive TBI or TBI of any kind in other populations [17]. It is therefore to be expected that the number of those at risk for the development of CTE is much higher than currently known. To date, CTE can only be diagnosed post-mortem by means of neuropathological evaluation. However, early in-vivo diagnosis is necessary to develop targeted treatment as well as effective preventative measures.

1.1.Etiology

Neuropathologically confirmed CTE is strongly associated with prior exposure to repetitive head impacts (RHI), including concussive and subconcussive hits [6, 18-25]. The traumatic deformation of the brain puts shear stress on axons which seems to be a key factor for the ensuing pathology. This supposedly involves multifocal damage to axonal membrane integrity, leading to ionic shifts impairing oxidative metabolism and cytoskeletal stability [26-28]. RHI exposure might not be the sole key factor though, as only some individuals exposed to RHI develop CTE [24, 29]. Most individuals with CTE have had a long history of RHI, yet neurodegeneration resembling CTE has also been reported after a single TBI [24, 29]. Additionally, the age of first exposure (AFE) under 12 years increases the risk of later-life cognitive impairment and altered brain structure [30, 31].
Furthermore, the individual risk of CTE is influenced genetically, most notably by the presence of the Apolipoprotein-epsilon 4 allele (APO ε4) [32-37]. This genetic variant is also a significant risk factor for Alzheimer's disease (AD) [38-40] and neurocognitive impairments and neurodegeneration following TBI [32-37].

1.2.Neuropathology

CTE presents with a set of distinct neuropathological findings in post-mortem examinations. These have been summarized as preliminary diagnostic criteria (**Table 1**) and later refined into a working protocol for the neuropathological diagnosis of CTE [41, 42]. It should be noted, that at the time the studies for this dissertation were conducted, the criteria were only available in their first version [42].

Pathognomonic lesion necessary for the CTE diagnosis	
	Aggregates of phosphorylated tau protein (p-tau) in neurons, astrocytes, and cell processes around small vessels in an irregular pattern at the depths of the cortical sulci
Findings supportive of CTE diagnosis	

Related to p-tau	• Abnormal p-tau pretangles and neurofibrillary tangles (NFTs) mostly in superficial layers (II–III) • Hippocampus: pretangles, NFTs (mostly CA2), proximal dendritic swelling, and pretangles (CA 4) • Neuronal and astrocytic p-tau accumulation in subcortical nuclei (mammillary bodies, amygdala, nucleus accumbens, thalamus, midbrain tegmentum, and isodendritic core (nucleus basalis of Meynert, raphe nuclei, substantia nigra, locus coeruleus) • p-tau immunoreactive thorny astrocytes at the glia limitans in subpial and periventricular regions • p-Tau immunoreactive large grain-like and dot-like structures, also some threadlike neurites
Not related to p-tau	• Macroscopic features: o disproportionate dilatation of the third ventricle o septal abnormalities, e.g., CSP o mammillary body atrophy o contusions or other signs of previous traumatic injury • 43 kDa TAR DNA binding protein (TDP-43) immunoreactive neuronal cytoplasmic inclusions and dot-like structures in the hippocampus, anteromedial temporal cortex, and amygdala
Exclusion criteria of CTE as sole diagnosis, signs of comorbidity	
	• Alzheimer's disease (AD): Neurofibrillary degeneration mostly in CA1 and the subiculum associated with amyloid-beta plaques as seen in AD [43], pretangles and NFTs in layers III and V

	• Progressive supranuclear palsy (PSP): cell loss in the cerebellar dentate nucleus, coiled bodies in oligodendroglia, tufted astrocytes [44] • Corticobasal degeneration (CBD): severe alterations of striatum and pallidum with cortical as well as subcortical astrocytic plaques [45] • Globular glial tauopathy (GGT): globular astrocytic inclusion [46]
Age-related p-tau astrogliopathy without diagnostic significance for CTE	
	• Thorn-shaped astrocytes [47] in subcortical white matter or mediobasal regions subependymal, periventricular, and perivascular, amygdala or hippocampus

Table 1: Preliminary National Institute of Neurological Disorders and Stroke (NINDS) criteria for the neuropathological diagnosis of CTE (adapted from [41, 42]).

1.3.In vivo diagnosis

To date, CTE cannot be diagnosed during lifetime but requires a post-mortem examination applying neuropathological criteria (**Table 1**) [41, 42]. This poses a significant limitation to provide adequate clinical care for those who might be afflicted and hinders the development of therapeutic approaches. It is, thus, essential to identify specific in-vivo markers of CTE.

Previous attempts to characterize and diagnose CTE in the living focused either on the retrospective analysis of symptoms in confirmed CTE or clinical syndromes following TBI. The former analyzed brain tissue from individuals with CTE and reviewed their clinical presentation from medical records and post-mortem interviews with next of kin [6]. The symptoms were mapped to four neuropathologically defined stages of CTE (**Table 2**).

Stage 1	• Headache • Loss of attention and concentration • Difficulties with short-term memory • Aggressive tendencies/explosivity

	• Executive dysfunction • Depression
Stage 2	• Headache • Loss of attention/concentration • Loss of short-term memory • Mood lability, mood swings, explosivity • Depression, • Less common: executive dysfunction, impulsivity, suicidality, language difficulties
Stage 3	• Difficulty with attention and concentration • Memory loss, • Mood swings, explosivity, aggression • Executive dysfunction, • Visuospatial difficulties • Depression, suicidality • Less common: impulsivity, apathy, headaches
Stage 4	• Loss of attention and concentration • Severe memory loss • Explosivity, aggressive tendencies • Executive dysfunction • Dementia • Gait and visuospatial difficulties • Depression, suicidality

	• Paranoia • Language difficulties • Less common: impulsivity, dysarthria, parkinsonism

Table 2: Clinical presentation of CTE stages [6]

While clinical symptoms can indicate different stages of CTE, they are not specific for CTE. It also remains unclear how proposed clinical subtypes might fit into these stages, considering the diversity of reported symptoms [48-50].
In addition, the time gap between trauma with ensuing neuropathological changes and the reported symptoms can range between years or even decades. We thus need methods that identify early pathologies and enable a risk prediction for diagnosis, prognosis, and potential treatment opportunities.
Looking at the clinical presentation after known TBI, Traumatic Encephalopathy Syndrome (TES) has been described as a clinically-defined chronic syndrome representing long-term consequences of exposure to RHI [51-53]. Depending on the primary symptoms, TES is divided into different subtypes (TES behavioral/mood variant, TES cognitive variant, TES mixed variant, and TES dementia) [53]. TES as a clinical syndrome is, however, not specific for CTE and its defining neuropathology.
While the diagnostic clinical approaches highlighted above are an essential step towards better understanding CTE and its consequences, they do not present an avenue to develop markers that allow early diagnosis, treatment, and outcome prediction. In trying to find more biological based markers, the field is looking at both fluid biomarkers and in-vivo imaging [54-58]. Indeed, the levels of tau in plasma and cerebrospinal fluid (CSF) have been found to be elevated in athletes with a history of RHI exposure and correlate with worse neurological outcome [55, 59, 60]. Further work is however needed regarding their relation to different patterns of RHI exposure [60, 61], possibilities of longitudinal disease monitoring [62], and specificity for in-vivo diagnostic use.

2. Neuroimaging

While neuropathology directly examines an individual's brain tissue, neuroimaging provides a non-invasive, in-vivo way to study the whole brain. The most common imaging method for brain structure is magnetic resonance imaging (MRI) [63-66]. Unlike computed tomography (CT) scans, no ionizing radiation is used, making it much safer. MRI relies on precise sequences of a strong static magnetic field, fast-switching magnetic gradient fields, and radiofrequency pulses to generate images with excellent contrast for different soft tissue properties.
These properties can be specifically targeted with MRI sequences allowing to analyze different components of the MRI signal. To generate high-resolution structural images the longitudinal relaxation time (T1) is especially useful. In this project a magnetization prepared rapid gradient-echo sequence (MPRAGE) was used [67]. In clinical practice the visual inspection of MR images by a trained radiologist is a quick and reliable method to detect relevant pathologies and check data quality. Considering the two-dimensional display of three-dimensional anatomical structures, the orientation of the body in the MRI scanner and the accurate definition of image planes is crucial for maximum accuracy, often requiring reorientation.
Beyond visual inspection, MRI data can be processed to detect subclinical pathologies or quantify anatomical properties. This not only facilitates an objective severity grading of pathologies, but also statistical comparisons across multiple subjects. For brain research a frequently used tool is FreeSurfer (http://surfer.nmr.mgh.harvard.edu/, Athinoula A. Martinos Center for Biomedical Imaging, Charlestown, MA, USA). After several preprocessing steps [68, 69] FreeSurfer delineates gray

matter nuclei including their volumes [70] and utilizes the folding pattern of gyri and sulci to parcellate the cerebral cortex for maps of cortical curvature, sulcal depth, and cortical thickness [70-75]. Separate processing pipelines for diffusion MRI [76, 77], positron-emission tomography [78, 79] and image registration methods for inter-subject, inter-modal or longitudinal data sets [68, 80-83] are also part of FreeSurfer. Despite a high level of automation, MRI processing still needs intermittent steps of manual quality assurance and sometimes time-consuming manual edits with consideration of inter- and intra-rater reliability.
Considering its immense potential to detect even the most subtle pathologies MRI has been used in patients who had sustained TBI or RHI and detected widespread changes in the brain, as we summarized in a review [84]. These included altered chemical composition [85-91], cerebral microbleeds and iron deposition [84, 92-94], altered cerebral activation patterns [95-98], cortical thinning [99], and reduced organization of the brain's white matter tracts [30, 100, 101].
As for routine use in clinical practice, structural MRI markers of CTE are needed, specific, easy to obtain, and ideally related to functional impairment. Unfortunately, it is unknown what MRI findings characterize CTE during lifetime. It is thus consequential to foremost consider CTE pathologies known from neuropathology and reevaluate these in the living brain with MRI.
CSP has been suggested as such marker, given its frequency and CTE-related enlargement [6, 42, 102-104]. In addition, general brain atrophy and reduction of the limbic brain volumes have been suggested to reveal potentially disease-specific patterns [6, 7, 19, 23, 105-124].

2.1.Structural alteration – the cavum septi pellucidi

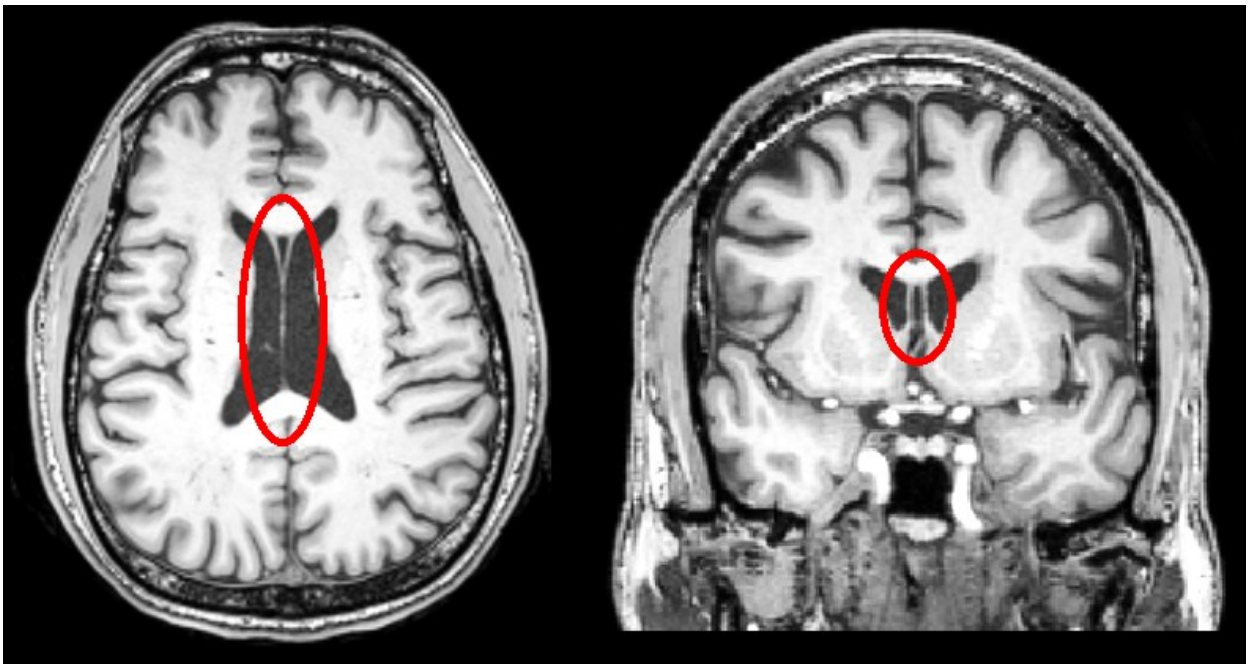

Figure 1: Septum pellucidum and CSP on structural MRI scans, adapted from Publication 1 [1]

A frequently noted pathology in CTE is a CSP [6, 42, 102-104], a cyst between the anterior leaflets of the septum pellucidum, delimited by the fornix and the corpus callosum [125].
The presence of CSP is often perceived as a developmental remnant with varying prevalence [126-129]. Other reports link it to genetic and developmental diseases, such as schizophrenia [130-134] or arguably premorbid impairment of intellectual function [135, 136]. Besides this developmental aspect, CSP is reported to be more frequent and larger following single TBI [127, 129, 136, 137] or exposure to RHI [6, 103, 128, 138-142] as well as in post-mortem neuropathological examination of CTE [6]. The underlying mechanism might be trauma-induced fluid waves in the lateral ventricles

and independent displacement of the cerebral hemispheres, resulting in shearing forces and subsequent separation of the septal leaflets [19, 127]. CSP is thus probably not directly affecting brain function, but rather a sign of the mechanical damage from trauma. Accordingly, CSP size has been observed to correlate with TBI severity [136] and ongoing RHI exposure [128]. Other studies found extensive cleft-shaped CSP in conjunction with severe axonal injury after a single TBI [127]. In CTE, CSP was found more frequently in brains with more severe neurodegenerative alterations [6]. Despite these associations, a possible role of CSP presence and length as markers of possible CTE in the living and its link to the clinical presentation has not been studied.

2.2.Regional brain atrophy - the limbic system

The limbic system is a very complex network of brain regions involved in emotional processing, memory modulation, learning, motivation, and attention [143-154]. Of note, there is a significant overlap of functions of the limbic system and symptoms attributed to CTE [6]. In addition, post mortem and imaging studies have related three parts of the limbic system: the cingulate gyrus, the amygdala, and the hippocampus with RHI, TBI, and CTE [6, 19, 23, 111-124].

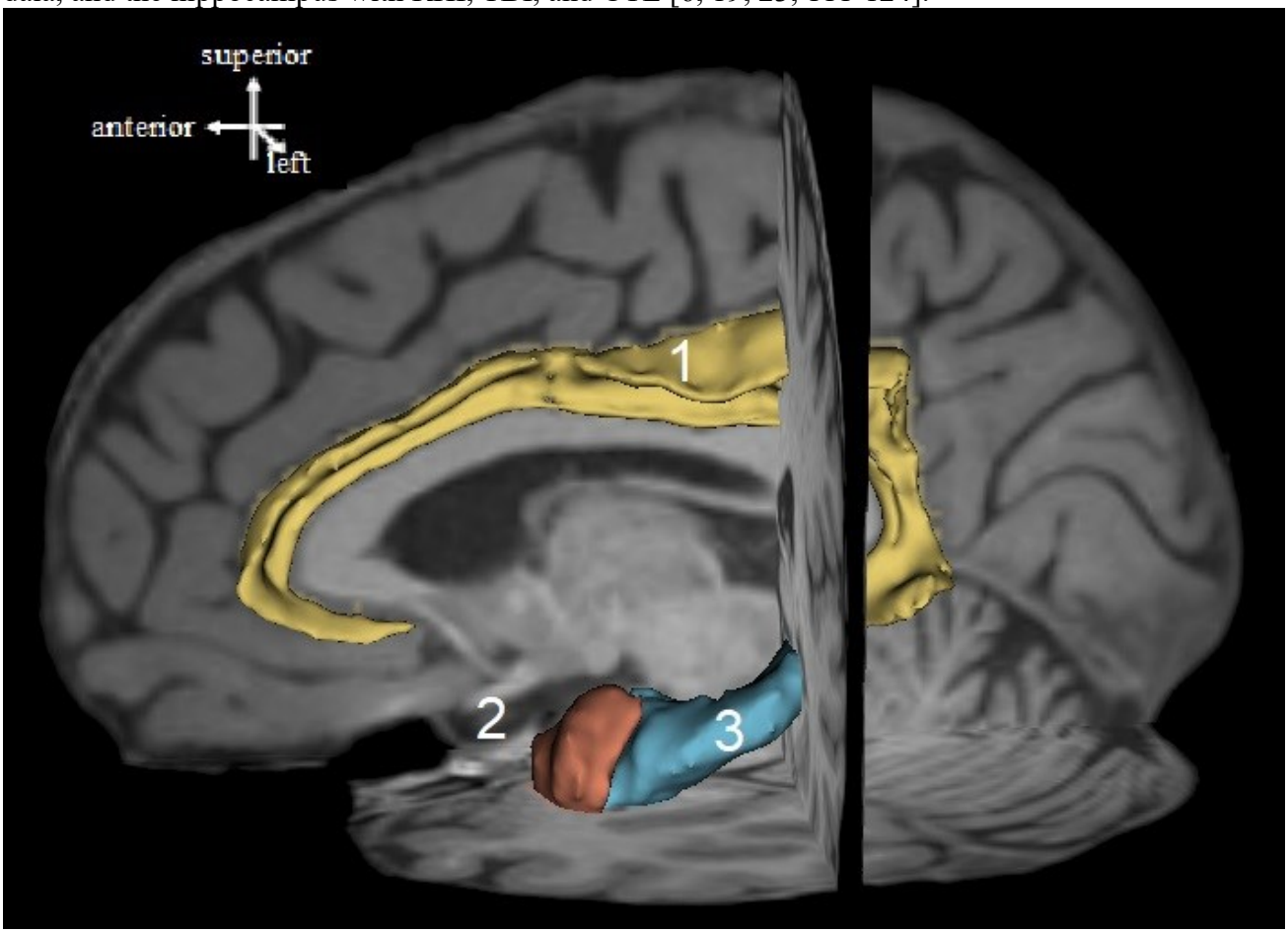

Figure 2: 3D reconstruction of ROIs based on Freesurfer segmentation: yellow (1): cingulate gyrus; blue (3): hippocampus; red (2): amygdala; adapted from Publication 2 [2]

The cingulate gyrus is a cortical structure that lies above the corpus callosum. It is involved in attention, memory, and internal cognition. Besides, it is also a crucial node in neuronal networks for an awake resting state [148-151, 155]. In CTE, RHI, and even after single TBI, the cingulate gyrus is often smaller [6, 19, 118, 119], and exhibits abnormal neurochemistry [112, 113], as well as altered glucose metabolism [114]. Functional MRI (fMRI) has also revealed abnormal activation patterns at resting state [115, 116] and using task-related paradigms [117].

The amygdala lies in the medial temporal lobe. It is involved in memory modulation, fear conditioning, and the regulation of social behavior [145-147]. Along with other structures in the medial temporal lobe, the amygdala shows atrophy in contact-sports athletes exposed to RHI [120, 121] and extensive neuropathological alterations in CTE [6, 19, 23]. Also, the amygdala is infrequently reported to be associated with cognitive dysfunction in the context of RHI [120, 121].
The hippocampus is a complex structure that is primarily involved in memory processing and learning [152-154]. According to in-vivo studies of RHI [121-124] and neuropathological examinations [6] of CTE, it is particularly susceptible to traumatic injury. Hence hippocampus atrophy correlates with impairment of memory and processing speed in individuals exposed to RHI [121, 123].

3. Motivation for this work

The lack of a technique for reliably diagnosing CTE during the lifetime is still a core problem for research and clinical practice.
First, standardized examinations would determine the actual prevalence of CTE and individuals at risk in society. Neurodegeneration could be specifically attributed to CTE, or a possible result of comorbidities. Furthermore, longitudinal studies could monitor disease progression to identify risk factors for CTE itself, and factors altering the course of the disease. These factors could be individual characteristics or medical interventions, thereby enabling the development of treatment options and assessment of their efficacy. For those afflicted by CTE, a verified diagnosis could help towards public recognition of their situation and facilitate subsequent support and compensation.
Given the potential benefits of an in-vivo CTE diagnosis, it is thus crucial to carefully consider any possible factor that could serve as a specific diagnostic marker and thoroughly assess their role in CTE. In doing that, the Diagnosing and Evaluating Traumatic Encephalopathy using Clinical Tests (DETECT) study was initiated as the first research project on CTE in the living, funded by the National Institutes of Health (NIH). Further support came from the National Institute of Child Health and Human Development (NICHD), the National Institute of Neurologic Diseases and Stroke (NINDS), and the National Institute on Aging (NIA). The necessary travel costs of participants from across the Unites States were partially covered by JetBlue Airlines, the National Football League, and the NFL Players Association.
DETECT studied a cohort of male former professional American Football players from the National Football League (NFL) and a set of non-contact sports athlete controls. The NFL players had suffered from behavioral and/or cognitive symptoms for at least six months before study participation. Given the combination of symptoms and documented RHI exposure, they were deemed high risk for CTE [156]. All participants underwent extensive multimodal testing. The MRI imaging protocol included structural imaging, diffusion tensor imaging (DTI), and magnetic resonance spectroscopy. Other examinations included a thorough neuropsychological evaluation covering memory, psychomotor speed, executive function and attention, mood and behavior, genetic testing, and analyses of blood and CSF.
Detailed study procedures and results can also be found in other publications of DETECT [1, 2, 30, 55, 59, 60, 101, 111, 156-159].
For this thesis, two studies were conducted, examining the DETECT cohort available at the respective time.

- The first study investigated CSP occurrence and size in former NFL players and evaluated the association between CSP measures and neurocognitive function. CSP was assumed to be more frequent and larger in former NFL players and to correlate with cognitive impairment.

- The second study focused on the volumes of the cingulate gyrus, the hippocampus, and the amygdala, and their relationship to memory, mood, behavior, attention, and psychomotor speed. Former NFL players were assumed to exhibit regional brain atrophy with impaired performance corresponding to the function of these anatomical structures.

Publication 1

1. Background

The CSP is a well-studied feature described in pathologically-confirmed cases of CTE [6], or after TBI, single [127, 129, 136, 137] as well as RHI [6, 103, 128, 138-142]. Besides its presence, its size is a crucial determinant for its relevance in the context of disease [6, 127, 128, 136]. However, it is unclear whether the CSP can be used to identify CTE in the living and is linked to clinical symptoms. We, therefore, studied CSP occurrence and size in a group of symptomatic former NFL players deemed at high risk of CTE.

2. Methods

The cohort studied for publication 1 included 72 former professional American football players and 14 former athletes of non-contact sports as controls who underwent MRI and neuropsychological testing as a part of DETECT. After an initial quality check, all images were reoriented using the anterior and posterior commissure and midsagittal plane as landmarks (3D Slicer version 3.6 Surgical Planning Laboratory, Brigham and Women's Hospital, Boston, USA). CSP and septum length were assessed on coronal slices **(Figure 3)** following previous studies [136, 160-163] by two independent raters in random order, blinded to groups.

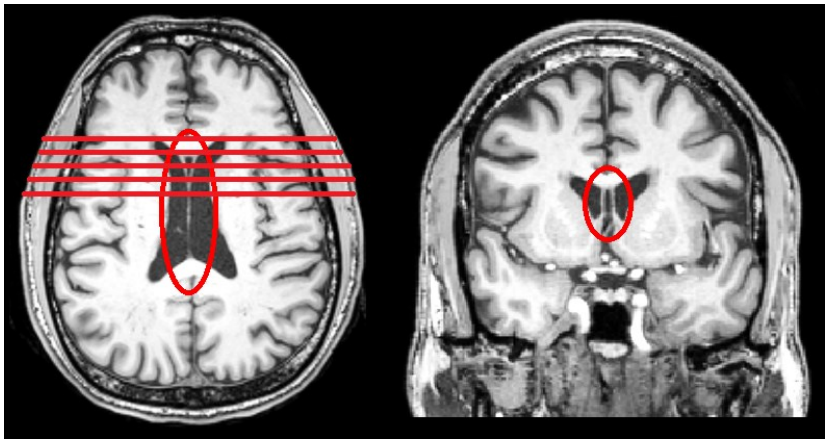

Figure 3: left: depiction of slice orientation for CSP ratings, right: slices as seen by raters to identify CSP, adapted from publication 1 [1]

Interrater reliability (intraclass coefficient for continuous variables, Cohen kappa for binary outcome), as well as possible influence of age and body mass index (BMI) (linear regression) were calculated. CSP length, septum length, and CSP to septum ratio were compared across groups using Wilcoxon two-sample tests. The CSP to septum ratio was introduced to account for a potential influence of individual septum length. In order to see whether CSP could be used to differentiate between groups, specificity, sensitivity, positive predictive value, and negative predictive value were calculated for multiple septum lengths. For former NFL players with a CSP $\leq$ 2mm and CSP $\geq$ 6mm [162], multivariate linear mixed effect models were used to analyze associations between CSP, adjusted for BMI, years of education, and years of professional football playing, and neuropsychological test performance as dependent variables [162]. This approach was chosen to model intra-subject correlations, as well as correlations between tests covering similar functions.

3. Results

Compared to controls the former NFL players had a significantly higher BMI (NFL mean=32.04 SD=4.47, controls mean=28.49 SD=3.60 p=0.007), fewer years of education (NFL mean=16.39y SD =0.87, controls mean=17.64 SD=2.10, p=0.045), and had had significantly more concussions (NFL

mean=446.9 SD=1077.4, controls mean=0.5 SD=1.53, p=0.001). Results of the group comparison of CSP measurements and the corresponding interrater reliability are summarized in **Table 3.**

	Mean of raters (Standard deviation)		Correlation of ratings	t-test
	NFL	Controls		p value
CSP present n (%)	66 (92%)	8 (57%)	Kappa = 0.83 p < 0.0001	0.0006
CSP length [mm]	7.7 (7.8)	4.4 (6.8)	rho = 0.98, ICC 0.99 p < 0.0001	0.03
Septum length [mm]	53.2 (4.6)	55.3 (5.1)	rho = 0.93, ICC 0.96 p < 0.0001	0.17
CSP/septum length ratio	0.15 (0.14)	0.08 (0.12)	rho = 0.98, ICC 0.97 p < 0.0001	p=0.03

Table 3: Group comparison of CSP measurements between former NFL players and controls and interrater reliability, adapted from publication 1 [1]

The best cutoff value to distinguish between groups was a CSP length of 2mm (sensitivity 87.5%, specificity 57%, positive predictive value 91.3%, negative predictive value 47.1%).
The neuropsychological evaluation showed significant differences between groups in 16 out of 24 tests. These revealed higher scores indicating abnormalities in most tests of the behavioral part (e.g., Behavioral Regulation Index BRI, Modified Scale for Suicidal Ideation MSSI), as well as lower scores for cognitive function. Detailed neuropsychological results can be found in the original publication [1].
In former NFL players, a CSP longer than 6mm compared to less than 2mm was associated with lower scores of letter processing (Wide Range Achievement Test WRAT-4 Reading p=0.0222) and verbal memory (Neuropsychological Assessment Battery NAB List Learning List A Immediate Recall p=0.0448).

4. Conclusions

We found CSP to be more frequent, longer and correlating with cognitive impairments in symptomatic former NFL players. These findings highlight the potential of the CSP to serve as a marker of CTE in the living. However, it should be noted that despite the former NFL players' risk of CTE, other diagnoses are possible. CSP measurements alone might be limited in their predictive value. However, they are easily obtainable and may serve as a part of a multimodal approach. Future studies should therefore use multiple biomarkers from neuroimaging, bloodwork, CSF, or clinical scores in conjunction to form a diagnostic framework. In addition, longitudinal approaches should be used to validate the connection between CSP and the clinical picture of CTE in neuropathologically confirmed cases of CTE.

Publication 2

1. Background

Regional brain atrophy is an often-reported key feature of CTE [6, 7, 23, 105-110]. Particularly parts of the limbic system, like the cingulate gyrus [6, 19, 112-119], the amygdala [6, 19, 23, 120, 121], and the hippocampus [6, 121-124], seem to be prone to injury and play a role in neurocognitive alterations following RHI. However, the connection between limbic system atrophy and subsequent neurocognitive impairment as well as their diagnostic value as possible in-vivo markers for CTE is poorly understood. Therefore, we measured the cingulate gyrus, amygdala, and hippocampus volumes in former NFL players and athlete controls in the present work. We compared volumes between groups and studied the link between volumes, and neurocognitive function within NFL players.

2. Methods

This study included 86 football players and 22 non-contact sports athletes from the DETECT cohort. Following quality assurance, all MR images were automatically segmented into anatomical regions of interest (ROI) using FreeSurfer (Version 5.3, http://surfer.nmr.mgh.harvard.edu/, Athinoula A. Martinos Center for Biomedical Imaging, Charlestown, MA, USA). This processing included a Talairach transformation, a segmentation of deep gray matter structures, and a parcellation of the cerebral cortex, based on the cortical folding pattern [70-72, 75]. Total intracranial volume was also calculated. The accurate fit of the ROI label maps was reviewed and adjusted when necessary by two independent raters and a neuroanatomist (Slicer 4.1 http://www.slicer.org, Surgical Planning Laboratory, Brigham and Women's Hospital, Boston, Massachusetts, USA [164]). Group differences of the volume of the cingulate gyri, hippocampi, and amygdalae were studied using mixed-effect regression models, controlling for age, BMI, estimated total intracranial volume, and years of education. Bootstrapping was used to account for multiple comparisons of all statistical tests [165]. The raw scores of cognitive function measures were converted and standardized for age, sex, and education. Then, a principal component analysis was performed, bundling the neuropsychological measures into four factors: Factor 1: Mood and behavior, Factor 2: attention and psychomotor speed, Factor 3: verbal memory, Factor 4: visual memory [156].
As for the volumes, mixed-effect regression models were used to compare the neurobehavioral factors between groups. Within the NFL group, associations between the neurobehavioral data and the regional brain volumes were analyzed utilizing partial correlations, adjusting for age, BMI, years of education, and estimated total brain volume.

3. Results

Compared to controls the former NFL players had a significantly higher BMI (NFL mean=32.90 SD=5.00, controls mean=28.50 SD=3.80 p=0.0002). The inter-observer reliability was between good and excellent for the exact fit of all ROI maps. All studied brain regions were significantly smaller in the group of former NFL players, as summarized in **Table 4**.

	Adjusted mean difference NFL-controls [mm³]	p-value	Interobserver reliability ICC
Left cingulate gyrus	575.014	0.036	0.723
Right cingulate gyrus	475.282	0.032	0.856

Left amygdala	176.216	<0.005	0.715
Right amygdala	157.425	0.012	0.887
Left hippocampus	158.439	0.024	0.764
Right hippocampus	146.091	0.032	0.627

Table 4: Limbic system structure volumes group comparison and inter-observer reliability adapted from publication 2 [2]

The former NFL players exhibited significantly worse scores in the domains of mood and behavior (Factor 1 $p<0.001$) as well as verbal memory (Factor 3 $p=0.0355$). In former NFL players, cognitive performance was linked to the ROI volumes. Smaller cingulate gyri were associated with worse attention and psychomotor speed (factor 2, both $p<0.001$), while a smaller right hippocampus correlated with impaired visual memory (factor 4 $p=0.027$).

4. Conclusion

In summary, we demonstrated limbic system structure atrophy and impaired neurocognitive function in RHI-exposed former NFL players compared to athlete controls. There was also a link between the regional atrophy and impaired function, precisely right hippocampus and visual memory (Factor 4), as well as cingulate gyri on both sides and attention and psychomotor speed (Factor 2). These links match previous reports of the structures' functions [121, 123, 151, 166], highlighting the clinical relevance and validity of volumetry from MRI.
However, it should be noted that the focal volume reduction in this cross-sectional study is not per se specific for CTE and could even have been preexistent. Therefore, future studies are needed to confirm these findings and evaluate volumetric measurements as part of a multi-modal diagnostic approach to CTE in the living. Also, connections between reported clinical subtypes and regional brain atrophy should be studied, as well as longitudinal data to identify factors modulating regional brain atrophy and its clinical repercussions.

Own Contribution

Both studies presented in this dissertation are part of the Diagnosing and Evaluating Traumatic Encephalopathy using Clinical Tests (DETECT) study, a 7 year project that assembled a consortium of researchers and respective research groups from Boston, USA (including: Psychiatry Neuroimaging Laboratory, Department of Psychiatry, Brigham and Women's Hospital, Harvard Medical School; BU Alzheimer's Disease and CTE Center, Boston University; Department of Biostatistics, Boston University School of Public Health; Data Coordinating Center, Boston University School of Public Health; Center for Clinical Spectroscopy, Brigham and Women's Hospital).
As DETECT was the first study to focus on possible in-vivo CTE biomarkers, it faced the challenge to cover a broad spectrum of possible pathological changes, all requiring specific analyses, while also meticulously paying attention to smallest details. The carefully selected study participants underwent a tightly packed 3-day testing program, which included extensive neurological and neuropsychological evaluations, state of the art blood work, a lumbar puncture for CSF and cutting-edge multimodal brain imaging. The imaging protocol included structural MRI, diffusion tensor imaging, positron emission tomography and magnetic resonance spectroscopy. For the different modalities, their conjunction in the imaging protocol, as well as the sequences themselves were meticulously tailored to meet the specific aims of DETECT. This included clinically available imaging sequences, as well as custom made research sequences. The resulting data was then analyzed by the respective expert research team.
As part of my dissertation project, I performed the analysis of structural MRI and diffusion tensor imaging at the Psychiatry Neuroimaging Laboratory of Harvard Medical School. As for the imaging sequences, the steps forming the image data processing pipeline were specifically customized for DETECT in numerous steps by a team of researchers, computer scientists, and programmers. Besides performing the processing steps as such, I ensured that the processing steps were closely linked with the subsequent analyses in a reiterative approach, meaning a constant discussion of the study design, and possible difficulties with the other authors. Here, I provided technical details to the debate, but also developed, programmed, and tested new processing software tools as part of this project. This dialogue led to further readjustments and tailoring of the processing for an ideal fit to the study aims, as well as the minimization of computational errors or systematic inaccuracies.
In addition to the many computational steps, there was a significant amount of manual work involved performing processing steps or recurring quality assurance. Besides researchers, computer scientists and programmers, there were up to 5 research assistants simultaneously working on data processing alone. Data preparation began with a visual slide-by-slide quality check of the raw MRI data, reorientation to anatomical landmarks and file conversions. These preprocessing steps were important for both studies presented in this dissertation, given that both relied on the same structural T1-weighted MRI, but also laid a reliable foundation for other specific computational analyses and studies.
Over the years of participant recruiting, testing, and data analysis, different members of the Psychiatry Neuroimaging Laboratory were involved in the processing and analysis of the MRI data for DETECT.
Their contribution is acknowledged in their respective rank in the list of co-authors. It should be noted that these lists also include members of other research teams involved in the conception, planning and study procedures of DETECT as a multi-center study.
The size and detail of the DETECT data set enabled a variety of detailed analyses and high-profile publications in peer-reviewed scientific journals, as can be seen from the attached list of other publications from the DETECT [1, 2, 30, 55, 59, 60, 101, 111, 156-159].

1. Publication 1

For publication 1, Prof. Dr. med. Inga K. Koerte and I developed the concept of CSP as an in-vivo MRI sign of trauma exposure in suspected CTE, hence the shared first-authorship. We began with an extensive literature search on the CSP itself, as well as its role in the context of brain trauma as a sign of trauma exposure, as opposed to pathologies indicating brain injury or subsequent biological responses. Then, I compared different imaging techniques to evaluate CSP and chose the final approach as an optimum to meet our study aims.
Accordingly, we set up the experiment with T1-weighted MRI, analyzed with two raters blinded to the subject's group. I then led the experiments, presented the preprocessed MRI to the raters ensuring randomization and blinding, structured the resulting ratings and derivate values and performed statistical analyses. We also developed further statistical models in close collaboration with a biostatistician.
All results were reviewed and interpreted together with Prof. Koerte. I then summarized our results and in preparation for publication 1 prepared illustrating figures, tables and a comprehensive summary of the literature. I further worked out the first draft of the publication. Later, I included feedback from co-authors and journal reviewers on multiple occasions in the writing and peer-review process.

2. Publication 2

For Publication 2, I contributed to the specific processing of the MRI-data and its interlinkage to the corresponding analyses. Besides setting up and applying the highly complex preprocessing pipeline outlined above, this meant initiating and executing the imaging segmentation into anatomical regions using FreeSurfer. The description of the computational process being automated is misleading though, as FreeSurfer processing is highly complex and still needs elaborate manual processing steps for every subject included by reviewing every slice of every imaging set of every participant at multiple stages, if done correctly. These steps include careful visual quality checks after each FreeSurfer processing step, such as image distortion removal or skull-strip, to remove skull and dura mater from images, or correct delineation between gray and white brain matter. Inaccuracies often require time-consuming manual edits and restarting the corresponding FreeSurfer step followed by quality reassessment. In case of continuous inaccuracies or software failures, systematic errors had to be carefully ruled out, as they might have translated into false study results. Similar to the raw image preprocessing described above, I used my technical knowledge here to analyze errors, trace their root causes and assess their impact on data integrity and subsequent study procedures, together with the first authors. Subsequently I contributed to adaptions and fine-tuning of the processing and analyses. I was then also involved in the interpretation and discussion of results, and revision of the final publication.

Original articles

1. **Publication 1: Cavum Septi Pellucidi in Symptomatic Former Professional Football Players**

Publication 1 can be found online at:

- https://www.liebertpub.com/doi/10.1089/neu.2015.3880?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub++0pubmed
- https://pubmed.ncbi.nlm.nih.gov/26414478/
- PMID: 26414478 PMCID: PMC4761807 DOI: 10.1089/neu.2015.3880

2. **Publication 2: Limbic system structure volumes and associated neurocognitive functioning in former NFL players**

Publication 2 can be found online at:

- https://pubmed.ncbi.nlm.nih.gov/29779184/
- https://link.springer.com/article/10.1007/s11682-018-9895-z
- PMID: 29779184 PMCID: PMC6854905 DOI: 10.1007/s11682-018-9895-z

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