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Cognitive Control Function and Moderate-to-Severe Traumatic Brain Injury

Functional and Structural Brain Correlates

Thesis for the degree of Philosophiae Doctor

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Norwegian University of Science and Technology
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Kognitiv kontroll og moderat til alvorlig traumatisk hjerneskade – funksjonelle og strukturelle hjernekorrelat

Hvert år rammes mange av traumatiske hjerneskader (traumatic brain injury - TBI) i Norge og resten av verden. For å kunne defineres som TBI må skaden være påført av en ytre kraft, og de vanligste årsakene til TBI er trafikk- og fallulykker. Kliniske tegn på TBI kan for eksempel være nedsatt- eller tap av bevissthet, andre nevrologiske utfall, eller funn ved bruk av konvensjonelle kliniske hjerneavbildningsmetoder. Nevropsykologiske tester kan også brukes i klinikken for å utrede mulige kognitive utfall etter skade. Alle disse kliniske metodene danner et viktig grunnlag for å kunne diagnostisere, behandle, og si noe om generell prognose for de som rammes. En utfordring i klinikken er imidlertid at ikke alle langtidsfølgevirkninger av TBI er påvisbare- eller kan forutsees ut fra disse metodene alene.

I denne avhandlingen ble det brukt avanserte hjerneavbildningsmetoder (funksjonell magnetresonans avbildning - fMRI, og diffusjon tensor avbildning - DTI) for å generere ny kunnskap om funksjonelle og strukturelle endringer i hjernen i kronisk fase (mer enn ett år siden skaden) etter moderat og alvorlig traumatisk hjerneskade. Det ble også undersøkt hvordan slike endringer var assosiert med kliniske variabler og andre funksjonsmål som tidligere har blitt vist å ha stor betydning for pasientenes funksjonsnivå i kronisk fase. Eksekutive funksjoner, også kalt kognitive kontrollfunksjoner, ble særlig undersøkt, siden disse funksjonene har vist seg å være betydningsfulle for hvordan pasienter med moderate og alvorlige traumatiske hjerneskader har det, og hvordan de klarer seg i hverdagen på lang sikt. Kognitive kontrollfunksjoner dreier seg om de mentale prosessene som er involvert i målrettet regulering av tanker, handlinger, og følelser.

Avhandlingen består av fire artikler. I første artikkel ble en stor gruppe friske deltakere inkludert i en studie for å validere en nyutviklet klinisk relevant fMRI protokoll som kunne måle hjerneaktivitet knyttet til kognitive kontrollprosesser med ulik temporal oppløsning. Resultat fra denne studien viste at det finnes et ”kjernenettverk” av hjerneområder, som aktiveres både under adaptive reaktive- (raske), samt mer stabile proaktive (mer langsomme) kognitive kontrollprosesser. Når det gjaldt de prosessene som ikke tilhørte

”kjernenettverket”, fant vi at de adaptive reaktive prosessene var lokalisert lengre fram i frontallappen, sammenlignet med de stabile proaktive prosessene. Videre ble det vist at hjerneaktiviteten knyttet til de stabile proaktive prosessene endret seg over tid utover i oppgaven, noe som indikerte at denne type aktivitet i særlig grad var sensitiv for å detektere adaptive endringer knyttet til å opprettholde målrettet atferd. For å forstå hjernedysfunksjon er det viktig å først gjøre seg kjent med hva som kjennetegner normal funksjon. Resultatene fra denne studien bidro til dette, og dannet et viktig grunnlag for å undersøke nevrale korrelater til kognitive kontrollprosesser etter TBI i artikkel nummer tre.

I artikkel nummer to ble det vist at personer med TBI rapporterte mer vansker (2-5 år etter skaden) knyttet til kognitiv kontrollfunksjon, samt emosjonelle og atferdsmessige problemer, enn kontrollgruppen. Studien viste også at diffus aksonal skade påvist med konvensjonell klinisk MR i tidlig fase, samt depressive symptomer målt ett år etter skaden, var særlige risikofaktorer for senere selvrapporterte plager. Samme studie viste for øvrig ingen statistisk signifikant sammenheng mellom resultater på kognitive tester fra det første året etter skade, og senere selvrapporterte plager.

I artikkel nummer tre ble det påvist ulik påvirkning av de nevrale korrelatene til henholdsvis adaptive reaktive-, og stabile proaktive kognitiv kontroll prosesser, som følge av TBI. Det ble også vist at TBI gruppen hadde økt hjerneaktivering, sammenlignet med kontrollene, knyttet til de stabile proaktive prosessene, jo lenger ut i oppgaven de var. Denne økte aktiveringen viste en doseavhengig lineær sammenheng med alvorligheten av hjerneskaden, med mer aktivering for de med høyere alvorlighetsgrad. Det ble også funnet at høyere hjerneaktivering etter TBI var relatert til mindre selvrapporterte kognitive kontrollproblemer i hverdagen. Dette indikerer at den økte hjerneaktiveringen under oppgaveløsning for TBI gruppen, synes å gjenspeile kompensatoriske mekanismer som også kan nyttiggjøres i mer hverdagslige situasjoner.

I artikkel fire ble det vist at mer alvorlig hjerneskade, basert på kliniske tegn, og funn på konvensjonell MR, var relatert til mer uttalte hvitsubstansforandringer i hjernen målt med DTI. Det ble også vist at mer uttalte hvitsubstansforandringer var relatert til dårligere fungering, både generelt, og også når det gjaldt test-basert kognitiv kontrollfunksjon. Det

ble imidlertid ikke funnet noen statistisk signifikant sammenheng mellom ulike DTI mål og selvrapportert kognitiv kontrollfunksjon i hverdagslige situasjoner.

Samlet sett viste funnene i avhandlingen at en bred kartlegging med flere metoder er viktig for å få en best mulig forståelse av de atferdsmessige og nevrale konsekvensene av TBI. Videre ble det vist at subtile endringer i hjernens struktur og funksjon, som ikke nødvendigvis er mulig å detektere med konvensjonelle hjerneavbildningsteknikker, kan ha stor innvirkning på hvordan mennesker med TBI har det, og hvordan de klarer seg i hverdagen. Et særlig interessant funn med mulige kliniske implikasjoner, var at test-basert kognitiv kontrollfunksjon, var relatert til subtile strukturelle endringer i hjernen (målt med DTI), mens selvrapporterte vansker knyttet til kognitive kontrollproblemer i hverdagen var relatert til adaptive endringer i hjerneaktivitet (målt med fMRI). Det er ikke helt uvanlig i klinisk sammenheng at pasienter kan skåre relativt godt på nevropsykologiske tester ment å måle kognitiv kontrollfunksjon, men allikevel rapporterer vansker i hverdagslivet. Å vite at slike selvrapporterte plager kan relateres til forskjeller i hjerneaktivitet, bidrar med et viktig perspektiv i så måte. I og med at det ble vist at økt hjerneaktivitet var relatert til kompensatoriske prosesser, indikerer dette også en mulig innfallsvinkel for målrettet behandling.

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All those who have directly or indirectly contributed to my work know whom you are and that your effort has meant a lot to me. If you have not been mentioned by name yet in this acknowledgement section, please feel free to insert it here:

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Insert your name here

Finally,

I would like to thank my parents Helen Svea Olsen and Per Harald Olsen, my sister Annikken Olsen Skjæran, and the rest of my extended family, for steady support, and for always being there.

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Trondheim September 12th 2014

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List of abbreviations

ACC = anterior cingulate cortex
AD = axial diffusivity
ASEBA-ASR = Achenbach system of empirically based assessment; Adult Self Report
BOLD = blood-oxygen-level-dependent
bPLS = behavioral least squares analysis
BRIEF-A = behavioral rating inventory of executive function-adult version
CBF = cerebral blood flow
CBV = cerebral blood volume
CCPT = Conners continuous performance test
CDE = common data elements
$CMRO_2$ = cerebral blood oxygen consumption
CPP = cerebral perfusion pressure
CPT = continuous performance test
CSF = cerebrospinal fluid
CT = computed tomography
DAI = diffuse axonal injury
DKEFS = Delis–Kaplan executive function system
DKI = diffusion kurtosis imaging
DLPFC = dorsolateral prefrontal cortex
DMN = default mode network
DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
DTI = diffusion tensor imaging
DWI = diffusion weighted imaging
EEG = electroencephalography
EPI = echo planar imaging
FA = fractional anisotropy
FEF = frontal eyefield
FLAIR = fluid attenuated inversion recovery
fMRI = functional magnetic resonance imaging
FSL = FMRIB's Software Library

FWHM = full-width at half-maximum
GCS = Glasgow coma scale
GLM = general linear model
GMT = goal management training
GOAT = Galveston orientation and amnesia test
GOS = Glasgow outcome scale
GOSE = Glasgow outcome scale extended
GRE = gradient echo
GRF = Gaussian random field
IBM = International Business Machines Corporation
ICP = intra cranial pressure
IPL = inferior parietal lobe
LOC = loss of conciousness
MCS = minimally concious state
MD = mean diffusivity
MEG = magnetoencephalography
MFC = medial frontal cortex
MNI = Montreal neurological imstitute
MPRAGE = magnetization-prepared rapid acquisition with gradient echo
MRI = magnetic resonance imaging
MRS = magnetic resonance spectroscopy
MVA = motor vehicle accident
NIRS = near infrared spectroscopy
NOK = Norwegian kroner
NSE = neuron-specific enolase
PET = positron emission tomography
PFC = prefrontal cortex
PTA = post traumatic amnesia
PTC = post traumatic confusion
RD = radial diffusivity
ROI = region of interest
SPECT = single-photon emission computed tomography

SPSS = statistical package for the social sciences
SWI = susceptibility imaging
T = tesla
TAI = traumatic axonal injury
TBI = traumatic brain injury
TBSS = tract based spatal statistics
TOT = time on task
TPJ = temporoparietal junction
VFC = ventral frontal cortex
VS = vegetative state
WM = white matter

List of papers

Paper I

Olsen, A., Brunner, J.F., Evensen, K.A.I., Garzon, B., Landrø, N. I., Håberg, A.K. The functional topography and temporal dynamics of overlapping and distinct brain activations for adaptive task control and stable task-set maintenance during performance of an fMRI-adapted clinical continuous performance test. *Journal of Cognitive Neuroscience* 2013; 25, 903-919.

Paper II

Finnanger, T., Olsen, A., Skandsen, T., Lydersen, S., Vik, A., Evensen, K.A.I., Håberg, A. K., Andersson, S., Indredavik, M. Self-reported executive, emotional and behavioural function 2-5 years after moderate-to-severe traumatic brain injury – a prospective follow-up study. *Submitted manuscript*.

Paper III

Olsen, A., Brunner, J. F., Evensen, K. A. I., Finnanger, T., Vik, A., Skandsen, T., Landrø, N. I., Håberg, A. K. Altered cognitive control activations after moderate-to-severe traumatic brain injury and their relationship to injury severity and everyday-life function. *Cerebral Cortex* 2014; Feb 20. [Epub ahead of print].

Paper IV

Håberg, A. K., Olsen, A., Moen, K. G., Schirmer-Mikalsen, K., Visser, E., Finnanger, T., Evensen, K. A. I., Vik., A., Skandsen, T., Eikenes, L. White matter microstructure in moderate-to-severe traumatic brain injury: the impact of acute phase injury related variables and associations with global outcome, performance-based and self-reported cognitive control function. *Submitted manuscript*.

Summary

Clinical signs of traumatic brain injury (TBI) such as altered- or complete loss of consciousness, other neurological signs, and findings based on conventional neuroimaging, represents important information for initial treatment and further follow-up of TBI survivors. However, not all real-life problems after TBI are easily detected by conventional imaging methods or neurological exams. This is particularly evident when trying to assess the more subtle effects of TBI, such as cognitive and emotional problems, that are often experienced in the chronic stage, after the initial recovery period has passed. The main aim for this thesis was to extend current knowledge on functional and structural changes in the brain after moderate-to-severe TBI by means of advanced neuroimaging methods, and to relate these findings to injury-related variables and functional measures known to be important for outcome. A particular focus was on investigating cognitive control function, as this has been demonstrated to play an especially important role for functional outcome after TBI. In order to reach this aim, several studies with different but related perspectives were performed, and four papers (Paper I – IV) based on these studies are included in this thesis.

In Paper I, a large group of healthy participants was included in a study in order to validate a clinically relevant task protocol that could measure both adaptive and stable cognitive control processes in the brain by means of blood-oxygen-level-dependent (BOLD) functional magnetic resonance imaging (fMRI). Results from this study gave further support for a core network of cognitive control, with overlapping activations for both stable and adaptive processes, comprised by brain regions bilaterally in the insula (and adjacent cortices) and dorsal medial frontal cortex. It was also established that in this particular task, adaptive cognitive control processes by and large were distributed in more anterior regions of the prefrontal cortex as compared to stable cognitive control processes. Another novel and important finding, was that only stable cognitive control processes were affected by time on task (TOT), indicating that this contrast might be particularly sensitive for detecting adaptive changes in the brain.

In Paper II, it was demonstrated that executive, emotional and behavioral problems were more frequently reported in chronic moderate-to-severe TBI survivors as compared to healthy controls. The results also indicated that identification of traumatic axonal injury (TAI) and symptoms of depression in an earlier phase after injury, might give a warning of later problems. Furthermore, self-report measures of cognitive control seemed to extend the information obtained from performance-based measures.

In Paper III, it was shown that neuronal correlates of adaptive and stable cognitive control processes were differently affected by moderate-to severe TBI. Moreover, TBI survivors exhibited increased TOT related BOLD activation related to stable cognitive control processes in the right inferior parietal lobe and right prefrontal cortex. Increases in BOLD activations had a dose-dependent relationship with injury severity, with increased activation with more severe injury. Interestingly, increased BOLD activations after TBI were related to better self-reported cognitive control function in everyday-life situations, indicating a compensatory role for these activations.

In paper IV, it was shown that more severe injury based on clinical signs, and findings on conventional MRI evaluations, was related to more pronounced alterations of white matter microstructure in a wide range of tracts as measured with diffusion tensor imaging (DTI). Reduced white matter integrity in TBI survivors was also associated with worse global outcome, and poorer cognitive control function as measured by performance-based measures. No association was found between any of the DTI measures and self-reported cognitive control function.

The findings presented in this thesis demonstrated that a broad assessment is warranted in order to optimize our understanding and follow-up of TBI patients. Also, it was shown that subtle changes in brain structure and function, not necessarily detectable with conventional imaging tools, might still have an important impact on how TBI survivors are able to cope with every-day life. A particularly interesting finding with possible clinical implications was that performance-based cognitive control function in chronic TBI was related to subtle structural changes in the brain as measured with DTI, whereas self-reported problems were exclusively related to functional adaptations as measured with

fMRI. In general, knowing that self-reported cognitive control function in chronic moderate-to-severe TBI survivors is associated with functional changes in the brain, gives an important perspective when seeing patients where such problems are not easily explained by conventional neuropsychological measures. More than that, as these functional changes were shown to play a potential compensatory role, this might indicate a potential target for neuro-rehabilitation.

Introduction

Definition of TBI

According to the International and Interagency Initiative toward Common Data Elements for Research on Traumatic Brain Injury and Psychological Health, TBI can be defined as *"…an alteration in brain function, or other evidence of brain pathology, caused by an external force"* (Menon et al., 2010). TBI is, however, a highly heterogeneous condition in terms of cause, injury severity, pathology, and prognosis (Maas et al., 2011). Recognizing the heterogeneity of TBI is important for both clinical work as well as research.

Causes of TBI

The most common causes of TBI are falls and vehicle accidents, followed by acts of violence and other reasons, such as for instance sports injuries (Langlois, Rutland-Brown, & Wald, 2006; Tagliaferri, Compagnone, Korsic, Servadei, & Kraus, 2006). Obvious external forces caused by such events are when the head is hit by an object, or hits an object. The brain is also particularly vulnerable to acceleration/deceleration forces, which can occur even without direct impact to the head. Foreign objects penetrating the skull may also cause brain trauma. Furthermore, increased attention in the later years has been given to TBI caused by forces created by blasts or explosions (Rosenfeld et al., 2013).

Incidence of TBI in Europe and Norway

A comprehensive systematic review of TBI epidemiology in Europe, demonstrated that the yearly incidence rates of hospital-treated TBI varied between 91 and 546 per 100,000 (Tagliaferri et al., 2006). The same review also revealed a great variability for how TBI was defined in different studies and how differences in health care systems and criteria for being registered affected the estimates. Despite these factors creating considerable uncertainty in the data material, the authors observed that most of the reported incidence rates were between 150-300/100,000, and concluded with a fairly conservative estimate of 235/100,000, when excluding the most extreme values. Mortality rates were found to be 15-20/100,000. As for injury severity, 70-80% was found to be mild. Moderate and severe TBI, which is the main focus in this thesis, represented around 10% each of the total rate.

Based on these numbers, European incidence rates are similar to other large regions of the world, such as Australia (Hillier, Hiller, & Metzer, 1997), however, possibly higher than in the US (Langlois et al., 2006). In Norway, findings from a study looking at data from 2005-2006 gathered from the Oslo population revealed an incidence rate of hospital treated TBI of 83.3/100,000 (Andelic, Sigurdardottir, Brunborg, & Roe, 2008). In this study the male-female ratio was 1.8-1, underlining the well known increased risk of TBI in the male population. The same study showed that 86% of the injuries were categorized as being mild, 7.9% moderate, and 6.1% severe. The main proportions of injuries were due to falls (51%) and motor vehicle accidents (29.7%), followed by assaults (12.8%) and other injuries (6.5%). Hence, although the most recent incidence rate seems to be lower in this Norwegian urban area compared to most other countries, the proportions of injury severities, gender, and external cause of injury were generally within the range of those previously reported elsewhere (Langlois et al., 2006; Tagliaferri et al., 2006).

Clinical evidence of TBI, early prognostic factors, and global outcome

An important clinical sign of TBI is a period of altered- or complete loss of consciousness (LOC) with onset at the time of injury. Other clinical signs of altered brain function after TBI include posttraumatic amnesia (PTA), and various neurological deficits within sensory and motor systems (Marmarou et al., 2007; Marshman, Jakabek, Hennessy, Quirk, & Guazzo, 2013). Both length and clinical presentation of LOC are important factors for evaluating injury severity and predicting outcome after TBI. The most extensively used tool for classification of injury severity after TBI is the Glasgow Coma Scale (GCS) (G. Teasdale & Jennett, 1974). GCS measures the level of consciousness by assessing motor-, verbal, and eye responses in the patient (table 1). Based on this assessment, patients get a score between 3 (deep coma) and 15 (fully alert and oriented). Most commonly, a GCS sum score of 3-8 is considered as severe-, 9-12 as moderate-, and 13-15 as mild TBI, respectively. However, it is increasing accept for categorizing a GCS score of 13 as moderate TBI (Maas, Stocchetti, & Bullock, 2008).

Table 1. Glasgow coma scale (GCS)

Domain	Response	Score
Eye opening	Spontaneous	4
	To speech	3
	To pain	2
	None	1
Best verbal response	Oriented	5
	Confused	4
	Inappropriate	3
	Incomprehensible	2
	None	1
Best motor response	Obeying	6
	Localizing	5
	Withdrawal	4
	Flexing	5
	Extending	3
	None	1
Total score	Deep coma or death	3
	Fully alert and oriented	15

Longer period of LOC and lower GCS score are both related to more severe injury and worse outcome after TBI (Maas et al., 2008). However, the validity and reliability of these measures are challenged by differences in timing of the assessment (at site of injury, hospital admission etc.), as well as other co-occurring confounders such as the presence of intoxication, medical sedation, and/or paralysis. In fact, it has been suggested that the GCS has lost some of its prognostic value due to changes in treatment protocols in pre-hospital acute care, involving increased use of intubation and medical sedation of patients (Stocchetti et al., 2004). Despite these limitations, GCS alone or together with other additional measures, currently provides the platform for most severity classifications after TBI. The GCS motor response is thought to be less prone to some of the abovementioned confounders, and has been shown to be the best outcome predictor in several studies, particularly for the more severely injured patients (Marmarou et al., 2007). Also, adding information about other neurological assessments of altered brain function, such as pupillary response, has shown to increase the predictive power of prognostic models (Marmarou et al., 2007). The head injury severity scale (HISS) is an example of a systematic approach including additional information on complications and other factors (such as neuroradiological findings) in combination with GCS score (Stein & Spettell, 1995). HISS is included as part of the Scandinavian guidelines for management of TBI, and the experience is

that it adds value to injury severity classification, particularly in the acute (neurosurgical) setting.

During the initial recovery after TBI, several levels of consciousness can be observed, ranging from full coma to fully alert and oriented patients. The different levels of altered consciousness are commonly categorized into coma, vegetative state (VS), minimally conscious state (MCS), and posttraumatic amnesia/confusion (PTA/PTC) (Giacino, Fins, Laureys, & Schiff, 2014; Marshman et al., 2013; Stuss et al., 1999). Although clear distinctions between each category is challenging to establish, and highly debated by experts in the field, each level is thought to indicate a progressively increased level of consciousness. Depending on injury severity, each patient may or may not go through all levels. For patients going through several phases of recovery, each level usually lasts longer than the previous one. The time spent recovering consciousness through these phases contains prognostic information for final outcome.

Particularly, a longer period of PTA has a negative impact on functional outcome (Marshman et al., 2013). PTA refers to the typically observed posttraumatic anterograde amnesia, and patients are thought to be out of PTA when they again can form continuous memories. However, such amnesia most often occurs in the context of a state of confusion in the patient, hence, the term posttraumatic confusion (PTC) has been advocated (Stuss et al., 1999). It has even been suggested that PTC is a main contributor to the lack of ability to form- and retrieve memories, and that this state should be understood as a condition more closely related to other delirious states (Nakase-Thompson, Sherer, Yablon, Nick, & Trzepacz, 2004; Stuss et al., 1999). Although widely recognized, no unitary and universally accepted definition of this posttraumatic phenomenon of altered brain function currently exists, and the terms PTA/PTC are used somewhat interchangeably. The clinical presentation of PTA can fluctuate, and the condition may eventually resolve quickly. It is therefore challenging to get an accurate measurement of the exact length of PTA in a clinical hospital setting. For practical reasons, PTA is most commonly measured from the time of injury and until a fully alert and oriented state is reach by the patient (including potential periods of coma, VS and MCS). Structured assessment tools such as the Orientation-log and Galveston Orientation and Amnesia Test (GOAT) has been

developed in order to aid the assessment of PTA, and have been shown to have reasonably good reliability and validity when used in an everyday clinical setting (Frey, Rojas, Anderson, & Arciniegas, 2007).

Clinical signs of altered brain function are susceptible to other confounding factors affecting the level of consciousness. Such confounders do not affect neuroimaging methods assessing the presence of structural brain injury. Neuroimaging therefore plays an important role in modern detection of TBI. Computed Tomography (CT) is the main modality in the acute stage, due to the quick assessment, and less restrictions when it comes to eligibility as compared to magnetic resonance imaging (MRI). However, MRI is often a preferred choice in the sub-acute stage for follow up scans and in the chronic phase, due to increased sensitivity for detecting certain types of brain injuries. Another advantage is that MRI does not expose subjects to radiation, which may be a potential risk factor for developing cancer with repeated CT assessments (Smith-Bindman et al., 2009).

The most common pathological characteristics of TBI detectable by use of various neuroimaging techniques are skull fractures, extra- and intra cerebral hematomas, contusions, diffuse/traumatic axonal injury (DAI/TAI), brain swellings/edema and mass effects (Haacke et al., 2010). Focal injuries such as contusions and intra cerebral hematomas are more commonly seen in older individuals after falls, whereas diffuse or traumatic axonal injuries are more prevalent and extensive in the upper end of the severity scale, and are often caused by motor vehicle accidents, probably due to the high-energy acceleration/deceleration- and rotational forces involved (Davceva, Janevska, Ilievski, Petrushevska, & Popeska, 2012). However, all types of pathological characteristics of TBI can potentially occur throughout the entire severity scale and across different causes. Also, the different pathological characteristics in individual patients are most often multifactorial and multifocal, providing considerable complexity to the information to be used for clinical prognosis and decision-making.

For CT, it has been developed classification schemes, such as the Marshall- (Marshall et al., 1991) and Rotterdam (Maas, Hukkelhoven, Marshall, & Steyerberg, 2005) CT classifications, in order to aid the work of researchers. These tools have proven valuable in the

acute stage, particularly for predicting mortality and categorization into broad outcome groups in severely injured patients (Bobinski, Olivecrona, & Koskinen, 2012; Maas et al., 2005). The classification systems are, however, less valuable for those presenting with less severe injuries, and for more fine-tuned estimation of long-term prognosis (de Oliveira Thais et al., 2014; Williams, Rapport, Hanks, Millis, & Greene, 2013).

Extending the qualities of CT, MRI sequences such as those based on standard T2-weighted, fluid attenuated inversion recovery (FLAIR), and T2* gradient echo (GRE), are generally more sensitive to detection of smaller lesions, such as those associated with DAI/TAI (Ashikaga, Araki, & Ishida, 1997; Kinoshita et al., 2005). The sensitivity of MRI increases with using stronger magnetic fields (within the conventional range for clinical use, e.g. 1.5T scanner vs. 3T). Further sensitivity for detecting DAI/TAI can be provided by adding MRI sequences such as susceptibility- (SWI) (Spitz, Maller, Ng, et al., 2013) and diffusion weighted imaging (DWI), which are now standard methods in many hospitals (Edlow & Wu, 2012).

Overall, the various neuroimaging modalities used in conventional clinical practice are instrumental for acute or sub-acute care of patients. Classification of type and location of the lesions seen in TBI has also been shown to be valuable for prediction of long-term global function (Skandsen et al., 2011). The full potential of conventional neuroimaging in TBI is, however, likely to be unfulfilled. With increased sensitivity, the amount and complexity of information increases, and hence makes classification and integration of this knowledge for meaningful clinical interpretation very challenging. There has also been a lack of universal standardization for imaging protocols and terms used to describe different pathologies. This issue has, however, been addressed recently, through the development of international recommendations for how to classify, define, and report the different TBI pathologies found on various neuroimaging methods data (Duhaime et al., 2010; Haacke et al., 2010). This will in time be integrated in in clinical research projects, which in turn may lead to an increased knowledge base to be used in future diagnostic and prognostic models.

Parallel to this, there is ongoing research focusing on development of new advanced imaging methods, as well as new applications of existing methods in order to increase the knowledge of about pathological characteristics after TBI. Diffusion tensor imaging (DTI), and more recently, diffusion kurtosis imaging (DKI), are particularly promising MRI based techniques for detection of DAI/TAI (Shenton et al., 2012). These methods are based on assessing the microscopic motion of water molecules in the brain, whose properties are closely correlated to white matter (axonal) integrity (Le Bihan et al., 2001). Other examples of more experimental non-invasive methods used to detect evidence of structural or functional brain injury in TBI are different kinds of perfusion MR and CT, MR spectroscopy (MRS), functional MRI (fMRI), positron emission tomography (PET), single-photon emission computed tomography (SPECT), near infrared spectroscopy (NIRS), magnetoencephalography (MEG), electroencephalography (EEG), and Doppler ultrasonography. The advanced neuroimaging work presented in this thesis utilized the properties of blood-oxygen-level dependent response (BOLD) fMRI, as well as metrics based on DTI, and belongs to this experimental line of neuroimaging research.

In addition to being a heterogeneous condition, TBI is also a dynamically evolving process. It should be stressed that TBI should not be understood as merely a single event, but encompasses a cascade of events, that can or cannot be treated, and that affects the development and progression of secondary injury and clinical signs, as well as the final outcome. For example, already in the pre-hospital setting it is important to avoid hypoxia and hypotension, as these are associated with poorer outcome (McHugh et al., 2007). At admission to the hospital, an important aim is to further stabilize the patient, and to treat or prevent neurological deterioration, for example through neurosurgery or medications (Morris, Juul, Marshall, Benedict, & Marshall, 1998). Further monitoring of the patient in a neurointensive care unit is often instrumental in order to inform different treatments related to for example reducing brain swelling, in order to avoid increased intra cranial pressure (ICP) and maintain cerebral perfusion pressure (CPP) (Bullock & Povlishock, 2007; M. Smith, 2008; Vik et al., 2008). Although specific neuroprotective treatments are a focus of research, and have shown promising effects especially in animal models (Kabadi & Faden, 2014), the main goal of current early TBI management is to prevent secondary injuries, and to provide optimal conditions for spontaneous neurorecovery. A consequence

of the dynamically evolving nature of TBI is that prognostic factors such as those based on neuroimaging (CT, MRI), GCS, and pupillary response, are commonly monitored multiple times throughout the early phase to guide treatment. It is therefore important to consider the multifactorial and temporal context of such data when estimating prognosis. It is also important to consider premorbid factors. For example, anticoagulant medications and older age are considered risk factors for worse outcome (Lingsma, Roozenbeek, Steyerberg, Murray, & Maas, 2010; Maas et al., 2008).

The main bout of recovery after moderate-to-severe TBI happens within the first 6 months post-injury (Ghajar, 2000). Most of this recovery is considered to be spontaneous, but may potentially be facilitated by specialized rehabilitation programs (Turner-Stokes, Disler, Nair, & Wade, 2005). The most common tools for assessing global outcome after TBI are the Glasgow Outcome Scale (GOS) (Jennett & Bond, 1975), and the extended GOS (GOSE) (G. M. Teasdale, Pettigrew, Wilson, Murray, & Jennett, 1998). The GOS allocates patients into 5 broad outcome categories based on their functional level, ranging from death to good recovery (table 2). The GOSE was later introduced in order to increase the resolution and sensitivity of the GOS, by introducing "upper" and "lower" levels for the disability- and good recovery categories (table 2). A structured interview protocol demonstrating satisfactory inter-rater reliability has been developed for administration of GOS and GOSE (Wilson, Pettigrew, & Teasdale, 1998).

Despite playing an undisputed major and important role in providing clinically meaningful classification of function after TBI, particularly in large cohort studies, these tools have limitations due to their broad categories (Lingsma et al., 2010). This is particularly evident when trying to assess the more subtle effects of TBI, which may still have a strong impact for the individual patient, and that are often experienced in the chronic stage, after the initial recovery period has passed. Such effects may for example present as cognitive and emotional problems only detectable through more fine-tuned assessment. Furthermore, some of these may be caused by subtle changes in brain function and structure, which may not be detected by conventional clinical neuroimaging. Gaining new knowledge on detecting such subtle effects of TBI falls within the main scope of the scientific work presented in this thesis.

Table 2. Glasgow outcome scale (GOS) and Glasgow outcome scale extended (GOSE)

GOS	GOSE	Interpretation
1 = Dead	1 = Dead	Dead
2 = Vegetative state	2 = Vegetative state	Absence of awareness of self and environment
3 = Severe disability	3 = Lower severe disability	Needs full assistance in ADL
	4 = Upper severe disability	Needs partial assistance in ADL
4 = Moderate disability	5 = Lower moderate disability	Independent, but cannot resume work/school or all previous social activities
	6 = Upper moderate disability	Some disability exists, but can partly resume work or previous activities
5 = Good recovery	7 = Lower good recovery	Minor physical or mental deficits that affects daily life
	8 = Upper good recovery	Full recovery or minor symptoms that do not affect daily life

ADL = activities of daily living.

Cognitive and emotional outcome after TBI

Cognitive impairments within a variety of domains have been documented from the sub-acute stage, to the chronic phase several years after TBI, across different mechanisms of injury, and have been shown to be associated with injury severity (Dikmen et al., 2009; Draper & Ponsford, 2008; Finnanger et al., 2013; Rabinowitz & Levin, 2014). In addition to injury severity, higher age at injury, and a lower level of education, have been related to worse cognitive outcome after TBI (Senathi-Raja, Ponsford, & Schonberger, 2010b; Sigurdardottir, Andelic, Roe, & Schanke, 2009; Spitz, Ponsford, Rudzki, & Maller, 2012). Cognitive function after TBI is most typically assessed by neuropsychological methods, using a large variety of different performance-based standardized tests, often categorized within domains such as attention, processing speed, memory and executive function. Deficits within all these domains have been found across all injury severities for TBI survivors. Common data elements (CDEs) for measuring cognitive outcome have been suggested, by and large covering these key domains (Hicks et al., 2013; Wilde et al., 2010). Also, as only partly appreciated in the CDEs, cognitive dysfunction after TBI is multifaceted and should be addressed through a range of methodologies, including self-report, both from the injured and significant others (Draper & Ponsford, 2009; Garcia-Molina, Tormos, Bernabeu, Junque, & Roig-Rovira, 2012; Gioia & Isquith, 2004; Isquith, Roth, & Gioia, 2013; Lannoo et al., 1998).

Emotional problems are also more prevalent in the TBI population, as compared with the general population. In the clinical range, an increased risk for developing Axis I disorders as defined by the DSM-IV criteria have been associated with TBI (Whelan-Goodinson, Ponsford, Johnston, & Grant, 2009). An increased risk for the clinical diagnosis of a wide range of psychiatric disorders (including depression, schizophrenia, bipolar disorder, and organic mental disorders) after TBI was also recently confirmed in a large population-based study in Denmark (Orlovska et al., 2014). However, it should also be appreciated that a broad assessment is needed in order to capture all the relevant emotional and psychosocial challenges TBI survivors might experience, including those in the sub-clinical range, which may still have an impact on long-term outcome and function (Draper, Ponsford, & Schonberger, 2007). Using extensive self-report questionnaires tapping into the different aspects of emotional and psychosocial problems often experienced after TBI may provide added value to both clinicians and researchers interested in capturing these phenomena (Warriner & Velikonja, 2006).

Although there are some studies of interest with regards to indicating a biological gradient for the development of emotional problems after TBI, results have varied, and it is considered premature to conclude on the association between injury severity and such problems (Rogers & Read, 2007). Studies have linked reduced grey matter volume in the hippocampus (Jorge, Acion, Starkstein, & Magnotta, 2007) and left prefrontal cortex (Jorge et al., 2004) to an increased risk for developing of mood disorders after TBI. Furthermore, a rationale for investigating certain properties of the white matter has been proposed (Maller et al., 2010), and there is some evidence supporting that white matter abnormality in fronto-temporal regions might be predictive of development of major depression after TBI (Rao et al., 2012). However, although the association between brain anatomy and the development of emotional problems has been a topic for several research papers which have provided interesting hypotheses (Jorge & Starkstein, 2005; Rogers & Read, 2007; Warriner & Velikonja, 2006), there is still a relative paucity of studies directly investigating such relationships after TBI by use of advanced neuroimaging.

Most of the recovery of cognitive problems occurs within the first 6-12 months after TBI (Christensen et al., 2008). However, changes in cognitive function have also been observed many years after injury (Draper & Ponsford, 2008). As for the trajectory of the development and recovery from emotional problems, the findings are less clear. A study focusing on the first year after injury, found that the average duration of major depression was <6 months for patients who developed the disorder (Jorge et al., 2004). This is similar to what has also been observed in the general population (Richards, 2011; Spijker et al., 2002). In a longer perspective (5-22 years) there is evidence indicating that older individuals experience higher emotional distress in the earlier phase after TBI, whereas younger individuals are more prone to such distress in the later phase (Senathi-Raja, Ponsford, & Schonberger, 2010a). That changes in both cognitive and emotional function may be observed many years after TBI underlines the importance of long term follow-up of patients, as well as the need for detecting risk factors as early as possible in the rehabilitation trajectory in order to plan for preventive measures.

Also interesting within this context is that cognitive function and the risk for developing emotional problems seem to be highly interrelated. Higher degree of cognitive impairment has for example been related to higher levels of anxiety and depression after TBI (Spitz, Schonberger, & Ponsford, 2013). In general, including information about cognitive function provides a more accurate representation of functional outcome, at least one year after injury (Finnanger et al., 2013; Spitz et al., 2012). In particular, executive function seems to have the strongest effect on functional outcome (Spitz et al., 2012). In fact, even when adjusting for injury severity, executive function appears to be most important for the ability to resume independent living, leisure activities and employment (Finnanger et al., 2013). Moreover, executive dysfunction after TBI is associated with the development of major depression, and common pathophysiologic mechanisms for these phenomena involving disruption of fronto-striatal-thalamic circuits has been suggested (Jorge et al., 2004). Understanding executive function and how it may be altered by injury, may therefore give particularly valuable knowledge for optimizing clinical follow-up of TBI survivors.

Executive function and cognitive control after TBI

Despite a wide range of empirical and theoretical work, there is no unitary agreed upon definition of executive function and its related sub-components, or terminology that is used to describe them. However, most models include the notion that executive functions are those involved in a goal-directed regulatory control of thoughts, emotions, and actions. In other words, executive functions are thought to control the use of domain-specific abilities (e.g. visuospatial functions, language, memory, motor skills, emotions etc.) in order to achieve a desired goal. The focus on the control aspect of executive functions is also highly evident through use of the term "cognitive control", which is used about the same functions. Executive function and cognitive control is used interchangeably in the literature, and will to some degree also be so in this thesis. However, the impression from the literature is that the term executive function is more used within the field of neuropsychology, whereas cognitive control is more frequently applied in the field of cognitive neuroscience. Hence, since this thesis mainly operates within the field of cognitive neuroscience, the term cognitive control will be used most frequently.

Examples of sub-components of cognitive control includes, but are not limited to, task-set maintenance and shifting, adaptive task control, monitoring, switching, inhibition, initiation, and regulation of emotions. Cognitive control is also highly interrelated- or even overlapping with functions (or terms) such as working memory and attention. Furthermore, different cognitive control functions have been found to be correlated, but separable from each other (Miyake & Friedman, 2012). Also important when attempting to measure cognitive control is to acknowledge the "task impurity" problem (Miyake & Friedman, 2012; Miyake et al., 2000). Although cognitive control is by most definitions separable from domain specific cognitive functions, it is always measured in context of these, meaning that the latter will always influence the result to some degree (e.g. language function will influence the result on a verbal fluency task, which is also believed to be a measure of cognitive control). Also important to acknowledge is that cognitive control is indeed multifaceted and can only to a certain degree be measured by performance-based neuropsychological tasks (Isquith et al., 2013; Toplak, West, & Stanovich, 2013). It is therefore particularly important to rely upon several forms of information in the assessment of cognitive control dysfunction after TBI. Self-report measures represent an alterna-

tive approach for structured and systematic assessment of executive functions in every-day situations (Isquith et al., 2013). Although overlapping to a certain degree, information from performance-based and self-report measures are clearly also measuring different aspects of cognitive control, and the questions of how they are related, or which methods that are most valid for predicting every-day functioning still remains to be resolved (Isquith et al., 2013; Toplak et al., 2013). This may partly be related to the fact that the definition, operationalization, and knowledge about cognitive control function are still premature, despite a huge amount of research effort in the field. Moreover, this not only highlights the importance of taking a broad approach when assessing cognitive control, but also the parallel need for improved and/or alternative complementary methods to extend todays knowledge.

Better cognitive control function after TBI, has been related to more frequent use of problem-focused (planful problem solving), compared to emotion-focused (escape avoidant), coping strategies (Krpan, Levine, Stuss, & Dawson, 2007). This finding was independent from other factors such as intelligence and injury severity, and no such relationship was found in a healthy control group. Neither was there a general between-group difference in coping style. It has therefore been suggested that TBI survivors actively engage cognitive control to implement an adaptive coping strategy, whereas this happens rather automatically or effortlessly in healthy controls (Krpan et al., 2007). Similar differences in coping style have also been observed in a real-life task (Krpan, Stuss, & Anderson, 2011b), and cognitive control dysfunction was the best predictor for an avoidant coping style in this task (Krpan, Stuss, & Anderson, 2011a). A problem-focused coping style has been associated with a favorable outcome (Curran, Ponsford, & Crowe, 2000; Dawson, Cantanzaro, Firestone, Schwartz, & Stuss, 2006), and may therefore be a mediator explaining the negative effects of cognitive control dysfunction on overall outcome (Finnanger et al., 2013; Spitz et al., 2012). Cognitive control function also plays an important role for the potential effects of rehabilitation strategies targeted at dealing with cognitive dysfunction. For example, the success of learning a compensatory strategy for memory disorders is clearly affected by cognitive control function (Fish, Manly, Emslie, Evans, & Wilson, 2008). Given its central role in regulation of other cognitive domains, cognitive control is therefore a particularly good candidate for mediating compensatory

mechanisms after TBI, and a promising target for neuro-rehabilitation (Levine et al., 2011).

Advancing the knowledge of cognitive control dysfunction after TBI, may improve the understanding of problems often experienced by TBI survivors, as well as guide future treatment and rehabilitation. Given the multifaceted nature of cognitive control, and the difficulty of measuring all of its aspects by use of conventional clinical measures, advanced neuroimaging may play an important part in extending the knowledge of cognitive control alterations after TBI. Such methods could also have a future role as biomarkers or proxies for dysfunction after TBI, as well as work as tools for evaluating the effect of treatment interventions (Nordvik et al., 2014). However, the potential success of such an approach relies on several factors, including well-designed studies informed by the theoretical neurocognitive models of cognitive control function. As always, when seeking to gain knowledge about brain dysfunction, the importance of first becoming familiar with normal function should be stressed.

Neurocognitive models of cognitive control function

Although there is no unitary agreed upon definition of cognitive control, a common element for most neurocognitive models of this phenomena is the separation between *processors* and *controllers* in the brain (Petersen & Posner, 2012; Posner & Petersen, 1990; Power & Petersen, 2013). This distinction highlights the difference between areas in the brain involved in *processing* domain-specific operations (e.g. memory, language, decision-making, movement etc.), and the regions involved in the domain-general operations related to *control* such processes (e.g. select and implement). How these domain-general processes operates, and are distributed anatomically in the brain, has been a central question through decades of research in neuroscience. Several theoretical frameworks have been developed, many of which are not exclusive of others, but rather highlights different aspects of cognitive control function. The most influential frameworks the later years within the field of neuroimaging have for example focused on dorsal- and ventral systems for top-down and bottom up control (Corbetta & Shulman, 2002), conflict monitoring involving the anterior cingulate cortex (ACC) and dorsolateral prefrontal cortex (DLPFC) (Botvinick, Braver, Barch, Carter, & Cohen, 2001; Carter & van Veen, 2007); Carter &

Krug, 2012), hierarchical distribution of cognitive control functions within the PFC (Badre, 2008; Badre & D'Esposito, 2007, 2009; Kim, Johnson, Cilles, & Gold, 2011; Koechlin, Ody, & Kouneiher, 2003; Koechlin & Summerfield, 2007; Venkatraman, Rosati, Taren, & Huettel, 2009), and organization based on the temporal aspect of cognitive control processing (Braver, 2012; Dosenbach, Fair, Cohen, Schlaggar, & Petersen, 2008).

In 2002 Corbetta and Shulman reviewed evidence for brain networks involved in goal-directed (top-down) and stimulus-driven (bottom-up) cognitive control (Corbetta & Shulman, 2002). The conclusion from their review was that it seems to be two partially segregated systems associated with these two types of control, and that they rely on different brain regions. Whereas the top-down system seem to mainly be related to dorsal fronto-parietal regions (including the inferior parietal lobe and frontal eye field), the bottom-up system seem to mainly rely on a right-lateralized ventral fronto-parietal network (including the temporoparietal junction and ventral frontal cortex). Being prepared through having prior knowledge has been shown to improve performance in a variety of task domains. This facilitation of performance is most likely related to a top-down implementation of perceptual-, motor and attentional task-sets, which are associated with prolonged neural activation within the dorsal fronto-parietal system (Corbetta & Shulman, 2002). On the contrary, if a sufficiently salient stimulus appears (such as a loud noise, low-frequent target stimuli, object with a feature that stands out from the crowd – *"pop out effect"*), this facilitates bottom-up processing associated with more transient activation within the ventral fronto-parietal system. Corbetta and Shulman suggest that the ventral system acts like a *"circuit breaker"* for the dorsal system, through detecting salient stimuli outside the focus of current processing, which may interrupt or redirect the ongoing task-set.

A similar interaction between two separate systems is described in the conflict-monitoring framework (Botvinick et al., 2001; Carter & van Veen, 2007); Carter & Krug, 2012). However, in this framework, the anterior cingulate cortex (ACC) is thought to detect stimuli- or response conflicts, and then signal the dorsolateral prefrontal cortex (DLPFC), which is considered a key area where cognitive control is carried out. According to this

framework, processors in the brain have limited processing capacity, and a conflict occurs if two different processes compete for this capacity. Such conflicts need to be detected, and solved or prevented through cognitive control. Typical behavioral consequences of high conflict are that processing time of the task at hand, as well as the likelihood for errors increases. The conflict-monitoring framework has gained quite some criticism more recently, after a study showed that increases in brain activity within the ACC, may be better explained by the typical increased time-on-task, rather than conflict processing per se (Grinband et al., 2011). This study therefore also highlight the importance of taking into account differences in task performance (in this case reaction time) when modeling brain activations (Price, Crinion, & Friston, 2006).

There are a multitude of different frameworks based on a notion of a hierarchical distribution of cognitive control functions within the PFC. Considerable evidence supports a rostro-caudal distribution of different cognitive control processes within the PFC (Badre, 2008; Badre & D'Esposito, 2007, 2009; Kim et al., 2011; Koechlin et al., 2003; Koechlin & Summerfield, 2007; Venkatraman et al., 2009). However, how the specific properties of these processes may govern their anatomical distribution is still highly debated (Badre, 2008). One framework suggests that cognitive control processes are distributed more rostral with higher task demand, for example through increasing task complexity or abstractness (Badre, 2008; Badre & D'Esposito, 2007, 2009). Moreover, according to this *"cognitive demand framework"*, processes with lower task demands, such as those more closely related to simple motor responses, are believed to be located in more caudal regions of PFC (Kim et al., 2011; Venkatraman et al., 2009). In contrast, the *"information cascade"* framework states that the anatomical distribution of cognitive control processes is rather based on their temporal context relative to action selection (Koechlin et al., 2003; Koechlin & Summerfield, 2007). Within this framework, information (cues) presented temporally remote from the action selection process itself, and that has to be maintained for an extended period of time (typically over several trials), is thought to be located in rostral regions of the PFC. In contrast, information that gets available in close proximity to the action selection process (e.g. properties of the current stimulus/trial), should be located more caudally. The former is referred to as *"episodic control"*, and the latter as *"contextual control"*, respectively. Although the cognitive demand framework and the

information cascade framework both originate from a rostro-caudal perspective of cognitive control, they therefore differ with regards to their emphasis on the temporal dimension of cognitive control.

There has been a sparked interest in the temporal dynamics of cognitive control the later years, and frameworks based more exclusively on this dimension have emerged. A large part of the scientific work included in this thesis was influenced by this trend in the field. Perhaps the most comprehensive frameworks focusing on the temporal dimension of cognitive control are the *"Dual Mechanisms"* (Braver, 2012), and the *"Dual Networks"* (Dosenbach et al., 2008) frameworks. These frameworks propose that cognitive control processes are indeed operating on (at least) two distinct temporal scales. Processes related to proactive control (Braver, 2012), or stable task-set maintenance (Dosenbach et al., 2008), are maintained over an extended period of time, typically across several trials in a cognitive task. Reactive- (Braver, 2012) or adaptive task control (Dosenbach et al., 2008), operates within a much narrower time-frame and is tightly coupled to moment-to-moment processing and rapid adjustments based on particular stimuli. Studies so far have shown that stable and adaptive cognitive control processes can be separated from each other on a behavioral level, and that their neural correlates are found in both overlapping and distinct brain regions. Regions that are overlapping for stable and adaptive task control have previously been found bilaterally in the anterior insula and adjacent areas, as well as in the medial frontal cortex (MFC) (Dosenbach et al., 2006). Moreover, these regions are among the most frequently activated areas in fMRI studies across different task types, which support their domain generality, and are hence strong candidates for serving as true *"controllers"* in the brain. Due to the strong overlap across tasks and temporal resolution, these areas have been suggested to represent a *"core system"* for cognitive control (Dosenbach et al., 2006). There is still more uncertainty with regards to the anatomical distribution of the neural correlates unique to stable- and adaptive task control processes. There is data suggesting that the two can be separated into distinct brain networks based on resting state fMRI, where adaptive task control is related to a fronto-parietal network (dorsolateral prefrontal cortex – intraparietal sulcus), whereas a cingulo-opercular (dorsal anterior cingulate cortex/medial superior frontal cortex - anterior insula/frontal operculum) network subserve stable task control (Dosenbach et al., 2007). The fronto-parietal

network overlaps with regions demonstrating solely transient brain activations during task performance. However, the cingulo-opercular network demonstrates both sustained and transient activation during task performance, and one may therefore argue that it is still premature to separate it from the earlier mentioned *"core system"* (Dosenbach et al., 2006). Hence, more research is needed to further delineate the controllers uniquely related to adaptive and stable task control, how they may be separated from a potential *"core network"*, as well as domain-specific processors of the brain.

Interesting observations of variability within the two different temporal systems of cognitive control have been made, that may suggest an explanatory framework for compensation after injury or disease (Braver, 2012). On an intra-individual level (state or task-related), it has been demonstrated that subjects shift towards relaying more on ongoing proactive control during performance of an interference task when there is a high expectancy for probes to occur. In contrast, during a low-expectancy condition, subjects were rather demonstrating increased reliance on reactive control (Burgess & Braver, 2010). Furthermore, inter-individual (trait related) variation was also demonstrated as relatively higher utilization of proactive control was associated with higher fluid intelligence (Burgess & Braver, 2010). On the other side, anxiety has been related to increased reliance on reactive control (Fales et al., 2008). Furthermore, a shift towards relying more on reactive- relative to proactive processes has been observed both as an effect of healthy aging (Paxton, Barch, Racine, & Braver, 2008) and schizophrenia (Edwards, Barch, & Braver, 2010), hence demonstrating between-group variability (related to changes in brain function or integrity in different populations) in the temporal aspects of cognitive control function. In summary, all these findings suggest that variability within the temporal dimension of cognitive control may explain differences in adaptive behavior, both in healthy individuals as well as after injury or disease.

As mentioned earlier, each of the different frameworks for cognitive control are not necessarily exclusive of the others. In fact, they have several similarities with regards to operationalization of various elements of cognitive control. For example, the constructs top-down control (Corbetta & Shulman, 2002), episodic control (Koechlin & Summerfield, 2007), proactive control (Braver, 2012), and stable task-set maintenance (Dosenbach et

al., 2008), seem to have a considerable overlap in their definitions. Likewise, bottom-up control (Corbetta & Shulman, 2002), conflict processing (Botvinick et al., 2001), contextual control (Koechlin & Summerfield, 2007), reactive control (Braver, 2012), and adaptive task control (Dosenbach et al., 2008), clearly share some important properties. That being said, the different frameworks each add some unique insight into the understanding of cognitive control functions, and do in specific instances provide different predictions for particular cognitive tasks. It is not within the scope if this thesis to delineate the entire picture of similarities and differences between each framework. However, although the main focus in large parts of the scientific work included in this thesis was on the temporal dimension of cognitive control (i.e. Dual Mechanisms/Dual Networks frameworks), our findings were indeed tested in relation to, or discussed within the context of several of the other frameworks. Common for all neurocognitive models for cognitive control function is that they involve several brain regions anatomically spread apart. Given the heterogenic pathophysiology of TBI, cognitive control deficits may be observed after injury or dysfunction in the controllers themselves, in the communication between controllers, and/or between controllers and processors.

Functional magnetic resonance imaging (fMRI) and TBI

BOLD fMRI has been the method of choice in the majority of fMRI studies in TBI. This is also the method used for the functional imaging studies in this thesis, and will be the main focus for this literature review. The neurovascular coupling as measured with the BOLD response is influenced by several factors, including cerebral blood flow (CBF), cerebral blood volume (CBV), and cerebral blood oxygen consumption ($CMRO_2$). When increased neural firing is elicited (e.g. by a cognitive task), CBF, CBV and $CMRO_2$ increase to provide neurons with more oxygen. However, the $CMRO_2$ increase is relatively lower than the increase in CBF, leading to a decrease of paramagnetic deoxygenated hemoglobin as compared to diamagnetic oxygenated hemoglobin. The BOLD response is based on detecting such differences in the ratio between diamagnetic oxygenated hemoglobin and paramagnetic deoxygenated hemoglobin (Ogawa et al., 1990).

Although some studies have shown hypo-activations when compared with controls (Sanchez-Carrion, Gomez, et al., 2008; Soeda et al., 2005), the most consistent finding

has been that moderate-to-severe TBI survivors exhibit increased and/or more widespread activation during performance of a wide range of cognitive tasks (Bonnelle, 2011; Christodoulou et al., 2001; Kohl, Wylie, Genova, Hillary, & Deluca, 2009; Maruishi, Miyatani, Nakao, & Muranaka, 2007; Raja Beharelle, Tisserand, Stuss, McIntosh, & Levine, 2011; Rasmussen et al., 2008; Scheibel et al., 2007; Scheibel et al., 2009; Sozda, Larson, Kaufman, Schmalfuss, & Perlstein, 2011; Turner & Levine, 2008; Turner, McIntosh, & Levine, 2011). Results from fMRI studies after TBI are consistent with those found in other neurological conditions such as multiple sclerosis (DeLuca, Genova, Hillary, & Wylie, 2008; Hillary et al., 2003), suggesting that increased activation during task performance may represent an adaptation due to compromised integrity of the brain. Increased activation, particularly in frontal brain regions, has also been observed in healthy subjects when task difficulty is increased (Arsalidou, Pascual-Leone, Johnson, Morris, & Taylor, 2013), and in healthy aging (Turner & Spreng, 2012). It therefore seems like increased BOLD activation may be related to increased engagement of neural resources as a function of increased challenges for the brain (Hillary, Genova, Chiaravalloti, Rypma, & DeLuca, 2006). *"Cerebral challenge"* (Hillary et al., 2006) may be transient or stable, and can be given by external demands in the environment, or related to different state- trait- or injury dependent factors within the individual.

It has been suggested that increased BOLD activation after TBI might represent compensatory mechanisms, related to upholding adequate performance levels during task performance (Kohl et al., 2009; Turner & Levine, 2008; Turner et al., 2011). Some studies have found increased BOLD activation after TBI to be positively correlated to better performance (Scheibel et al., 2009; Turner et al., 2011), whereas others have found a negative relationship (Bonnelle et al., 2012), or both (Newsome et al., 2007). A positive relationship between BOLD activation and better performance has also been observed in a study, even when TBI survivors displayed hypo-activation as compared with healthy controls on a group level (Sanchez-Carrion, Gomez, et al., 2008). Although a positive association between increased BOLD activation and better performance, as well as increased BOLD activation in the context of highly similar performance (Maruishi et al., 2007; Newsome et al., 2007; Scheibel et al., 2009; Turner et al., 2011) might support the compensation hypothesis, the variability of findings indicate that this issue needs further elucidation.

Furthermore, most studies of altered BOLD activation after TBI has been observed in the context of group differences in fMRI task performance, which has not been accounted for (Bonnelle et al., 2012; Christodoulou et al., 2001; Hillary et al., 2011; Raja Beharelle et al., 2011; Rasmussen et al., 2008; Sanchez-Carrion, Gomez, et al., 2008; Scheibel et al., 2007; Sozda et al., 2011). Moreover, in some of the studies that have reported highly similar performance or adjusting for performance differences, this has been true for performance accuracy, but not reaction time (Bonnelle, 2011; Kohl et al., 2009; Turner & Levine, 2008).

As modeling task-related BOLD signal changes directly or indirectly is affected by fMRI-task performance, failing to adjust for group differences in performance may lead to circular reasoning, when interpreting such relationships. Accordingly, it has been stressed that the validity of fMRI group differences observed in neurologically impaired participants, is highly dependent on keeping task performance similar across groups and/or statistically adjusted for (Price et al., 2006). One important factor is that the degree of compensation may be individual, in the sense that even though an individual performs at a sub-optimal level as compared to others (and/or with less activation), they may still have performed worse without neuronal compensation. This may for example explain why increased activation still can be observed in the context of poorer task performance after TBI (Christodoulou et al., 2001), or that BOLD activation might be related to better task performance despite observing hypo-activation on a group level (Sanchez-Carrion, Gomez, et al., 2008). Without adjusting for fMRI task performance in situations like this, correlations between the BOLD response and an external functional measure could potentially be flawed. Another implication from this is that validation of the functional role of BOLD differences ideally should not rely on measures highly correlated with the particular fMRI task used, such as very similar neuropsychological task paradigms. Furthermore, TBI survivors often do not display deficits on neuropsychological tasks administered in highly controlled settings, despite reporting problems in everyday life. This is particularly true for cognitive control function, where performance-based and self-report measures seem to measure different aspects of this function (Isquith et al., 2013; Toplak et al., 2013). Relating increased BOLD activation after TBI to self-report measures, while adjusting for fMRI task performance, might shed new light on potential compensatory

mechanisms, more closely related to everyday function as perceived by TBI survivors. However, no previous studies have investigated such relationships.

An interpretation related to the compensation hypothesis is that increased BOLD activations after TBI might represent a failure to effectively enhance neuronal efficiency due to practice effects, or more automatic processing as the task progresses. Very few studies have investigated such effects as a function of time-on-task (TOT). However, some support for this interpretation has been found in a study of a small group of severe TBI survivors (Newsome et al., 2007). Another study demonstrated increased within-group TOT related activation for TBI survivors, as well as compared with healthy controls (Kohl et al., 2009). Healthy controls in the same study on the other hand exhibited decreased activation on a within-group level (Kohl et al., 2009), indicating that habituation and compensation mechanisms might be displayed differently in healthy, as compared to injured brains. Upholding performance throughout a prolonged task is clearly a *"cerebral challenge"* (Hillary et al., 2006), and is typically associated with performance decline even in healthy subjects (Langner, Steinborn, Chatterjee, Sturm, & Willmes, 2010). Engaging more neuronal resources due to compensation or a failure to habituate to the task may therefore be related to the often-reported experience of cognitive fatigue, which is prevalent for the TBI group (Kohl et al., 2009; Ponsford et al., 2012). Investigating TOT effects is hence potentially informative for many important aspects of subtler dysfunction after TBI.

Another question is also whether the increased activation is related to transient alteration of functional engagement in task-relevant brain regions that have been preserved after injury, or if it is better explained by permanent reorganization through recruitment of novel regions, not normally activated in healthy brains. This question is still up for debate (Hillary, 2011), however, a study investigating this issue by means of behavioral partial least squares analysis (bPLS) of fMRI data from eight TBI survivors, gave preliminary evidence in favor of the altered functional engagement hypothesis (Turner et al., 2011). This study showed that areas of the PFC that were co-activated in healthy controls as a function of increased task difficulty in a working memory task were engaged at lower levels of difficulty in TBI survivors. More studies like this, also including investigation of

within-task changes (e.g. TOT effects or longitudinal studies) are needed in order to gain traction on this issue (Hillary, 2011).

Injury severity might represent increased *"cerebral challenge"* with more severe injury, and if so, should therefore be related to an increased need for compensation. A study investigating severe TBI found a positive association between increased activation during performance of an N-Back task and lower GCS score when the task load was low (Newsome et al., 2007). However the opposite was observed when the task load was increased. Results from this study should, however, be interpreted with caution, because of a small sample size (n = 10) and an extremely narrow range of GCS scores (3-5). A study investigating the relationship between GCS and BOLD activation in 14 TBI survivors, initially found no relationship between GCS and BOLD activation (Scheibel et al., 2007). However, after tweaking the statistical threshold some indications for increased activation with more severe injury were found. However, this study did not adjust for task-performance, or relevant demographic factors known to be important for functional outcome after TBI (Scheibel et al., 2007). In a later study that in fact also adjusted for age, education, estimated IQ, and task accuracy, lower GCS score was related to increased cognitive control related activation within the MFC and thalamus (Scheibel et al., 2009). However, this study failed to adjust for task reaction time in the regression model, which has been demonstrated to affect activation within the same MFC region (Grinband et al., 2011). Moreover, although including a larger sample of TBI survivors (n = 30), this as many other fMRI studies in the field, applied a relatively liberal statistical threshold. In conclusion, there is some evidence pointing in the direction that increased BOLD activation is related to more severe injury, however, larger studies with sufficient statistical power to validate these findings are needed.

The variety of different tasks used in previous fMRI studies in TBI, raises the question whether the observed alterations in BOLD activation are domain specific, or whether they represent more domain general operations. Heterogeneity of the TBI samples, as well as in the methodology used to analyze the data, further complicate this issue. However, although there are quite some findings unique to each study, some commonalities can be observed across many of them when it comes to anatomical distribution of brain activa-

tions. The most consistently altered BOLD activations after TBI have been found within particular fronto-parietal areas, including the dorsolateral PFC and MFC, encompassing brain regions typically associated with domain general cognitive control functions. In fact, most studies have used tasks with strong cognitive control components such as the n-back task (Christodoulou et al., 2001; Hillary et al., 2011; Maruishi et al., 2007; Newsome et al., 2007), the Stroop paradigm (Soeda et al., 2005; Sozda et al., 2011), dual-tasking (Rasmussen et al., 2008), stop-signal task (Bonnelle et al., 2012), alpha-span task (Turner & Levine, 2008; Turner et al., 2011), stimulus response compatibility task (Scheibel et al., 2007; Scheibel et al., 2009), paced visual sustained attention test (Maruishi et al., 2007), symbol digit modality task (Kohl et al., 2009) and choice reaction time task (Bonnelle, 2011). As cognitive control is needed in all these tasks (and virtually any other task), it is therefore plausible that the common findings are related to this domain general function. Furthermore, given the heterogeneity of the TBI samples, focusing on domain general activations related to cognitive control for future investigations may be particularly valuable, as more domain specific activations may be more susceptible to individual pathology. As cognitive control dysfunction has a particularly important role for functional outcome after TBI (Finnanger et al., 2013; Spitz et al., 2012), and is a promising target for cognitive rehabilitation interventions (Levine et al., 2011), hypothesis driven investigation of its neuronal correlates, carefully integrated within innovative neurocognitive theoretical frameworks, may provide extended and important insight.

In summary, there is some evidence that TBI leads to hyper activations, particularly observed in fronto-parietal cognitive control regions in the brain. Moreover, these hyper activations have been suggested to be compensatory, and associated to the degree of *"cerebral challenge"* represented by such factors as injury severity and task demands. However, as pointed out earlier, several methodological issues need to be improved/addressed, and larger studies providing sufficient statistical power to detect subtle BOLD changes are needed in order to validate and extend previous studies.

Diffusion tensor imaging (DTI) and TBI

White matter injuries have been observed in all severities of TBI. Diffusion tensor imaging (DTI) is based on a modification of diffusion-weighted imaging (DWI), and has shown to

be a promising technique for assessing white matter integrity in vivo, also where no sign of injury is seen on conventional clinical MR images (Newcombe et al., 2011). DTI measures diffusion properties of water molecules in the brain, which are closely correlated to white matter microstructure (Le Bihan et al., 2001; Tournier, Mori, & Leemans, 2011). Isotropic diffusion is observed when the water molecules can move unrestricted (such as in cerebrospinal fluid), whereas if they are restricted (such as when restricted by the myelin of white matter tracts), the diffusion is anisotropic. When measuring the properties of anisotropic diffusion in six or more non-collinear directions, a diffusion tensor can be calculated. This tensor can be represented as an ellipsoid, where three eigenvectors represents the long axis (e_1), width (e_2) and depth (e_3), respectively. The length of the different eigenvectors is represented as eigenvalues (λ_1, λ_2 and λ_3), and can be used to calculate summary measures to infer representation of different diffusion properties of the underlying tissue. Several different summary measures can be calculated based on DTI data, where the most common for use in TBI studies are fractional anisotropy (FA) and mean diffusivity (MD) (Hulkower, Poliak, Rosenbaum, Zimmerman, & Lipton, 2013). Mean diffusivity is calculated by making an average of the three eigenvalues, and is reflecting the magnitude of the mean diffusion in all directions (regardless of its directionality). FA on the other hand is an expression of the directionality of diffusion, and is normalized so that it provides a number between 0 and 1 (where 0 represents isotropy and 1 full anisotropy). FA does only express the degree of anisotropic directionality, not the particular direction within the ellipsoid; however, in order to get more information about this, axial and radial diffusivity can be calculated. Axial diffusivity (AD) is based on the largest eigenvalue, and radial diffusivity (RD) is calculated from the two smaller eigenvalues. In general, in TBI, increased AD (diffusion along the fibers) has been suggested to be associated with axonal damage, while increased RD (diffusion perpendicular to WM fibers) is more likely to be associated with demyelination (Budde et al., 2007; J. Li, Li, Feng, & Gu, 2011; S. Li et al., 2013; Song et al., 2003). However, it is important to bear in mind that there is no one to one relationship between DTI metrics and white matter microstructure.

Information about the main direction of water diffusion locally within each voxel can be used to infer long-range directionality of whole tracts. This is what is referred to as DTI tractography, or white matter tractography (Lazar, 2010). Tractography analyses can be

performed in many ways, and results may vary across different methods. Different methods of tractography generally fall into two major categories, namely those that utilize deterministic- and those that utilize probabilistic algorithms. In general, deterministic algorithms are based on directly following the main diffusion direction (e_1) from voxel to voxel, whereas the probabilistic algorithms estimate the likelihood of two regions being connected (Tournier et al., 2011). Tractography have an important role for in-vivo mapping of specific white matter tracts, and for parceling out such tracts to be used as ROIs in further analysis (e.g. of MD and FA). A big challenge when performing tractography is to correctly estimate the direction when there is crossing, kissing, or bending fibers within the same voxel. As this is a clear limitation of this approach, there has been a considerable focus on method development to further improve both acquisition and analysis techniques to overcome this challenge (Tournier et al., 2011). Another challenge is that DTI in general, and tractography methods in particular, are complex and computationally time-consuming. Most methods are also limited by the subjective factor of manually placing ROIs prior to fiber tracking. In order to make this approach more available, and relevant for large-scale studies and clinical purposes, another focus should therefore be on developing automated or semi-automated methods with sufficiently high validity and reliability (Edlow & Wu, 2012).

DTI has been shown to be more sensitive to detecting white matter abnormalities after TBI than conventional clinical imaging, and disrupted white matter integrity has been demonstrated to be more extent with more severe injury and worse global outcome (Benson et al., 2007; Newcombe et al., 2011). This indicates that DTI may be a promising method for increasing the precision of detection and grading of TBI. Alterations of both FA and MD have been observed in chronic TBI of all severities (Hulkower et al., 2013). Despite some variations, the most consistent finding from DTI studies have been decreased FA in various brain regions in the chronic stage (Bendlin et al., 2008; Hulkower et al., 2013; Inglese et al., 2005; Kumar et al., 2009; Xu, Rasmussen, Lagopoulos, & Haberg, 2007). Animal studies from the acute and sub-acute stage after experimental injury, have demonstrated that reduced FA and AD is primarily related to axonal injury in the initial phase, whereas RD increase over time, further contributing to reduced FA, and is probably reflecting demyelization (J. Li et al., 2011; S. Li et al., 2013). This suggests

that DTI can be used as an in vivo tool, not only for detection of injury, but also for evaluating the progression of injury, and estimate time since injury. However, these experiments were performed in highly controlled settings, and caution should be exercised when extrapolating these findings to humans. There are relatively few studies that have investigated longitudinal within-group changes in moderate-to-severe TBI from the acute stage into the sub-acute or chronic phase, and results are not uniform, reflecting the complexity of TAI in humans. A study of severe TBI demonstrated reduced FA (compared to healthy controls) in the sub-acute phase (~8 weeks) that was caused by decreased AD and increased RD (Sidaros et al., 2008). At follow up ~12 months after injury, within-group FA increases (normalization) were observed in several anatomical regions (posterior limb of the internal capsule and centrum semiovale), with increased AD and mainly unchanged RD, suggesting increased axonal integrity. The areas of increased FA were mainly found in patients with more favorable outcome, which may indicate that signs of possible reorganization processes can be detected by DTI. However, in other regions (posterior corpus callosum and cerebral peduncle) both AD and RD increased with time, and FA decreased (Sidaros et al., 2008). Moreover, other longitudinal studies have mainly found reductions in FA from the sub-acute to the chronic phase (Kumar et al., 2009; Perez et al., 2014). As most longitudinal DTI studies have included acute scans from several weeks after injury, important information from the very acute phase might also have been missed (J. Li et al., 2011; S. Li et al., 2013). A very recent study demonstrated no FA changes within 24 hours of injury, but that FA was decreased 7 months later (Perez et al., 2014), demonstrating the importance of considering the time-window of obtained scans when interpreting findings. White matter tract volume has not been examined as extensively as FA and MD in TBI, and the results are so far inconsistent (Brandstack, Kurki, & Tenovuo, 2013; Kurki, Laalo, & Oksaranta, 2013). Given that total white matter volume has been shown to decline slowly, and not be significantly reduced before 1 year after injury (Brezova et al., 2014), it might be that white matter tract volume loss is best portrayed in a late chronic phase.

Several studies have shown that white matter integrity in a wide range of anatomical regions as measured with DTI is associated with domains of cognitive dysfunction commonly observed after TBI (Hulkower et al., 2013). For example, memory dysfunction after

TBI has been related to reduced white matter integrity of the fornix, uncinate fasciculus, corpus callosum, forceps, saggital stratum, fronto-occipital faciculus, superior and inferior longitudinal fasciculus (Kinnunen et al., 2011; Kraus et al., 2007; Niogi et al., 2008; Spitz, Maller, O'Sullivan, & Ponsford, 2013). Furthermore, particularly interesting for this thesis is that cognitive control dysfunction after TBI has been associated with reduced white matter integrity in several widespread white matter tracts such as the corpus callosum, superior and inferior longitudinal fasciculus, the cingulum bundle, anterior and superior corona radiata, and the internal capsule (Kinnunen et al., 2011; Leunissen et al., 2014; Niogi et al., 2008; Spitz, Maller, O'Sullivan, et al., 2013). White matter disruptions in thalamo-cortical projection fibers have also been demonstrated to be associated with poorer cognitive control function (Little et al., 2010). Interestingly, none of the previous DTI studies have investigated the association between white matter microstructure and self-reported cognitive control function. Moreover, although there is an indication of double dissociation between cognitive domains such as memory (bilateral uncinate fasciculus) and cognitive control (left anterior corona radiata) after mild TBI (Niogi et al., 2008), there is still great variability of findings in the literature across injury severities as to which tracts are related to a particular cognitive dysfunction.

The majority of DTI studies in TBI have used an ROI based approach. However, the anatomical distribution of white matter disruption after TBI is difficult to predict a priori in an individual un-stratified (e.g. with regards to lesion location) sample of TBI patients. Also, although certain cognitive functions have been associated with particular tracts in healthy brains (Johansen-Berg, 2010), the functional changes due to injury might not be expressed with equal specificity. This may be partly because the pathology of TBI is rather heterogeneous, but also because the total *"white matter load"* (Kraus et al., 2007) regardless of anatomical location might have a high impact on behavioral changes, particularly in tasks relying on integration of several anatomical areas. Another factor to consider is that different methods of analysis are not equally sensitive in all anatomical regions (Szczepankiewicz et al., 2013; Wakana et al., 2007). Disruptions of large tracts such as the corpus callosum have been significantly related to many factors, including injury severity and a range of cognitive functions. This probably reflects the importance of this structure for many different brain functions, but could also be related to that the particular method

used might be more robust in reliably detecting changes in this region, compared to other smaller and anatomically less pronounced tracts. Further complicating the interpretation of results is that the abundance and size of axons and other components such as glial cells and blood vessels vary within different parts of the white-matter (Rabi, Madhavi, Antonisamy, & Koshi, 2007). Partly based on the inconsistency of findings, it has been suggested that investigations of white-matter changes in TBI group-data ideally should rely on a two-stage analysis including both whole-brain (e.g. tract based spatial statistics – TBSS) and ROI based approaches (Leunissen et al., 2014; S. M. Smith et al., 2006; Spitz, Maller, O'Sullivan, et al., 2013). Although there are some regions in the brain more susceptible to TBI than others, performing only ROI based analysis may lead to missing out on important regions of disrupted white matter regions, also those that might only be represented in specific parts of tracts. This is also particularly relevant when aiming to investigate cognitive control function, which relies on integration and communication between several controllers in widespread anatomical regions.

In summary, DTI has proven to be a valuable method for gaining information about changes in white matter microstructure after TBI. However, as described earlier, not all DTI findings regarding white matter microstructure have been uniform. The variability of findings may be related to the time-window after injury being investigated, differences in patient samples, type of analysis, clinical variables included in the analyses, or the particular ROIs investigated (Hulkower et al., 2013). More studies taking a combined whole-brain and ROI based approach are therefore still needed in order to further elucidate the consequences of TBI on white matter microstructure, and to establish the relationship between various DTI measures, clinical variables, and functional outcome.

Aims for the thesis

The main aim for this thesis was to extend current knowledge on functional and structural changes in the brain after moderate-to-severe TBI, and to relate these findings to injury-related variables and functional measures known to be important for outcome. In order to reach this aim, several studies with different but related perspectives were performed, and four papers based on these studies are included in this thesis (hereafter referred to as Paper I-IV).

It is known that cognitive control function plays a particularly important role for functional outcome after moderate-to-severe TBI. Furthermore, recent neurocognitive models of cognitive control emphasize the importance of measuring both adaptive and stable cognitive control processes, as this may shed new light on potential compensatory mechanisms after injury. No previous studies have investigated both adaptive and stable cognitive control processes in the same study after TBI. However, in order to detect dysfunction, it is important to first be familiar with normal function.

In Paper I, the focus was on developing a task that was clinically relevant for typical cognitive control deficits after TBI, and that could reliably measure both adaptive and stable cognitive control processes in the healthy brain. Another important aim in Paper I was to validate this fMRI-adapted version of a widely used clinical paradigm against innovative neurocognitive models based on recent neuroimaging literature.

Cognitive control is multifaceted and can only to a certain degree be measured with performance-based measures. Also, the validity of interpretations of the functional significance of BOLD alterations might be flawed if it is correlated merely to fMRI task performance or highly similar performance based measures. No previous fMRI study of TBI has included other measures of cognitive control in such investigations. A new approach was therefore taken in the work presented in this thesis where a self-report measure of behavior related to cognitive control in every-day life was used in order to investigate the functional significance of TBI-related alterations in BOLD activation.

In Paper II, cognitive, emotional, and behavioral problems in chronic moderate-to-severe TBI were delineated by use of self-report, and related to injury related variables and early clinical MRI findings. Also, in a subgroup analysis, these measures were related to performance-based measures of cognitive function. Although taking a rather broad approach in this paper, the analyses regarding cognitive control function was most important for the focus of this thesis.

In Paper III, the perspectives from Paper I and II were combined to provide for hypothesis driven investigation of altered cognitive control activations after moderate-to-severe TBI and its relationship to injury severity and every-day life function.

Studies with larger samples taking a combined whole-brain and ROI based approach are needed in order to further elucidate white matter microstructure changes after moderate-to-severe TBI as measured with DTI and their functional significance. Furthermore, in order to make the DTI approach more available and relevant for large-scale studies after TBI, the properties of automated and semi-automated methods should be investigated in relevant samples.

In Paper IV, Tract-based spatial statistics (TBSS) and an automated method for tractography not previously used in TBI were applied in order to investigate white matter integrity and its relationship to injury related variables and functional outcome in general, and both performance-based and self-reported cognitive control function in particular.

Materials and methods

Participants

TBI survivors were recruited from a cohort of 236 consecutive patients admitted to the Department of Neurosurgery at St. Olavs Hospital, Trondheim University Hospital, Norway, between October 2004 and July 2008. All TBI survivors had moderate-to-severe TBI according to the Head Injury Severity Scale (Stein & Spettell, 1995). All patients except for 5 consented to participating in follow-up research studies and to be registered in a database. Data regarding acute- and sub acute measures were also registered in this database, and some of these data have also been described in previous studies (Finnanger et al., 2013; Skandsen, Finnanger, et al., 2010; Skandsen, Kvistad, et al., 2010). The data collection specific for the studies included in this thesis was performed between February 2009 and August 2010. An attempt was made to contact all TBI survivors registered in the database if they fulfilled the following criteria: between 14-65 years of age the year of testing, >1 year since injury, fluency of the Norwegian language, and being eligible for task fMRI (GOSE ≥5 and no MRI incompatible implants). Other exclusion criteria were previous moderate-to-severe TBI, and diagnosed neurologic or psychiatric condition.

Out of the 231 TBI survivors originally registered in the database, 51 died, 40 were excluded for being outside the age-limit, 28 due to premorbid or ongoing medical conditions, 4 not being fluent in the Norwegian language, and 13 for not being eligible for fMRI. This left a total of 95 TBI survivors eligible for the studies in this thesis, whereof 74 consented to participation. The qualitative impression was that very few (~2) potential participants actively declined to participate, as the main reason for non-participation was that we could not get ahold of some individuals for various reasons. Unfortunately, the exact reason for non-participation was not systematically registered. In total, one hundred and three healthy controls were also recruited. Healthy controls were recruited from friends and relatives of TBI survivors, healthy controls from a cohort database from a study of young adults born with very low birth weight (VLBW), as well as from different workplaces in Trondheim, Norway. All participants received financial reimbursement of NOK 1000. The study protocols were approved by the Regional Committee for Research Ethics, and adhered to the Helsinki Declaration.

The final samples included for each individual paper differs slightly due to exclusion based on study specific factors (e.g. missing data, or compromised data quality) as well as age, sex and education matching that are described in detail in each paper. However, a non-trivial difference in the study sample for Paper IV is worth an extra note here. A considerable lower number of TBI survivors (N=49) were included in Paper IV, mainly due to technical problems with the scanner, leading to pronounced vibration artifacts in some of the DTI images. This problem selectively affected DTI scans, and none of the other imaging protocols. This hardware problem with the scanner was sought solved several times, however without success. Particular focus was therefore on quality control of individual data (Tournier et al., 2011), and only including participants with sufficient data quality. A consequence of this was also that age, sex, and education matched healthy controls with artifact free DTI images (N=50) were selected to match the final sample of TBI survivors in this paper.

All data acquisition performed specifically for the work of this thesis included ~6 hours of assessments, all completed during one day. In addition to the data included in this thesis, assessments of high-level mobility and recording of EEG data was also performed. The order of the different tests was randomized for each individual to avoid systematic effects of fatigue or other relevant factors.

MRI data acquisition

All scans were performed on the same scanner at St. Olavs Hospital, which was a 3-T Siemens Trio with a 12-channel head coil (Siemens AG, Erlangen, Germany). A blood-oxygen-level dependent (BOLD) sensitive echo planar imaging (EPI) pulse sequence was applied to investigate neuronal correlates during performance of an in-house developed cognitive control task. The diffusion tensor imaging (DTI) sequence was a single-shot balanced-echo EPI sequence (acquired in 30 non-collinear directions). Two spin echo sequences with opposite phase encoding were acquired immediately after each EPI sequence (fMRI and DTI). These spin echo sequences were used for correction for static magnetic field distortions (Holland, Kuperman, & Dale, 2010). For anatomical reference, a T1 weighted 3D volume obtained with a magnetization-prepared rapid acquisition with

gradient echo (MPRAGE) sequence was applied. More details about imaging sequences can be found in each individual paper.

NOT-X continuous performance test (CPT) - fMRI paradigm

A novel fMRI task was developed and implemented specifically for the work in this thesis. Previous work had shown that measuring both adaptive and stable cognitive control processes might provide new insight on potential compensatory mechanisms after injury or disease. Previous studies taking this approach had used tasks mainly developed within cognitive neuroscience. We therefore wanted to develop a task that was more clinically relevant, but could still be adapted to measure both adaptive and stable cognitive control processes by means of fMRI, and validate it with respect to recent neurocognitive models of cognitive control. Also important was that the task demands were not too high, as we wanted both healthy controls and TBI survivors to have similar performance, as this is important for the validity of the interpretations of BOLD differences in neurological samples (Price et al., 2006).

After considering several different options, we landed on modifying a version of the continuous performance test (CPT) paradigm. This test paradigm is among the 5 most frequently used tests for clinical assessment of cognitive control and attention (Rabin, Barr, & Burton, 2005). Furthermore, a proof of principle fMRI study only investigating stable processes had demonstrated that key cognitive control areas could be detected during performance of this task (Ogg et al., 2008). The CPT paradigm is based on detecting low-frequency stimuli within a consecutive presentation of high-frequency stimuli (Riccio, Reynolds, Lowe, & Moore, 2002). The Conner's CPT (Conners, Epstein, Angold, & Klaric, 2003) is probably the most popular commercially available CPT paradigm used in clinics throughout the world. In this CPT, the subject is told to respond as fast as possible by pressing a response button each time a letter from A-Z (high-frequency stimuli – 90% of the time) is presented on the screen, but to withhold their response if the letter is "X" (low frequency stimuli – 10% of the time). As the subjects are instructed to withhold their response when there is an X presented on the screen, the generic name of this CPT paradigm is *"Not-X CPT"* (Riccio et al., 2002).

For the purpose of the work in this thesis, an fMRI-adapted version of the Not-X CPT paradigm inspired by the Conners CPT (Conners et al., 2003) was developed. In order to be able to measure both stable (block-related) and adaptive (event-related) cognitive control processes, the task was optimized for a mixed block- and event related fMRI design (Petersen & Dubis, 2012). Furthermore, as we were specifically interested in also investigating TOT effects, a great deal of work was put into balancing out potential order effects, as well as reducing the potential effects of global signal changes in the design. Technical details on how this was done are presented in the respective papers (Paper I and III).

Implementation of the Not-X CPT design was done in MATLAB 2008 (Math Works, Inc., Natick, MA), and presentation was done with E-Prime (Psychology Software Tools, Pittsburgh, PA). The test was presented to participants through either MRI-compatible video-goggles (VisualSystem, Nordic NeuroLab, Bergen, Norway) or an MRI-compatible monitor (Siemens AG, Erlangen, Germany). A switch to using the monitor instead of the goggles had to be made because of technical problems with the latter. Potential effects of this change were controlled for in all analyses. Responses were recorded using fiberoptic response grips (ResponseGrip, Nordic NeuroLab, Bergen, Norway). Stimulus timing and behavioral data was stored in log files using a Python-based script interacting with the E-Prime.

BOLD fMRI data analysis

All fMRI data were analyzed with the FMRIB's Software Library (FSL) toolbox 4.1.6 (FMRIB Centre, Oxford, UK). A custom algorithm was used in order to perform correction for geometrical distortions in EPI images before these analyses (Holland et al., 2010). Non-brain structures were first removed. BOLD fMRI data was motion corrected, grand mean intensity normalized and smoothed with a 6 mm full-width at half-maximum (FWHM) Gaussian filter. Temporal high pass filtering of 50s for block-related analyses, and 25s for event-related analyses were applied. Functional MRI data was linearly registered to each individual's native high-resolution T1 image using 7 degrees of freedom. Non-linear registration of native high-resolution images to a 1 mm MNI standard space template was then performed, using 12 degrees of freedom and a warp resolution of 8

mm. The functional image series were then transformed into standard space by applying the transformation matrix obtained from the high-resolution T1 image.

The hemodynamic response function was convolved with a standard Gamma variate, and a general linear model (GLM) was used to model BOLD activations as an effect of different contrasts. For each individual, the different contrasts were computed from 2 different runs and combined in a fixed effects analysis. Within- and between group effects were investigated by means of mixed effect analyses. Both Paper I and Paper II included whole-brain analyses. In these whole-brain analyses, thresholding and corrections for multiple comparisons were performed with a voxel based approach in Paper I (GFR-theory-based maximum height thresholding with $p < 10^{-13}$ and $p < 0.01$) and with a cluster threshold of $Z > 2.3$ ($p < 0.05$) in Paper III. In addition, in Paper III parameter estimates of BOLD activation were extracted from particular ROIs in each individual and used in further analyses. The Harvard Oxford cortical- and subcortical structural brain atlases as well as visual inspection were used for anatomical denotation.

DTI data analysis

The FSL toolbox was also used to perform DTI analyses. All DTI acquisitions were registered to the b0 image using affine registration in order to minimize distortions due to motion and eddy currents. Correction for geometrical distortions was performed utilizing a custom algorithm (Holland et al., 2010). Non-brain structures were removed, and FMRIB's diffusion toolbox was used to fit a diffusion tensor model to the raw data in each voxel. Tract based spatial statistics (TBSS) (S. M. Smith et al., 2006) was used for voxel-wise statistical analysis of the diffusion data. The Camino package was used for tractography, and an interpolated deterministic streamlining method was applied (Cook PA, 2006). A clustering approach based on clustering the streamlines based on their pair-wise distances was used in order to find consistent bundles of streamlines across subjects (Visser, Nijhuis, Buitelaar, & Zwiers, 2011).

Other statistical analyses

All other statistical analyses (e.g. demographic, behavioral and ROI based data) were performed with IBM SPSS 18.0 (Paper II), 19.0 (Paper I), and 20.0 (Paper III and IV). In depth description of the statistical methods can be found in the individual papers.

Summary of the papers

Paper I

Title: The functional topography and temporal dynamics of overlapping and distinct brain activations for adaptive task control and stable task-set maintenance during performance of an fMRI-adapted clinical continuous performance test.

Background: Stable and adaptive cognitive control processes seems to be subserved by partly overlapping, but also distinct anatomical areas. Brain regions in the MFC and bilaterally in the anterior insula have been suggested to represent a core network of cognitive control. The existence of such a core network, as well as the unique topography for different adaptive and stable cognitive control processes are still highly debated, and needs further elucidation.

Overall objective: Develop and validate a clinically relevant task for measuring both adaptive and stable cognitive control processes.

Methods: BOLD fMRI was acquired in 87 healthy participants during performance of a Not-X CPT adapted for use in a mixed block- and event related fMRI paradigm.

Research questions: Is there a core network of cognitive control comprised by the MFC and bilateral anterior insula? How are areas related to stable and adaptive cognitive control processes organized within the PFC? How is stable and adaptive cognitive control processes affected by TOT?

Main findings: Overlapping areas of activation related to both adaptive and stable cognitive control processes were observed in the MFC, and bilaterally in the anterior insula (and adjacent cortices), right IPL, and middle temporal gyrus. Within the PFC, there was a rostro-caudal distribution of adaptive- relative to stable processes. BOLD activation related to stable cognitive control processes decreased in task typical task related areas, and increased in typical task negative/default mode network (DMN) regions, as an effect of TOT. No TOT effects were seen for adaptive cognitive control activation.

Conclusions: Results from this study provides further evidence for a core network of cognitive control. Extending previous studies, important knowledge on the functional organization of adaptive and stable cognitive control processes, and their temporal dynamics in the context of an extensively used clinical CPT paradigm was provided. This knowledge could provide a platform for future hypothesis driven studies investigating the neuronal correlates of cognitive control dysfunction.

Paper II

Title: Self-reported executive, emotional and behavioral function 2-5 years after moderate and severe traumatic brain injury - a prospective follow-up study.

Background: Moderate-to-severe TBI is a risk factor for developing executive, emotional, and behavioral problems.

Overall objective: Investigate the properties of two self-report measures, namely the Behavioral Rating Inventory of Executive Function (BRIEF-A) and the Achenbach System of Empirically Based Assessment (ASEBA); Adult Self Report (ASR), in a cohort of moderate-to-severe TBI survivors.

Methods: The BRIEF and ASEBA-ASR was administered to 67 survivors of moderate-to-severe TBI, and a group of 72 age- sex- and education matched healthy controls.

Research questions: Does survivors of moderate-to-severe TBI experience more executive, emotional and behavioral problems in the chronic phase? How is self-reported executive, emotional, and behavioral function related to demographic factors and injury related variables such as GCS, PTA, and early MRI findings? How are self-reported executive, emotional and behavioral function in the chronic phase associated with performance-based measures of cognitive function, symptoms of depression, and global outcome as measured during the first year after injury?

Main findings: TBI survivors reported more executive, emotional and behavioral problems, as compared with healthy controls. Presence of traumatic axonal injury (TAI) as detected in early clinical MRI, was associated with later problems. Self-reported executive, emotional and behavioral problems in the late chronic phase were associated with symptoms of depression 1 year after injury. There were no statistically significant associations between self-reported executive, emotional and behavioral function and performance-based measures of cognitive control.

Conclusions: Executive, emotional and behavioral problems were frequently reported in chronic moderate-to-severe TBI survivors. Identification of TAI and symptoms of depression in an earlier phase, may give a warning of later problems, and should therefore be assessed systematically in the clinic. Self-report measures seem to extend information obtained from performance-based measures, and may therefore provide extra value when used in parallel with these in the clinic.

Paper III

Title: Altered cognitive control activations after moderate-to-severe traumatic brain injury and their relationship to injury severity and everyday-life function.

Background: Increased BOLD activation during task performance after moderate-to-severe TBI has been suggested to represent compensatory mechanisms. However, whether this alteration of the BOLD signal truly are compensatory remains to be elucidated. Moreover, no previous study has investigated the neuronal correlates of both adaptive- and stable cognitive control processes after TBI. Most previous studies have included small samples, reported imaging results uncorrected for multiple comparisons, and/or failed to adjust for known outcome moderators such as age and education.

Overall objective: Investigate the functional significance of cognitive control related BOLD alterations after TBI.

Methods: BOLD fMRI was undertaken in 62 moderate-to-severe TBI survivors, and 68 age- sex and education matched healthy controls during performance of a Not-X CPT adapted for use in a mixed block- and event related fMRI paradigm.

Research questions: Does TBI survivors demonstrate a shift toward relying more on adaptive processes within an a priori "core" cognitive control region in the MFC? Will TBI survivors exhibit increased and more widespread BOLD activation related to stable processes as a function of TOT? Will altered BOLD activations show a dose-dependent relationship to injury severity? How are BOLD alterations related to self-reported cognitive control function in every-day life situations?

Main findings: TBI survivors demonstrated increased BOLD activation related to adaptive cognitive control processes within an a priori "core" MFC region. TBI survivors exhibited increased TOT related BOLD activation related to stable cognitive control processes in the right IPL and right PFC. Increases in BOLD activations had a dose-dependent relationship with injury severity, with increased activation with more severe injury. Finally, increased BOLD activations after TBI were related to better self-reported cognitive control function in everyday-life situations.

Conclusions: The neuronal correlates of adaptive and stable cognitive control processes are differently altered after moderate-to severe TBI. Increased BOLD activation commonly observed after TBI might represent injury specific compensatory mechanisms also related to every-day life cognitive control function.

Paper IV

Title: White matter microstructure in chronic moderate-to-severe traumatic brain injury: the impact of acute phase injury related variables and associations with global outcome, performance-based and self-reported cognitive control functions.

Background: DTI is a valuable method for investigating white matter integrity after moderate-to-severe TBI. However, inconsistencies in results exist, which may partly be related to differences in study samples, types of analyses, and time-windows for investigation. It

has been suggested that taking a combined approach by using both whole-brain and ROI based methods may provide important insight into the white matter alterations after TBI. Moreover, automated or semi-automated methods may make DTI more available and relevant for large-scale studies.

Overall objective: Investigate the consequences of chronic moderate-to-severe TBI on various DTI measures such as FA, MD and tract volume by taking a combined whole-brain and automated tractography approach.

Methods: Tract based spatial statistics (TBSS) and automated tractography was performed in 49 chronic moderate-to-severe TBI survivors and 50 age- sex- and education matched healthy controls.

Research questions: What is the impact of acute phase injury, neuroimaging, and clinical variables on various DTI measures in the chronic phase? What is the association between various DTI measures and different chronic phase outcome measures including GOSE, as well as both performance-based and self-reported cognitive control function?

Main findings: Moderate-to-severe TBI was associated with widespread FA decrease, MD increase, and tract volume loss. More severe injury, as measured with clinical MRI evaluations of TAI, GCS, and length of PTA was related to more pronounced white matter microstructure alterations. Reduced white matter integrity in TBI survivors was also associated with worse global outcome, and poorer cognitive control as measured by performance-based measures. No association was found between any of the DTI measures and self-reported cognitive control function.

Conclusion: Extended knowledge about the clinical significance of various DTI measures was provided. Taking a combined whole-brain and automated tractography approach was demonstrated as valuable as the methods yielded both overlapping and complementary results. Support for a distinction between performance-based and self-reported cognitive control function was found, as DTI measures were exclusively associated with the former.

General discussion

The scientific work presented in this thesis took a multimodal approach in order to investigate subtle effects of chronic moderate-to-severe TBI. It was shown that various clinical measures of altered brain function and injury after TBI (Menon et al., 2010) were associated with self-reported cognitive and emotional function, as well as structural and functional alterations in the brain as measured by advanced MRI methods in the chronic phase. Furthermore, important new insight was gained on how both performance-based and self-reported cognitive control function in chronic moderate-to-severe TBI were related to subtle structural and functional changes in the brain. Reflecting the heterogeneity and complexity of TBI (Maas et al., 2011), different modalities each provided both unique and interrelated information that extend previous findings, and give rise to new valuable questions for further clinical- and basic TBI research. The individual results are discussed in detail in each paper (I-IV). However, in the following discussion, more emphasis will be given to understanding findings across studies, as well as going more into depth with methodological considerations and future perspectives.

Findings associated with cognitive control function in healthy participants

In Paper I we found support for a core network for cognitive control comprised by brain regions bilaterally in the insula and adjacent cortices and dorsal MFC. Additional candidates for core regions were found in the right IPL and middle temporal gyrus. The core network has previously been identified by use of a conjunction analysis across different types of tasks (Dosenbach et al., 2006). Some caution should therefore be exercised when interpreting parts of the results, as the additional candidates for core regions found in Paper I might be task specific, or contaminated with *"task impurity"* effects (Miyake & Friedman, 2012; Miyake et al., 2000). Further validation of those regions is therefore granted. The study also established that in this particular Not-X CPT task, adaptive cognitive control processes by and large were distributed in more anterior regions of the PFC as compared to stable cognitive control processes, and therefore was best explained by the cognitive demand- (Badre, 2008; Badre & D'Esposito, 2007, 2009), rather than the information cascade framework (Koechlin et al., 2003; Koechlin & Summerfield, 2007). Another novel and important finding, was that only stable cognitive control processes

were affected by TOT. This indicated that this contrast might be particularly sensitive for detecting adaptive changes in the brain, such as those related to increased *"cerebral challenge"* (Hillary et al., 2006) or cognitive fatigue (Kohl et al., 2009; Ponsford et al., 2012). Overall, findings in Paper I anchored our novel fMRI paradigm to current influential neurocognitive models of cognitive control, and established a platform for hypothesis driven investigation of TBI-related alterations in cognitive control activations.

The findings regarding associations between other measures of cognitive control function (D-KEFS TMT and BRIEF-A) and imaging parameters in healthy participants were relatively sparse. No associations between BOLD activations and self-reported cognitive control function were found. Furthermore, no statistically significant correlations between any DTI measure and self-reported cognitive control function were observed. For the performance-based measures (D-KEFS TMT), there was a negative correlation between the letter-sequencing subtest and white matter integrity in several of the major tracts. This indicates that there is some association between the efficiency of processing in the healthy brain and white matter integrity (Johansen-Berg, 2010). However, there were no statistically significant associations between white matter integrity and any of the other subtests, including the letter-number sequencing, which is the subtest placing the highest demand on cognitive control. Regrettably, due to the focused hypothesis driven approach in Paper III, we did not include an independent (in addition to the Not-X CPT) performance-based measure of cognitive control function in this study. However, in an ad-hoc analysis of this data for the purpose of this discussion (unpublished), we only found a positive correlation between the number sequencing subtest (D-KEFS TMT 2) and TOT related BOLD activation in healthy participants within the right IPL ROI (r = .303, $p < 0.05$). Notably, in this ad-hoc analysis, no statistically significant associations between TOT related activations and the D-KEFS TMT subtests were present in TBI group.

All DTI analyses were corrected for gender and age, as these factors have been shown to explain a considerable amount of the variability in white-matter integrity in healthy subjects (Johansen-Berg, 2010; Kanaan et al., 2012). In our particular study there were no gender effects with regards to FA or MD. There was, however, a strong negative correlation between age and FA and MD in all major white matter tracts. Therefore, in healthy

participants, such age effects might explain more of the variance in white-matter integrity than the normal variation in cognitive control function. Importantly, as our selection of cognitive control measures were restricted to only the D-KEFS TMT and BRIEF-A, we cannot rule out the possibility that other assessment tools would be more sensitive to detecting relationships to DTI measures. However, the observation of limited associations between DTI variables and measures of cognitive function in healthy participants is in accordance with other studies using different tests (Eikenes, Lohaugen, Brubakk, Skranes, & Haberg, 2011; Eikenes et al., 2012).

In TBI survivors there were extensive negative correlations between performance and white matter integrity on all subtests of the D-KEFS TMT, except for the one aiming to isolate motor speed. We also found several associations between BOLD activation and self-reported cognitive control function in TBI survivors. Hence, the methods and designs used in the work presented in this thesis proved to be more sensitive for detecting injury-related correlates than those related to normal variation in healthy participants.

Findings related to clinical signs of TBI

Altered brain function in the acute and sub-acute phase as for example measured by GCS score, HISS and length of PTA, as well as pathological changes detected by conventional neuroradiological methods, are important clinical signs of TBI which have shown to have prognostic value for global outcome in the chronic phase (Frey et al., 2007; Skandsen, Kvistad, et al., 2010). However, more knowledge on how these measures are associated to more subtle signs of TBI in the chronic phase is needed.

In Paper IV it was shown that TBI survivors exhibited extensive white-matter disruptions in several major tracts as measured with DTI. Reduced white matter integrity was associated with lower GCS score and longer period of PTA, confirming the link between injury severity and white matter disruption (Benson et al., 2007; Newcombe et al., 2011; Skandsen, Kvistad, et al., 2010). Moreover, there was an association between the grading of TAI, number of micro hemorrhages, and FLAIR lesion volume, as obtained from conventional early phase MRI, and later white matter integrity as measured by DTI in the chronic phase. These findings support the importance of detecting TAI lesions early

(Moen et al., 2012), as the consequences of these persist into the chronic phase. Episodes of decreased cerebral perfusion pressure (CPP) as observed in the ICU ensuing TBI had only minor effects on white matter (specific to increased MD), while increases in ICP, as well as Rotterdam CT scores reflecting mass lesions/increased ICP, did not significantly affect any DTI measures. This supports previous findings in animal models demonstrating that the integrity of axons might be relatively resistant to increases in ICP itself (Lafrenaye, McGinn, & Povlishock, 2012). Interestingly, lower FA was observed in those who had been injured in motor vehicle accidents, as compared with falls, probably reflecting the effects of generally higher acceleration-deceleration forces involved in the former type of injury (Davceva et al., 2012). The automatic tractography method demonstrated that the volume of WM tracts was significantly reduced in the chronic phase of TBI, concurring with the WM atrophy taking place during the first year after TBI (Brezova et al., 2014).

In line with previous studies, we found that survivors of moderate-to-severe TBI reported more cognitive control and emotional problems both in the clinical and sub-clinical range (Paper II, see also Paper III and IV). However, GCS score and length of PTA were not significantly associated with self-reported function within these domains. Also, despite the fact that a sub-group analysis demonstrated that TBI survivors had reduced performance-based cognitive function at 3 months after injury, the scores from these tests were not associated with the later self-reported problems in the chronic phase. This indicates that self-reported problems in the chronic phase might be better predicted by other measures. Indeed, findings in Paper II rather points at the importance of assessing factors such as the degree of early depressive symptoms and TAI lesions, as both of these were associated with more self-reported emotional and cognitive control problems. Notably, however, this relationship was stronger for later self-reported emotional- as compared to cognitive control function.

Although there was no indication of a biological gradient with regards to injury severity (Rogers & Read, 2007), the relationship to TAI indicates a biological vulnerability for developing emotional problems after TBI (Jorge & Starkstein, 2005; Rogers & Read, 2007; Warriner & Velikonja, 2006), particularly involving white matter (Maller et al., 2010; Rao et al., 2012). However, our findings also indicated that experiencing cognitive

and emotional problems in the chronic phase might be moderated by other factors. Particularly interesting, our findings pointed towards functional adaptations in the brain as a potential candidate. In Paper III we demonstrated that TBI survivors had several areas of increased BOLD activation during performance of a Not-X CPT as compared with healthy controls. This is in accordance with the majority of previous fMRI studies after TBI (Bonnelle, 2011; Christodoulou et al., 2001; Kohl et al., 2009; Maruishi et al., 2007; Raja Beharelle et al., 2011; Rasmussen et al., 2008; Scheibel et al., 2007; Scheibel et al., 2009; Sozda et al., 2011; Turner & Levine, 2008; Turner et al., 2011). Substantiating and extending previous studies (Newsome et al., 2007; Scheibel et al., 2007; Scheibel et al., 2009), it was demonstrated that these increases were related to injury severity in a dose-dependent fashion in such a way that BOLD activation increased with more severe injury. We believe that this strong link between increased BOLD activation and this early clinical sign of TBI, demonstrates that this is indeed a particularly interesting candidate for a neuronal correlate to potential functional adaptations in the brain after TBI.

In summary, findings from the scientific work included in this thesis support that various early clinical signs of TBI are related to more subtle behavioral, structural and functional changes in the chronic phase. However, not all these relationships could be interpreted in a straightforward manner, and another important focus of the work was therefore to further delineate the functional significance of alterations in the brain observed in the chronic moderate-to-severe TBI survivors, with an emphasis on cognitive control function.

Cognitive control function and compensatory mechanisms after TBI

Our studies confirmed that TBI survivors are burdened with a higher degree of every-day cognitive control problems as compared with healthy controls. This underlines the importance of further investigation of their potential underlying mechanisms. In Paper III we found evidence that increased BOLD activations after TBI were related to less self-reported problems with cognitive control in every-day settings, and might serve a compensatory role. This goes beyond previous studies in supporting the compensation hypothesis of increased BOLD activation after TBI (Kohl et al., 2009; Turner & Levine, 2008; Turner et al., 2011), as it links BOLD alterations to a measure of every-day function that is somewhat independent of fMRI task performance or highly similar neuropsychological

tasks (Isquith et al., 2013; Price et al., 2006). A particular strength of this finding was that these results were adjusted for injury severity (GCS score), fMRI task performance, and established outcome moderators such as age and education. This strengthens the interpretation that increased BOLD activation after TBI has a functional role, also independent of the aforementioned factors.

Findings from Paper II and IV raise several important questions as for how to understand potential functional compensatory mechanisms. In paper II it was demonstrated that the presence of TAI detected on conventional MRI in the sub-acute phase was related to increased self-reported emotional and cognitive control problems in the chronic phase. On the contrary, in Paper IV, no statistically significant associations were found between any DTI measure and self-reported cognitive control function. This points to a potential presence of an initial vulnerability due to TAI in the early phase, which may be moderated by adaptive functional changes, for example by those reflected in altered BOLD activations as TBI survivors progress into the chronic phase (Sanchez-Carrion, Fernandez-Espejo, et al., 2008). In Paper II an association was also found between symptoms of depression during the first year after injury and increased self-reported cognitive control problems later in the chronic phase. Also, no association between self-reported and performance-based measures of cognitive control was found in this study. As the neuronal correlates of concurrent emotional problems were not investigated in Paper III, this opens up for the possibility that the observed BOLD alterations might also be influenced by such problems, either directly, or through an interaction with self-reported cognitive control function. It has been shown previously that self-reported emotional and cognitive problems are highly interrelated (Jorge et al., 2004; Spitz, Schonberger, et al., 2013). Furthermore, the relationship between performance-based and self-reported measures of cognitive control is not fully understood (Isquith et al., 2013; Toplak et al., 2013). More research is needed to investigate these matters, however, our findings are still convincing with regards to linking increases in the BOLD signal to every-day problems experienced by TBI survivors, regardless of their phenomenological quality or category.

It has been suggested that emotional problems are mediated by cognitive control dysfunction through the development of an emotion focused coping style (Krpan et al., 2007;

Krpan et al., 2011a, 2011b). Problem-focused coping is performed with less cognitive control (i.e. automatically) in healthy controls, whereas more cognitive control (hence effort) might be needed for TBI survivors to implement the same strategies (Krpan et al., 2007). It is therefore plausible that the increased BOLD activations related to self-reported cognitive control function in Paper III represent the ability for TBI survivors to mobilize extra resources that might also benefit every-day coping. The lack of relationship between BOLD activation and self-reported cognitive control function in the healthy controls might also be explained in a similar manner, as implementation of a problem-focused coping style is believed to be relatively effortless in this group (Krpan et al., 2007).

In TBI survivors, a strong association was found between performance-based measures of cognitive control and most major white matter tracts (Paper IV). It has been proposed that self-reported cognitive control function is more related to the success of actual goal pursuit in every-day life, and that performance-based measures are rather more directly linked to the efficacy of processing (Toplak et al., 2013). Based on this, we suggest that measures of white-matter integrity is representative of the basic capacity for effective processing in the brain after TBI, whereas functional adaptations detected with fMRI may still enhance the basic processing capacity through compensatory mechanisms that are influencing (in some cases possibly normalizing) measures of every-day life function. If this is the case, disrupted white matter integrity should be positively associated to increased BOLD activation after TBI. Indirect support for this has been found in a study that demonstrated that disrupted white-matter integrity between typical task-positive regions in the brain such as the insula and MFC, lead to increased BOLD activations in DMN regions (Bonnelle et al., 2012). As our studies were conducted in parallel, we did not investigate possible interactions between white-matter integrity and BOLD activations. Future longitudinal studies investigating such structural and functional interactions, also in relation to self-reported measures of emotional and cognitive control function, might serve to further disentangle the complexity of cognitive control function and potential compensatory mechanisms after TBI.

Clinical implications

Real-life deficits experienced by chronic moderate-to-severe TBI survivors are not always easily detected by conventional neuropsychological or neurological assessments. Furthermore, although conventional imaging methods provide information instrumental for detection of TBI, findings from such methods often fall short in explaining more subtle problems that are frequently experienced by patients. DTI and BOLD fMRI are still experimental methods, not yet suitable for clinical assessment of individual TBI patients. However, as demonstrated in this thesis, the knowledge gained from such methods may still be informative for our understanding of problems exhibited by patients that we see in the clinic.

First of all, the findings presented in this thesis remind us that a broad assessment is warranted in order to optimize our assessment and understanding of our patients. Also, it was demonstrated that subtle changes in brain structure and function not necessarily detectable with conventional tools might still have an important impact on how TBI survivors cope with every-day life. A particularly interesting finding with possible clinical implications was that performance-based cognitive control function in chronic TBI was related to subtle structural changes in the brain as measured with DTI, whereas self-reported problems were exclusively related to functional adaptations as measured with fMRI. In general, knowing that self-reported cognitive control function in chronic moderate-to-severe TBI survivors is associated with functional changes in the brain, gives an important perspective when seeing patients where subtle problems are not easily explained by performance-based measures. More than that, as these functional changes were shown to play a potential compensatory role, this might indicate a potential target for neuro-rehabilitation.

Methylphenidate treatment has been demonstrated to reduce cognitive control related BOLD activation in the MFC after TBI, despite no behavioral difference (Newsome et al., 2009). Although only 4 TBI survivors were included in the treatment group in this double-blind placebo controlled study, this finding serves as a proof of principle that fMRI might serve as a proxy for measuring the effects of medical interventions after TBI. In this particular case the effect of methylphenidate might be interpreted as improved efficiency of neuronal processing, as the treatment group seemed to require less of what we hypothe-

size to be compensatory BOLD activation. Future pharmacological fMRI studies investigating both the acute effects of candidate drugs, as well as their long-term effects on functional brain reorganization, might give important insight for improving treatment strategies.

Cognitive control function is probably the most targeted cognitive domain for non-medical neuro-rehabilitation after TBI. One example of a theory driven approach to rehabilitation of cognitive control, is Goal Management Training (GMT). GMT is based on a theory of maintenance of task-sets, in order to implement higher order goal-driven behavior (Levine et al., 2011). Interestingly, this system has been hypothesized to be supported by a right lateralized fronto-thalamic-parietal brain network, that if compromised (e.g. by TBI), will lead to more cue-dependent or distracted behavior in the individual (Levine et al., 2011). Some evidence has been provided from an fMRI study that enhanced control over processing of visual stimuli in the extra striate cortex, accompanied with modulation of prefrontal activation, may be associated with successful improvement of cognitive control after completing a highly similar intervention (Chen et al., 2011). This demonstrates that neuronal correlates of altered cognitive control function due to a focused rehabilitation intervention after TBI can be detected with fMRI. Our findings related to the potential compensatory role of right fronto-parietal cognitive control regions during stable-task set maintenance over a longer period of time are in line with the hypothesized underlying brain network targeted by GMT. It would therefore be particularly interesting to investigate whether GMT or a similar intervention would affect this type of BOLD activation specifically.

Methodological considerations

TBI sample

TBI survivors in our studies were recruited from a database of patients who had initially been admitted to a level I trauma center. This sample may therefore differ from those from other studies where TBI survivors have been included from rehabilitation units or other clinics where patients seek help due to experiencing problems in the chronic phase. Also, as the HISS (Stein & Spettell, 1995) was used in the inclusion and for categorizing injury severity, several patients with GCS score of 13 were included. Although still debated, there is an increasing trend to include patients with a GCS score of 13 in the moderate TBI category, due to the higher risk of complicating factors in these patients than others classified as mild (Maas et al., 2008). All our participants also had to be eligible for fMRI, which excluded some patients with more severe disabilities. As a consequence of these factors, our final sample was relatively well functioning for a moderate-to-severe TBI sample, as reflected by the fact that they all had GOSE scores in the moderate disability to good recovery range (GOSE ≥5). The exclusion of certain premorbid conditions also limits the generalizability of our results to certain TBI survivors that are commonly treated in the clinic. In particular, the exclusion of participants with diagnosed psychiatric conditions might have influenced the results obtained in Paper II regarding self-reported emotional problems. However, a strength of our sample was that it was rather large compared with other studies using advanced MRI, spanned across a wide age range, and by and large was in concordance with gender ratios and injury mechanism distributions as reported from epidemiological studies (Tagliaferri et al., 2006).

Cognitive control- and emotional function measures

The narrow selection of cognitive control- and emotional function measures is a limitation to our work. The performance-based (D-KEFS TMT, Not-X CPT) and self-report measures of cognitive control function (BRIEF-A) were included due to their clinical use and previous findings in TBI and other neurological samples (Delis, Kaplan, & Kramer, 2001; Finnanger et al., 2013; Garcia-Molina et al., 2012; Lovstad et al., 2012; Riccio et al., 2002; Roth, 2005; Waid-Ebbs, Wen, Heaton, Donovan, & Velozo, 2012). The ASEBA-ASR (Achenbach, 2003) has not previously been used in adult TBI. However,

given its comprehensiveness, and the popularity of its pediatric equivalent, we included this tool as we saw it as a potentially good candidate for detecting subtle emotional problems often reported in chronic adult TBI (Warriner & Velikonja, 2006). Although selected based on their particular properties and our hypotheses, the narrow selection was also a consequence of practical logistic aspects. The study was logistically challenging as all participants completed a total of ~6 hours of assessment during one day (6 hours x 177 participants = 1062 hours). A considerable proportion of the TBI survivors had to travel to the assessment site, and also stay at a hotel. As we reimbursed all expenses for the participants, this also restricted our possibility of extending the assessments to several days, and therefore limited our time to include a broader assessment. Another limitation regarding the assessment tools was that not all tools were used for analyses in each individual paper. This was partly due to the fact that the papers were developed in parallel with specific hypotheses. However, as previously discussed in this thesis, many of the interpretations of our findings could benefit from including other measures, which is a lesson that provides an important direction for our future studies.

Functional MRI

As increased BOLD activations after TBI might be related to injury severity, it is important to also consider injury-related factors not associated with altered neuronal function as such. Neurovascular changes due to injury or disease may alter the neurovascular coupling, and thereby weaken the correlation between the BOLD response and neural activity. This issue should always be kept in mind when interpreting BOLD activations in general (as neurovascular coupling might be different in various brain regions), and in particular after injury or disease (Price et al., 2006). Changes in baseline cerebrovascular parameters have been demonstrated in small samples of moderate and severe TBI survivors (Hillary & Biswal, 2007; Newsome et al., 2012), and suggestions for how to control for such changes have been presented (Hillary & Biswal, 2007). However, knowledge of such factors in different types and severities of TBI is rather limited, and corrections for this is not part of standard fMRI analysis methods at the present time, and was neither performed in the work presented in this thesis. On the other hand, previous work from our research group has demonstrated that the hemodynamic response seems to be intact, at least in primary visual regions, despite of disrupted optic tracts after severe TBI (Palmer et

al., 2010). This indicates that standard fMRI methodology has some validity for studying neuroplasticity after injury.

The ability to reliably measure the BOLD response may also be influenced by signal artifacts due to larger pathological- (e.g. lesions) and postoperative changes. Lesions might also influence the quality of the spatial normalization of individual high-resolution images to standard space. Although theoretically valid (Brett, Leff, Rorden, & Ashburner, 2001), masking out lesion areas in the TBI survivors represents a challenging approach due to the heterogenic pathology also including small lesions that might attenuate on conventional imaging from the acute to the chronic phase (Moen et al., 2012). Parameters obtained from voxel-based morphometric methods have previously been used in fMRI analysis after TBI in order to adjust for anatomical differences caused by injury (Bonnelle et al., 2012). However, this method also has its limitations as the accuracy of tissue segmentation methods is far from perfect after TBI, and even varies between different anatomical regions in healthy controls (Oakes et al., 2007). In order to avoid effects of sub-optimal registration from high-resolution native- to standard space, all individual registrations in our study were manually inspected. Using a non-linear registration procedure with a warp resolution of 8 mm, we observed strikingly successful registrations for most subjects. Our experience was that the registration of EPI images to native high-resolution space was more challenging for both injured and healthy brains. This was, however, significantly improved by the custom procedure to correct for geometrical distortions in the EPI images (Holland et al., 2010). We cannot completely rule out any effects of lesions in our findings. However, the expected effect would be decreased sensitivity, as the models used assumed that there was no variability in the underlying anatomy or neuronal reorganization (Price et al., 2006). We are therefore confident that such effects would at least not represent a big risk of making type I errors.

Changes in BOLD activation may also be related to inefficient neuronal processing, due to pathophysiological mechanisms not related to functional output (behavior). However, both anatomical- as well as general pathophysiological changes would not be expected to create systematic changes in specific brain regions across different TBI samples and studies. As described in the introduction of this thesis, such TBI related BOLD alterations

have been found in typical cognitive control regions within the brain, and have also been seen to vary with transient changes in task performance and task demands (Scheibel et al., 2009; Turner et al., 2011). This was also the case in Paper III, as the anatomical areas associated with TBI related BOLD alterations were not only found in typical cognitive control areas, but also in areas overlapping with task related activations in the healthy controls (e.g. dorsolateral PFC, IPL, and MFC). The fact that similar findings have also been observed in TBI survivors presenting with only TAI and no other lesions (Maruishi et al., 2007; Raja Beharelle et al., 2011; Turner & Levine, 2008; Turner et al., 2011), further points towards that these are systematic changes not likely to be related to general non-functional mechanisms. Furthermore, demonstrating within-subject differences such as transient TOT- (Paper III) and longitudinal effects (Sanchez-Carrion, Fernandez-Espejo, et al., 2008) after TBI that are related to function, is also in support of the validity of this method. Despite its pitfalls, it can hence be argued that BOLD fMRI has great potential for providing new knowledge about the neuronal correlates of TBI, given that proper effort is put into the study design and data analysis.

The task design used in Paper I and III had the same distribution of targets (432) and non-targets (48) as well as general task demands as the CCPT (Conners et al., 2003). However, due to the fMRI adaptations, there were two main differences between the task designs. In order to allow for particular block-related analyses, task-blocks were interleaved with fixation-blocks (rest condition). This adaptation made the total length of our Not-X CPT considerably longer than the CCPT (~30 min vs. 14 min). Also, in order to allow for event-related analysis, the inter stimulus intervals (ISIs) were randomly scrambled within each block in order to sample different time points of the hemodynamic response for all trial types (Petersen & Dubis, 2012). This is different from the CCPT as ISIs in this task is stratified into different block types with identical ISIs for several consecutive trials. On the one hand, the constantly changing ISIs might explain why the mean reaction times observed in our studies are seemingly higher (~420ms vs. ~380ms) than in studies using the original paradigm (Egeland & Kovalik-Gran, 2010), as participants do not fall into a habitual state of predicting responses as easily. On the other hand, this might have potentially have helped the TBI survivors to stay more alert throughout the task, which could explain the highly similar task performance across groups. Although such potential effects

of task design are relevant for relating our findings to other behavioral studies, adaptations of the task for use in a mixed block- and event related fMRI design were inevitable. The strength of our studies was large sample sizes facilitating the internal validation of the particular task. However, further studies using the exact same Not-X CPT paradigm in other populations are needed in order to gain further external validation of the design.

Generally, the statistical thresholding of activations in our studies was more conservative than in most other comparable studies. In Paper I, a particularly conservative threshold was chosen in order to detect a true *"core network"* for cognitive control. In Paper III, a more liberal threshold was chosen, however, still more conservative than the majority of other BOLD fMRI studies after TBI. In addition, many of our analyses were adjusted for several covariates. This may explain why some of our contrasts revealed fewer differences between TBI survivors and healthy controls than what has been described in previous studies. Although a risk of making type II errors was present (Lieberman & Cunningham, 2009), we still think this conservative hypothesis driven approach extends previous studies and represents a general strength.

Diffusion tensor imaging

For our DTI analyses we applied a combined whole-brain and ROI based approach. Although the TBSS analysis is not truly a whole-brain approach since it is restricted to the most robust parts of the white-matter skeleton (S. M. Smith et al., 2006), this voxel-based method still represents a much wider approach than typical ROI-based analyses. In the tractography approach, ROIs representing particular white matter-tracts were automatically selected based on the properties of the data (Visser et al., 2011). Both approaches therefore have the advantage that no a priori placement of anatomical ROIs is necessary, thereby increasing the potential generalizability and reproducibility of the findings. That being said, the quality of all DTI measures depends on acquisition parameters, as well as decisions made along the analysis pipeline, which might affect the final results (Jones & Cercignani, 2010; Tournier et al., 2011). It is not within the scope of this thesis to address all these, however, some comments about the practical differences between the two methods with regards to our own findings are warranted.

Similar issues with regards to registration from native to standard space, as have been discussed for fMRI, are also present for the DTI analyses. For the TBSS analysis, effects of misalignment errors can also occur in the skeleton projection step. Such errors might be susceptible to microstructure pathology, and can contribute to assignment of voxels to the wrong anatomical tract, particularly in regions with complex fiber architecture (Bach et al., 2014). Despite this limitation of the method, skeletonizing is in general considered an advantage, as the principal idea is that the skeleton only represents tracts that are common to all individuals in a particular study. Similarly, as tract size and shape varies between individuals, a strong feature of the tractography method is that tracts are first determined in native space before being registered to a common space. In order to perform group comparisons, bundles of streamlines that were consistent across participants were detected by means of an automated method clustering them based on their pair-wise distances within a common space (Visser et al., 2011). Although increasing the probability of comparing the same tracts across participants, it should be acknowledged that this analysis relies on data exceeding the tracking FA threshold in each individual, and might therefore contain some deviations from the actual underlying anatomy. This highlights the obvious, but nevertheless important methodological consideration with regards to interpretation of all DTI metrics, namely that it reflects the diffusion properties of water in and around the underlying tissue, and not the tissue itself.

Although yielding similar results to some extent, TBSS seemed to be more sensitive than automated tractography, meaning that more significant findings were exhibited by means of the former method. This can partly be explained by the fact that TBSS yields voxel-based results, and is therefore also able to detect differences in parts of tracts, as compared to the tractography method that relies on average measures within whole tracts. Moreover, another limitation of the tractography method was that only certain tracts were included, whereas the whole white-matter skeleton (although thresholded) was included in the TBSS analyses.

Although MD provided similar results, for both methods, and in concordance with previous studies (Edlow & Wu, 2012), FA seemed to be the most sensitive DTI measure for describing white matter alterations after TBI. Furthermore, TBSS provided considerably

higher FA values (e.g. in the corpus callosum) than the tractography method, for both healthy controls and TBI survivors. This was probably related to the fact that the tractography method encompasses the whole tract including the more peripheral parts of the white-matter tracts, compared to the TBSS procedure, which only encompasses the central part of the tract. Although tract volume itself demonstrated more limited information with regards to its relationship to function, the fact that there were between-group volume differences, could also have affected the measurement of mean FA and MD in the tractography based analyses (Kurki et al., 2013). Taken together, both methods revealed similar results to a large extent, but did also provide unique information, partly reflecting the strengths and limitations of each approach. This supports the use of a combined approach when investigating white matter integrity and its clinical relevance after TBI (Leunissen et al., 2014; Spitz, Maller, O'Sullivan, et al., 2013).

A limitation in Paper IV was that a considerable proportion of the original data had to be discarded, mainly due to vibration artifacts caused by problems with the scanner. As described in the methods section this left only 49 TBI datasets available for complete DTI analysis. Our approach to handling artifacts was rather conservative, as participants were excluded from analysis even in cases where only a few slices were affected. This was important, as removing only grossly affected slices may potentially introduce a positive bias in scalar calculations (Ling et al., 2012). The samples for some of the subgroup analyses were also limited by the availability of certain variables. For example, only 21 TBI survivors were admitted to the ICU, and ICP and CPP data was only obtained from 16 subjects. However, we still think the results obtained from these analyses are informative, in particular for planning future studies, as there is a relative paucity of studies that have investigated these variables in relation to DTI measures in the chronic phase.

Future perspectives and conclusion

The scientific work presented in this thesis was to a large degree performed in parallel, but with different, specific research questions. Each study therefore contributed with new knowledge from different modalities laying the groundwork for new research questions, some of which has already been touched upon in this thesis.

One focus for our future work will be to combine the knowledge from the individual papers in order to further delineate the neuronal and behavioral effects of moderate-to-severe TBI. This will for example involve a multimodal approach combining DTI and fMRI for hypothesis driven investigation of cognitive control networks and function. This will also include investigation of the intrinsic properties of such networks by use of resting state fMRI, which was acquired in parallel to the data included in this thesis.

As all fMRI and DTI analyses included in this thesis were cross-sectional and based on investigations of chronic TBI, several questions regarding the trajectory of brain alterations from the sub-acute to the chronic phase still remains to be investigated. I am currently involved in a project at the University of California Los Angeles (UCLA) where we are investigating such longitudinal changes in children and adolescents with moderate-to-severe TBI (primary investigator: Professor Robert Asarnow). A continuation of this project is also to investigate the utility of fMRI as a tool for detecting the effects of a clinical intervention (cognitive training in combination with a novel drug) in the chronic phase in a subgroup of these patients. Investigating how alterations in BOLD activation may be affected in such an experimental design can provide important insight for further development of targeted treatment interventions for this patient group.

The work of this thesis includes novel methods and research designs for investigation of both functional and structural brain alterations due to brain injury. To further develop and validate our approach, a parallel line of our research is related to applying similar methodology in order to investigate brain alterations caused by a different etiology than TBI. Parallel to the work in this thesis, we therefore collected the same type of data from young adults that were prematurely born with a very low birth weight (VLBW). Brain

injury occurs in 20-50% of children born with VLBW. Perinatal brain injury may in some instances have a biological advantage due to a high level of neuroplasticity in the newborn. However, other evidence points towards less potential for functional compensation in young brains, due to the fact that many cognitive functions have yet to be developed, hence also causing accumulative developmental problems due to the initial injury. Despite the different etiologies of perinatal and adult (traumatic) brain injury, there are several similarities with regard to the cognitive and emotional problems experienced (Finnanger et al., 2013; Lohaugen et al., 2010; Lund et al., 2012) (and Paper II). Another similarity is that injuries in white-matter are particularly prevalent (Eikenes et al., 2011; Skandsen, Kvistad, et al., 2010). Given that cognitive control function relies on widespread brain networks and the connectivity between these, both groups therefore serve as particularly interesting models for investigating reorganization in these systems (Skranes et al., 2009) (and Paper IV). Based on our work in healthy controls and adult TBI presented in this thesis, work is now in progress to analyze data to investigate both structural and functional brain alterations in young adults born with VLBW.

In conclusion, the work presented in this thesis represents a step towards increased understanding of functional and structural changes in the brain after moderate-to-severe TBI, and their relation to injury-related variables and functional measures known to be important for outcome. Just as important is that this work has provided an opportunity for our research group to gain further experience on running a truly multidisciplinary research program on TBI. I have been lucky to be part of this experience, where I have had the chance to learn from the best. Future work, some of which has been described above will clearly benefit from this experience. The work presented in this thesis therefore only represents the beginning of my research career, and an endeavor towards new scientific discoveries and adventures in collaboration with the fantastic team of researchers and clinicians that I have had the pleasure of working with the last few years.

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Paper I-IV

Paper I

The Functional Topography and Temporal Dynamics of Overlapping and Distinct Brain Activations for Adaptive Task Control and Stable Task-set Maintenance during Performance of an fMRI-adapted Clinical Continuous Performance Test

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Abstract

■ Previous studies have demonstrated that stable and adaptive attention processes are mediated by partly overlapping, but distinct, brain areas. Dorsal medial PFC and anterior insula may form a "core network" for attention control, which is believed to operate on both temporal scales. However, both the existence of such a network as well as the unique functional topography for adaptive and stable attention processes is still highly debated. In this study, 87 healthy participants performed a clinical not-X continuous performance test optimized for use in a mixed block and event-related fMRI design. We observed overlapping activations related to stable and adaptive attention processes in dorsal medial PFC and anterior insula/adjacent cortex as well as in the right inferior parietal lobe and middle temporal gyrus. We also identified areas of activations uniquely related to stable and adaptive attention processes in widespread cortical, cerebellar, and subcortical areas. Interestingly, the functional topography within the PFC indicated a rostro-caudal distribution of adaptive, relative to stable, attention processes. There was also evidence for a time-on-task effect for activations related to stable, but not adaptive, attention processes. Our results provide further evidence for a "core network" for attention control that is accompanied by unique areas of activation involved in domain-specific processes operating on different temporal scales. In addition, our results give new insights into the functional topography of stable and adaptive attention processes and their temporal dynamics in the context of an extensively used clinical attention test. ■

INTRODUCTION

A considerable body of evidence suggests that attention is supported by widespread brain areas located in cortical (Ogg et al., 2008; Fan, McCandliss, Fossella, Flombaum, & Posner, 2005), subcortical (Balleine, Delgado, & Hikosaka, 2007; Heyder, Suchan, & Daum, 2004), and cerebellar (Ghajar & Ivry, 2009; Dosenbach et al., 2007) regions, which in turn are organized into neural networks supporting different attentional processes (Dosenbach et al., 2007; Posner & Rothbart, 2007; Raz & Buhle, 2006; Corbetta & Shulman, 2002). Some properties of attention are considered to be stable ongoing processes related to functions such as sustained attention (Ogg et al., 2008) and task-set maintenance (Altmann & Gray, 2002). Other aspects of attention are thought to be related to rapid adaptive processes such as conflict processing (Desmet, Fias, Hartstra, & Brass, 2011), error processing (Mathiak et al., 2011; Nee, Kastner, & Brown, 2011), and successful response inhibition (Boehler, Appelbaum, Krebs, Hopf, & Woldorff, 2010). Stable and adaptive attention processes are subserved by partly overlapping, but distinct, brain networks (Wilk, Ezekiel, & Morton, 2012; Dosenbach, Fair, Cohen, Schlaggar, & Petersen, 2008; Dosenbach et al., 2006, 2007; Seeley et al., 2007). Overlapping regions have been suggested to include the dorsal medial PFC as well as the insula and adjacent prefrontal regions, which may form a "core network" for task control comprising both adaptive and stable processes (Dosenbach et al., 2006). These regions are among the most commonly reported brain areas in imaging studies across a wide variety of tasks (Nelson et al., 2010), further underlining their potential role as core task regions. However, whether insula and dorsal medial PFC play a substantial role for stable task maintenance is highly debated. Other studies imply that these structures are primarily involved in a salience network that works

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on a more rapid time scale (Wilk et al., 2012; Menon & Uddin, 2010; Seeley et al., 2007). Also, despite several informative studies, the functional topography of the unique adaptive task control and stable task-set maintenance activations has yet to be elucidated.

The PFC has drawn particular interest from researchers investigating the functional topography of attentional control. Accumulated evidence supports a rostro-caudal distribution of control functions within PFC (Kim, Johnson, Cilles, & Gold, 2011; Badre & D'Esposito, 2007, 2009; Venkatraman, Rosati, Taren, & Huettel, 2009; Badre, 2008; Koechlin & Summerfield, 2007; Koechlin, Ody, & Kouneiher, 2003). However, controversy exists regarding which factors govern this distribution (Badre, 2008). One distinction between two acknowledged frameworks originating from the rostro-caudal perspective is to what degree they emphasize the temporal dimension of attentional control. The cognitive demand framework states that control functions should be located more rostral within PFC as control demands are increased, that is, by increasing task complexity or abstractness (Badre & D'Esposito, 2007, 2009; Badre, 2008). Accordingly, processes with lower cognitive demands, such as those more closely related to motor responses, should be located in more caudal regions (Kim et al., 2011; Venkatraman et al., 2009). In contrast, the episodic and contextual control framework (Koechlin & Summerfield, 2007; Koechlin et al., 2003) suggests that processing relying on immediate stimuli-related cues (contextual control) should be located caudally relative to processes based on cues more distant in time that have to be maintained throughout the task (episodic control). Although these two different frameworks both originate from the rostro-caudal perspective and overlap to a certain degree on a theoretical level, they provide different predictions for specific task paradigms. Determining whether the distribution of stable task-set maintenance and adaptive task control within PFC is best accommodated by the control demand or the episodic and contextual control framework may yield valuable information for delineating the functional organization of attentional control.

Another temporal aspect of attention is the effect of time-on-task (TOT). Typical TOT effects are fatigue and decrements in behavioral performance (Langner, Steinborn, Chatterjee, Sturm, & Willmes, 2010; Lim et al., 2010; Conners, Epstein, Angold, & Klaric, 2003). Self-reported levels of fatigue have been found to correlate with increased activity in typical task-positive brain regions and decreased activity in "default mode network" (DMN) or task-negative regions (Kelly, Uddin, Biswal, Castellanos, & Milham, 2008; Cook, O'Connor, Lange, & Steffener, 2007; Weissman, Roberts, Visscher, & Woldorff, 2006; Fox et al., 2005). However, other studies report both decreased and increased activations of both task-positive and task-negative regions using different types of tasks and with or without accompanying behavioral or state changes (Lim et al., 2010; Tana, Montin, Cerutti, & Bianchi, 2010; Cook et al., 2007; Butti et al., 2006). In context of these results, it is worth mentioning that limitations of most previous studies of TOT effects are relatively few participants, the use of predefined ROIs, and liberal statistical thresholding. Also, there are currently no published studies that have investigated the effects of TOT for both stable task-set maintenance and adaptive task control in the same study.

An excellent task for investigating the temporal dynamics of stable task-set maintenance and adaptive task control is the continuous performance test (CPT; Riccio, Reynolds, Lowe, & Moore, 2002; Riccio & Reynolds, 2001). The main feature of CPTs is that participants are asked to detect low-frequency target stimuli within a consecutive presentation of nontargets in a task that typically lasts for >10 min. The CPT is among the top five most frequently used test paradigms for assessment of attention in the U.S. and Canada (Rabin, Barr, & Burton, 2005). Among the most extensively used CPTs for assessment of dysfunctions of attention is the Conners' CPT (Conners et al., 2003). Conners' CPT falls within the category of CPTs, where participants are asked to respond to nontargets (letters from A–Z) and withhold their response to targets (the letter X), also commonly described as a not-X CPT (Riccio et al., 2002). Moreover, a previous proof of concept study using a block fMRI design has demonstrated that brain regions typically involved in attention function are reliably activated during this task (Ogg et al., 2008).

For this study, an in-house version of a not-X CPT, optimized for use in a mixed block and event-related fMRI design, was used to determine common and distinct brain areas related to stable task-set maintenance and adaptive task control. On the basis of previous research, the existence of a core network for attentional control consisting of anterior insular and dorso-medial prefrontal brain regions was investigated. In addition, domain-specific not-X CPT activations within cortical, cerebellar, and subcortical areas uniquely related to stable and adaptive processes were mapped. Extending previous research, this study aimed to answer two novel research questions, namely (1) how areas related to stable versus adaptive task processing are organized within PFC and (2) how stable task-set maintenance and adaptive task control are affected by TOT. In detail, for research question 1, two different frameworks giving opposite predictions for our particular not-X CPT were tested. The episodic and contextual control framework (Koechlin & Summerfield, 2007; Koechlin et al., 2003) made the prediction that stable task-set maintenance (episodic control) would be located rostral, relative to adaptive task control (contextual control). Contrary to this, the cognitive demand framework (Badre & D'Esposito, 2007, 2009; Badre, 2008) predicted that stable task-set maintenance (low complexity: task set dominated by 90% simple motor responses) would be located caudal, relative to adaptive task control (higher complexity: decision making/response inhibition). Finally, for research question 2, the prediction was that adaptive task control and stable task-set maintenance would be affected differently as an effect of TOT, something that would provide further evidence for dissociation between the proposed networks.

METHODS

Participants

One hundred three healthy participants were recruited through a cohort database from a clinical study as well as advertisements at a wide variety of workplaces in Trondheim, Norway. Volunteers were financially reimbursed with NOK 1000 for their participation. Inclusion criteria were absence of diagnosed neurological or psychiatric condition, ongoing substance abuse, previous head injury, ability to cooperate during fMRI testing, and fluency in the Norwegian language. Number of years of completed formal education was assessed using a self-report form, which was quality assured through a short interview performed by the experimenters. Of the 103 participants first enrolled, 16 were excluded from further analysis: two because of diagnosed psychiatric or neurological condition uncovered in the initial screening interview at site, one because of excessive fMRI artifacts, eight because of technical problems (missing data or aborted scans), and five because of excessive movement artifacts (defined as mean relative displacement > 0.5 mm in any direction), leaving 87 participants (34 women) ranging in age from 14.5 to 64.5 years, with a median age of 31.4 years in the final sample. The participants had between 9 and 18 years of completed formal education with a median of 12 years. All participants (and their parents if the participant was under 18 years old) gave written informed consent. The study protocol was approved by the National Ethics Committee in Norway and adhered to the Helsinki Declaration.

Design of fMRI Task

The fMRI attention task was an in-house developed variant of the not-X CPT, inspired by the Conners' CPT (Conners et al., 2003), and modified to allow for both block and event-related fMRI analysis, giving the opportunity to investigate both adaptive task control (event-related) and stable task-set maintenance (block-related). Targets were randomly chosen from all letters other than X (A–Z), whereas the nontarget was the letter X. The task was presented in two consecutive runs, each lasting ~15 min. Each run consisted of 240 stimuli with 24 (10%) of them being nontargets. Each stimulus was presented on the screen for 250 msec. The stimuli within run 1 were split into 16 blocks of different types (containing zero, one, two, or three nontarget/s). Block types were presented pseudorandomly with the constraint that no more than two consecutive blocks of the same type could be presented. Inside each block, which was composed of 15 stimuli, targets and nontargets were randomly scrambled, not allowing two consecutive nontargets to occur or nontargets to be the first stimulus of any block. The ISIs were randomly scrambled within each block (with five ISIs of 1 sec, five ISIs of 2 sec, and five ISIs of 4 sec) to ensure sampling at different time points of the hemodynamic response curve for all trial types, allowing for event-related fMRI analysis (Petersen & Dubis, 2012). ISIs preceding nontargets (X) were evenly distributed (eight of 1 sec, eight of 2 sec, and eight of 4 sec). Interblock intervals (IBIs) were randomly scrambled within the run (with six IBIs of 14 sec, five IBIs of 16 sec, and five IBIs of 18 sec). Run 2 was an inverse presentation of run 1, meaning that the same blocks with the same stimuli, stimuli order, ISIs, and IBIs as in run 1 were presented in the opposite order, thereby counterbalancing possible order effects after the two runs were collapsed. The total number of stimuli of both runs combined was 480 with 48 (10%) nontargets elements. Implementation of the CPT was done in MATLAB 2008 (The MathWorks, Inc., Natick, MA), using the functions randperm() and rand() for the generation of pseudorandom permutations and values.

CPT Paradigm Procedure

Participants were instructed to press a response button as fast as possible whenever a letter appeared on the screen, except for the letter "X." They were also instructed to strive to make as few errors as possible. All participants completed a training session using a standard desktop computer, and the experimenter made sure that the participant performed the test as intended before entering the scanner room. Instructions were also repeated before each fMRI run during scanning. Stimulus presentation and timing of stimuli were achieved using E-prime 1.2 (Psychology Software Tools, Pittsburgh, PA). The paradigm was presented using MRI-compatible video-goggles (VisualSystem, Nordic NeuroLab, Bergen, Norway) for 41 participants. Because of technical problems with the goggles, an MRI-compatible monitor (Siemens AG, Erlangen, Germany) and a head-coil mounted mirror were used for the remaining 46 participants. The video goggles and monitor were tested for differences in timing of stimuli presentation using photodiodes and an oscilloscope. The test revealed that the monitor had a ~60-msec stimulus onset delay relative to the video goggles. This was adjusted for during postprocessing of response and fMRI data. Responses were measured using fiberoptic response grips (ResponseGrip, Nordic NeuroLab, Bergen, Norway) and stored in log files by utilizing a custom-made Python-based log script that interacted with the E-Prime software.

MRI Scanning

Scanning was performed on a 3-T Siemens Trio scanner with a 12-channel head matrix coil (Siemens AG, Erlangen, Germany). Foam pads were used to minimize head motion. In both fMRI runs, 380 T2*-weighted BOLD sensitive images were acquired using an EPI pulse sequence (repetition time [TR] = 2400 msec, echo time [TE] = 35 msec, field of view [FOV] = 244 mm, slice thickness = 3.0 mm, slice number = 40, matrix = 80 × 80, giving an in-plane resolution of 3 × 3 mm) with slices positioned transversal along the A–P axis. For anatomical reference, a T1-weighted

3-D volume was acquired with a magnetization prepared rapid gradient echo sequence (TR = 2300 msec, TE = 2.88 msec, FOV = 256 mm, slice thickness = 1.20 mm, matrix 256 × 256, giving an in-plane resolution of 1.0 × 1.0 mm). In addition, two spin echo volumes were sampled to be used for distortion correction (Holland, Kuperman, & Dale, 2010): one acquired in the A–P direction, and the other, in P–A. Apart from different phase encoding directions, the spin echo protocols were identical (TR = 2010 msec, TE = 35 msec, FOV = 244 mm, slice thickness = 3 mm, matrix 80 × 80, giving an in-plane resolution of 3 × 3 mm).

Analysis of Behavioral Data

Calculation of CPT Performance Measures

The following measures were computed based on the behavioral raw data: omission errors, the number of targets a participant failed to respond to; commission errors, the number of nontargets a participant mistakenly responded to; hit RT, the mean RT of correct responses; and hit RT standard error of the mean (*SEM*), the standard error of the mean of hit RT. In addition, measures derived from signal detection theory (Green & Swets, 1966) were computed, namely detectability (d') and response style (β). Detectability (d') represents the relation between the signal (targets) and noise (nontargets) distribution and is considered to be a good measure of the discriminative power of an individual. The rationale behind this measure is that a participant with a good ability to distinguish and detect target and nontarget stimuli will have large differences between the signal and noise distributions, whereas an individual with decreased ability to distinguish and detect target and nontarget stimuli will have small differences. Detectability (d') was computed by applying the equation $d' = z_H - z_{FA}$ where H represented hits and FA represented false alarms, and the functions z_H and z_{FA} represented the inverse of the cumulative normal distribution of the hit rate and the false alarm rate. Hits were defined as correct responses to targets, whereas false alarms were defined as erroneous responses to nontargets (commission errors). Hit rate was found by dividing the actual number of hits in the CPT task by the number of possible hits (432), and false alarm rate was calculated by dividing number of false alarms by the number of possible false alarms (48), respectively. Response style (β) is a measure representing response tendency, which is considered related to how risky an individual is when responding to stimuli on a CPT. High β value reflects a cautious response style with emphasis on avoiding commission errors, whereas a low β value reflects a risky response style with more emphasis on avoiding omission errors. Response style (β) was computed in the following manner: $C = -0.5(z_H - z_{FA})$, $\ln \beta = d' \times C$, $\beta = \exp(\ln \beta)$. For participants who had hit rates or false alarm rates of 1, d' and β were calculated using a maximum value for hit rate to $(N - 1)/N$, which is a commonly used approximation in signal detection theory. Furthermore, if participants had a false alarm rate of 0, β was calculated using a minimum false alarm rate of $1/N$.

Statistical Analyses

All behavioral data were analyzed with IBM SPSS 19.0. Means, standard deviations (*SD*), and confidence intervals (CI) for the overall means of not-X CPT measures were calculated. To investigate TOT effects, the CPT was divided into four equally long time epochs after collapsing run 1 and run 2. Each of the six CPT measures was included in separate repeated-measures ANOVAs with time epoch (1, 2, 3, and 4) as a fixed factor. Mauchley's test was used to investigate the assumption of sphericity of the data, and a Greenhouse–Geisser correction was utilized if this assumption was violated. Subsequent polynomial trend analyses were performed to explore the nature of significant effects from the repeated-measures ANOVAs. For all tests, the acceptance level for significant results was set to $p < .05$, and a Bonferroni correction giving a critical $p > .0083$ (Bonferroni corrected, $\alpha/n = 0.05/6 = 0.0083$) was applied to control for multiple statistical tests where appropriate (univariate ANOVAs). Eta squared (η^2) was calculated as a measure of effect size.

Analysis of MRI Data

Preprocessing

All fMRI data were processed utilizing the FMRIB's Software Library (FSL) toolbox version 4.1 (FMRIB Centre, Oxford, United Kingdom) and a custom algorithm for correction of susceptibility artifacts (Holland et al., 2010). After nonbrain removal using the Brain Extraction Tool (Smith, 2002), MCFLIRT (Jenkinson, Bannister, Brady, & Smith, 2002) was applied for affine motion correction. Correction of inhomogeneous static magnetic field-induced distortion was done by calculating displacement fields using spin-echo EPI sequences with opposite phase encoding, which was then applied for correction of the gradient EPI sequences (Holland et al., 2010). A Gaussian kernel of 6-mm FWHM was applied for spatial smoothing. Grand-mean intensity normalization of the entire 4-D data set was performed, and high-pass temporal filtering was set to 50 sec for the block-related analysis and 25 sec for the event-related analysis. Linear registration (7 *df*) using FLIRT (Jenkinson et al., 2002; Jenkinson & Smith, 2001) was performed to register each individual's fMRI data to their own high-resolution structural image. Nonlinear registration (12 *df*) from high-resolution structural to MNI152 1-mm standard template using an 8-mm warp resolution was done by utilizing FNIRT (Anderson, Jenkinson, & Smith, 2007a, 2007b). BOLD activity related to task blocks and individual trials was modeled using a general linear model (GLM). The hemodynamic response function was convolved using a Gamma

variate, which is a normalization of the probability density function of the Gamma function (phase = 0 sec, *SD* = 3 sec, mean lag = 6 sec).

Main Contrasts

For each run, the following main contrasts were performed for all participants: (1) stable task-set maintenance (task block > fixation block) and (2) task-negative activation (fixation block > task block) for block analysis and (3) conflict processing (nontargets > targets), (4) hits (targets > nontargets), (5) error processing (commission errors > successful inhibition), and (6) successful inhibition (successful inhibition > commission errors) for event-related analysis (adaptive task control). Both runs were then combined in a higher level analysis for each individual using a fixed effects model. Finally, a mixed effects model was applied to create group average statistic images, which were corrected for multiple comparisons using GRF-theory-based maximum height thresholding with $p < 10^{-13}$ (voxel corrected) for contrasts 1–4. Because of very robust activations, this stringent threshold was necessary to generate meaningful statistical parametric maps for interpretation. For the error processing and successful inhibition contrast, a more standard GRF-theory-based maximum height threshold of $p < .01$ (voxel corrected) was applied because of the lower number of trials included in this contrast as compared with the other two. Omission errors were not included in any separate contrasts because of low statistical power because of a large number of participants with very few or no such errors (floor effect). However, for exploratory purposes, omission errors were investigated in a subsequent regression model (see below). A conjunction analysis was performed to investigate brain areas that were activated above the statistical threshold ($p < 10^{-13}$) in both adaptive task control (conflict processing) and stable task maintenance and therefore would represent a "core network." Error processing was not included in this formalized conjunction analysis because of the considerable difference in statistical threshold for this contrast compared with the other two. However, all contrasts were also evaluated more qualitatively with regard to overlap in standard Montreal Neurological Institute (MNI) space.

TOT Effects

To investigate TOT effects, two separate repeated-measures GLMs were applied. In the first GLM, we investigated the TOT effect with the stable task maintenance contrast as a dependent variable and time epoch (1, 2, 3, and 4) as a fixed factor. In the second GLM, the same procedure was performed for investigating the TOT effect for adaptive task control by using the conflict processing contrast as the dependent variable. Significant main effects were followed up by individual contrasts comparing the first time epoch (epoch 1) to each of the subsequent ones (2, 3, and 4; progressively more distant). Statistical images were thresholded using GRF-theory-based maximum height thresholding with $p < .05$ (voxel corrected).

Correlations with CPT Measures

Positive and negative neural correlates to the measures of attention (except commission errors, which were included in a separate contrast) computed from the behavioral data were investigated by including hit RT, hit RT *SEM*, omission errors, detectability (d'), and response style (β) in separate regression models for the two the main contrasts, stable task maintenance and conflict processing (adaptive task control). The final statistical images from the correlation analyses were thresholded using GRF-theory-based maximum height thresholding with $p < .05$ (voxel corrected).

Cluster Algorithm and Presentation of Imaging Data

For all contrasts, a cluster algorithm was applied to obtain the main peak *Z* values and size of clusters (number of voxels) in 1 × 1 × 1 mm MNI space. Only clusters consisting of >40 voxels were included. The Harvard Oxford cortical and subcortical structural brain atlases as incorporated in the FSL software and visual inspection were used to denote relevant anatomical structures.

RESULTS

Behavioral Results

Overall means, *SD*, and 95% CI for the different not-X CPT measures are presented in Table 1.

TOT Effects

Mauchley's test indicated that the assumption of sphericity was violated for the main effect of hit RT, hit RT *SEM*, omission errors, and response style (β). For these variables, the degrees of freedom were corrected using the

Table 1. Overall Not-X CPT Performance Data

	N	*Mean*	*SD*	*95% CI of the Mean*
Hit RT (msec)	87	419.79	54.48	[408.18, 431.41]
Hit RT *SEM*	87	6.31	2.44	[5.79, 6.83]
Omission errors	87	7.69	13.49	[4.81, 10.57]
Commission errors	87	15.57	8.12	[13.84, 17.30]
Detectability (d')	87	2.92	0.79	[2.75, 3.09]
Response style (β)	87	0.12	0.17	[0.09, 0.16]

Greenhouse–Geisser estimates of sphericity ($\varepsilon = 0.657$ for the main effect of hit RT, $\varepsilon = 0.684$ for the main effect of hit RT *SEM*, $\varepsilon = 0.621$ for the main effect of omission errors, and $\varepsilon = 0.675$ for the main effect of response style). All effects are reported as significant at $p < .05$ (Bonferroni corrected, $\alpha/n = 0.05/6 = 0.0083$). Results from separate one-way repeated-measures ANOVAs showed a main effect of TOT for hit RT, $F(1.971, 85.029) = 12.3$, $p = .000$, $\eta^2 = 0.125$, omission errors, $F(1.863, 85.137) = 9.309$, $p = .000$, $\eta^2 = 0.098$, detectability, $F(3, 84) = 6.104$, $p = .001$, $\eta^2 = 0.066$, and response style, $F(2.024, 84.976) = 6.344$, $p = .002$, $\eta^2 = 0.069$. Statistically significant results are presented in Figure 1. There were no significant main effects of TOT for hit RT *SEM*, $F(2.053, 84.947) = 1.954$, $p = .144$, $\eta^2 = 0.022$, or commission errors, $F(3, 84) = 3.187$, $p = .024$. A polynomial trend analysis indicated that there was a significant linear increase in hit RT with TOT, $F(1, 86) = 16.004$, $p = .000$, $\eta^2 = 0.157$. Furthermore, there was a significant cubic trend, $F(1, 86) = 13.133$, $p = .0000$, $\eta^2 = 0.132$, indicating that hit RT first increased from block 1 to 2, then slightly decreased from block 2 to 3, and then increased from block 3 to 4 (Figure 1). There was also a significant linear increase in omission errors with TOT, $F(1, 86) = 13.271$, $p = .0000$, $\eta^2 = 0.134$, and response style, $F(1, 86) = 9.614$, $p = .003$, $\eta^2 = 0.101$, as well as a linear decrease in detectability score, $F(1, 86) = 10.605$, $p = .002$, $\eta^2 = 0.110$. The detectability score also demonstrated a significant cubic trend, indicating that detectability was relatively stable from block 1 to 2, decreased substantially from block 2 to 3, and then slightly increased from block 3 to 4 (Figure 1).

Imaging Results

Activations for Stable Task-set Maintenance and Adaptive Task Control

Brain activation related to performance of the not-X CPT task was found in frontal, parietal, subcortical, and cerebellar regions of the brain. The conjunction analysis revealed overlapping areas of activation between stable task-set maintenance and adaptive task control in insular and adjacent cortices bilaterally, paracingulate gyrus, right inferior parietal cortex, and right middle temporal gyrus (Figure 2, Table 4). Nonoverlapping activity unique for stable task-set maintenance was found in the dorsocaudal parts of the medial frontal cortex (MFC), left precentral gyrus, and dorsal striatum (bilaterally in the caudate and left putamen), in addition to the right thalamus and cerebellum (Table 2, Figure 2). There were also unique activations for adaptive task control. Conflict processing showed unique activity in more anterior parts of the MFC (relative to stable task-set maintenance), left precentral gyrus, posterior cingulate, right thalamus, and left caudate (Table 3, Figure 2). Error processing revealed unique activations within the MFC, right posterior insula, right precentral gyrus, left postcentral gyrus, and bilaterally within the temporal lobes and parietal regions (including the precuneus) as well as the lingual gyrus (Tables 4 and 5, Figure 3). Successful inhibition had unique activations in the frontal poles as well as in areas bilaterally in the occipital lobe (Table 5). Within the adaptive task control network, there was an overlap in activation between conflict processing and error processing in the anterior

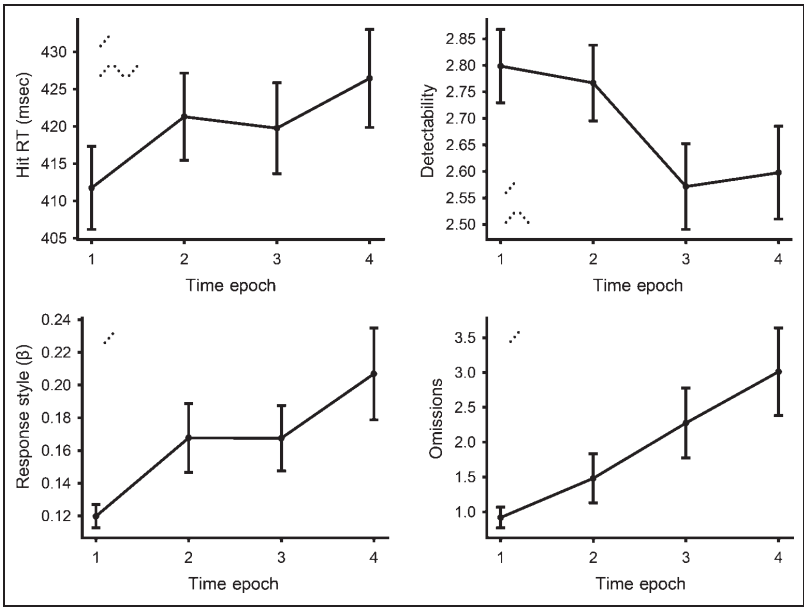

Figure 1. TOT effects for not-X CPT performance. The graphs show the development of CPT performance (group means ± standard error) with TOT. Only CPT measures with a statistically significant ($p < .05$, Bonferroni corrected) effect of TOT are included. Results from a polynomial trend analysis ($p < .05$) are indicated by ⋰ = linear trend, ⋰⋱ = quadratic trend, ⋰⋱⋰ = cubic trend.

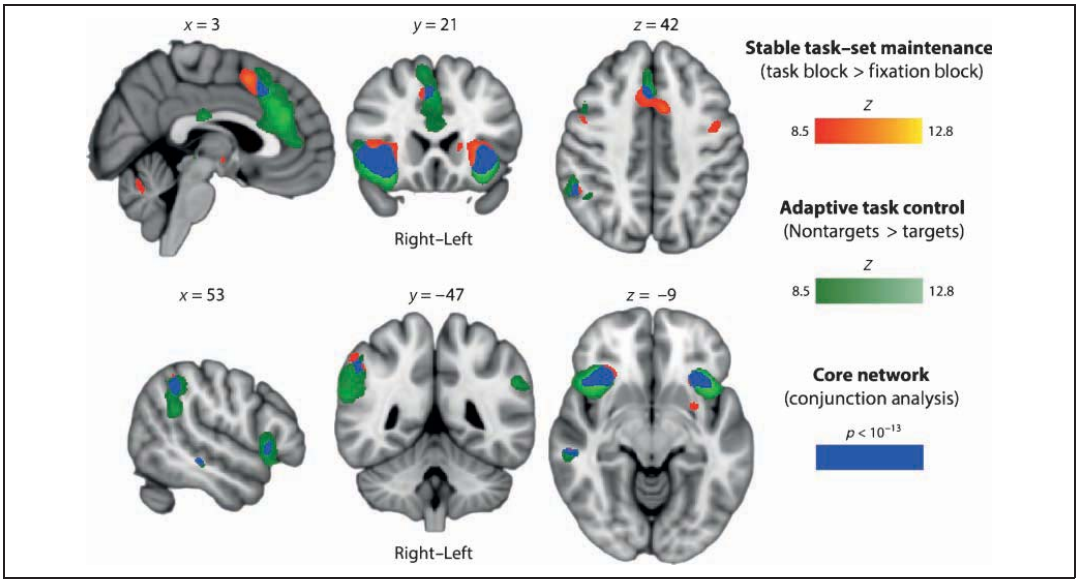

Figure 2. Stable task-set maintenance, adaptive task control, and core network for cognitive control. The figure shows SPMs for the contrasts in stable task-set maintenance (task block > fixation block, $p < 10^{-13}$, voxel corrected) and adaptive task control (conflict processing, nontargets > Targets, $p < 10^{-13}$, voxel corrected) and a conjunction analysis indicating areas that are activated above the statistical threshold for both adaptive task control and stable task-set maintenance ($p < 10^{-13}$, voxel corrected). Targets = all letters except the letter X. Nontargets = the letter X. Results are presented on a 1 × 1 × 1 mm MNI template.

cingulate gyrus and between conflict processing and successful inhibition in the right inferior parietal lobe (IPL). Finally, there was task-negative activation (fixation block > task block) in parietal (including the precuneus and posterior cingulate cortex [PCC]) and occipital regions (Table 2, Figure 3) as well as activation related to hits (targets > nontargets) in the left precentral gyrus (Table 3).

TOT Effects

Repeated-measures GLMs revealed a significant main effect of TOT for stable task-set maintenance, but no such effect for adaptive task control (conflict processing). For stable task-set maintenance, follow-up analyses showed increased activation in the left frontal pole and bilaterally in the occipital poles in time epochs 3 and 4 relative to epoch 1 (Table 6, Figure 3). The activations in the occipital poles were clearly overlapping with task-negative areas described in the previous section (Figure 3). For epoch 4 relative to epoch 1, there was also increased activation in other frontal, parietal, temporal, and occipital areas that, to some degree, overlapped or were adjacent to the task-negative network (Table 6, Figure 3). We also found decreased activity as an effect of TOT from time epoch 1 to epoch 4. Areas of decreased activations were located to frontal, parietal, and temporal brain regions in addition to the cerebellum and were, to a large degree, overlapping with the task-positive regions described in the previous section (Table 6, Figure 3).

Correlation Analyses

There was a positive correlation between brain activation related to adaptive task control (conflict processing) and detectability (d'), with main peak in the juxtapositional (former SMA) cortex (main peak MNI coordinates: $x = -4$, $y = -6$, $z = 55$, size = 83 voxels, $Z = 4.9$). None of the other CPT measures correlated with brain activation in neither the adaptive task control (conflict processing) nor stable task maintenance contrasts.

DISCUSSION

The present fMRI study investigating the neural underpinnings of not-X CPT performance revealed three main findings: (1) overlapping as well as nonoverlapping brain activation in cortical, subcortical, and cerebellar regions related to stable task-set maintenance and adaptive task control (including conflict processing, error processing, and successful inhibition); (2) activations within the frontal cortex were by and large localized to more rostral regions during adaptive task control as compared with stable task-set maintenance; and (3) brain activity decreased in task-positive and increased in task-negative/

Table 2. Peak Activations across Whole Brain for Stable Task Control (Task Block vs. Fixation Block)

				Coordinates for Peak Activation (MNI)		
Anatomical Region	*R/L*	*Size (Number of Voxels)*	*Z*	*x*	*y*	*z*
Stable Task-set Maintenance						
Frontal orbital cortex	R	6,212	10.8	30	26	−3
Insular cortex	L	5,437	10.5	−28	24	−3
Paracingulate gyrus	R	4,450	10.7	1	10	50
Precentral gyrus	L	1,086	9.56	−44	−2	35
Supramarginal gyrus, posterior division	R	533	9.01	53	−45	42
Cerebellum	R	494	9.33	9	−75	−20
Precentral gyrus	R	209	8.99	45	1	38
Middle temporal gyrus	R	195	9.04	56	−28	−11
Putamen	L	180	8.97	−29	3	−8
Caudate	R	171	9.21	8	4	14
Thalamus	R	64	8.76	4	−7	−5
Caudate	R	42	8.68	16	23	3
Task-negative						
Occipital pole	R	3,249	10.8	31	−97	−11
Occipital pole	R	2,201	10.2	−25	−98	−13
Precuneus	R	1,380	9.98	−15	−65	20
Precuneus	L	1,360	9.85	16	−61	20
Precuneus	L	936	9.39	2	−69	61
Cingulate gyrus, posterior division	R	124	8.94	3	−49	9

Results were achieved using a mixed effects model corrected for multiple comparisons using GRF-theory-based maximum height thresholding with $p < 10^{-13}$ (voxel corrected). Only the most significant (main) peak within each cluster is reported in the present table. $n = 87$ (34 women). Naming of anatomical regions associated with main peaks was based on the Harvard Oxford cortical and subcortical structural atlases as implemented in the FSL software. R = right, L = left. Note that some clusters are particularly large and therefore span over several brain regions (see Figures 2 and 3 as well as the Results and Discussion sections in the main text for more information).

DMN regions with TOT for stable task-set maintenance, whereas no TOT effects were found for adaptive task control.

A Core Network for Cognitive Control

During the not-X CPT task, a widespread cortical–subcortical cerebellar network was engaged, where overlapping areas of activation in stable set maintenance and adaptive task control were located to the insula and adjacent cortex, paracingulate cortex, right inferior partial lobe, and right middle temporal gyrus.

Our findings support the existence of a core system for task control, which includes the insula and the MFC (Dosenbach et al., 2006). By using a conservative threshold ($p < 10^{-13}$, voxel corrected) compared with most studies, there was an increased risk for type II errors in this study, which could potentially lead to a bias toward large effects (Lieberman & Cunningham, 2009). However, the proposed core network has previously been found to be relatively robust (Dosenbach et al., 2006). Taking this into consideration, in addition to the large sample size (Thyreau et al., 2012), a conservative threshold was chosen in this study, as type I errors were considered to be less desirable than type II errors when trying to determine a true core network.

Contrary to previous research, we failed to find overlapping activity directly related to error processing in the anterior insula and MFC (Dosenbach et al., 2006). Neither did we find overlapping activity there for successful inhibition. This indicates that, although adaptive task control in general may belong to a core network together with stable task-set maintenance, certain adaptive properties are likely to be domain or task specific. A more con-

Table 3. Peak Activations across Whole Brain for Adaptive Task Control (Nontargets vs. Targets)

				Coordinates for Peak Activation (MNI)		
Anatomical Region	*R/L*	*Size (Number of Voxels)*	*Z*	*x*	*y*	*z*
Conflict Processing						
Cingulate gyrus, anterior division	R	14,547	11.8	6	34	25
Frontal orbital cortex	R	11,272	12.7	37	22	−7
Frontal orbital cortex	L	6,643	12.8	−35	19	−12
Angular gyrus	R	5,411	10.1	60	−47	21
Cingulate gyrus, posterior division	R	738	9.68	4	−21	24
Supramarginal gyrus, posterior division	L	653	9.98	−55	−46	30
Middle temporal gyrus, posterior division	R	588	9.78	57	−27	−13
Caudate	R	369	9.03	12	7	5
MFG	R	283	8.92	48	8	44
Right Thalamus	R	82	8.87	5	−25	−4
Caudate	L	72	8.81	−11	7	3
Hits						
Precentral gyrus	L	340	9.08	−40	−27	62

Results were achieved using a mixed effects model corrected for multiple comparisons using GRF-theory-based maximum height thresholding with $p < 10^{-13}$ (voxel corrected). Only the most significant (main) peak within each cluster is reported in the present table. $n = 87$ (34 women). Naming of anatomical regions associated with main peaks was based on the Harvard Oxford cortical and subcortical structural atlases as implemented in the FSL software. Targets = all letters except the letter X; nontargets = the letter X. Note that some clusters are particularly large and therefore span over several brain regions (see Figures 2 and 3 as well as the Results and Discussion sections in the main text for more information).

ventional threshold was used when investigating error processing and successful inhibition ($p < .01$, voxel corrected), because of the fact that there were considerably less trials included in these contrasts (lower statistical power) as compared with the more-general conflict processing contrast. The lack of overlap, despite more liberal thresholds, supports the interpretation that they do not belong to the core network but rather are domain specific.

We also found overlapping activation for stable task-set maintenance and adaptive task control in the IPL and middle temporal gyrus. The IPL is recognized as part of

Table 4. Peak Activations across Whole Brain for Conjunction Analysis (Adaptive Task Control and Stable Task-set Maintenance), Representing the "Core Network" of Cognitive Control

				Coordinates for Peak Activation (MNI)		
Anatomical Region	*R/L*	*Size (Number of Voxels)*	*Z*	*x*	*y*	*z*
Conjunction Analysis						
Frontal orbital cortex/insula	R	4,838	10.8	32	26	−3
Insula/frontal orbital cortex	L	3,029	10.4	−29	23	−4
Paracingulate gyrus	R	451	9.23	5	20	41
Supramarginal gyrus, posterior division	R	353	8.95	54	−45	43
Middle temporal gyrus, posterior division	R	191	9.04	56	−28	−11

Brain areas activated above the statistical threshold ($p < 10^{-13}$) in both conflict processing (adaptive task control) and stable task-set maintenance were investigated in a conjunction analysis. The most significant (main) peak within each cluster is reported in the present table. $n = 87$ (34 women). Naming of anatomical regions associated with main peaks was based on the Harvard Oxford cortical and subcortical structural atlases as implemented in the FSL software.

Table 5. Peak Activations across Whole Brain for Adaptive Task Control (Commission Errors vs. Correct Inhibition)

Anatomical Region	*R/L*	*Size (Number of Voxels)*	*Z*	*Coordinates for Peak Activation (MNI)*		
				x	*y*	*z*
Error Processing						
Lingual gyrus	L	19,334	7.11	−8	−62	6
Lingual gyrus	R	4,981	6.16	17	−55	−1
Central opercular cortex	R	4,443	7.02	59	−15	11
Precentral gyrus	R	2,703	6.66	55	−5	36
Postcentral gyrus	L	1,699	6.38	−49	−15	38
Precuneus	L	1,583	6.33	−1	−53	63
Cingulate gyrus, anterior division	L	1,356	5.89	−3	22	28
Superior frontal gyrus	L	451	5.75	−7	11	61
Temporal pole	R	310	5.94	28	9	−28
Cingulate cortex, anterior division	L	224	5.38	−1	−10	38
Parahippocampal gyrus, posterior division	L	177	5.29	−19	−26	−13
Superior temporal gyrus, anterior division	R	137	5.12	66	−1	5
Temporal pole	L	91	5.15	−29	15	−36
Successful Inhibition						
Occipital pole	L	2,108	5.78	−28	−95	11
Frontal pole	R	757	6.04	18	48	−19
Supramarginal gyrus, posterior division	R	724	5.39	42	−44	46
Frontal pole	L	588	5.69	−38	54	−8
Frontal pole	R	559	5.29	47	36	22
Frontal pole	R	389	5.51	37	58	−4
Lateral occipital cortex, superior division	R	213	5.41	32	−69	36
Lateral occipital cortex, inferior division	L	180	5.37	−43	−75	−3

Results were achieved using a mixed effects model corrected for multiple comparisons using GRF-theory-based maximum height thresholding with $p < .01$ (voxel corrected). Only the most significant (main) peak within each cluster is reported in the present table. $n = 87$ (34 women). Naming of anatomical regions associated with main peaks was based on the Harvard Oxford cortical and subcortical structural atlases as implemented in the FSL software. Commissions = failure to withhold button press when the letter X was presented; successful inhibition = correctly withholding the button press when the letter X was presented. Note that some clusters are particularly large and therefore span over several brain regions (see Figures 3 and 4 as well as the Results and Discussion sections in the main text for more information).

a dorsal attention system that is connected to orienting (Fan et al., 2005; Corbetta & Shulman, 2002), but has also been related to not-X CPT performance (Tana et al., 2010; Ogg et al., 2008) and moment-to-moment adjustment during task performance (Wilk et al., 2012) as well as semantic and phonological processing and categorization of visual stimuli (Stoeckel, Gough, Watkins, & Devlin, 2009). This brain region was also activated for the individual types of control networks in the study performed by Dosenbach and colleagues; however, they failed to find a direct overlap (Dosenbach et al., 2006), indicating that these brain areas may represent more domain (task) specific processing rather than a generalized top–down cognitive control. Whereas Dosenbach and colleagues based their analyses on data from several tasks with different task demands and stimulus types (Dosenbach et al., 2006), this study is limited by the use of only one task. This may simply lead to a larger degree of overlap because both block- and event-related analyses are likely to be affected by the same domain-specific demands of the task. If this is the case, low demand on spatial orienting in our task makes it plausible that the overlapping IPL activity we found could be partly related to semantic and phonological processing and categorization of the letters (Stoeckel et al., 2009) rather than spatial orientation (Fan et al., 2005). The most pronounced and explicit demand on

semantic processing in the not-X CPT was the instruction to distinguish between the semantic meaning given to the letter X ("stop responding") versus that of all the other letters ("respond"). In addition to this, participants were engaged in continuously processing letters throughout the task. Such processing could have activated the IPL, as semantic and phonological processing of meaningful stimuli has previously shown to recruit this region regardless of explicit task demands (Binder, Desai, Graves, & Conant, 2009; Stoeckel et al., 2009). Overlapping activity in the right middle temporal gyrus is also likely associated with semantic processing (Visser, Jefferies, Embleton, & Lambon Ralph, 2012; Laufer, Negishi, Lacadie, Papademetris, & Constable, 2011; Binder et al., 2009). Increased activity in both the IPL and middle temporal gyrus during successful inhibition further supports the view that these regions are involved in successful performance.

Interestingly, conflict processing revealed additional activation in the left supramarginal gyrus, indicating that additional resources may be recruited specifically in relation to the cognitive conflict that arises when processing nontargets as opposed to targets (Ettinger et al., 2008). Conflict cannot easily be distinguished from differences related to responding or not responding (Kim, Chung, & Kim, 2012). However, it is unlikely that the additional activation in the left supramarginal gyrus in the current study is merely caused by differences related to responding and not responding. Typical activation related to responding was found only in motor areas when investigating activation directly related to hits (targets > nontargets). Also, if the activation had been directly related to responding versus not responding, it would be expected that this difference would be isolated in the successful inhibition or error processing contrasts. This was not the case, as the activation in the left supramarginal gyrus was unique for the conflict processing contrast (nontargets > targets). Finally, a recent study demonstrated that the left supramarginal gyrus has a causal role in relation to the left dorsal premotor cortex in rapid action reprogramming (Hartwigsen et al., 2012). Evidence from this study supports that the supramarginal gyrus is involved in controlling the release of action programs regardless of whether they involve responding or not responding (Hartwigsen et al., 2012).

Anteriorization of Adaptive Relative to Stable Task Control in the Frontal Cortex

In addition to the "core" activation located within the MFC, stable task-set maintenance activated caudal parts of the medial superior frontal gyrus, whereas adaptive task control (conflict and error processing) activated

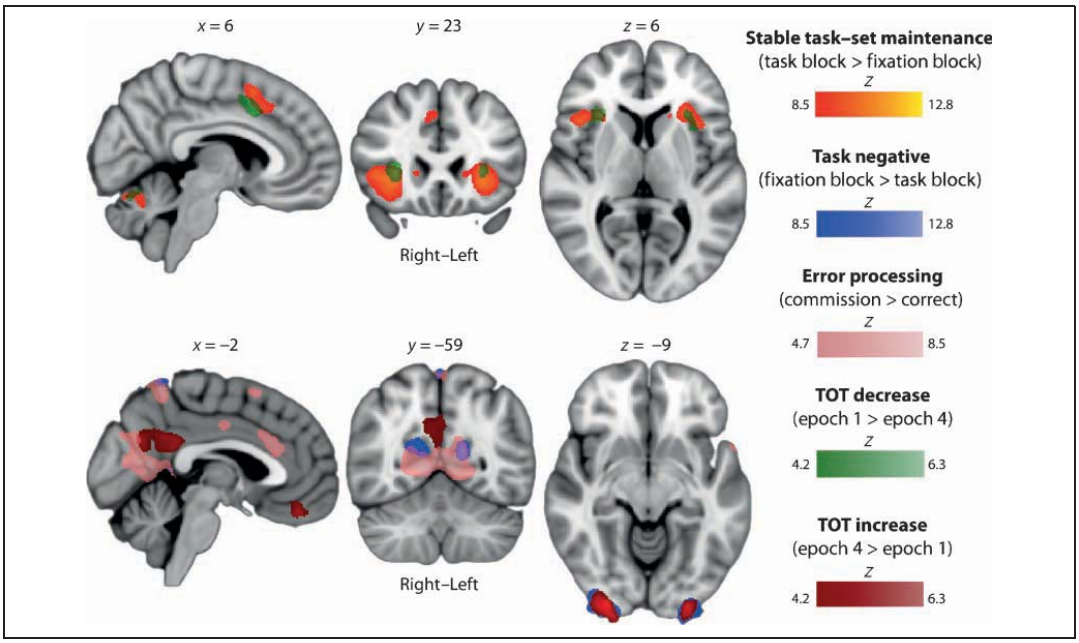

Figure 3. Stable task-set maintenance, task-negative activity, error related activity, and TOT effects. The figure shows SPMs for stable task-set maintenance ($p < 10^{-13}$, voxel corrected), task-negative activity ($p < 10^{-13}$, voxel corrected), error processing ($p < .01$), and TOT increase and decrease ($p < .05$). Commissions = failure to withhold button press when the letter X was presented. Correct = correctly withholding the button press when the letter X was presented. Results are presented on a 1 × 1 × 1 mm MNI template.

Table 6. Peak Activations across Whole Brain for TOT Effects for Stable Task-set Maintenance

Anatomical Region	*R/L*	*Size (Number of Voxels)*	*Z*	*Coordinates for Peak Activation (MNI)*		
				x	*y*	*z*
Time Epoch 1 > 4						
Cingulate gyrus, anterior division	R	2,400	5.19	6	11	41
Precentral gyrus	L	1,794	5.53	−42	−4	60
Insular cortex	R	1,514	5.29	30	21	7
Cerebellum	L	1,421	5.47	−1	−74	−18
Insular cortex	L	1,303	5.34	−42	11	−2
Precentral gyrus	R	685	5.12	42	−4	44
Frontal pole	R	260	4.68	32	42	23
Parietal opercular cortex	L	249	4.63	−47	−34	22
Juxtapositional Lobule cortex	L	208	5.10	−8	−6	60
Superior frontal gyrus	R	193	4.77	14	2	59
Superior temporal gyrus, posterior division	L	143	4.90	−66	−34	18
Cerebellum	L	90	4.76	−35	−60	−29
MFG	R	79	4.59	44	0	59
Superior frontal gyrus	L	42	4.61	−30	−50	70
Time Epoch 3 > 1						
Occipital pole	R	1,586	6.06	30	−97	−11
Occipital pole	L	927	5.59	−26	−98	−12
Frontal pole	L	59	4.67	−18	37	−18
Time Epoch 4 > 1						
Precuneus	R	4,610	5.08	4	−64	26
Frontal pole	L	3,437	6.32	−19	37	−18
Occipital pole	R	1,671	6.15	29	−97	−11
Occipital pole	L	1,354	6.18	−25	−98	−12
Frontal pole	L	353	4.79	−41	40	−19
Frontal pole	L	266	4.81	−5	69	16
Frontal orbital cortex	R	166	4.57	19	34	−18
Superior frontal gyrus	L	120	4.74	−14	34	39
Precentral gyrus	R	88	4.62	14	−28	66
Frontal pole	L	79	4.61	−13	48	37
Precentral gyrus	L	58	4.59	−10	−30	69
Subcallosal cortex	L	56	4.72	−7	7	−17
Lateral occipital cortex	L	52	4.54	−38	−71	31
Middle temporal cortex	L	49	4.48	−52	−4	−25

After a repeated-measures GLM yielded a statistically significant main effect of TOT, subsequent paired *t* tests were performed which compared time epoch 1 with each of the other time epochs (2, 3, and 4) progressively further away in time. Only statistically significant results from these analyses are presented in this table. Results were achieved using a mixed effects model corrected for multiple comparisons using GRF-theory-based maximum height thresholding with $p < .05$ (voxel corrected). Only the most significant (main) peak within each cluster is reported in the present table. $n = 87$ (34 women). Naming of anatomical regions associated with main peaks was based on the Harvard Oxford cortical and subcortical structural atlases as implemented in the FSL software. Note that some clusters are particularly large and therefore span over several brain regions (see Figures 3 and 4 as well as the Results and Discussion sections in the main text for more information).

rostral regions of ACC. The present results are therefore best accommodated by the cognitive demand framework (Badre & D'Esposito, 2007, 2009; Badre, 2008) rather than the episodic and contextual control framework (Koechlin & Summerfield, 2007; Koechlin et al., 2003). Accordingly, the results indicate that, with an event-related analysis, we can identify activation related to the more specific and perhaps demanding actions of conflict and error processing, whereas the activity present in the block analysis appears to be dominated by the ongoing task-set related to simple motor responses (Kim et al., 2011; Venkatraman et al., 2009).

Moreover, evidence has demonstrated that the more dorsal region of ACC as well as the pre-SMA are involved in action selection and conflict resolution (Forstmann, van den Wildenberg, & Ridderinkhof, 2008; Taylor, Nobre, & Rushworth, 2007), whereas the relatively more ventro-rostral part of ACC is mainly activated during error detection and anticipatory prediction of response selection (Nee et al., 2011). In accordance with this, our results revealed that main activations related to conflict and error processing was located in more ventro-rostral regions of ACC, relative to that of stable task-set maintenance.

One exception from the anteriorization of adaptive task control within the PFC was present in our data, namely the error-related activation in the very posterior ACC. The activated region is, however, bordering the PCC and may hence not be representative for the prefrontal region. Activation of the PCC has been related to both a task-negative network involved in lapses of attention (Weissman et al., 2006) and preparatory motor inhibition (Hu & Li, 2012). The rostral PCC may be specifically involved in processing errors, as the more general conflict processing contrast activated an area far more caudal in the same region. From this, it could be hypothesized that there is a rostro-caudal distribution within the PCC with regards to more general versus complex processing.

The pre-SMA and adjacent areas were activated by both stable task-set maintenance and error processing, with the latter located more rostral (and somewhat dorsal). Block-related fMRI analysis has previously demonstrated a larger number of activated voxels in dorsal, relative to ventral, areas during a not-X CPT performance (Ogg et al., 2008). Furthermore, stable task-set maintenance has been found to activate more dorsally within the MFC relative to adaptive task control (Wilk et al., 2012). Novel in our study is that we investigated error processing more directly. The pre-SMA area is hypothesized to be involved in switching between and/or reactivating task-sets when this is required, and error-related activity in the same area may signal re-engagement of decaying task-sets (Nee et al., 2011; Altmann & Gray, 2002). Memory for task-sets is thought to be a noisy system, where decay in task-sets leads to lower discriminative power (given by lower d') for distinguishing one stimulus from the other (Altmann & Gray, 2002). In our task, we found a positive correlation between the conflict processing and detectability (d') in the pre-SMA area, giving direct support for its role in separating signal from noise.

There was also evidence for a distribution gradient within the lateral prefrontal lobe, where adaptive task control was associated with more anterior activation than stable task-set maintenance. Stable task-set maintenance activation spreads from its main peak in the precentral gyrus into the middle frontal gyrus (MFG), which is known to be involved in maintaining task goals as well as manipulating items in working memory (Rypma, Prabhakaran, Desmond, Glover, & Gabrieli, 1999). Conflict processing was also associated with activation more anterior in the MFG relative to stable task-set maintenance. Moreover, in addition to enhanced activity in primary visual areas, successful inhibition revealed increased activation with main peaks bilaterally in the frontal poles. In the right hemisphere, this activation spreads into the MFG, anterior to both stable task-set maintenance and conflict processing, indicating that successful inhibition relies on endogenous control processes located in the most anterior regions in the PFC (Kim et al., 2011; Taren, Venkatraman, & Huettel, 2011).

Distinct Subcortical and Cerebellar Regions Recruited by Stable Task-set Maintenance and Adaptive Task Control

Activations related to stable task-set maintenance were found in the dorsal striatum (bilaterally in the caudate and left putamen), right thalamus, and cerebellum. The dorsal striatum has an important role in cognitive control and categorization of visual stimuli (Seger, 2008; Balleine et al., 2007; Heyder et al., 2004). Stable task-set maintenance activated anterior parts (the head) and also more posterior parts spreading into the body of the caudate, in addition to the left putamen. These areas are thought to be key structures in separate cortico-striatal loops, namely the executive (head) and visual (body) loop (Seger, 2008). Conflict processing also activated the head of the caudate, although separated from, and located dorso-caudal relative to the stable task-set maintenance activation.

Largely overlapping thalamic activations related to both alerting and executive control have been reported in a previous event-related fMRI study (Fan et al., 2005). In our study, using a more stringent threshold, we were able to find separate thalamic activation for stable task-set maintenance and adaptive task control. Whereas stable task-set maintenance showed activation in the ventral anterior nuclei region previously known to be involved in executive function (Little et al., 2010; Van der Werf, Witter, Uylings, & Jolles, 2000), conflict processing revealed activation in the pulvinar region (in vicinity of the peak activation related to executive control in the Fan et al. study), which plays a role in working-memory-guided visual selection (Rotshtein, Soto, Grecucci, Geng, & Humphreys, 2011). Previous research has suggested a role for the thalamus as a part of a cingulo-opercular network, which

is supposed to mainly engender stable task-set maintenance (Dosenbach et al., 2008). Our results refine this view, suggesting that distinct subregions of the thalamus may be specifically involved in both stable task-set maintenance and adaptive task control.

The cerebellum has also been proposed to be involved in a cingulo-opercular network by providing error codes through interacting with the thalamus and a fronto-parietal network through connections via the dorsolateral PFC and IPL (Dosenbach et al., 2007). Another theoretical perspective sees the cerebellum as crucial for maintenance of anticipatory brain activity that is subsequently synchronized with the expected sensory stimuli, facilitating a more sustained "predictive brain state" (Ghajar & Ivry, 2009). In our study, we failed to directly relate activation in the cerebellum to error processing, as we only found activations related to stable task-set maintenance. These results support a role for the cerebellum as a comparator or internal template in attention and executive control (Ghajar & Ivry, 2009) and not an error detector as such.

Task-negative Network and Error Processing

Task-negative not-X CPT activations were located to posterior brain regions similar to those previously found in a CPT study (Ogg et al., 2008) and coinciding with the DMN (Fox et al., 2005). We also found error-related activity in several of the same regions (lateral and medial parietal regions including the precuneus), possibly indicating a failure to effectively deactivate the task-negative network when errors occurred (Weissman et al., 2006). However, not all error processing areas overlapped with the task-negative regions. Also, in addition to the previously described activations in PFC, PCC, and task-negative regions, error processing was uniquely supported by the right posterior insula, left postcentral gyrus, bilaterally in the temporal lobes, and central opercular cortices. This activity may be related to more specific error activity such as affective or cognitive reactions related to making errors (Mathiak et al., 2011) or reactive activation of domain-/task-specific neural networks.

TOT Effects

This study is the first to investigate TOT effects for both stable task-set maintenance and adaptive task control in the same fMRI experiment. Interestingly, we found a statistically significant TOT effect only for stable task-set maintenance and not for adaptive task control. This finding gives further support for dissociation between adaptive versus stable networks. Furthermore, for stable task-set maintenance, there was primarily a decrease of activation in task-positive and an increase in task-negative (our task) or DMN regions (Fox et al., 2005; Fransson, 2005) as a function of TOT.

A previous study found reduction of CBF in a fronto-parietal task-positive attention network after 20 min of performing a psychomotor vigilance task, which was related to decreased task performance (Lim et al., 2010). Others have found decreased BOLD response in task-positive networks that were unrelated to behavioral performance as the task progressed, leading the authors to attribute their findings mainly to habituation effects (Tana et al., 2010; Butti et al., 2006). The fact that TOT effects in our study were both positive and negative and overlapping with the original task-positive and task-negative networks makes it unlikely that the BOLD response changes are because of general habituation effects or global signal changes (Fox, Zhang, Snyder, & Raichle, 2009). The global fMRI signal may change over time, particularly in paradigms lasting for an extended period (e.g., because of scanner drift). Such effects were minimized in this study, both by application of conventional filtering of the data as well as by using a well-balanced task design and analysis approach (see Methods section). Although this balanced design theoretically reduced the sensitivity for detecting TOT effects (e.g., by collapsing two runs), it actually increased the specificity. Global signal effects are also unlikely for the present findings in particular, as there is evidence that the global signal is primarily not localized in the currently activated regions, resembling anticorrelated regions typically found in resting-state fMRI studies (Fox et al., 2009).

Both increases in attentional demands and self-reported level of fatigue have previously been associated with increased activations within typical task-positive areas and decreased activations in typical task-negative areas (Cook et al., 2007; McKiernan, Kaufman, Kucera-Thompson, & Binder, 2003), which is the opposite of the TOT effect in this study. Moreover, stimulus-independent thoughts have been associated with decreased activity in task-positive areas and increased activity in task-negative regions (McGuire, Paulesu, Frackowiak, & Frith, 1996). However, it has also been suggested that activation in DMN areas is involved in prospective planning (Buckner, Andrews-Hanna, & Schacter, 2008), which may suggest that increased activation in DMN areas may play a role in a proactive attention control system (Braver, 2012).

The general behavioral effect of TOT in our task was a linear decrease in performance on detectability and increase in RT and omission errors as well as increased β. This general worsening of performance with increased TOT is in accordance with previous research (Langner et al., 2010). Although there was a general decrease in performance, the RT and detectability curves could not be fully understood without also investigating nonlinear effects. The fact that these measures were more fluctuating with time could mean that they are supported by different underlying neural networks than those that elicit omission errors and higher β. However, we were not able to confirm this hypothesis in our fMRI analyses, which failed to reveal any statistically significant relationships between any of the behavioral CPT measures and BOLD activity for the stable task-set maintenance contrast.

Interestingly, there was a lack of significant TOT effects for commission errors. Along with increased RT, omission errors, and response style (β) scores, this may be an indication of a change to a more cautious response style with TOT, represented by an increased threshold for not-X responses. This interpretation may shed further light on the finding that TOT affected only neural activity related to stable task-set maintenance rather than dynamic control adjustments, as changes in the overall strategy (task-set) would be expected to mainly influence the former.

Summary and Conclusion

This study demonstrates novel aspects of the neural underpinnings of stable task-set maintenance and adaptive task control in 87 healthy participants, using a mixed block and event-related fMRI design. The results support the existence of an overlapping core network for cognitive control. In addition, we were able to map distinct brain regions underlying cognitive control during not-X CPT performance, which operates and reacts on different temporal scales. The results also indicate a rostro-caudal distribution in the frontal cortex where stable task-set maintenance is located more posteriorly in regions considered to be related to more general functions, whereas adaptive task control is located more anteriorly where more demanding and perhaps domain-specific operations are considered to be performed. Only the stable task-set maintenance network, and not the adaptive task control network, exhibited a TOT effect. The TOT effects in the stable task-set maintenance network were related to a decrease in task-positive activation and a parallel increase in task-negative/DMN activation.

A particular strength of the current study is the high number of participants and statistical power, which allowed for whole-brain analyses without abandoning strict thresholds for statistical significance and correction for multiple comparisons. This study contributes new knowledge by combining one of the most commonly administered cognitive tests with more recent, innovative neurocognitive theoretical perspectives and methods. This knowledge may give rise to valuable new questions within basic and clinical attention research as well as new perspectives for interpretation of clinical CPT results.

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Paper II

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Paper III

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Altered Cognitive Control Activations after Moderate-to-Severe Traumatic Brain Injury and Their Relationship to Injury Severity and Everyday-Life Function

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This study investigated how the neuronal underpinnings of both adaptive and stable cognitive control processes are affected by traumatic brain injury (TBI). Functional magnetic resonance imaging (fMRI) was undertaken in 62 survivors of moderate-to-severe TBI (>1 year after injury) and 68 healthy controls during performance of a continuous performance test adapted for use in a mixed block- and event-related design. Survivors of TBI demonstrated increased reliance on adaptive task control processes within an a priori core region for cognitive control in the medial frontal cortex. TBI survivors also had increased activations related to time-on-task effects during stable task-set maintenance in right inferior parietal and prefrontal cortices. Increased brain activations in TBI survivors had a dose-dependent linear positive relationship to injury severity and were negatively correlated with self-reported cognitive control problems in everyday-life situations. Results were adjusted for age, education, and fMRI task performance. In conclusion, evidence was provided that the neural underpinnings of adaptive and stable control processes are differently affected by TBI. Moreover, it was demonstrated that increased brain activations typically observed in survivors of TBI might represent injury-specific compensatory adaptations also utilized in everyday-life situations.

Keywords: cognitive control, compensation, continuous performance test, executive function, fMRI, time-on-task

Introduction

Moderate-to-severe traumatic brain injury (TBI) can cause varying degrees of cognitive control deficits, which in turn have negative impact on long-term functional outcome (Draper and Ponsford 2008; Ponsford et al. 2008). Cognitive control is supported by overlapping and distinct brain regions operating on different temporal scales (Dosenbach et al. 2006; Olsen et al. 2013). Processes such as response conflict- and error processing (Desmet et al. 2011; Nee et al. 2011) operate within a rapid reactive "adaptive" temporal scale, whereas sustained attention (Ogg et al. 2008) and stable task-set maintenance (Altmann and Gray 2002) are believed to be supported by proactive "stable" processes. The balance between adaptive and stable control processes has been shown to shift in aging (Paxton et al. 2008) and schizophrenia (Edwards et al. 2010) toward relying more on adaptive processes relative to stable. This emphasizes the dissociation between the different temporal systems and demonstrates their vulnerability to ageing and disease as well as indicates potential compensatory mechanisms (Braver 2012). Furthermore, only the stable control system seems to be altered as an effect of time-on-task (TOT) (Olsen et al. 2013), suggesting that this network may be particularly prone to the effects of cognitive fatigue (Cook et al. 2007). Cognitive fatigue is prevalent after TBI and has been related to the need for increased effort during task performance (Ponsford et al. 2012). It is still an open question whether adaptive and stable control systems are affected differently by TBI.

A region active during both adaptive and stable control processes has reliably been observed in the medial frontal cortex (MFC) in healthy participants (Dosenbach et al. 2006; Olsen et al. 2013). Interestingly, this brain region is also of particular interest after TBI, as demonstrated in several functional imaging studies (Scheibel et al. 2007; Hillary 2008; Rasmussen et al. 2008; Cazalis et al. 2011; Sozda et al. 2011). Indeed, the MFC is among the brain regions most consistently demonstrated to have altered blood oxygen level–dependent (BOLD) signal in several neurologic populations, including TBI (Hillary 2008). Accordingly, the core region for cognitive control within the MFC is potentially a key region for understanding how both adaptive and stable control processes are affected by TBI.

Previous functional magnetic resonance imaging (fMRI) studies have typically shown that survivors of moderate-to-severe TBI exhibit both increased and more widespread brain activations during performance of various cognitive tasks (Christodoulou et al. 2001; Scheibel et al. 2007; Rasmussen et al. 2008). It has been proposed that TBI survivors engage more neuronal resources to uphold adequate performance levels related to cognitive control (Turner and Levine 2008; Kohl et al. 2009; Turner et al. 2011). Increased BOLD activation after TBI has been positively correlated with both more severe injury and better fMRI task performance (Newsome et al. 2007; Scheibel et al. 2007, 2009), lending some support to its role as an injury-specific compensatory mechanism. However, whether increased activation after TBI represent true compensatory mechanisms

has yet to be elucidated (Hillary 2008, 2011). Moreover, the majority of previous fMRI studies on the effects of TBI have included relatively small heterogeneous samples, often reported imaging results uncorrected for multiple comparisons and/or failed to adjust for established outcome moderators such as age and education. It is therefore a need for further validation in sufficiently powered samples in order to establish the significance of previous findings.

Furthermore, a limitation when interpreting the functional role of BOLD activations in relation to task performance is that the 2 are inevitably related merely due to the way analyses are traditionally performed (Price et al. 2006; Hillary 2008). Consequently, it is considered crucial for the validity of BOLD activation differences between healthy controls and neurologically impaired participants that fMRI task performance is kept highly similar between groups and/or adjusted for (Price et al. 2006). Another implication of the tight coupling between fMRI task performance and brain activations is that validation of the functional significance of BOLD alterations should ideally rely on other measures than fMRI task performance (or highly similar neuropsychological tests) as such. Consequently, in contrast to previous studies, the present study implemented an alternative approach by utilizing the Behavioral Rating Inventory of Executive Function-Adult version (BRIEF-A) (Roth et al. 2005), which is a comprehensive and well-validated self-report measure of cognitive control function in everyday-life situations (Garcia-Molina et al. 2012; Lovstad et al. 2012; Waid-Ebbs et al. 2012).

In this study, the neuronal correlates of adaptive and stable control processes in moderate-to-severe TBI were investigated using a continuous performance test (Conners et al. 2003) adapted for use in a mixed block- and event-related fMRI design (Olsen et al. 2013). This particular test was chosen because of its extensive use in clinical settings (Rabin et al. 2005), well-described psychometric abilities (Riccio et al. 2002; Conners et al. 2003), capacity to measure both stable and adaptive control processes (Olsen et al. 2013), as well as having relatively simple task demands. The latter was important to ensure that both TBI survivors and healthy controls could perform the test accurately, which is a prerequisite for the validity of fMRI studies with neurological populations (Price et al. 2006).

Extending previous studies, both stable and adaptive control processes were investigated in order to delineate adaptations of these neural systems as a consequence of brain injury. First, 1) it was hypothesized that TBI survivors would demonstrate a shift toward relying more on adaptive task control processes (Paxton et al. 2008; Edwards et al. 2010; Braver 2012) within a predefined core region for cognitive control in the MFC (Olsen et al. 2013). Secondly, 2) it was predicted that TBI survivors would exhibit increased and more widespread BOLD activation (Christodoulou et al. 2001; Scheibel et al. 2007; Rasmussen et al. 2008) related to stable task-set maintenance TOT increases (Olsen et al. 2013), possibly in order to uphold adequate performance levels despite cognitive fatigue (Cook et al. 2007; Kohl et al. 2009). Finally, in order to explore the functional significance of possible BOLD alterations, 3) it was investigated whether such alterations would show a dose relationship with injury severity, and 4) if it was correlated with cognitive control function in everyday-life situations as measured with BRIEF-A (Roth et al. 2005), while controlling for fMRI task performance and the established outcome moderators age and education.

Materials and Methods

Participants

A total of 73 survivors with chronic moderate-to-severe TBI according to the criteria set by the Head Injury Severity Scale (HISS) (Stein and Spettell 1995) and 78 age-, sex-, and education-matched healthy controls were recruited for the present study. TBI survivors were recruited from a database of patients previously admitted to the Department of Neurosurgery, St. Olavs Hospital, Trondheim University Hospital, Norway. Details on how demographic and injury-related data were prospectively collected in the acute stage have been previously described (Skandsen et al. 2010). Glasgow outcome scale extended (GOSE) was administered at the time of fMRI. A self-report form and an interview were used to assess years of completed education. Healthy controls were recruited from friends and family of TBI patients, as well as from workplaces in Trondheim, Norway.

Inclusion criteria for both groups included being between 14- and 65-years old the year the testing was performed, fluency in the Norwegian language, ability to cooperate during fMRI testing, absence of previous moderate or severe head injury, diagnosed neurologic or psychiatric condition, as well as MRI incompatible implants. Eleven TBI survivors were excluded from further analysis: 3 due to missing fMRI data, 5 due to excessive movement (defined as relative displacement of >0.5 mm in any direction), 2 due to falling asleep during scanning, and 1 due to previously diagnosed psychiatric or neurologic disease that was not discovered before the day of scanning. This left 62 TBI survivors (17 women), for the full analyses in this study. Patient characteristics are presented in Table 1. Ten healthy controls were excluded: 3 because of missing data due to technical problems, 2 due to previously diagnosed psychiatric or neurologic conditions discovered at the day of testing, 4 due to excessive movement (defined as relative displacement of >0.5 mm in any direction), and 1 due to excessive fMRI artifacts. A total of 68 healthy controls (20 women) were hence included in the full analyses in this study. An independent t-test revealed no statistically significant age difference ($P = 0.86$) between TBI survivors (M = 32.4, SD = 14.2) and healthy controls (M = 33.8, SD = 13.6).

Table 1
Descriptive data characterizing TBI survivors

Variable	Total ($n = 62$)		Moderate ($n = 35$)		Severe ($n = 27$)	
	No.	Percent	No.	Percent	No.	Percent
Years since injury[a]	2.8	1.5–5.4	2.7	1.5–5.4	3	1.5–5.4
GCS score[a]	9	3–14	12	9–14	6	3–8
PTA duration						
Short (<7 days)	35	56.5	24	68.6	11	40.7
Long (≥7 days)	24	38.7	10	28.6	14	51.9
Missing data	3	4.8	1	2.9	2	7.4
Injury mechanism						
Vehicle accident	30	48.4	15	42.9	15	55.6
Falls	25	40.3	13	37.1	12	44.4
Skiing accident	3	4.8	3	8.6	0	0
Other/unknown	4	6.5	4	11.5	0	0
Early MRI: TAI grading						
No TAI	18	29.0	14	40.0	4	14.8
TAI 1	18	29.0	7	20.0	11	40.7
TAI 2	18	29.0	11	31.4	7	25.9
TAI 3	6	9.7	2	5.7	4	14.8
Missing data	2	3.2	1	2.9	1	3.7
Early MRI: cortical contusions						
No contusions	15	24.2	9	25.7	6	22.2
One	14	22.6	7	20	7	25.9
2 or more	31	50.0	18	51.4	13	48.1
Missing data	2	3.2	1	2.9	1	3.7
GOSE score at fMRI testing						
Moderate disability	25	40.3	13	37.1	12	44.4
Good recovery	37	59.7	22	62.9	15	55.6

Note: Descriptive data for the total TBI group, and moderate and severe TBI as defined by the Head Injury Severity Scale (HISS). TAI, traumatic axonal injury based on radiological evaluation of T2*, FLAIR and T2 images in the early phase (see Skandsen et al. 2010 for details).
GCS, Glasgow coma scale; PTA, post-traumatic amnesia; GOSE, Glasgow outcome scale extended; Good recovery, GOSE score 7–8; Moderate disability, GOSE score 5–6.
[a]Numbers representing GCS and years since injury are given as medians and ranges.

Neither was there a statistically significant difference in years of completed education ($P = 0.57$) between TBI survivors (M = 12.0, SD = 2.3) and healthy controls (M = 12.1, SD = 2.2). Written informed consent was obtained (also from parents if participants were under the age of 18). The study protocol adhered to the Helsinki Declaration and was approved by the Regional Committee for Medical Research Ethics.

Design of fMRI Task

An in-house-developed Not-X CPT (Olsen et al. 2013) inspired by the Conners' CPT (Conners et al. 2003) was presented to the participants in a mixed block- and event-related BOLD fMRI design (Petersen and Dubis 2012). The task consisted of a total of 480 stimuli, divided into 432 targets and 48 non-targets (10%). Targets consisted of randomly chosen letters (A–Z) other than "X," and non-targets were the letter X. Each stimulus was presented on the screen for 250 ms. The task was presented as 2 consecutive ~15-min runs, where each run consisted of 16 interleaving task blocks and 16 baseline (fixation cross) blocks. Each block contained 15 stimuli, and both inter-block intervals (IBIs) and inter-stimuli intervals (ISIs) were randomly scrambled within each block (with 6 IBIs of 14 s, 5 IBIs of 16 s, and 5 IBIs of 18 s and 5 ISIs of 1 s, 5 ISIs of 2 s, and 5 ISIs of 4 s). The jittered presentation of ISIs ensured sampling of different time points of the hemodynamic response curve, allowing for event-related fMRI analysis (Petersen and Dubis 2012). Counterbalancing was applied to eliminate systematic effects of ISI, IBI, or order of the different stimulus types (targets and non-targets). The task design was implemented using Matlab (The MathWorks, Inc., Natick, USA).

Not-X CPT Paradigm Procedure

Participants were instructed to respond as fast and accurately as possible by pressing a response button whenever a target (A–Z) was presented on the screen, and to withhold their response whenever the letter X appeared. All participants went through a practice session using a desktop computer outside the scanner room together with an experimenter who ensured that each individual performed the task as intended before the actual fMRI session. E-prime 1.2 (Psychology Software Tools, Pittsburgh, USA) was used for stimulus presentation and timing of stimuli. MRI-compatible video-goggles (VisualSystem, Nordic NeuroLab, Bergen, Norway) were used for visual presentation during scanning for 95 subjects. Due to technical problems with the goggles, the remaining subjects had to use a head-coil–mounted mirror system and a MRI compatible monitor (Siemens AG, Erlangen, Germany). Using photo diodes and an oscilloscope, a difference of ~60-ms stimulus onset delay was detected for the monitor relative to the goggles, which was adjusted for during post-processing of response- and fMRI data. A fiber optic response grip (ResponseGrip, Nordic NeuroLab, Bergen, Norway) was used for registration of subject responses, and all behavioral data were stored in individual log files by utilizing a customized Python-based log-script interacting with E-prime.

Self-Report Measure of Cognitive Control

The BRIEF-A was used as a self-report measure of cognitive control (Roth et al. 2005). BRIEF-A is a 75-item self-report questionnaire that provides 9 subscales measuring different domains of cognitive control: 1) inhibit, 2) Shift, 3) Emotional Control, 4) Self-Monitor, 5) Initiate, 6) Working Memory, 7) Plan/Organize, 8) Task Monitor, and 9) Organization of Materials. Participants were asked to indicate the frequency of the statement belonging to each item on a 3-point Likert scale (1—never, 2—sometimes, and 3—often). Based on these subscales, a Behavioral Regulation Index (BRI, sum of subscales 1–4), Metacognition Index (MI, sum of subscales 5–9), and a Global Executive Composite score (GEC, sum of subscales 1–9) were calculated and used for further analyses in this study.

Three healthy controls had one missing single item score each. In these cases, missing scores were handled according to recommendations in the BRIEF-A manual, by replacing the missing value with the value 1 (never). One healthy control had 7 missing single item scores and was excluded from further analyses involving BRIEF-A. There was no missing data for BRIEF-A in the TBI group.

MRI Scanning

All MRI data were acquired on a Siemens Trio with a 12-channel Head Matrix Coil (Siemens AG). Head motion was reduced by the use of foam pads around the subjects' heads. During Not-X CPT performance ~380 T2* weighted, BOLD-sensitive volumes were acquired for each "run," using an echo-planar imaging pulse sequence with TR of 2400 ms, TE of 35 ms, FOV of 244 mm, matrix of 80 × 80, slice thickness of 3 mm, and a total of 40 slices, giving an in-plane resolution of 3 × 3 mm. Slices were positioned transversal along the A–P axis. Before each "run," 2 spin echo sequences (TR = 2010 ms, TE = 35 ms, FOV = 244 mm, slice thickness = 3 mm, and matrix 80 × 80, giving an in-plane resolution of 3 × 3 mm) with opposite phase encoding (A–P and P–A) were acquired for correction of static magnetic field-induced distortion (Holland et al. 2010). For anatomical reference, a T1-weighted 3D MPRAGE volume was acquired (TR = 2300 ms, TE = 30 ms, FOV = 256 mm, slice thickness = 1.2 mm, and matrix 256 × 256, giving an in-plane resolution of 1 × 1 mm).

Analysis of Behavioral Data

IBM SPSS 20.0 was used for statistical processing of behavioral data. Based on the behavioral raw data from the Not-X CPT task, the following CPT measures were calculated: "Hit Reaction Time," "Hit Reaction Time Standard Error," "Omission Errors," "Commission Errors," "Response style (β)," and "Detectability (d')" (Conners et al. 2003; Olsen et al. 2013). To investigate TOT effects, the Not-X CPT task was divided into 4 time epochs after collapsing "run 1" and "run 2." Each time epoch was of equal length and balanced with regard to all task demands. A previous study demonstrated that the majority of TOT-related brain activation changes could be detected by comparing time epoch 1 with time epoch 4 of the test (Olsen et al. 2013). The focus was therefore on the first and last quarter of the task when investigating TOT effects in this study. To get a representation of each individuals change in behavioral performance with TOT, difference scores (Δ) were computed for each Not-X CPT measure by subtracting the value from time epoch 1 from the value from time epoch 4: Δ = time epoch 4 – time epoch 1.

In order to assess group differences, separate (for Not-X CPT performance and Δ Not-X CPT performance) 2 × 6 multivariate analyses of variance (MANOVA) were applied, with group as a fixed factor (healthy controls, TBI survivors), and the 6 performance measures as dependent variables. As it is considered to be important for the validity of fMRI studies with neurological populations that performance is similar between the groups that are compared (Price et al. 2006), type II errors were a bigger concern than type I errors for these particular analyses. For exploratory and descriptive purposes, it was therefore decided to also assess and report univariate results and 95% CI for the difference of each single measure, even when the MANOVA did not reveal a statistically significant main effect. Partial ETA squared (ηp^2) was calculated in order to investigate effect sizes.

A similar MANOVA as described earlier was applied for investigating between-group differences in self-reported (2 × 3 MANOVA, BRIEF-A) measures of cognitive control.

Analysis of MRI Data

Non-brain structures were removed with BET (Smith 2002) and motion correction done with MCFLIRT (Jenkinson et al. 2002). Correction of geometrical distortions was done as described by Holland et al. (2010). Then, the data were smoothed (Gaussian kernel FWHM 6 mm), grand mean intensity normalized, high pass temporal filtered (50 s for block analysis and 25 s for event-related analysis), before linear registration of fMRI data to native high-resolution space (T1 MPRAGE) using 7 degrees of freedom (Jenkinson and Smith 2001; Jenkinson et al. 2002), followed by nonlinear registration of individual high-resolution structural image to MNI152 1-mm standard template using 12 degrees of freedom and a 8-mm warp resolution (Anderson et al. 2007a, 2007b).

Whole-Brain and ROI Analyses

BOLD activity related to task blocks and individual trials was modeled using the general linear model. The hemodynamic response function

was convolved with a standard Gamma variate. Initially, all contrasts were computed for each of the 2 "runs" separately and then combined using a fixed-effects model. Finally, mixed-effects models were used to create group average statistical images as well as investigate group differences for each individual contrast. Both whole-brain and ROI-based analyses were performed. For all whole-brain analyses, SPMs were corrected for multiple comparisons by using a cluster threshold of $Z > 2.3$, and a corrected cluster significance threshold of $P < 0.05$. Main peak Z-values with up to 5 local maxima and size of clusters (number of voxels) in standard $1 \times 1 \times 1$ mm MNI space were extracted. For anatomical denotation of location of activation, visual inspection and the Harvard Oxford cortical and subcortical structural brain atlases as incorporated in the FSL software were applied.

The stable task-set maintenance (task block > rest block) and adaptive task control (non-targets > targets) contrasts were created including data from the task as a whole (time epoch 1, 2, 3, and 4). First, an omnibus whole-brain analysis was performed in order to explore overall effects between healthy controls and TBI survivors. Second, according to the hypothesis regarding a shift toward more adaptive task control processing in TBI survivors, an ROI analysis was performed to specifically investigate differences in stable task-set maintenance and adaptive task control in an a priori chosen 10-mm sphere region in the MFC ($x = 5$, $y = 20$, $z = 41$). This region was chosen due to its role in a core network for cognitive control, which activates reliably in relation to both stable and adaptive cognitive control processes (Dosenbach et al. 2006; Olsen et al. 2013). Also, this particular brain region is among the brain regions that most reliably have shown increased task-related activation in TBI survivors as compared with healthy controls (Hillary 2008). For this analysis, parameter estimates for BOLD signal changes were extracted from each individual participant, compared between patients and controls, and finally also related to TBI injury severity as defined by HISS (Stein and Spettell 1995). As age and education was originally matched on the whole group level (TBI vs. healthy controls), a 3×2 multivariate analysis of covariance (MANCOVA) was used with group as a fixed factor (healthy controls, moderate TBI, and severe TBI), BOLD contrasts as dependent variables (stable task-set maintenance and adaptive task control), and age, years of completed education, and the 6 Not-X CPT performance measures as covariates.

In order to investigate TOT effects, the following contrasts were created: stable task-set maintenance TOT increase (task block time epoch 4 > task block time epoch 1), stable task-set maintenance TOT decrease (task block time epoch 1 > task block time epoch 4), adaptive task control TOT increase (non-targets time epoch 4 > non-targets time epoch 1), and adaptive task control TOT decrease (non-targets time epoch 1 > non-targets time epoch 4). In addition to the a priori MFC ROI also used for the previously described stable and adaptive contrasts, ad-hoc ROI analyses were performed to demonstrate the between-group effects with regard to injury severity as defined by HISS (Stein and Spettell 1995). Spherical ROIs (10 mm) were based on main peaks in the right inferior parietal lobe (IPL) ($x = 53$, $y = -43$, $z = 36$) and PFC ($x = 35$, $y = 27$, $z = 38$) demonstrating statistically significant differences between TBI survivors and healthy controls in the whole-brain analyses of the TOT effect contrast (Table 4). As for the main contrasts, a MANCOVA was used, with group as a fixed factor (healthy controls, moderate TBI, and severe TBI) and ROIs as dependent variables. Age, years of completed education, and Δ Not-X CPT measures (the relevant performance measure for these particular contrasts) were used as covariates.

Relationships between fMRI and BRIEF-A

In order to investigate the functional significance of the Not-X CPT fMRI results, findings were related to a self-report measure of cognitive control (BRIEF-A). Separate partial correlation models were applied for TBI survivors and healthy controls. First, parameter estimates extracted from the "core network" MFC ROI in both the overall stable task-set maintenance and adaptive task control contrasts and BRIEF-A measures were included in a partial correlation model. This model controlled for age, years of completed education, and Not-X CPT performance measures. For the TBI group, the model additionally controlled for GCS score, in order to adjust for general effects of injury severity. GCS was used as a covariate instead of HISS, as it is based on a continuous scale, which provided more variability in the scores, and hence represented a more appropriate and conservative approach for use in the partial correlation model. A similar partial correlation model was applied using the ad-hoc TOT stable task-set maintenance ROIs, controlling for Δ Not-X CPT measures in lieu of the overall Not-X CPT measures.

Results

Behavioral Results

Overall and Δ Not-X CPT performance was highly similar between TBI survivors and healthy controls, and no statistically significant differences were found between the groups (Table 2). However, TBI survivors reported significantly more everyday problems with cognitive control than healthy controls, on all 3 BRIEF-A measures (Table 3).

Imaging Results for Overall Stable Task-Set Maintenance and Adaptive Task Control

A MANCOVA was used to investigate differences across healthy controls and TBI survivors in BOLD activation in the a priori MFC ROI, related to stable task-set maintenance and adaptive task control during the whole task. The assumption of homogeneity of regression slopes was not violated, indicating that the relationship between the dependent variables (stable task-set maintenance and adaptive task control) did not vary as a function of group (healthy controls, moderate TBI, and severe TBI), $F_{6,\ 252} = 1.828$, $P = 0.094$, and $\eta\rho^2 = 0.42$. There was a statistically significant main effect of group, $F_{4,\ 238} = 2.591$, $P = 0.037$, and $\eta\rho^2 = 0.042$. Univariate analyses revealed that the main effect was driven by an effect for adaptive task control, $F_{10,\ 119} = 4.248$, $P < 0.001$, and $\eta\rho^2 = 0.263$. There was no statistically significant effect for stable task-set maintenance, $F_{10,\ 119} = 0.822$, $P = 0.608$, and $\eta\rho^2 = 0.065$. The planned polynomial contrast demonstrated a significant linear trend for adaptive task control, $P = 0.004$, indicating that BOLD activation increased proportionally with injury severity when adjusted for age, years of completed education, and Not-X CPT measures (Fig. 1). There were no statistically significant differences between TBI survivors and healthy controls for the 2 main contrasts, stable task-set maintenance (task block > rest block) and adaptive task control (non-targets > targets) in the omnibus whole-brain analyses.

Imaging Results for TOT Effects

TBI survivors had statistically significant larger increase in activation as an effect of TOT for the stable task-set maintenance contrast in right parietal and frontal areas, as compared with healthy controls (Table 4, Fig. 2). The assumption of homogeneity of regression slopes was met for the MANCOVA used for further investigation of stable task-set maintenance TOT effects within ROIs, $F_{9,\ 378} = 1.486$, $P = 0.151$, and $\eta\rho^2 = 0.034$. A significant main effect of group (healthy controls, moderate TBI, and severe TBI) was evident, $F_{6,\ 236} = 2.210$, $P = 0.043$, and $\eta\rho^2 = 0.053$. This effect was driven by the effects of the right PFC ROI, $F_{10,\ 119} = 2.523$, $P = 0.009$, and $\eta\rho^2 = 0.175$, as well as the right IPL ROI, $F_{10,\ 119} = 2.919$, $P = 0.003$, and $\eta\rho^2 = 0.197$, whereas no statistically significant effect was present for the a priori chosen MFC ROI. Planned polynomial contrasts demonstrated that BOLD activation in the right PFC ROI ($P = 0.002$) and the right IPL ($P = 0.001$) were both linearly related to injury severity when adjusted for age, years of completed education, and Δ Not-X CPT measures (Fig. 1).

Table 2
Not-X CPT and Δ Not-X CPT measures across TBI survivors and healthy controls

Variable	MANOVA	Group	*n*	Mean	95% CI of means	95% CI of difference	*P*	ηp^2
Not-X CPT								
Hit RT (ms)	F (6, 123) = 1.09, $P = 0.373$, and $\eta p^2 = 0.050$	TBI	62	416.73	402.21, 431.24	−25.80, 14.35	<0.573	0.002
		Control	68	422.45	408.59, 436.31			
Hit RT SEM		TBI	62	6.16	5.61, 6.72	−0.92, 0.61	<0.692	0.001
		Control	68	6.32	5.79, 6.85			
Omissions		TBI	62	9.18	6.18, 12.18	−0.55, 7.76	<0.088	0.023
		Control	68	5.57	2.71, 8.44			
Commissions		TBI	62	16.90	14.68, 19.13	−1.78, 4.38	<0.405	0.005
		Control	68	15.60	13.48, 17.73			
Response style (β)		TBI	62	0.14	0.11, 0.18	−0.01, 0.92	<0.098	0.021
		Control	68	0.10	0.06, 0.13			
Detectability (d')		TBI	62	2.75	2.54, 2.96	−0.522, 0.06	<0.123	0.018
		Control	68	2.98	2.78, 3.18			
Δ Not-X CPT								
Δ Hit RT (ms)	F (6, 123) = 0.421, $P = 0.864$, and $\eta p^2 = 0.020$	TBI	62	8.25	0.77, 15.73[a]	−17.17, 3.51	<0.194	0.013
		Control	68	15.08	7.94, 22.24[a]			
Δ Hit RT SEM		TBI	62	0.59	−0.90, 2.09	−1.91, 2.22	<0.884	<0.001
		Control	68	0.44	−0.99, 1.87			
Δ Omissions		TBI	62	1.90	0.69, 3.12[a]	−1.31, 2.06	<0.661	0.002
		Control	68	1.53	0.37, 2.69[a]			
Δ Commissions		TBI	62	0.19	−0.40, 0.79	−0.65, 0.98	<0.692	0.001
		Control	68	0.03	−0.54, 0.59			
Δ Response style (β)		TBI	62	0.08	0.03, 0.12[a]	−0.05, 0.08	<0.697	0.001
		Control	68	0.06	0.02, 0.11[a]			
Δ Detectability (d')		TBI	62	−0.21	−0.38, −0.03[a]	−0.32, 0.17	<0.527	0.003
		Control	68	−0.13	−0.30, 0.04			

Note: The table presents multi- and uni-variate results from a comparison of Not-X CPT and Δ Not-X CPT performance measures across TBI survivors and healthy controls.
MANOVA, multivariate analysis of variance; Δ, difference score (time epoch 4 − time epoch 1); SEM, standard error of the mean; TBI, traumatic brain injury; CI, confidence interval; ηp^2, partial ETA squared.
[a]Within-group univariate TOT effects for Δ Not-X CPT performance measures at the $P < 0.05$ level.

Table 3
Self-report measures of cognitive control across TBI survivors and healthy controls

Variable	MANOVA	Group	*n*	Mean	95% CI of means	95% CI of difference	*P*	ηp^2
BRIEF-A								
BRI	F (3,125) = 4.89, $P = 0.003$, and $\eta p^2 = 0.11$	TBI	62	43.82	41.77, 45.88	2.57, 8.27	<0.001	0.100
		Control	67	38.40	36.43, 40.38			
MI		TBI	62	60.55	57.36, 63.74	0.49, 9.33	<0.030	0.037
		Control	67	55.64	52.58, 58.71			
GEC		TBI	62	104.37	99.49, 109.25	3.57, 17.10	<0.003	0.067
		Control	67	94.05	88.35, 98.74			

Note: The table presents multi- and uni-variate results from comparisons of BRIEF-A measures across TBI survivors and healthy controls. One healthy control was excluded from the analyses involving BRIEF-A due to too many missing item scores (see Methods).
MANOVA, multivariate analysis of variance; BRI, Behavioral Regulation Index; MI, Metacognition Index; GEC, Global Executive Composite; TBI, traumatic brain injury; CI, confidence interval; ηp^2, partial ETA squared.

There were also noteworthy within-group effects for stable task-set maintenance TOT effects in the explorative whole-brain analysis. Healthy controls had large clusters of significant activations related to stable task-set maintenance TOT increase in midline posterior and anterior regions, including the precuneus, posterior cingulate cortex, ventromedial prefrontal cortex, and frontal poles (Fig. 2). Parallel to this, healthy controls had significant decreases of activation as an effect of TOT in the right anterior insula/frontal operculum, as well as in frontal midline regions encompassing the anterior cingulate-, paracingulate-, and supplementary motor cortices. TBI survivors also had stable task-set maintenance TOT increase of activation in midline posterior and anterior regions (e.g., in the precuneus, posterior cingulate cortex, ventromedial prefrontal cortex, and frontal poles), however far more extensive and widespread than for the healthy controls (Fig. 2). In addition to the midline regions also activated in the healthy controls, TBI survivors had particularly pronounced additional areas of increased activation bilaterally in the inferior parietal lobules, as well as bilaterally in dorso-lateral regions of the frontal cortex, in addition to several subcortical regions. Contrary to healthy controls, TBI survivors had no statistically significant decreases in activation as a function of TOT. There were no within- or between-group TOT effects for adaptive task control.

Relationships between BOLD Activation and BRIEF-A Scores

The partial correlation model revealed several statistically significant findings for the TBI group. The general finding was that BOLD signal increases in several ROIs were related to lower levels of self-reported problems associated with cognitive control (Table 5). There were no statistically significant relationships between the BOLD signal in any of the ROIs and BRIEF-A scores for healthy controls (Table 5).

Discussion

The present study revealed 4 main findings with importance to understanding alterations of neuronal correlates to cognitive

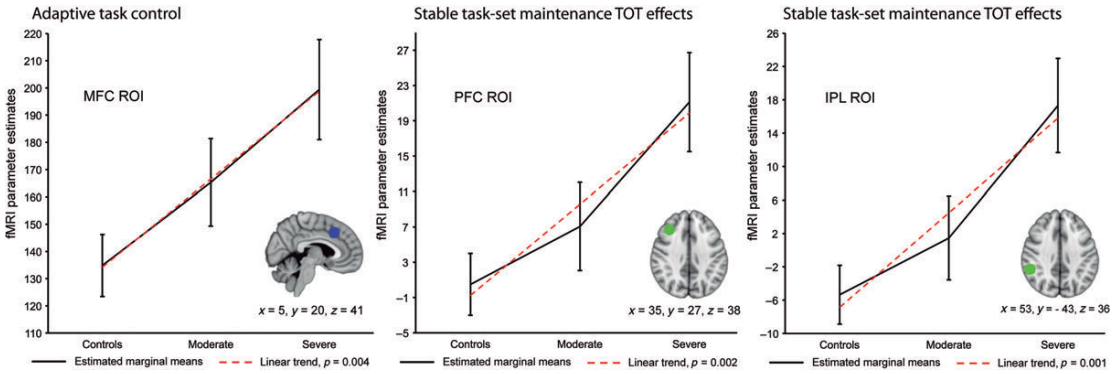

Figure 1. ROI analyses across healthy controls, moderate- and severe TBI survivors. The figure shows the results of planned polynomial contrasts following statistically significant MANCOVAs. Only statistically significant results are shown. Results are adjusted for age, education, and Not-X CPT performance (Δ Not-X CPT performance for TOT effects). TOT, time-on-task; ROI, region of interest; MFC, medial frontal cortex; IPL, inferior parietal cortex; PFC, prefrontal cortex. Error bars represent ± standard error of estimated marginal means.

Table 4
Differences between TBI survivors and healthy controls on TOT activations related to stable task-set maintenance (Δ stable task-set maintenance)

Anatomical region	R/L	Size (number of voxels)	*Z*	Coordinates for peak activation (MNI)		
				X	*Y*	*Z*
TBI survivors > healthy controls (Δ stable task-set maintenance)						
Supramarginal gyrus, posterior division	R	24 769	4.21	53	−43	36
Supramarginal gyrus, posterior division	R	lm	4.1	50	−43	36
Angular gyrus	R	lm	4.05	47	−45	29
Angular gyrus	R	lm	3.78	56	−54	49
Angular gyrus	R	lm	3.76	49	−49	47
Angular gyrus	R	lm	3.63	54	−55	49
Middle frontal gyrus	R	16 777	3.98	35	27	38
Frontal pole	R	lm	3.87	34	46	5
Frontal pole	R	lm	3.80	37	45	6
Middle frontal gyrus	R	lm	3.73	54	15	44
Middle frontal gyrus	R	lm	3.72	56	15	41
Frontal pole	R	lm	3.58	16	53	14

Note: Results were corrected for multiple comparisons by using a cluster threshold of $Z > 2.3$, and a corrected cluster significance threshold of $P = 0.05$. Main peak *Z*-values (and up to 5 local maxima within each cluster) and size of clusters (number of voxels) in standard 1 × 1 × 1 mm MNI space were extracted and presented in the table. For anatomical denotation, visual inspection, and the Harvard Oxford cortical and subcortical structural brain atlases as incorporated in the FSL software were applied.
lm, local maxima; R/L, right/left; Δ stable task-set maintenance, stable task-set maintenance time epoch 1 vs. stable task-set maintenance time epoch 4.

control after TBI: 1) during Not-X CPT performance, TBI survivors demonstrated an overall shift toward utilizing more adaptive task control processes in a core region for cognitive control in the MFC, 2) accompanied by increased stable task-set maintenance BOLD activations as an effect of TOT in the right IPL and PFC, as compared with healthy controls. Increases in BOLD activation were related to 3) injury severity in a linear dose-dependent fashion and 4) to lower levels of self-reported problems with cognitive control, a relationship only present in TBI survivors, and not in healthy controls.

Increased Reliance on Adaptive Task Control in the MFC After TBI

In the context of no general whole-brain differences and highly similar performance, TBI survivors had increased activation related to adaptive task control in an a priori chosen ROI in the MFC known to be extremely reliably activated during both adaptive and stable control processes (Dosenbach et al. 2006; Olsen et al. 2013). Interestingly, this increase in activation had a linear dose relationship to injury severity, with stronger activation with more severe TBI, when adjusted for age, education, and fMRI task performance. Moreover, there was no difference in activation between healthy controls and TBI survivors for the overall stable task-set maintenance contrast in the same MFC ROI.

Increased activations after TBI within the MFC have been found in several other studies using other cognitive tasks (Christodoulou et al. 2001; Scheibel et al. 2007; Rasmussen et al. 2008) and been related to injury severity in a study that included 30 patients with sub-acute (3 months after injury) TBI (Scheibel et al. 2009). Our study extends previous findings by showing that adaptive and stable control processes are affected differently by injury severity and that these changes are persisting into the chronic stage. More specifically, in a task where TBI survivors could uphold similar performance to healthy controls, they recruited more neuronal resources related to adaptive task control. This can be interpreted as a compensatory mechanism, similar to findings in other populations (Paxton et al. 2008; Edwards et al. 2010; Braver 2012). It should, however, be noted that in these previous studies, both increased probe related, and at the same time reduced cue related, PFC activation was observed. This was not the case in the present study, as there was no significant group difference for the stable task-set maintenance contrast. One possible explanation for this result could be that it was partially influenced by increased variability, in particular in the TBI group, due to TOT-related changes in this contrast.

Increased TOT Effects for Stable Task-Set Maintenance in TBI Survivors

A whole-brain exploratory analysis investigating differences between healthy controls and TBI survivors revealed differences in TOT effects for stable task-set maintenance, but not for adaptive task control. This supports that stable task-set maintenance is particularly susceptible to cognitive fatigue as a

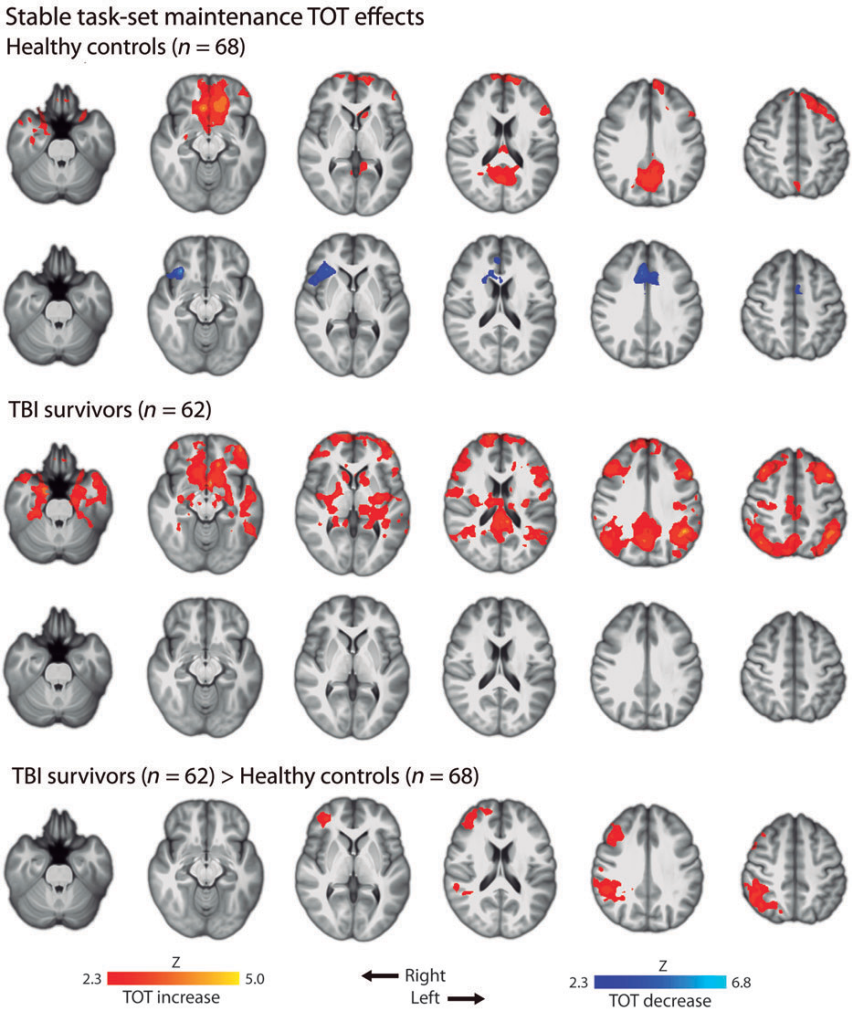

Figure 2. Whole-brain TOT effects for stable task-set maintenance. SPMs are corrected for multiple comparisons using a cluster threshold of $Z > 2.3$, $P = 0.05$. Results are presented on a 1-mm MNI standard space template. SPM, Statistical Parametric Mapping; MNI, Montreal Neurological Institute.

function of TOT (Olsen et al. 2013). Clusters of increased BOLD activation as a function of TOT were found in TBI survivors, as compared with healthy controls, with main peaks in the IPL and PFC in the right hemisphere. The IPL and PFC have been suggested to play a crucial role in a right lateralized attention control network (Corbetta and Shulman 2002). The right IPL has also previously been related to Not-X CPT performance (Ogg et al. 2008; Tana et al. 2010) and suggested to be part of the core network for cognitive control (Olsen et al. 2013). Moreover, in addition to PFC regions, a region just posterior to this right IPL region has previously been related to cognitive fatigue after TBI (Kohl et al. 2009).

The right PFC in particular is more extensively recruited in response to increased task demands in several neurological populations, including TBI (Hillary 2008). This recruitment may indicate that increased cognitive control resources are allocated. It has also been observed that PFC activations in TBI increase from the early stage after TBI until 6 months later (Sanchez-Carrion et al. 2008), suggesting that such increases represent an adaptive change in this region developing in the rehabilitation phase after injury.

In TBI survivors, the TOT effect was shown to be linearly related to injury severity, after adjusting for age, education, and fMRI task performance. This implies underlying injury-specific changes involved in the stable task-set maintenance TOT increase differences. Both in this and in a previous study (Olsen et al. 2013), there were no within-group changes in commission errors as an effect of TOT. There were, however, changes in response time, omission errors, and response style, suggesting that the threshold for Not-X responses was

Table 5
Correlations between BOLD activation and self-report measures of cognitive control for TBI survivors and healthy controls

	BRIEF-A		
	BRI	MI	GEC
TBI survivors ($n = 62$)			
Overall main contrasts[ab]			
Stable task-set maintenance MFC	−0.177	−0.363**	−0.305*
Adaptive task control MFC	−0.077	−0.058	−0.069
Stable task-set maintenance TOT effects[bc]			
MFC	−0.346*	−0.281*	−0.322*
Right IPL	−0.423**	−0.400**	−0.431**
Right PFC	−0.369**	−0.317*	−0.355**
Healthy controls ($n = 67$)			
Overall main contrasts[a]			
Stable task-set maintenance MFC	−0.091	0.009	−0.048
Adaptive task control MFC	−0.078	−0.062	−0.077
Stable task-set maintenance TOT effects[c]			
MFC	−0.081	−0.074	−0.085
Right IPL	−0.222	−0.067	−0.145
Right PFC	0.100	0.089	0.103

Note: Partial correlations (r) between NOT-X CPT fMRI ROI parameter estimates and BRIEF-A measures. One healthy control was excluded from the analyses involving BRIEF-A due to several missing item scores (see Methods).
[a]Controlled for age, education, and Not-X CPT performance measures. [b]Additionally controlled for GCS score. [c]Controlled for age, education, and Δ Not-X CPT performance measures.
*$P < 0.05$ (two-tailed). **$P < 0.01$ (two-tailed).

increased, implying a top-down regulation through strategy change. It makes sense that compensatory mechanisms are more readily implemented in a top-down fashion, rather than in a system relying on reactive bottom-up processes. A disadvantage of proactive- (stable) as opposed to reactive (adaptive) control is that it is computationally more demanding and thereby uses more neural resources (Braver 2012). By engaging the stable task-set maintenance network, there are fewer resources available for other tasks over a prolonged period of time. It is therefore plausible that an increased reliance on stable task-set maintenance relative to adaptive task control may lead to increased fatigue after TBI (Kohl et al. 2009; Ponsford et al. 2012), despite partially compensating for some of the cognitive deficits after injury (Braver 2012). However, this needs to be further investigated as the present study was limited by the lack of an independent measure of fatigue to specifically evaluate this interpretation.

In order to activate the bottom-up adaptive system, particularly salient stimuli are needed (Seeley et al. 2007; Menon and Uddin 2010). In light of this, it can be speculated whether the shift toward increased adaptive processing within the MFC as found in the overall adaptive task control contrast represents an increased burden on the adaptive system due to insufficient compensation (preparation) by the use of stable task-set maintenance (Jahfari et al. 2012). Since the number of commission errors was stable throughout the task and TOT effects were not seen for BOLD activation related to adaptive task control in this study, future studies should aim to investigate nonlinear relationships or functional connectivity interactions between the 2 networks in order to test this hypothesis (Dosenbach et al. 2007; Hillary et al. 2011; Bonnelle et al. 2012; Gratton et al. 2012).

Both TBI survivors and healthy controls had pronounced within-group increases of activation in areas of the DMN as an effect of TOT. Activations in DMN regions have been linked to prospective planning (Buckner et al. 2008), hence suggesting a possible role in a proactive compensatory control system (Braver 2012). However, increased activity in DMN areas such as the precuneus and posterior cingulate cortex has previously also been related to impairments of sustained attention in TBI patients (Bonnelle et al. 2011), possibly due to a failure in successfully deactivating these regions (Weissman et al. 2006). Moreover, disrupted structural white-matter integrity between typical task-positive regions, such as anterior insula and pre-supplementary motor cortex/anterior cingulate gyrus, may be related to this failure (Bonnelle et al. 2012). TBI survivors in our study also seemed to recruit more pronounced DMN node activation; however, despite the already mentioned findings in the right IPL, no other DMN regions survived the statistical threshold in a direct comparison between the groups.

According to the within-group analysis of TOT effects, TBI subjects also recruited additional subcortical regions, including the basal ganglia. Previous fMRI studies have highlighted the role of the interaction between the basal ganglia and frontal cortex for proactive selective response suppression (Majid et al. 2013), as well as decision-making under time pressure (Forstmann et al. 2008). Moreover, in their model of central fatigue, Chaudhuri and Behan (2000) proposed that fatigue observed in a range of patient groups might be caused by a failure of the non-motor function of the basal ganglia, which in turn may affect the striatal–thalamic–frontal cortical system. Particularly interesting in this context is that increased activation in the basal ganglia related to cognitive fatigue in TBI survivors was observed in a study utilizing an ROI analysis specifically aimed at investigating this model (Kohl et al. 2009). Furthermore, an interesting line of very recent TBI research demonstrated that reduced fronto-striatal white-matter integrity (Leunissen et al. 2013a) and possibly related subcortical atrophy changes (Leunissen et al. 2013b) were associated with task-switching impairments.

Another interesting within-group observation was that healthy controls demonstrated a stable task-set maintenance TOT decrease in the MFC and right insula, which are part of the core network for cognitive control (Dosenbach et al. 2006; Olsen et al. 2013), whereas no such effect was apparent within the TBI group. Such a TOT decrease can be interpreted as a habituation effect or reduced processing needs due to a practice effect. An important factor to consider is that compensation and/or habituation may be displayed differently in healthy controls and TBI survivors. In accordance with the compensation hypothesis, it has been found that TBI survivors exhibit increased TOT-related activation during performance of a modified coding task, both within-group and as compared with healthy controls (Kohl et al. 2009). However, healthy controls in the same study demonstrated decreased TOT-related activation on a within-group level, which is better accommodated by a habituation hypothesis (Kohl et al. 2009). The finding that compensation/habituation mechanisms may be different in injured- as compared with healthy-brains was also supported by our study. This was demonstrated by the fact that stable task-set maintenance TOT activity increase during Not-X CPT was functionally related to BRIEF-A only in TBI survivors and not in healthy controls.

In mixed fMRI designs, there is generally a tendency for lower statistical power for event-related, relative to block-related, contrasts (Miezin et al. 2000; Petersen and Dubis 2012). Additionally, in the present study, there were relatively few non-targets as compared with targets in the Not-X CPT (48 vs. 432), potentially introducing additional concerns regarding the sensitivity and precision of this contrast. However, as

demonstrated in our previous study in healthy participants (Olsen et al. 2013) as well as the ROI analysis in the present study, this contrast yielded extremely robust results on a within-group level. It is therefore highly unlikely that the observation of less between-group differences related to adaptive task control, as compared with stable task-set maintenance, was merely caused by a lack of statistical power. An alternative explanation for more general TBI-related increases in the BOLD signal without presence of differences in task performance may be that they are driven by permanent functional brain reorganization (Hillary 2008), or physiological and structural factors not related to function as such (Hillary and Biswal 2007). However, the finding of significant between-group TOT effects makes this explanation unlikely, as these are within-task transient changes, more likely to be related to compensation (Hillary 2008). Another potentially confounding factor is that the presence of global signal change may introduce noise in the data when investigating the BOLD signal over an extended time period. We used a well-balanced task design and analysis approach (e.g., by combining 2 runs) in addition to conventional filtering to minimize this effect. Furthermore, the fact that TOT effects were present in typical task-positive regions for this task, and that they were different between groups, also gives a strong indication that our results were not due to such effects (Fox et al. 2009).

TBI-Related BOLD Increases Might Play a Compensatory Role for Everyday Cognitive Control Function

Stable task-set maintenance BOLD signal increases during the task as a whole and in particular as an effect of TOT were related to experiencing less everyday problems with cognitive control as measured with BRIEF-A. This was only evident in TBI survivors, and not healthy controls, suggesting that the increased BOLD activations may represent injury-specific compensatory mechanisms successfully applied in unrestricted everyday-life situations after injury. Considering the underlying positive linear association between BOLD increase and injury severity, it is noteworthy that the association between self-reported cognitive control function and increased activation was present after adjusting for injury severity. Consequently, the increased BOLD activation appears to represent both injury severity mechanisms and compensatory mechanisms associated with improved self-reported cognitive control function.

An important implication from these findings is that caution should be applied when generalizing relationships between cognitive control and BOLD activation in healthy controls to those of neurological populations such as TBI (Hillary and Biswal 2007), also due to the fact that differences in signal changes appear to be multifactorial. As discussed earlier, differences with regard to habituation and compensatory mechanisms in the healthy and injured brain (Kohl et al. 2009) may further complicate the interpretation of differences in neuronal activation between healthy controls and neurological populations such as TBI.

An alternative explanation of our results may be that TBI survivors who exhibit BOLD increases underreport their cognitive deficits, due to impaired self-awareness, which may be present in some TBI survivors (Hart et al. 2005). This is, however, rather unlikely, given the temporally dynamic TOT effects, and that impaired self-awareness in chronic TBI usually is considered a more stable trait. Also, previous studies have demonstrated relatively strong agreement on the magnitude of cognitive deficits between family informants and TBI survivors (Lannoo et al. 1998; Lovstad et al. 2012). However, future studies should aim to investigate this aspect more directly, for example by relating BOLD increases after moderate-to-severe TBI to scores on the informant version of the BRIEF-A.

Summary and Conclusions

This study demonstrated that the neural underpinnings of adaptive and stable task control processes are differently affected by injury and that increased BOLD activations observed in moderate-to-severe TBI survivors might represent injury-specific compensatory mechanisms also utilized in everyday-life situations. A particular strength of this study was that results were adjusted for the effects of fMRI task performance, as well as the established outcome moderators, age and education.

To this date, this is the largest fMRI study in survivors of moderate-to-severe TBI. New knowledge was provided utilizing a validated fMRI-adapted version of a commonly administered clinical continuous performance test, carefully integrated within an innovative neurocognitive theoretical framework. By relating fMRI findings to the most comprehensive and increasingly popular self-report form for cognitive control function (BRIEF-A), this knowledge has the potential for giving rise to valuable new questions within basic and clinical TBI research, as well as new perspectives for interpretation of clinical test results.

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Notes

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Paper IV

White matter microstructure in moderate-to-severe traumatic brain injury: the impact of acute phase injury related variables and associations with global outcome, performance-based and self-reported cognitive control function

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Abstract

The first aim of this study was to elucidate the impact of acute phase injury related and neuroimaging variables on white matter fractional anisotropy (FA), mean diffusivity (MD) and tract volumes in chronic moderate-to-severe traumatic brain injury (TBI) survivors. The second aim was to examine the association between different chronic phase outcome measures (Glasgow Outcome Scale Extended scores, performance-based and self-reported cognitive control functioning) and FA, MD and tract volumes. Diffusion tenor imaging (DTI) at 3T was acquired >1 year after TBI in 49 moderate-to-severe TBI survivors and 50 matched controls. DTI data was analyzed with tract based spatial statistics and automated tractography. Moderate-to-severe TBI led to widespread FA decrease, MD increase and tract volume loss. FA was the primary denominator of injury severity demonstrated in comparisons of severe vs. moderate TBI, motor vehicle vs. fall accidents, and presence of diffuse axonal injury versus not. Reduced FA in thalamus and brain stem were specific to all grades of DAI. In chronic TBI, FA and MD were associated with Glasgow Comas Scale scores, number of microhemorrhages, and lesion volume on fluid attention inversion recovery images from the acute phase. In severe TBI, number of days with ≥3 episodes of cerebral perfusion pressure <70 mmHg was specifically associated with reduced MD, no effect of intracranial pressure (ICP) >20 mmHg on FA or MD was observed. Rotterdam computer tomography scores, mostly reflecting increased ICP due to edema and/or mass lesion, did not influence chronic phase FA or MD. Poor global outcome and performance-based cognitive control functioning were associated with widespread FA and MD changes in the TBSS analysis. Only MD from the automated tractography analysis correlated consistently with general outcome. Self-reported cognitive control function was not related to FA, MD or tract volumes. In conclusion, the primary traumatic injury mechanism and severity had significant impact on loss of FA and its distribution, while possible secondary pathophysiological mechanisms such as increased ICP or decreased CPP had no or limited effects on white matter microstructure in the chronic phase. General and performance-based outcomes in the chronic phase were associated with both FA and MD, but highly inconsistently with tract volume.

Keywords: MRI, head injury, intensive care unit, executive function, BRIEF

Introduction

The axons of white matter (WM) are particularly vulnerable to stretch associated with acceleration-deceleration forces in traumatic brain injury (TBI) (STRICH 1956, Peerless & Rewcastle 1967). The ensuing WM pathology is a diffuse, predominantly secondary axotomy described as diffuse axonal injury (DAI) (Smith *et al.* 2003, Povlishock 1992). Oligodendrocytes and myelin sheaths are also affected in DAI, and the changes in these structures take place over a very protracted time course (Coleman & Freeman 2010, Johnson *et al.* 2013b). DAI has been observed in all TBI severities (Bigler 2013b, Bigler 2013a).

Diffusion tensor imaging (DTI) is a magnetic resonance imaging (MRI) technique for assessing WM microstructure *in vivo* (Pierpaoli *et al.* 1996, Basser & Pierpaoli 1996, Beaulieu 2002). This technique has been shown to depict DAI in TBI survivors even when there is no sign of injury on conventional MRI (Newcombe *et al.* 2011, Kumar *et al.* 2009). From DTI, several measures can be derived of which fractional anisotropy (FA) and mean diffusivity (MD) are commonly reported. FA is a measure considered to reflect primary and secondary axonal injury in TBI (Bigler 2013a, Li *et al.* 2013), while mean diffusivity (MD) in general is considered a measure of disorders of myelination as well as loss of axons (Song *et al.* 2005, Song *et al.* 2002, Li et al. 2013). DTI data can be analyzed with different approaches, and it has been suggested that a combination of several methods should be used to explore the complexity of WM injury in TBI (Spitz *et al.* 2013, Leunissen *et al.* 2014). In the current study tract based spatial statistics (TBSS) (Smith *et al.* 2006) and an automated tractography method (Visser *et al.* 2011) not previously used in TBI, were implemented.

Earlier studies have shown that both WM FA and MD are altered in chronic TBI of varying severity (Bendlin *et al.* 2008, Inglese *et al.* 2005, Kumar et al. 2009, Xu *et al.* 2007). WM tract volume reduction has not been examined as extensively as FA and MD in TBI, and the results so far are inconsistent (Brandstack *et al.* 2013, Kurki *et al.* 2013). However, total WM volume has been shown to decline slowly, and not be significantly reduced

before 1 year after injury (Brezova *et al.* 2014). Thus, it is possible that WM tract volume loss is better portrayed in a late chronic phase as in the current study. Moreover, the histopathological changes in WM take place over several years following TBI (Johnson *et al.* 2013a, Johnson et al. 2013b), and therefore time since injury may impact on WM FA, MD and volumes.

A particular goal of the current study was to verify if FA, as opposed to MD, is the DTI measures primarily reflecting injury severity, as would be expected based on the specific increase in axonal loss in all WM regions with more severe injury (Gennarelli *et al.* 1982, Povlishock 1992). It follows that the FA decrease should be greater in severe than moderate TBI. Likewise, presence of DAI and increasing severity of DAI grade should be associated with a more notable FA decrease. As DAI results from strong acceleration/deceleration forces, present in motor vehicle accidents (MVA) to a larger extent than in falls (Adams *et al.* 1984, Adams *et al.* 1982, Davceva *et al.* 2012, Meythaler *et al.* 2001), we predicted that TBI survivors of MVA had more conspicuous FA decreases than those surviving falls.

The second aim was to explore the relationship between WM FA and MD and common clinical and neuroimaging variables from the acute and subacute phase of TBI. Since the propagation of traumatic forces through WM has direct impact on the level of consciousness after TBI (Meythaler et al. 2001), we predicted that Glasgow coma scale (GCS) scores would be associated with both FA and MD changes in the corpus callosum (CC), hemispheric WM, and mesencephalon (Chatelin *et al.* 2011, Levin *et al.* 1988, Ommaya & Gennarelli 1974). Correlations between GCS scores and tract volumes were also investigated. Posttraumatic amnesia (PTA) describes alterations in alertness, emotional responses and processing in several cognitive domains, not only memory, following TBI (Marshman *et al.* 2013). To date only the relationship between PTA and FA in mild TBI has been studied using a whole brain WM region of interest (ROI) approach (Benson *et al.* 2007). DAI grading based on conventional MRI is used to assess the severity of DAI in TBI in the clinic (Gentry 1994). The presence of micro hemorrhages versus no micro hemorrhages has been shown to reduce FA and increase MD in several WM tracts, indi-

cating a relationship between conventional MRI based DAI grading and DTI measures (Kinnunen *et al.* 2011). How DAI, as reflected in number of micro hemorrhages and lesion volume load on fluid attention inversion recovery MRI in the early phase of TBI, is associated with chronic phase FA and MD is yet unknown. By elucidating this relationship the potential of everyday clinical practice for assessing extent of WM involvement in TBI can be reappraised. Rotterdam computer tomography (CT) scores (Maas *et al.* 2005) from acute phase CT scans are used as an outcome predictor in TBI patients. These scores reflect mainly the presence of brain edema and mass lesions, and therefore increasing intracranial pressure (ICP). Whether the increased ICP associated with such changes have long term effects on WM microstructure remains relatively unexplored. The results from an animal study (Lafrenaye *et al.* 2012) and a patient study (Newcombe et al. 2011) in the acute and subacute phase, respectively, indicate that elevated ICP does not increase WM injury in the adult. To further elucidate the role of ICP on WM, we examined the effect of ICP increases as measured in the intensive care unit (ICU) in a subgroup of severe TBI patients. The effect of decreased cerebral perfusion pressure (CPP), which is associated with risk of ischemic brain injury (Bullock & Povlishock 2007), was also investigated in the same TBI group. In other pathologies (e.g. premature birth, cerebrovascular disease), as well as in aging, reduced CPP leads primarily to demyelination, and if sufficiently severe also axonal damage (Børch *et al.* 2010, Back 2006, Vernooij *et al.* 2008, Fazekas *et al.* 1993). Hence CPP decreases in TBI may affect MD more than FA. Normal aging leads to both lower FA and increased MD (Bendlin *et al.* 2010). TBI impacts on the normal age related changes in WM microstructure, remains unknown.

The third main aim of this study was to investigate the relationship between WM microstructure and different types of outcome. The outcome measures included general outcome as measured with Glasgow Outcome Scale Extended (GOSE), as well as both performance-based and self-reported cognitive control function. Cognitive control or executive control function appears to be particularly important for independent living and mental health following TBI (Finnanger *et al.* 2013, Spitz et al. 2013). One key challenge in the clinical assessment of cognitive control function is that it is multifaceted, and not considered not to be fully captured by performance-based neuropsychological tests

(Toplak *et al.* 2013, Isquith *et al.* 2013). As a consequence, structured self-report measures of cognitive control function have gained popularity, and are now widely used in clinical evaluations of TBI survivors. Despite a certain degree of overlap, information from performance-based and self-report measures is clearly measuring different aspects of cognitive control (Toplak et al. 2013, Isquith et al. 2013). Whether self-reported and performance-based cognitive control measures are supported by the same neuronal correlates remain unexplored. Previous studies in TBI have primarily examined the relationship between outcome measures and FA (Niogi *et al.* 2008, Spitz et al. 2013, Hulkower *et al.* 2013), but some have included for instance MD or other combinations of DTI measures (Betz *et al.* 2012, Kinnunen et al. 2011, Sidaros *et al.* 2008). In the current study the associations between FA, MD and tract volumes as obtained from TBSS and automated tractography and different outcome variables were examined with the goal of establishing which of the WM measure(s) best describes outcome.

Materials and methods

The study protocol adhered to the Helsinki Declaration and was approved by the Regional ethics committee. All participants received financial reimbursement of 1000 Norwegian kroner. Written informed consent was obtained (also from parents if participants were under the age of 16).

TBI group

A total of 73 survivors with chronic (> 1 year after injury) moderate to severe TBI according to the Head injury severity scale (HISS) (Stein & Spettell 1995) were recruited from the prospective and consecutive head injury database at St. Olav's Hospital, Trondheim University Hospital, Norway (Skandsen et al. 2009). All were admitted in the period 2004-2008. Inclusion criteria in the present study were age between 14-66 years at time of DTI, fluency in the Norwegian language, ability to cooperate during neuropsychological testing as indicated by GOSE scores of ≥ 5 at 12 months after injury, absence of head injury before the injury leading to inclusion in the head injury database, neurologic or psychiatric condition, as well as standard MRI contraindications. Data from the acute phase related to injury mechanism, TBI severity, CT and MRI neuroimages, and

clinical data. For severe TBI patients admitted to the ICU, ICP and CPP data was obtained from the ICU part of the head injury database (Schirmer-Mikalsen *et al.* 2013). At time of the DTI investigation in the chronic phase of TBI, outcome data were collected.

Healthy control group

In total, 78 healthy age, sex and education matched controls were recruited (from friends and family of TBI patients, as well as from different workplaces). The healthy controls underwent the same examinations as the TBI survivors at time of DTI scanning.

Acute phase data

Injury mechanism was classified as motor vehicle accident (MVA), fall or other. Classification of the TBI as moderate or severe was done using HISS scores (Stein & Spettell 1995) which in turn is also based on the Glasgow Coma Scale (GCS) on admission (Teasdale & Jennett 1974). GCS score was assessed at time of arrival in the emergency room, or before intubation in case of a pre-hospital intubation. All patients included had GCS score ≤13 that could not be explained by other factors than the head injury (Skandsen *et al.* 2010, Moen *et al.* 2012). A GCS score ≤ 8 is considered as severe while GCS score between 9-13 as moderate TBI according to the HISS criteria (Stein & Spettell 1995).

The Rotterdam CT score (Maas et al. 2005) used was from the worst CT scan obtained in the acute phase. The Rotterdam CT scoring was performed by one radiologists.

MRI at 1.5T (Siemens Symphony Sonata; Siemens Medical, Erlangen, Germany) was acquired as soon as feasible and the clinical condition allowed for it, between 2-41 (mean 12) days post injury. Sagittal turbo spin-echo (TSE) T2 weighted, sagittal, coronal and transverse T2 fluid attenuated inversion recovery (FLAIR) weighted, transverse T2* weighted gradient echo imaging (GRE) and diffusion weighted imaging (DWI) with diffusion gradients in x, y and z dimensions and images at b=0, 500 and 1000 s/mm^2 were used for DAI classification by two experienced senior neuroradiologists (Skandsen et al., 2010). DAI was classified into Grade 1; traumatic lesions confined to lobar WM, Grade

2; lesions also detected in CC, and Grade 3; presence of brainstem lesions (Gentry 1994). Total number of microbleeds was counted in the T2* scans and total FLAIR lesion volume obtained from manually drawn FLAIR lesion masks (Moen *et al.* 2014, Moen et al. 2012).

In the TBI patients duration of PTA was assessed and recorded during the subacute phase by experienced clinicians based on notes from nurses in the records, patients recall of events or, for patients referred to rehabilitation, with the orientation log (Jackson *et al.* 1998). PTA duration was categorized into intervals of 0-1 week, 1-2 weeks, 2-3 weeks, 3-4 weeks and >4 weeks (RUSSELL & SMITH 1961).

A total of 21 included severe TBI survivors were treated in the ICU. There is no level 1evidence for recommending thresholds for ICP or CPP (Bullock & Povlishock 2007). The guideline suggests ICP to be kept below 20-25 mmHg, which has been shown to improve outcome (Vik *et al.* 2008, Karamanos *et al.* 2014). In this study ≥ 3 episodes of ICP >20 mmHg during one day was registered as deviating from the treatment goal. For CPP the data are less consistent with regard to outcome, perhaps due to variable methods of deriving CPP (Rao *et al.* 2013), and/or the presence of varying degrees of autoregulation deficits in TBI patients (White & Venkatesh 2008). The guidelines from 2007 recommend a CPP of <60 mmHg, but CPP <70 mmHg is advocated under certain circumstances to avoid risk of ischemia (Bullock & Povlishock 2007). The earlier guidelines used a cut off of CPP <70 mmHg (Maas *et al.* 1997). The patients in this study were admitted to the ICU before as well as after the guidelines for CPP treatment goals were changed. In the ICU database ≥ 3 episodes per day with CPP <70 mmHg, 60-69 and <60 mmHg are registered. Since there were few days with ≥ 3 episodes of CPP <60 mmHg, the number of days with ≥ 3episodes <70 mmHg were used in this study. For details on ICU treatment after implementation of the 2007 guidelines see (Schirmer-Mikalsen et al. 2013).

Chronic phase data

Time since injury was calculated as number of days between the time of injury and the DTI scan was performed.

Global outcome was assessed with Glasgow Outcome Scale Extended (GOSE) assessing social reintegration and independent living after TBI (Wilson *et al.* 1998, Jennett *et al.* 1981). GPOSE was scored face-to-face, using a structural interview by trained experimenters at the time of DTI. GOSE scores range from 1 (dead, minimum score) to 8 (upper level good recovery, maximum score).

Number of years of completed education was assessed based on both a self-report form and an interview at time of scanning.

The Behavioral Rating Inventory of Executive Function Adult version (BRIEF-A) was included as a self-report measure of cognitive control function (Roth 2005). BRIEF-A consists of 75 items measuring behavioral, emotional and cognitive aspects of cognitive control functioning. Each item is rated on a three-point frequency scale (0 = never; 1 = sometimes; 2 = often). Five of the 75 items are designed to detect invalid response styles (inconsistencies or negativity), while the remaining 70 items make up three composite index scores: the global executive composite score, behavioral regulation index, and metacognitive index. The global executive composite score consists of items measuring inhibition, shift, and emotional control, while behavioral regulation index reflects self-monitoring items, and the metacognitive index includes items describing initiation, working memory, planning/organization, task monitoring, and organization of materials.

The D-KEFS Trail Making Test (D-KEFS TMT) (Delis DC 2001) was included as a performance based measure of cognitive control functions. D-KEFS TMT consists of five different subtests where subtest 1 is visual scanning, subtest 2 is letter sequencing, subtest 3 is number sequencing, subtest 4 is letter-number sequencing, and subtest 5 is motor speed. Time used to complete each subtest was included in further analyses.

Statistical comparisons of demographics and cognitive control measures between TBI and controls

Independent t-tests were applied in order to test group differences in age, years of completed education, and scores on the performance-based cognitive control measure D-KEFS TMT and the self-reported measure, BRIEF-A. A chi square analysis was used to test differences in proportions between groups with regard to sex distribution. The level of statistical significance was set to $p < 0.05$ (two sided).

Chronic phase MRI acquisition

DTI scans were acquired in the chronic phase of TBI on a 3 T Siemens Trio with Quantum gradients (30 mT/m) with a 12-channel Head Matrix Coil (Siemens AG, Erlangen, Germany). The DTI sequence was a single-shot balanced-echo EPI sequence acquired in 30 non-collinear directions with b = 1000 s/mm^2 using the following parameters: TR = 6800 ms, TE = 84 ms, FOV 240 x 240 mm, slice thickness 2.5 mm, acquisition matrix 96 x 96, giving isotropic voxels of 2.5 mm. Fifty-five transversal slices with no gap were acquired giving full brain coverage. For each slice, six images without diffusion weighting (b=0), and 30 images with diffusion gradients were acquired. The DTI sequence was repeated twice to increased signal to noise ratio. In order to correct for image distortion caused by magnetic susceptibility artifacts two additional b=0 images were acquired with opposite phase-encoding polarity (Holland *et al.* 2010).

DTI analyses

DTI data was analyzed with the tools of the FMRIB software library (FSL, Oxford Centre for Functional MRI of the Brain, UK; www.fmrib.ox.ac.uk/fsl) and automated tractography as described by Visser et al. (2011). First the two DTI acquisitions and extra b=0 images were merged into a single 4D file, and image artifacts due to motion and eddy current distortions were minimized by registration of the DTI acquisitions to the b=0 image using affine registration. Image distortion caused by magnetic susceptibility artifacts was minimized with a nonlinear B0-unwarping method using paired images with opposite phase-encoding polarities, resulting in opposite spatial distortion patterns, and align-

ment of the resulting images using a fast nonlinear registration procedure (Holland et al. 2010). The brain was extracted using Brain Extraction Tool (BET, part of FSL).

Tract-based spatial statistics (TBSS)

FMRIB's Diffusion Toolbox (FDT) was used to fit a diffusion tensor model to the raw diffusion data in each voxel. Voxelwise maps of the eigenvalues (λ_1, λ_2, λ_3), FA and MD were calculated for the TBI and control groups. Voxelwise statistical analysis of the diffusion data was performed using Tract-Based Spatial Statistics (TBSS, part of FSL) (Smith *et al.* 2007, Smith et al. 2006). Briefly, all subjects' FA data was aligned to each other, thereby identifying the "most typical" subject in the study, which was used as the target image. This target image was affine-aligned to the MNI152 standard space using a nonlinear registration tool IRTK (part of FSL) (Rueckert *et al.* 1999), and all the FA images were transformed into 1x1x1mm MNI152 space by combining the nonlinear transform to the target FA image with the affine transform from that target to MNI152 space. A mean FA image was created from all the aligned FA images, and thinned to create a skeletonized mean FA representing the centers of all WM tracts common to all the subjects in the analysis. The mean FA skeleton was thresholded to FA $\geq$ 0.2 to include the major WM pathways, but exclude peripheral tracts and grey matter. Each subject's aligned FA data was then projected onto the skeleton by searching perpendicular from the skeleton for maximum FA values in individual subject's FA map. Statistical comparisons were then restricted to voxels in the skeleton. Voxelwise statistics of the skeletonized FA, MD and eigenvalue data were carried out using Randomise (part of FSL) to test for group differences (FA, MD and eigenvalues) and to examine the relationship between FA and MD and the different independent variables. Randomise carries out permutation-based testing and inference using Threshold-Free Cluster Enhancement (TFCE) (Nichols and Holmes, 2002) with a correction for multiple comparisons, and the statistical threshold for all the analysis were $p<0.05$, corrected for sex and age at MRI. Two sample independent t-tests were performed to investigate the presence of significant group differences in FA and MD between the entire TBI group versus healthy control group, and for dichotomized TBI groups: moderate versus severe TBI, injury mechanism MVA versus fall, no DAI (grade 0) versus all DAI (grades 1+2+3), DAI (grade 1) versus DAI (grade

2+3) groups. Randomise was also used to examine the relationship between FA and MD and the demographic (age at time of DTI), injury related (GCS score and time since injury), clinical (duration of PTA, number of days with ≥ 3 episodes of ICP >20 mmHG or CPP < 70 mmHg), neuroimaging (number of micro hemorrhages, volume of FLAIR lesions and Rotterdam CT scores), global outcome (GOSE scores), self-reported (BRIEF sub-indices), and performance-based (D-KEFS TMT subtests 1-5) cognitive control function, performed as separate regression analyses. The anatomical locations of regions with significant group differences or associations with regard to FA and/or MD were identified in a WM atlas (Mori *et al.* 2005).

Automated tractography segmentation method

Tractography

The Camino package was used for diffusion analysis and generation of streamlines (Cook PA 2006). To parameterize voxel diffusion profiles, q-ball reconstruction was used, as it is computationally efficient and provides adequate resolution of crossing fibers in many white matter regions (Tuch 2004). Spherical harmonics up to fourth order were used as basis functions. Up to three principal diffusion directions were determined in each voxel and these were used as a basis for tractography. Streamlines were generated using the interpolated deterministic streamlining method, as implemented in Camino, with an FA threshold of 0.15. All voxels with an FA value greater than 0.25 were used as seed voxels.

Nonlinear registration

The mean b=0 volumes for all subjects were affinely registered with FLIRT (part of FSL) to the MNI152 template. A custom group template was created by averaging the registered volumes. The original b=0 volumes were then nonlinearly registered with FNIRT (part of FSL) to the group template. The streamlines were warped from subject space to the group template using the deformation fields produced by FNIRT.

Clustering

To find consistent bundles of streamlines across subjects, a clustering approach previously described in Visser et al. (2011) was used, clustering the streamlines based on their pair wise distances. Before clustering, all streamlines were linearly resampled to 25 points, and the streamlines from all 99 subjects were concatenated. Clustering was performed on the merged dataset consisting of streamlines from all subjects, allowing for the identification of clusters that are consistent across all subjects. To allow for the processing of the full set of data, the multi-subject dataset was randomly partitioned into subsets of 10.000 streamlines. In each of these subsets, 250 clusters were identified using hierarchical clustering. The hierarchical clustering process is based on repeatedly finding clusters with the lowest mutual distance and merging them until 250 clusters are identified. The clustered subsets were then combined to obtain segmentations with the same number of clusters for the full dataset, using a distance-based matching procedure to find corresponding labels across subsets. The clustering step was repeated 100 times with different random partitions to obtain a stable segmentation, by selecting the cluster assignments that occurred most often for each streamline, and to find statistics indicating the consistency of these assignments between repetitions. White matter structures were then identified in 10 randomly selected subjects from both groups by extracting the corresponding labels from the multi-subject clustering result. These labels could be applied to either the original or resampled streamlines, and are consistent in all the individuals in the study. For each subject, the clusters were extracted with pruning (thresholding), and concatenated to form the corresponding fiber tracts: corpus callosum (CC), superior longitudinal fasciculus (SLF) and inferior longitudinal fasciculus/inferior fronto-occipital fasciculus (ILF/IFOF). ROIs were made for the extracted fiber tracts and converted into subject diffusion space, to extract mean FA, MD, λ_1, λ_2, λ_3 and volume for each tract separately in the left and right hemisphere in each subject. Tract volume was calculated for each WM tract by summing the number of voxels containing at least one streamline and multiplying by voxel volume. It is important to note that this value reflects the number of voxels within the tract that exceeded the tracking FA threshold, and might deviate from the actual volume.

For further analyses, values obtained from the tractography method was extracted and analyzed in SPSS. Mann-Whitney U tests (two-tailed) with significance set to p> 0.05 were used to compare FA, MD, λ_1, λ_2, λ_3 and volume of CC, left and right SLF and ILF/IFOF in the TBI and the healthy control groups due to lack of normal distributions. Separate partial correlation models adjusting for age and sex were applied for TBI survivors and healthy controls in order to investigate the relationship between the DTI measures obtained from tractography and injury severity (GCS score), global outcome (GOSE score), and cognitive control measures (BRIEF-A and D-KEFS TMT subtests1-5). For the TBI survivors, the relationship between the volumes of the tracts and DAI and time since injury was also investigated by partial correlation models adjusted for age and sex.

To more directly compare the FA values in CC from the TBSS and the automated tractography method, a ROI was manually drawn on the TBSS' WM-skeleton which only included voxels in CC. Mean FA was calculated from the CC TBSS ROI and compared with the mean FA in CC from the automated tractography method using a Mann-Whitheny U test (two tailed) with significance set to p>0.05.

For images used in figures, the FSL 1mm mean FA template was used as the background image. The images are shown in radiological convention, i.e. the right side of the subjects is on the left side of the images.

Results

In total 49 DTI scans (36 male) were suitable for analysis in the TBI group. Of the 73 TBI subjects initially included, 14 subjects were excluded due to vibration artifacts in the DTI scans, 2 due to missing DTI, 2 due to missing correction scans, and 6 due to DTI acquisitions in only 12 directions. There was ~50-50% moderate and severe TBI patients included, ¾ had any grade of DAI and about half had PTA>1 week (Table 1). The mean GOSE score at time of DTI was 6.7 (range 5-8), i.e. all TBI survivors in the current study recovered with moderate disability or better. The GOSE scores were not significant different between the moderate (6.8±1.1) and the severe TBI groups (6.5±1.1) (p=0.36).

There were 50 healthy controls matching the 49 TBI survivors that were included in the current study. They were chosen among the controls with high quality DTI scans.

A summary of the group characteristics for the TBI and control subjects included in the analyses is given in Table 1. There were no statistical significant differences with regard to age, sex distribution, length of completed education, or on the different scores on the performance-based test of cognitive control, D-KEFS TMT, between the TBI and the control groups (Table 1). With regard to the self-reported cognitive control measure, the TBI group scored significantly higher on the BRIEF-A global executive composite score and behavior regulation index than the healthy controls, but there was no group difference for the metacognitive index (Table 1).

TBSS analyses of group differences between TBI and control groups

Significantly decreased FA and increased MD were present in all major WM tracts and the brain stem in the TBI group compared to the control group (Figure 1). The reduced FA was mainly caused by an increase in the radial eigenvalues (data not shown). In the control group a strong negative association was found between FA and age at time of scanning in all major WM tracts, except for very limited involvement of the anterior and posterior limb of the internal capsule (Figure 2). A positive association between MD and age was more circumscribed and included the anterior CC, fornix, external capsule and optic radiation in the healthy controls (Figure 2). No associations between FA or MD and age were present in the TBI group.

Impact of acute phase injury related, neuroimaging and clinical variables on chronic phase FA and MD in the TBI group

Injury severity and mechanism had significant impact on FA in particular. The severe TBI group had significantly lower FA in the truncal part of CC compared to the moderate TBI group, but there was no difference in MD (Figure 1). The MVA group had significantly lower FA in the right hemisphere SLF, posterior corona radiata, ILF/IFOF and external capsule compared to the fall group (Figure 1). No differences in MD were ob-

served between the MVA and fall groups. The group with DAI had significantly lower FA in the entire CC, anterior and posterior limbs of the internal capsule, peripheral parts of intra- and inter-hemispheric tracts, thalamus and brain stem compared to the no DAI group (Figure 1). MD was not decreased in the deeper, midline structures (i.e. thalamus and brain stem), only in the long intrahemispheric tracts and CC in the DAI group compared to the non-DAI group (Figure 1). In the DAI grade 2+3 group, FA was significantly lower in the CC, and right anterior corona radiate plus external capsule compared to DAI grade 1 group, but there were no MD difference (Figure 1).

Time since injury was not associated with FA or MD values. GCS scores were positively associated with FA, most notably in CC and thalamus, but also in the external capsule, SLF, ILF/IFOF and the more peripheral hemispheric tracts (Figure 3). The MD increases associated with lower GCS scores were more or less the inverse of the FA decreases (Figure 3). PTA duration was negatively associated with FA values in all WM tracts including the peripheral hemispheric tracts and temporal lobe tracts as well as the thalamus, but excluding the posterior limb of internal capsule (Figure 3). MD was similarly, but inversely, related to PTA duration (Figure 3). Both the number of micro hemorrhages and the FLAIR lesion volume were significantly associated with reduced FA in all major WM tracts including the peripheral parts of the hemispheric WM tracts and thalamus (Figure 3). The associations between number of micro hemorrhages and FLAIR volumes with MD were the inverse of that of FA (Figure 3). Rotterdam CT scores were not associated with FA or MD values. Number of days with ≥3 episodes of ICP >20 mmHg was not associated with FA or MD changes. Number of days with ≥3 episodes of CPP <70 mmHg was associated with increased MD in the anterior CC and corona radiate (Figure 3), but no FA changes.

Associations between different outcome measures in chronic phase and FA and MD from the TBSS analysis in TBI and control groups

In the TBI group GOSE scores were positively associated with FA in CC, external capsule, SLF and ILF/IFOF including some of the more peripheral tracts, plus the brain stem (Figure 3). For MD a significant negative association was present also in the thalamus

(Figure 3). In the TBI group the scores for D-KEFS TMT subtests 1-4 were negatively correlated with FA and positively with MD in all central and peripheral WM tracts. The correlations were most striking between FA and subtest 1, 3 and 4, while the significant correlations between FA and subtest 2 were predominantly located to the right hemisphere (Figure 4). For subtests 1-4, FA and MD changes mirrored each other (Figure 4). There were no associations between FA or MD and subtest 5, i.e. the motor speed test. In the control group FA correlated with subtest 3, similarly to that in the TBI group, although the more superior brain regions and thalamus were not involved in the controls (Figure 4). There were no statistically significant correlations between FA and the other D-KEFS TMT subtests in the controls. There were no associations between the BRIEF-A sub indices and FA or MD in the TBI or control groups.

Automated tractography in TBI and control groups

Representative tractographies of CC, SLF and ILF/IFOF in one TBI survivor and one control subject are shown in Figure 5. TBI survivors had significantly lower tract volumes for all studied tracts except left SLF (Table 2). Moreover, all tracts' median FA values were significantly lower while median MD, λ_1, λ_2, and λ_3 values were significantly higher in the TBI group compared to the control groups (Table 2). The direct comparison between FA in CC obtained from TBSS and automated tractography showed that FA was significantly higher ($p<0.001$) in the TBSS analysis in both the TBI and control groups (TBI: mean FA = 0.65±0.06 (median=0.66); controls: mean FA=0.72±0.04 (median=0.72)) compared to FA from automated tractography (TBI: FA=0.41±0.02 (median=0.42); controls: FA=0.44±0.02 (median=0.43)).

In the TBI group, GCS scores were associated with volume loss in CC and right ILF/IFOF (Table 3). Furthermore, the volume of ILF/IFOF (left: r=-0.346, p=0.02; right: r=-0.470, p=0.001) was negatively correlated with DAI grade, no similar correlations were present for the other tracts' volumes. Time since injury correlated positively with CC volume (r=0.304, p=0.043), but not with the other tracts' volumes. Mean MD was the parameter from the tractograhy which was most consistently correlated with GOSE scores (Table 3). For the tract volumes, only the ILF/IFOF volumes were correlated with

GOSE scores. No other consistent findings were present (Table 3). No significant relationships between BRIEF-A sub indices scores and the automated tractography parameters were demonstrated in the TBI or healthy control groups (Table 4). D-KEFS TMT subtests 1-5 scores were somewhat inconsistently associated with FA and MD values obtained from the automated tractography analysis (Table 4). The associations with tract volumes and performance on D-KEFS TMT were even less consistent (Table 4). In the controls D-KEFS TMT subtests 1 and 3 was significantly correlated with volume of the CC, and FA plus volume of the right ILF/IFOF. No other correlations were found between the automated tractography measures and D-KEFS TMT scores in the controls.

Discussion

The present study revealed extensive changes in WM FA, MD and tract volumes in chronic moderate and severe TBI survivors with relatively good overall outcome and highly similar performance-based cognitive control function as compared to a well-matched healthy control group. There were six main findings in this study: (1) FA was the primary denominator of injury severity, (2) DAI of any grade led to lower FA in the thalamus and brain stem, (3) in severe TBI, days with CPP <70 mmHg had minor effects specifically on MD, (4) days with ICP >20 mmHg, as well as Rotterdam CT scores reflecting brain edema and /or mass lesions and thereby increasing ICP, did not significantly affect chronic phase FA or MD, (5) the relationship between chronic phase outcome and DTI measures varied between DTI analysis methods as well as between types of outcomes, but appeared in general to be associated with both FA and MD, and to a very limited extent tract volumes, (6) decreased performance-based cognitive control function following TBI was associated with widespread FA and MD changes, while self-reported cognitive control functions were not.

Impact of acute phase injury, clinical and neuroimaging variables on FA, MD and volumes in chronic moderate and severe TBI

The reduced FA in TBI resulted from increased diffusivity perpendicular to the tract axis, which implies loss of axons but also myelin (Beaulieu 2002, Song *et al.* 2003). FA was shown to be a particular sensitivity marker of injury severity as seen in the group compar-

isons between severe versus moderate TBI, MVA versus fall injuries, and DAI grade 2+3 versus DAI grade 1. These findings extend previous claims that FA is a representative measure, describing the distribution and severity of WM changes in TBI (Bigler 2013b, Bigler 2013a, Kinnunen et al. 2011).

Since DAI and GCS scores are connected (Skandsen et al. 2010, Ommaya & Gennarelli 1974, Gennarelli et al. 1982), it was not surprising that GCS scores were associated with FA as well as MD values in CC, long intra hemispheric tracts, thalamus and brainstem. This agrees with predictions of propagation of traumatic forces through WM based on biomechanical modeling as well as previously published results on the correlations between GCS scores and DTI parameters obtained in studies in several severities of TBI and using different types of DTI analysis approaches (Sorg *et al.* 2013, Adams *et al.* 1989, Chatelin et al. 2011, McAllister *et al.* 2012, Bayly *et al.* 2012). The duration of PTA was significantly associated with FA and MD in both central and peripheral WM tracts, and the thalamus. Furthermore, tracts connecting the temporal lobe with both posterior and anterior brain regions were affected. This suggests that PTA duration is a result of widespread disconnection of WM, including the temporal lobes and thalamus, which corresponds well with the overall disorientation and reduction in several cognitive domains often observed during PTA (Marshman et al. 2013). The brain correlates of PTA, however, needs further study, since few studies have examined patients during PTA. The lack of normal age related FA and MD changes in the TBI group further emphasized the impact of TBI on WM, demonstrating that moderate and severe TBI leads to WM pathology superseding normal physiological processes. There was no effect of time since injury on FA or MD in the TBSS analysis. This may be related to the fact that all TBI survivors were in the chronic phase, well past the first year after injury. One longitudinal study of FA changes over time in severe TBI showed no further decline in FA between 2 and 5 years after injury (Dinkel *et al.* 2013), and two other longitudinal studies during the first 6 months to 1 year after the injury reported changes within the time period of the studies (Kumar et al. 2009, Ljungqvist *et al.* 2011, Sidaros et al. 2008). There is also a study which showed that when taking age into account, FA and MD changes over time was not present in WM after TBI (Kinnunen et al. 2011). Taken together, FA and MD appear to

stabilize 1 year after TBI although histopathologically changes in WM continue (Vargas & Barres 2007, Johnson et al. 2013a). Surprisingly a positive correlation between time since injury and CC volume was demonstrated in the current study. It is difficult to reconcile this finding with the previous finding of total WM loss of ~ 2% of the intracranial volume during the first year after TBI (Brezova et al. 2014). One might speculate that reorganization is more prominent in the CC due to its sheer size, and/or that gliosis formation is more marked since the CC suffers the greatest strain (Chatelin et al. 2011, Levin et al. 1988, Ommaya & Gennarelli 1974), thence leading to volume increase with time since injury.

The presence and severity of DAI as described from the acute phase MRI scans (FLAIR lesion volumes, number of micro hemorrhages as well as DAI grade) were demonstrated to be closely linked to both FA and MD changes in the TBI survivors. Hence, early phase conventional MRI of DAI is a valuable tool for describing WM injury in TBI. As expected based on the distribution of DAI lesions (Gentry 1994), reduced FA and increased MD was observed in the CC in DAI grade 2 + 3 group versus DAI grade 1 group. However, there was no significant difference in brain stem FA or MD between the DAI grades. This may be due to DAI of any grade impacting on the brainstem. This interpretation is supported by the comparison no DAI versus DAI group which revealed significant FA changes in both the brainstem and thalamus in the latter group. Indeed, the brainstem appears to be particularly sensitivity to DAI as significantly smaller brain stem volumes are observed in all grades of DAI versus non DAI already in the acute phase of TBI (Brezova et al. 2014). Furthermore, the present results demonstrated that the thalamus was particularly sensitive to DAI. The thalamic FA changes in the chronic phase may reflect secondary changes resulting from disconnection of the thalamus and cortex due to DAI in corona radiata, and/or represent primary thalamic injury as DAI lesions in thalamus are present in early phase after TBI (Moen et al. 2014, Moen et al. 2012, Little *et al.* 2010). Only the volume of ILF/IFOF was correlated with DAI grade. This finding may point to deeper hemispheric tracts as being more affected with increasing DAI grade.

Number of days with ≥3 episodes of CPP <70 mmHg was associated with increased MD, but no changes in FA in the TBI group admitted to ICU. This suggests that oligodendrocytes are particularly vulnerable to CPP decreases in TBI, similar to observations in other cerebral pathologies and in normal aging (Børch et al. 2010, Back 2006, Vernooij et al. 2008, Fazekas et al. 1993). The cut-off of CPP<70 mmHg is high according to today's guidelines (Bullock & Povlishock 2007), and may include normal physiological CPP fluctuations. However, since the number of events was based on number of days with at least 3 episodes of CPP <70 mmHg, it seems likely that CPP dysregulation was present in the severe TBI patients included in the analysis. The MD changes associated with the CPP measures were located to the arterial territory shared by the middle and anterior cerebral arteries, pointing to an ischemic origin and the vulnerability of the water shed areas to CPP drops. It should be noted that a possible effect of decreased CPP on MD is unlikely to affect overall outcome, which is the most common end point used to evaluate ICU treatment protocols. Still, the MD increase in anterior CC and corona radiata may influence cognitive outcome as MD in these regions was associated with performance on D-KEFS TMT subtests. There was no measurable influence of days with ≥3 episodes of ICP >20mmHg on WM FA or MD in the severe TBI group admitted to ICU. This is in line with acute experimental data (Lafrenaye et al. 2012), and results from the early phase of TBI (Newcombe et al. 2011). In a study of the long term effect (~5 years) of raised ICP in the acute phase after TBI on CC microstructure in children, the patient group with ICP >20 mmHg and/or treatment for lowering ICP for >3 days was shown to have reduced FA and increased MD in the CC compared to the group without ICP elevation (Tasker *et al.* 2010). It may be that children are more sensitive to ICP >20 mmHg as their normal ICP is lower than in the adult (Rangel-Castilla *et al.* 2008). Taken together with the lack of associations between FA or MD and Rotterdam CT scores, which also reflect increased ICP, the current study does not find support for elevated ICP per se leading to additional WM injury in adults surviving TBI.

White matter in chronic moderate and severe TBI as described by automated tractography

The automatic tractography method demonstrated that the volume of WM tracts was significantly reduced in the chronic phase of TBI, concurring with the WM atrophy taking place during the first year after TBI (Brezova et al. 2014). Previous studies have used other tractography methods, more mixed TBI groups, and shorter follow up which may have lead to less consistent findings with regard to tract volumes in TBI groups (Brandstack et al. 2013, Kurki et al. 2013). In this study the FA, MD, eigenvalues and volumes were consistent between SLF and ILF/IFOF in the two hemispheres in both the TBI and the control groups. The current study demonstrated that CC had the greatest volume loss (~16% of controls), followed by ILF/IFOF (~10%), and SLF (0-7%).

In the TBI group GCS scores were associated with greater volumes loss in CC, but not consistently with the volume of the other tracts. CC is considered to be the tract experiencing the largest force in TBI (Chatelin et al. 2011, Levin et al. 1988, Ommaya & Gennarelli 1974). It is therefore not surprising that the largest and most consistent effect on volume was found in this structure. However, as described above, CC volume was also found to be positively associated with time since injury. Together these findings suggest that both the initial traumatic forces as well as inherent responses in CC following TBI lead to the observed macro- and microstructural CC changes.

Even though the tractography results appeared to be consistent with regard to tract FA, MD and volumes in both the TBI and control groups, the associations between these measures and the acute phase and outcome measures were highly inconsistent compared to the TBSS results. The most consistent finding for GCS scores were increased MD in CC, right and left SLF and right ILFO/IFO. Thus, mean FA value of an entire tract does not appear to reflect injury severity to the same extent as MD of the tract. These results concur with a previous study which showed that FA values obtained with tractography are significantly affected by the methodology used and often deviate considerably from that in central parts of the tract (Kurki et al. 2013). The impact of analysis method on FA is clearly illustrated in the present study in the direct comparison between FA in the CC

from tractography and from the CC ROI using TBSS which showed significantly lower FA with tractograhy. This result is to be expected since the automated tractography encompasses larger parts of the CC and therefore includes more peripheral parts with lower FA values. By including WM with lower FA, the effect of injury severity on WM will not be as striking. These results point to TBSS as the method of choice for depicting injury severity.

Chronic phase outcome measures and associations with WM FA, MD and tract volumes

In the TBSS analysis widespread FA decreases and MD increases in the same regions were demonstrated to be associated with poorer general outcome measured with GOSE and performance-based cognitive control measured with D-KEFS TMT subtests 1-4. The tractography analysis, on the other hand, showed that mean MD in all tracts was associated with GOSE scores while FA was not. Furthermore, FA, MD and tract volumes from automated tractography were found to be associated with D-KEFS TMT subtests 1-5, but the findings were inconsistent both with regard to subtests and tracts involved. Taken together, these results demonstrated that both FA and MD changes determine outcome, but that different approaches to DTI analysis as well as the type of outcome measured give somewhat varying results. Tract volumes were to a very limited and inconsistent extent associated with outcome, and will not be discussed further.

In the TBI group widespread regions of reduced FA and increased MD were associated with poorer performance on D-KEFS TMT subtests 1-4, but not subtest 5 measuring motor speed. This result illustrates how subtests 1-4 might rely more upon integration and communication within a distributed cognitive control brain network (Power & Petersen 2013, Dosenbach *et al.* 2007) than pure motor speed. Previous studies have demonstrated associations between reduced FA and increased MD in several of the same WM tracts and poorer cognitive control performance after TBI (Leunissen *et al.* 2013, Kinnunen et al. 2011, Niogi et al. 2008, Spitz et al. 2013). In addition, the present data supports an important role of microstructural integrity of the thalamus for cognitive control functions in particular, but not overall outcome as indicated by the lack of significant association between GOSE scores and FA and MD in thalamus in the TBSS analysis. In the healthy

control group, FA was positively associated with D-KEFS TMT subtest 3. In general, significant associations between FA or MD and performance based scores on neuropsychological tests are infrequently observed in healthy controls, but is a common finding in groups with different cerebral pathologies (Eikenes *et al.* 2012, Eikenes *et al.* 2011, Nir *et al.* 2013, Deng *et al.* 2013) concurring with the current results.

The significant self-reported deficits in cognitive control functions measured with BRIEF-A in the TBI group, were not correlated with FA, MD or tract volumes from the TBSS or automated tractography analyses. The lack of a relationship between self-reported changes in cognitive control function and changes in FA and MD combined with the presence of such associations for performance-based measures of cognitive control, supports the suggested distinction between cognitive control function measured by self-report as opposed to performance (Toplak et al. 2013, Isquith et al. 2013). In a recent study, we demonstrated that increased BOLD activation in prefrontal and parietal cortex after moderate to severe TBI was associated with less self-reported cognitive control problems, thus possibly representing a compensatory mechanism (Olsen *et al.* 2014). Taken together, WM integrity appears to determine the objective effectiveness (i.e. performance based measure) of cognitive control processing while grey matter changes, such as those detected with fMRI, seems to underlie the individual's experience of effort with regard to cognitive control (i.e. self-report) following TBI.

Limitations

The strength of the study is the prospective design with clinical and neuroimaging data, plus the well-matched healthy control group. Still, some clinical data was available only in subgroups of TBI survivors, as shown in Table 1. For instance not all severe TBI patients had ICP and CPP monitoring, and data was therefore available in 16 out of 23 severe TBI survivors. Moreover, when the TBI group was divided into clinical subgroups, the number of individuals in some of the groups was small, e.g. in the DAI 3 group, which made it impossible to study the different DAI grades separately. Furthermore, many statistical tests were performed in this study, and only the TBSS analyses were corrected for multiple comparisons. This increases the risk of type 1 errors. In addition, not

all data had a normal distribution parametric correlation analysis was implemented, e.g. GCS scores and number of days with CPP and ICP deviations, which may have caused type II errors. Finally, although representing key measurement tools of self-reported and performance-based cognitive control function, the selection of only the D-KEFS TMT and BRIEF-A leaves some uncertainty whether other assessment tools could have provided different results.

The associations between the automated tractography measures and the different acute phase and outcome measures were rather inconsistent compared to that obtained with TBSS. The use of tractography needs further refinement and investigations to verify its role in TBI studies.

Conclusions

Loss of FA, MD and tract volumes following moderate to severe TBI is widespread, and reflects the propagation of the traumatic forces through the brain. FA is particularly sensitive to injury severity and mechanism, while FA and MD are both important for outcome. Tract volume on the other hand was not consistently found to be related to outcome. DAI of all grades in the acute phase specifically affects thalamus and brainstem microstructure in the chronic phase. Performance-based, but not self-reported, cognitive control functions were associated with WM FA and MD changes suggesting that the brain correlates differ between self-reported and performance-based cognitive control measures. Based on previous and current findings performance impairments are more closely related to WM microstructure while self-reported problems are associated with changes in cortical activations.

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Table 1. Demographics, injury characteristics, global outcome, and cognitive control measures in the traumatic brain injury and healthy control groups

	TBI group		**Control group**		
Variable	No.	mean (SD) or %	No.	mean (SD) or %	P-value
Age (mean, SD)	49	29.2 (12.1)	50	32.7 (12.1)	n.s.
Male (%)	36	73.5	36	72	n.s.
Years of completed education (mean, SD)	49	11.9 (2.3)	50	12.16 (2.16)	n.s.
Moderate TBI (%)	26	53.1			
Severe TBI (%)	23	46.9			
Time since injury in years (mean, SD)	49	2.8 (1.1)			
Injury mechanism	49				
Motor vehicle accident (%)	23	46.9			
Fall (%)	22	44.9			
Other injury mechanism (%)	4	8.2			
GCS score (mean, SD)	49	8.8 (3.6)			
Rotterdam CT score (mean, SD)	38	2.7 (1.1)			
DAI grading	47	95.9			
No DAI (%)	12	25.5			
DAI 1 (%)	14	29.8			
DAI 2 (%)	16	34.0			
DAI 3 (%)	5	10.6			
Flair lesion volume (mean, SD)	38	1708.3 (2310.8)			
Number of microhemorrhages (mean, SD)	38	13.8 (12.2)			
ICP* (mean, SD)	16	2.8 (5.1)			
CPP** (mean, SD)	16	5.6 (5.1)			
PTA duration	47	95.9			
0-1 week (%)	24	49.0			
1-2 weeks (%)	9	18.4			
2-3 weeks (%)	5	10.2			
3-4 weeks (%)	3	6.1			
> 4 weeks (%)	5	10.2			
GOSE score (mean, SD)	49	6.7 (1.4)			
BRIEF-A					
GEC (mean, SD)	48	105.4 (25.4)	49	94.7 (14.5)	**< 0.05**
BRI (mean, SD)	48	44.6 (10.9)	49	38.7 (6.8)	**< 0.01**
MI (mean, SD)	48	60.8 (15.9)	49	56.0 (9.2)	n.s.
D-KEFS TMT					
Subtest 1 (mean, SD)	48	22.1 (6.8)	50	21.0 (5.5)	n.s.
Subtest 2 (mean, SD)	48	28.5 (11.5)	50	25.0 (8.1)	n.s.
Subtest 3 (mean, SD)	47	28.3 (11.2)	50	27.3 (14.9)	n.s.
Subtest 4 (mean, SD)	47	79.8 (29.1)	50	76.6 (33.3)	n.s.
Subtest 5 (mean, SD)	48	22.9 (7.3)	50	20.7 (5.2)	n.s.

Between group differences for age, years of completed education, and cognitive control measures were investigated with independent t-tests. A chi square test was applied in order to test differences between groups with regard to sex distribution. $P < 0.05$ (two-sided) was considered statistically significant. Statistically significant results are highlighted as bold text. TBI = traumatic brain injury. MRI = Magnetic Resonance Imaging. DAI = traumatic axonal injury. GCS = Glasgow Coma Scale. CT = Computer Tomography. ICP = Intra Cranial Pressure. CPP = Cerebral Perfusion Pressure. BRI = Behavioral Regulation Index. MI = Metacognitive Index. GEC = Global Executive Composite. TMT = Trail Making Test. SD = standard deviation. PTA = Post Traumatic Amnesia. GOSE = Glasgow Outcome Scale Extended. * Number of days with ≥3 episodes of ICP >20 mmHg only measured in a subgroup of severe TBI. ** Number of days with ≥3 episodes of CPP <70 mmHg only measured in a subgroup of severe TBI.

Table 2. Median (in italic) and mean fractional anisotropy, diffusivity, λ1, λ2, λ3 and tract volumes with standard deviations (in parenthesis) obtained with automated tractography in TBI and healthy control groups.

White matter tract		TBI group		Control group		p-value
Corpus callosum (CC)	FA	*0.416*	(0.414 ± 0.018)	*0.434*	(0.436 ± 0.018)	**<0.001**
	MD	*0.82*	(0.83 ± 0.04)	*0.78*	(0.78 ± 0.03)	**<0.001**
	λ 1	*1.23*	(1.23 ± 0.05)	*1.19*	(1.19 ± 0.03)	**<0.001**
	λ 2	*0.72*	(0.73 ± 0.04)	*0.68*	(0.67 ± 0.03)	**<0.001**
	λ 3	*0.53*	(0.54 ± 0.04)	*0.48*	(0.49 ± 0.03)	**<0.001**
	vol (ml)	*117.30*	(117.71 ± 28.21)	*135.09*	(137.07 ± 17.01)	**<0.001**
Left inferior longitudinal	FA	*0.375*	(0.377 ± 0.02)	*0.398*	(0.397 ± 0.012)	**<0.001**
fasciculus/ inferior	MD	*0.81*	(0.83 ± 0.07)	*0.77*	(0.78 ± 0.03)	**<0.001**
fronto-occipital fasciculus	λ 1	*1.16*	(1.18 ± 0.08)	*1.13*	(1.13 ± 0.04)	**<0.001**
(L ILF/IFOF)	λ 2	*0.74*	(0.75 ± 0.07)	*0.70*	(0.70 ± 0.03)	**<0.001**
	λ 3	*0.54*	(0.55 ± 0.06)	*0.51*	(0.50 ± 0.03)	**<0.001**
	vol (ml)	*39.36*	(38.53 ± 10.78)	*45.60*	(44.74 ± 9.01)	**<0.001**
Right inferior longitudinal	FA	*0.373*	(0.374 ± 0.021)	*0.397*	(0.396 ± 0.022)	**<0.001**
fasciculus/ inferior	MD	*0.81*	(0.82 ± 0.04)	*0.77*	(0.77 ± 0.03)	**<0.001**
fronto-occipital fasciculus	λ 1	*1.17*	(1.17 ± 0.05)	*1.12*	(1.12 ± 0.04)	**<0.001**
(R ILF/IFOF)	λ 2	*0.74*	(0.75 ± 0.04)	*0.70*	(0.70 ± 0.03)	**<0.001**
	λ 3	*0.54*	(0.55 ± 0.04)	*0.50*	(0.50 ± 0.03)	**<0.001**
	vol (ml)	*39.17*	(37.38 ± 9.32)	*43.45*	(43.61 ± 7.95)	**<0.001**
Left superior longitudinal	FA	*0.378*	(0.376 ± 0.018)	*0.390*	(0.388 ± 0.016)	**<0.001**
fasciculus (L SLF)	MD	*0.77*	(0.77 ± 0.03)	*0.73*	(0.73 ± 0.03)	**<0.001**
	λ 1	*1.08*	(1.09 ± 0.04)	*1.05*	(1.05 ± 0.03)	**<0.001**
	λ 2	*0.71*	(0.71 ± 0.03)	*0.67*	(0.67 ± 0.03)	**<0.001**
	λ 3	*0.50*	(0.5 ± 0.03)	*0.47*	(0.47 ± 0.02)	**<0.001**
	vol (ml)	*19.20*	(19.83 ± 4.47)	*21.16*	(21.05 ± 5.3)	**<0.001**
Right superior longitudinal	FA	*0.348*	(0.347 ± 0.015)	*0.361*	(0.362 ± 0.016)	**<0.001**
fasciculus (R SLF)	MD	*0.77*	(0.78 ± 0.03)	*0.73*	(0.73 ± 0.03)	**<0.001**
	λ 1	*1.07*	(1.07 ± 0.04)	*1.03*	(1.03 ± 0.03)	**<0.001**
	λ 2	*0.72*	(0.72 ± 0.03)	*0.68*	(0.68 ± 0.03)	**<0.001**
	λ 3	*0.53*	(0.53 ± 0.03)	*0.49*	(0.49 ± 0.03)	**<0.001**
	vol (ml)	*35.73*	(36.26 ± 6.08)	*41.11*	(39.6 ± 5.69)	**<0.001**

MD = mean diffusivity. FA = Fractional Anisotropy. λ = Lambda (eigenvalue). SD= standard deviation. MD, λ1, λ2 and λ3 are given in 10^{-3} mm^2/s. Between group differences were investigated with a Mann-Whitney U test. $p < 0.05$ (two-sided) was considered statistically significant, not corrected for multiple comparisons.

Table 3. Partial correlations (adjusted for age and sex) between mean fractional anisotropy and mean diffusivity, and tract volumes obtained with automated tractography, and GCS and GOSE scores in the TBI group**.**

	Value	Score	Partial correlation (*r*)	*p*-value
Corpus callosum (CC)	Mean FA	GCS	242	.101
		GOSE	.232	.116
	Mean MD	GCS	-.391	**.007**
		GOSE	-.300	**.040**
	volume	GCS	.326	**.025**
		GOSE	.279	.057
Left inferior longitudinal fasciculus/	Mean FA	GCS	.247	.094
inferior fronto-occipital fasciculus		GOSE	.260	.078
(L ILF/IFOF)	Mean MD	GCS	-.281	.056
		GOSE	-.447	**.002**
	Volume	GCS	.242	.101
		GOSE	.481	**.001**
Right inferior longitudinal fasciculus/	Mean FA	GCS	.345	**.018**
inferior fronto-occipital fasciculus		GOSE	.117	.435
(R ILF/IFOF)	Mean MD	GCS	-.360	**.013**
		GOSE	-.318	**.029**
	Volume	GCS	.417	**.004**
		GOSE	.379	**.009**
Left superior longitudinal fasciculus	Mean FA	GCS	.163	.273
(L SLF)		GOSE	.446	**.002**
	Mean MD	GCS	-.377	**.009**
		GOSE	-.399	**.005**
	Volume	GCS	-.122	.416
		GOSE	.082	.582
Right superior longitudinal fasciculus	Mean FA	GCS	.251	.089
(R SLF)		GOSE	.222	.134
	Mean MD	GCS	-.316	**.030**
		GOSE	-.346	**.017**
	volume	GCS	.063	.676
		GOSE	.154	.303

Partial correlations (*r*) between white matter integrity (Tract FA, MD, volume), Glasgow Coma Scale (GCS) and Glasgow Outcome Scale Extended (GOSE) scores. Results are adjusted for age and sex. Statistically significant was set o $p < 0.05$ (two-sided), uncorrected for multiple comparisons. FA = Fractional Anisotropy. MD = Mean Diffusivity.

Table 4. Partial within-group correlations (adjusted for age and sex) between mean fractional anisotropy, mean diffusivity, mean tract volumes, and self reported (BRIEF-A) and performance-based (D-KEFS subtests) cognitive control function in the TBI and healthy control groups.

	Self-reported (BRIEF-A)			**Perfomance-based (D-KEFS TMT)**				
	BRI	MI	GEC	Subtest 1	Subtest 2	Subtest 3	Subtest 4	Subtest 5
TBI group (n=46)								
FA								
Corpus callosum	-.093	.027	-.025	-.291	-.233	**-.333***	**-.325***	-.172
Right ILF/IFOF	-.062	-.061	-.012	**-.297***	**-.361***	-.093	-.281	-.130
Left ILF/IFOF	-.034	-.131	-.099	-.263	-.135	**-.341***	-.236	-.173
Right SLF	-.044	-.062	-.059	**-.423****	-.348*	-.288	**-.344***	-.278
Left SLF	-.013	-.100	-.071	**-.504*****	**-.368***	**-.482*****	**-.397****	**-.392****
MD								
Corpus callosum	-.007	-.064	-.040	**.450****	**.304***	**.401****	.374*	.216
Right ILF/IFOF	-.073	-.118	-.103	**.546*****	**.414****	**.320***	.375*	.282
Left ILF/IFOF	.161	.221	.210	.183	.055	.209	.047	.088
Right SLF	.021	.050	.043	**.485*****	**.369***	**.337***	.295	**.327***
Left SLF	.018	-.085	-.043	**.405****	**.305***	**.422****	**.402****	.242
Volume								
Corpus callosum	-.059	-.061	-.066	**-.400****	-.130	**-.340***	-.217	-.267
Right ILF/IFOF	-.206	-.100	-.154	**-.364***	-.295	-.126	**-.302***	-.204
Left ILF/IFOF	-.251	-.288	-.292	-.085	.084	-.043	.037	-.031
Right SLF	-.206	-.229	-.234	-.271	-.103	-.046	-.200	-.100
Left SLF	-.121	-.116	-.127	-.096	.750	-.229	-.053	.039
Control group *(n=49)*								
FA								
Corpus callosum	-.041	.116	.050	-.139	.014	-.244	-.027	-.016
Right ILF/IFOF	.148	.150	.161	-.251	-.216	**-.370***	-.125	-.063
Left ILF/IFOF	.055	.056	.060	-.138	-.129	-.249	-.112	-.121
Right SLF	-.041	.088	.033	-.189	-.018	-.193	-.039	.036
Left SLF	.109	.209	.177	-.008	-.120	-.109	.047	.014
MD								
Corpus callosum	-.053	-.038	-.048	.033	-.091	.125	.054	-.072
Right ILF/IFOF	-.073	-.164	-.134	-.025	-.167	.072	.045	-.069
Left ILF/IFOF	-.167	-.226	-.215	-.165	-.014	.189	.015	-.170
Right SLF	-.109	-.129	-.130	.014	-.032	.229	-.003	-.111
Left SLF	-.011	-.059	-.041	.021	-.168	.118	-.081	-.149
Volume								
Corpus callosum	.197	.125	.169	-.061	-.180	**-.290***	-.173	-.234
Right ILF/IFOF	.028	.047	.041	-.312	-.265	**-.344***	-.180	-.162
Left ILF/IFOF	.490	.096	.081	.128	-.081	-.245	.096	-.001
Right SLF	-.122	.006	-.055	-.255	-.166	-.264	-.089	-.088
Left SLF	.116	.171	.158	.091	-.235	-.249	-.020	.144

Partial correlations (*r*) between white matter integrity (Tract FA, MD, volume), performance-based (D-KEFS Trails) and self-report (BRIEF-A) measures of cognitive control function. Results are adjusted for age and sex. BRI = Behavioral Regulation Index. MI = Metacognitive Index. GEC = Global Executive Composite. ILF/IFOF = Inferior Longitudinal Fasciculus/ Inferior Fronto-Occipital Fasciculus. SLF = Superior Longitudinal Fasciculus. Statistically significant results are highlighted as bold text. * = $p < .05$ (two-tailed). ** = $p < .01$ (two-tailed), *** = $p < .001$ (two-tailed). Corrections for multiple comparisons were not applied.

Figure legends

Figure 1. Between-group tract based spatial statistics (TBSS) results for fractional anisotropy and mean diffusivity.

The statistical threshold for significant group differences was $p < 0.05$, corrected for gender, age at MRI, and multiple comparisons as implemented in Randomise. The FSL 1mm mean FA template was used as the background image. The images are shown in radiological convention, i.e. the right side of the subjects is on the left side of the images. The x, y and z refer to MNI template coordinates. TBI = Traumatic Brain Injury, FA = Fractional Anisotropy, MD = Mean Diffusivity. DAI = Diffuse Axonal Injury.

Figure 2. Association between age and fractional anisotropy and mean diffusivity as obtained with tract based spatial statistics (TBSS) in the control group.

No effect of age on FA or MD was found in the TBI group. The statistical threshold was set to $p < 0.05$, corrected for multiple comparisons as implemented in Randomise. The FSL 1mm mean FA template was used as the background image. The images are shown in radiological convention, i.e. the right side of the subjects is on the left side of the images. The x, y and z refer to MNI template coordinates. FA = fractional anisotropy, MD = mean diffusivity.

Figure 3. Associations between acute phase injury related variables and neuroradiological findings, as well as chronic phase global outcome, and fractional anisotropy and mean diffusivity as obtained with tract based spatial statistics (TBSS).

The statistical threshold was set to $p < 0.05$, corrected for gender, age at MRI, and multiple comparisons as implemented in Randomise. The FSL 1mm mean FA template was used as the background image. The images are shown in radiological convention, i.e. the right side of the subjects is on the left side of the images. The x, y and z refer to MNI template coordinates. FA = fractional anisotropy, MD = mean diffusivity, GCS = Glasgow coma scale, FLAIR = fluid attenuated inversion recovery, PTA = post traumatic amnesia, GOSE = Glasgow outcome scale extended.

Figure 4. Associations between performance-based cognitive control function (D-KEFS TMT) and fractional anisotropy and mean diffusivity as obtained with tract based spatial statistics (TBSS) in the TBI and control groups.

The statistical threshold was set to $p < 0.05$, corrected for gender, age at MRI, and multiple comparisons as implemented in Randomise. The FSL 1mm mean FA template was used as the background image. The images are shown in radiological convention, i.e. the right side of the subjects is on the left side of the images. The x, y and z refer to MNI template coordinates. TBI = Traumatic Brain Injury, FA = Fractional Anisotropy, MD = Mean Diffusivity, D-KEFS TMT = Delis-Kaplan Executive Function System Trail Making Test, ns = non-significant.

Figure 5. Representative tractography images of corpus callosum (a), superior longitudinal fasciculus (b) and inferior longitudinal fasciculus/inferior fronto-occipital fasciculus (c) in one TBI survivor (male with severe TBI, age 21 at time of DTI) and one healthy control (female, age 20).

Figure 1

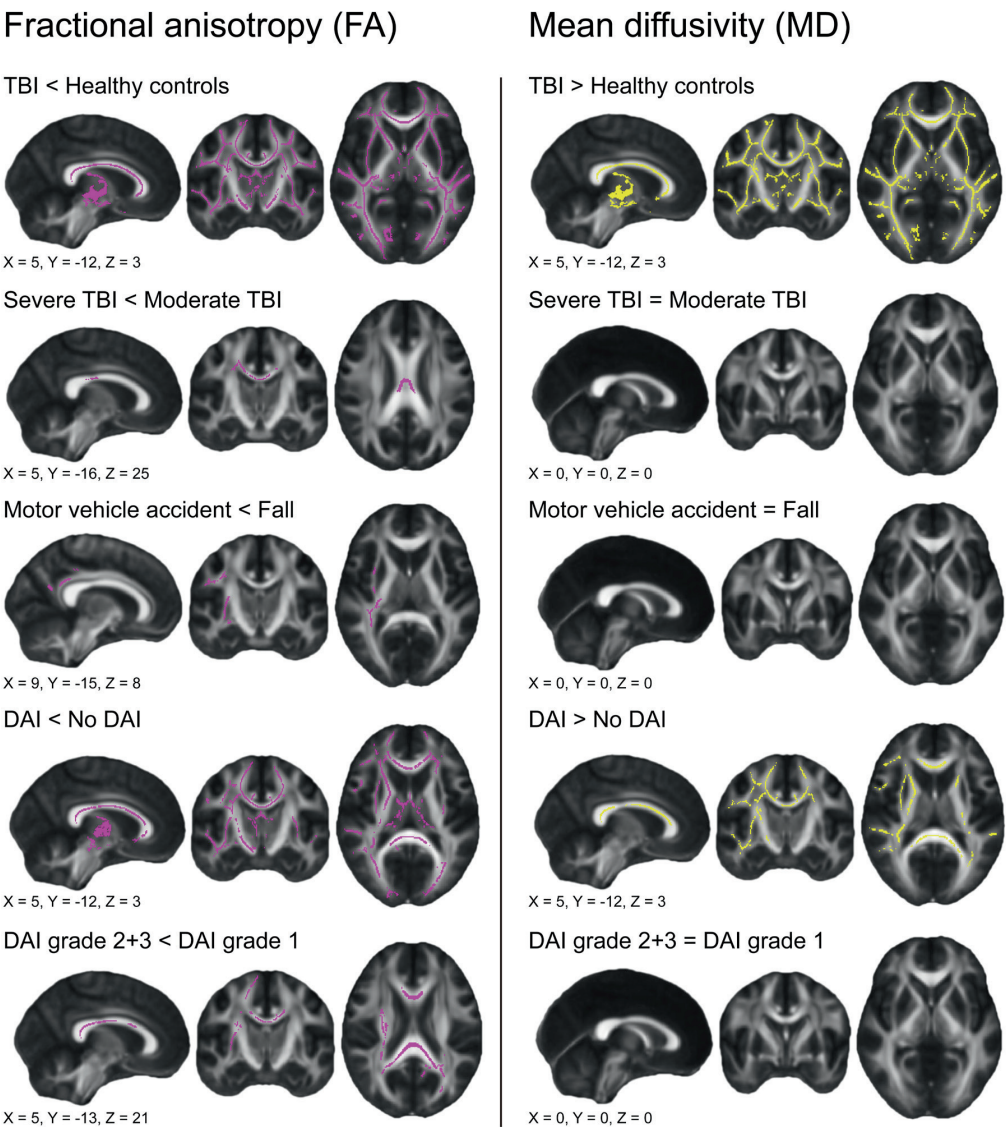
Fractional anisotropy (FA)
Mean diffusivity (MD)
TBI < Healthy controls
X = 5, Y = -12, Z = 3
TBI > Healthy controls
X = 5, Y = -12, Z = 3
Severe TBI < Moderate TBI
X = 5, Y = -16, Z = 25
Severe TBI = Moderate TBI
X = 0, Y = 0, Z = 0
Motor vehicle accident < Fall
X = 9, Y = -15, Z = 8
Motor vehicle accident = Fall
X = 0, Y = 0, Z = 0
DAI < No DAI
X = 5, Y = -12, Z = 3
DAI > No DAI
X = 5, Y = -12, Z = 3
DAI grade 2+3 < DAI grade 1
X = 5, Y = -13, Z = 21
DAI grade 2+3 = DAI grade 1
X = 0, Y = 0, Z = 0

Figure 2

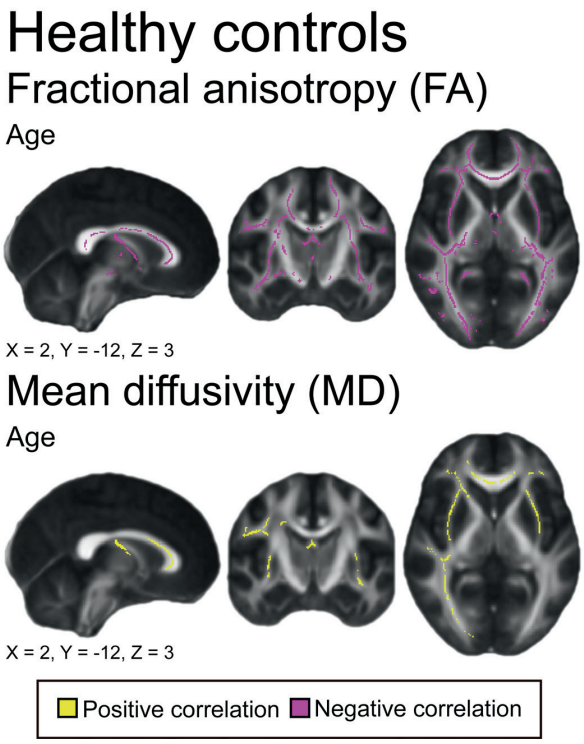
Healthy controls
Fractional anisotropy (FA)
Age
X = 2, Y = -12, Z = 3
Mean diffusivity (MD)
Age
X = 2, Y = -12, Z = 3
Positive correlation
Negative correlation

Figure 3.

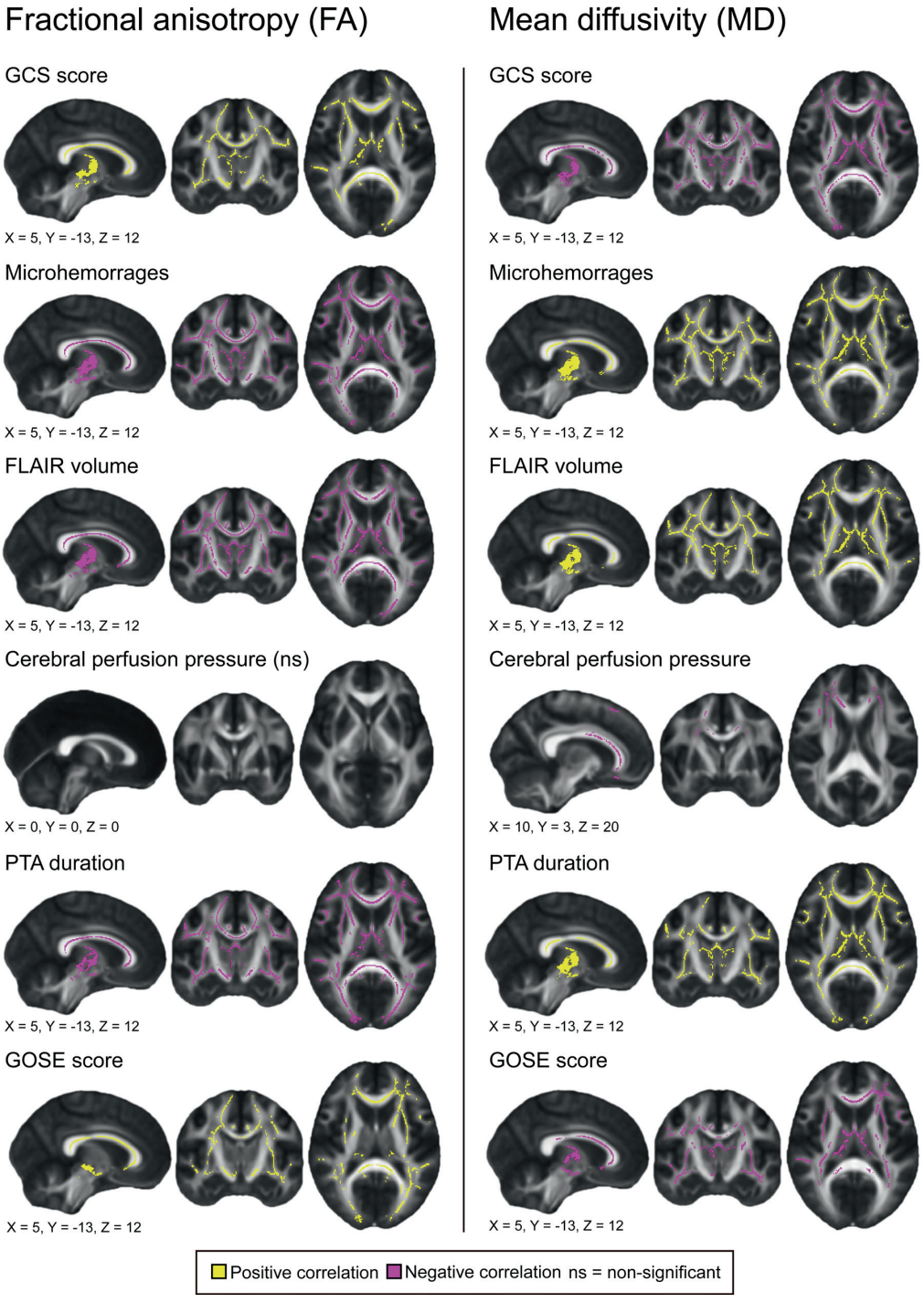
Fractional anisotropy (FA)
Mean diffusivity (MD)
GCS score
X = 5, Y = -13, Z = 12
Microhemorrages
X = 5, Y = -13, Z = 12
FLAIR volume
X = 5, Y = -13, Z = 12
Cerebral perfusion pressure (ns)
X = 0, Y = 0, Z = 0
PTA duration
X = 5, Y = -13, Z = 12
GOSE score
X = 5, Y = -13, Z = 12
Cerebral perfusion pressure
X = 10, Y = 3, Z = 20
Positive correlation
Negative correlation
ns = non-significant

Figure 4.

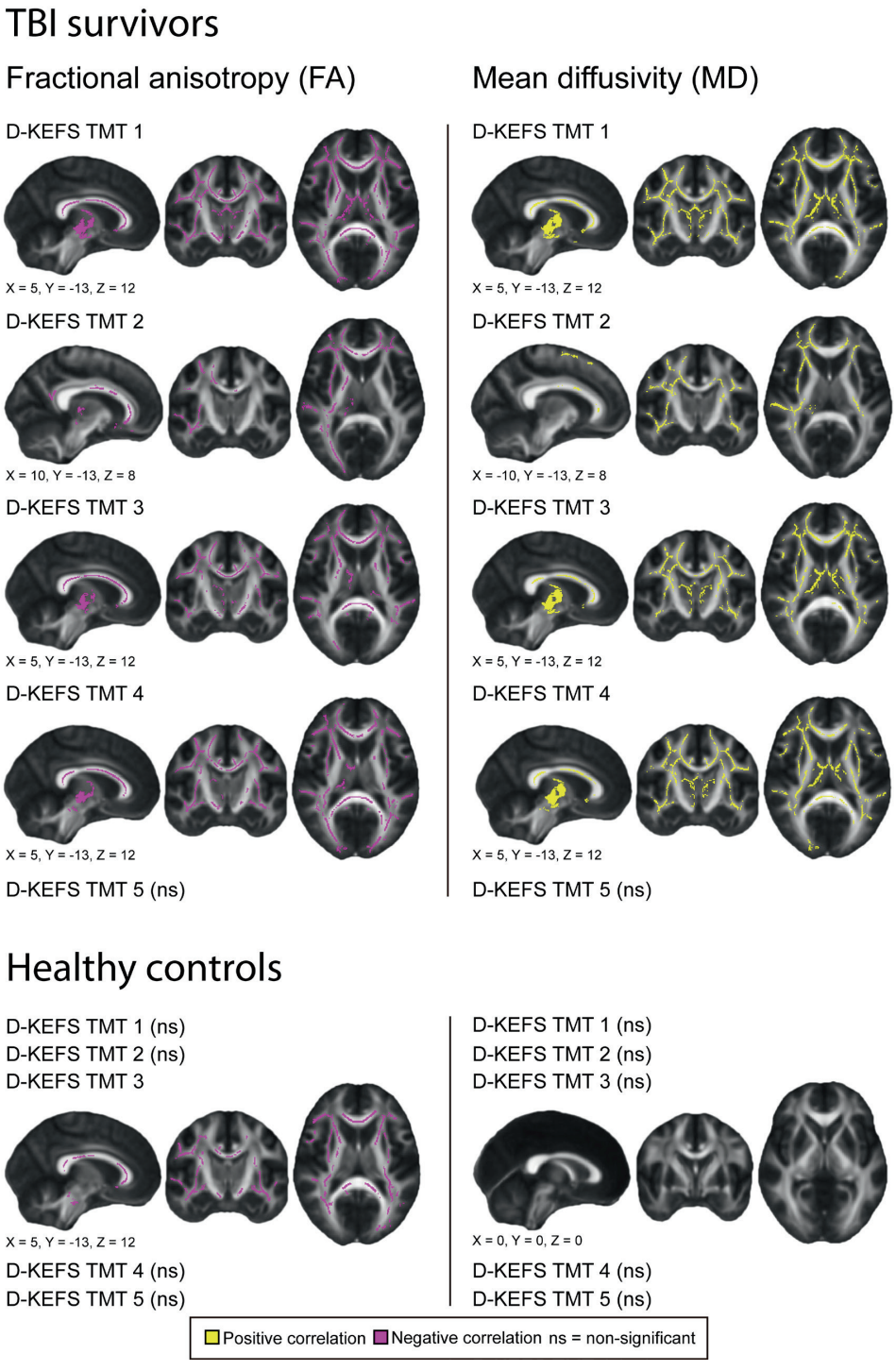
TBI survivors
Fractional anisotropy (FA)
Mean diffusivity (MD)
D-KEFS TMT 1
X = 5, Y = -13, Z = 12
D-KEFS TMT 2
X = 10, Y = -13, Z = 8
X = -10, Y = -13, Z = 8
D-KEFS TMT 3
X = 5, Y = -13, Z = 12
D-KEFS TMT 4
X = 5, Y = -13, Z = 12
D-KEFS TMT 5 (ns)
Healthy controls
D-KEFS TMT 1 (ns)
D-KEFS TMT 2 (ns)
D-KEFS TMT 3
D-KEFS TMT 3 (ns)
X = 0, Y = 0, Z = 0
D-KEFS TMT 4 (ns)
D-KEFS TMT 5 (ns)
Positive correlation
Negative correlation
ns = non-significant

Figure 5.