Shedding light on cognitive control

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Gothenburg 2020

Cover illustration by Jenny Nyberg

It is a trivial, but important, truth
that daggers look exactly like things
that look exactly like daggers; and
some of these latter may not be daggers.
A.D. Smith 2002

Sammanfattning på svenska

Vår förmåga att flexibelt anpassa och korrigera våra tankar, känslor och vårt agerande kallas för kognitiv kontroll. Det är en förmåga som utvecklas under barn- och ungdomsåren och når sin fulla potential i mitten av tjugoårsåldern. Förmågan att kunna kontrollera sina tankar och känslor spelar en betydande roll i dagens samhälle, därför kan problem med kognitiv kontroll ha stora effekter på barn och vuxnas resultat i utbildning och arbete och kan påverka den generella livskvalitén. Den här avhandlingen handlar om kognitiv kontroll och dess underliggande hjärnbarksaktivitet. I de studier som utgör den här avhandlingen har hjärnavbildningstekniken funktionell närainfraröd spektroskopi (fNIRS) används. fNIRS mäter förändringen av den relativa syresättningen i blodet, ett par centimeter ner i hjärnbarken, som ett indirekt mått på hjärnaktivitet. I jämförelse med andra hjärnavbildningstekniker innebär en fNIRS-undersökning mindre stränga begränsningar för den som undersöks vilket möjliggör mer vardagsnära studiedesigner.

I de två första arbetena undersökte vi individer som lider av hjärntrötthet (pathological mental fatigue) minst 5 månader efter skallskada (n=20) och individer diagnostiserade med utmattningssyndrom (n=20) med friska vuxna kontroller (n=20). Hjärntrötthet kan uppstå till följd av skallskada eller annan påverkan på hjärnan så som stroke, hjärnhinneinflammation eller långvarig stress. Idag lider uppskattningsvis över 200 000 svenskar av hjärntrötthet och ca 35 000 svenskar är sjukskrivna i utmattningssyndrom. Många som lider av dessa problem rapporterar problem med kognitiv kontroll men kan allt som oftast prestera bra på neuropsykologiska tester. Trots detta klarar de inte av att återgå till arbete/studier på heltid, blir snabbt utmattade och behöver väldigt lång återhämtning. I ett försökte att återskapa en arbetsdag och fånga förändringen i hjärnaktivitet när de blev trötta, fick deltagarna göra olika neuropsykologiska tester och fylla i formulär under två och en halv timme. fNIRS mätningar gjordes under hela experimentet och sex av de sju neuropsykologiska testerna gjordes två gånger. När vi jämförde hjärnaktivering från början och slutet av undersökningen kunde vi inte se någon skillnad för någon av grupperna. Däremot hade båda patientgrupperna lägre aktivitet i pannlobsbarken under test av kognitiv kontroll och involveringen av vänstra ventrolaterala prefrontala barken var associerad med nivån av hjärntrötthet.

I det tredje arbetet undersöktes relationen mellan mental trötthet (trait mental fatigue), förmågan att använda proaktiv kognitiv kontroll och hjärnbarksaktivitet hos friska vuxna (n=30). Kognitiv kontroll kan vara proaktiv

eller reaktiv. Vid proaktiv kognitiv kontroll förutser eller förbereder vi oss på hur vi ska reagera medan en reaktiv kognitiv kontroll innebär att vi reagerar på en händelse när den redan har skett. Resultaten visade att ökad mental trötthet hos friska vuxna var förknippad med en tendens att använda kognitiv kontroll på ett reaktivt sätt. Ökningen i mental trötthet hos deltagarna var också förknippad med ökad hjärnaktivitet i högra dorsolaterala prefrontala barken och vänstra posteriora hjässlobsbarken under reaktiva uppgifter jämfört med proaktiva uppgifter.

I de två sista arbetena tog vi med oss fNIRS maskinen till två skolor för att studera matematiskt tänkande samt proaktiv kognitiv kontroll hos barn i åtta till nio års åldern (n=53). Resultatet av det fjärde arbetet visade att barnen hade mer hjärnaktivering i högra anteriora dorsolaterala prefrontal barken när de löste matematikuppgifter som enbart var textbaserade jämförelse med när de fick visuellt hjälpmedel som bilder eller figurer. Resultatet av det femte arbetet var att barn som tenderar att vara mindre reaktiva eller mer proaktiva involverar högra posteriora hjässlobsbarken mer under reaktiva uppgifter än proaktiva uppgifter.

Abstract

This thesis aimed to investigate the ability to adjust cognitive processes and behavior, i.e., cognitive control, and its related functional activity in the cortex. The optical imaging technique functional near-infrared spectroscopy (fNIRS) was used to detect change in cortical activity during neuropsychological tests of conflict processing and proactive cognitive control

The two first studies used a test-retest design and investigated how prolonged mental activity, neuropsychological testing for two and a half hours, affects cognitive performance and functional activity in the frontal cortex in individuals suffering from pathological mental fatigue after traumatic brain injury (**paper I**) and exhaustion disorder (**paper II**). We were able to show that both patient groups have reduced functional activity during cognitive control, especially in the left ventrolateral prefrontal cortex, and that this reduction was associated with the level of pathological mental fatigue. There was no indication that prolonged mental activity induced a change in functional activity during the test session.

Paper III showed that increased trait mental fatigue in healthy adults was associated with a tendency to use cognitive control in a reactive way. The increase in trait mental fatigue was also associated with an increased functional activity in frontal and parietal cortex during reactive conflict processing situations compared to proactive ones.

In the last studies, we brought the fNIRS machine to two schools to investigate functional brain activation during mathematical cognition (**paper IV**) and cognitive control (**paper V**) in children between the age of 8- to 9-years in a school environment. The result suggested that the visual aid in mathematical tasks reduces the cognitive load and the functional activity in the right anterior dorsolateral prefrontal cortex, compared to equivalent tasks without visual aid. Children who tend to be less reactive or more proactive in a conflict processing test involve the right posterior parietal cortex more during reactive situations than proactive ones.

Keywords:
Cognitive control, fNIRS, mental fatigue, exhaustion disorder, TBI, children, mathematical cognition, proactive cognitive control

List of papers

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I.   Skau, S. Bunketorp-Käll, L., Kuhn, H.G., and Johansson, B.
Mental Fatigue and Functional Near-Infrared Spectroscopy (fNIRS) - Based Assessment of Cognitive Performance After Mild Traumatic Brain Injury
Frontiers in Human Neuroscience (2019) 13: 145

II.   Skau, S. Jonsdottir, I., Sjörs Dahlman, A., Johansson, B., and Kuhn H.G.
Exhaustion disorder and altered brain activity in frontal cortex detected with fNIRS
Manuscript

III.   Skau, S. Bunketorp-Käll, L., Johansson, B., and Kuhn H.G.
Proactive cognitive control, trait mental fatigue and cortical brain activation: an fNIRS study
Manuscript

IV.   Skau, S. Bunketorp-Käll, L., Helenius, O., and Kuhn H.G.
Difference in functional activity in frontal and parietal cortex for spatial and written mathematics in primary school children: an fNIRS study
Manuscript

V.   Skau, S. Bunketorp-Käll, L., Helenius, O., and Kuhn H.G.
Proactive cognitive control and cortical brain activation in 8- to 9-year old children: an fNIRS study
Manuscript

Content

Abbreviations

α	the probability of rejecting H_o when it is true
β	the probability of not rejecting H_o when it is false
ACC	Anterior cingulate cortex
AMR	Additive and multiplicative reasoning
AS	Additive situations
AR-G	Additive reasoning with geometric support
AR-T	Additive reasoning text based
AX-CPT	AX Continues performance task
BANUCA	Basic numeracy and calculations
BF_{IO}	Bayes factor support for H_I over H_o
CC	Stroop congruent and Simon congruent stimuli
CI	Stroop congruent and Simon incongruent stimuli
CSE	Congruency sequence effect
Deoxy-Hb	Deoxygenated hemoglobin
DLPFC	Dorsolateral prefrontal cortex
DMC	Dorsal motor cortex
DMC theory	Dual mechanism of control theory
DS	Digit Span
DSC	Digit Symbol Coding
ED	Exhaustion disorder
EEG	Electroencephalography
FDR	False discovery rate
fMRI	functional magnetic resonance imaging
fNIRS	functional near infrared spectroscopy
FPA	Frontal polar area
H_o	Null hypothesis
H_I	Alternative hypothesis
IC	Stroop incongruent and Simon congruent stimuli
II	Stroop incongruent and Simon incongruent stimuli
LD	Lilla duvan
LPC	Lateral parietal cortex
LPPC	Lateral posterior parietal cortex
MFS	Mental Fatigue Scale
MoCA	Montreal Cognitive Assessment

MPC	Medial parietal cortex
MPPC	Medial posterior parietal cortex
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
NHST	Null hypothesis significant testing
n	Number of observations
Oxy-Hb	Oxygenated hemoglobin
PaSMO	Parallel serial mental operation test
PBI	Proactive behavioral index
PET	Positron emission tomography
PFC	Prefrontal cortex
PPC	Posterior parietal cortex
ROI	Region of interest
RSI	Response to stimuli interval
SAWM	Speed, divided attention and working memory test
SD	Standard deviation
SMA	Supplementary motor cortex
SS	Symbol Search
TBI	Traumatic brain injury
TBI-MF	Traumatic brain injury suffering from mental fatigue
TVPS-III	Test of Visual Perception Skills-III
VAS	Visual Analogue Scale
VLPFC	Ventrolateral prefrontal cortex
VMC	Ventral motor cortex
WAIS-IV	Wechsler adult Intelligence Scale 4th edition
WISC-IV	Wechsler Intelligence Scale for Children 4th edition

1. Introduction

Cognitive control is the ability to flexibly adjust cognitive processes in order to maintain and execute appropriate goal-directed behavior. It is an essential part of our ability to direct our cognition, emotion, and motor activity into purposeful, organized, strategic and self-regulated behavior [1]. Since it is such an integral part of what it means to be a functioning person in modern society, problems with cognitive control are related to quality of life and success in school and the job market [2]. Having problems with cognitive control can also be an indicator of many developmental, neurological, and psychiatric disorders such as ADHD, autism, dementia, schizophrenia, and depression[3-5]. Understanding and mapping the mechanism behind cognitive control is thus crucial for medical diagnosis and treatment as well as understanding cognitive development and what it means to be a human being.

This thesis examines the effects of prolonged mental activity on cognitive control and cortical activation in the frontal cortex in individuals suffering from mental fatigue after traumatic brain injury (TBI) (**paper I**) and exhaustion disorder (ED) (**paper II**); how the difference in trait mental fatigue in healthy adults is related to proactive cognitive control (**paper III**); the functional activity in frontal and parietal cortex in 8- to 9-year old children when presented with different mathematical situations (**paper IV**) and; the functional differences in frontal and parietal cortex in 8- to 9-year old children for proactive and reactive cognitive control (**paper V**).

1.1 Cognitive control

Cognitive control is often used interchangeably with executive function, and occasionally other times it is used synonymously with the term central executive, part of Baddeley's theory of working memory [6]. As a matter of fact, within the research fields of psychology and neuropsychology, the framework of *executive functions* is more prominent, whereas, within cognitive neuroscience, *cognitive control* is the more frequently adapted concept. I will here discuss cognitive control for two reasons. Firstly, there is more agreement on what it is and how to measure it. Secondly, inherent in many definitions of executive function is that it is an ability used to overcome new and novel situations, which is not part of idea of cognitive control [1]. Thirdly, I will apply in my thesis theoretical frameworks

developed out of the research on cognitive control, the congruency sequence effect (CSE), or the Gratton effect [7] and the dual mechanism of control theory (DMC) [8].

Since cognitive control covers such a wide range of functions, many researchers have investigated if there is a need for some more basic functions in place for, and make up, the other cognitive control functions. It has been postulated that these necessary core functions are working memory, inhibitory capacity, and cognitive flexibility [9-12]. Empirical work seems to support that around the age of 7 years, the cognitive functions of working memory, inhibition, and cognitive flexibility have both separated and become relatively stable constructs [9, 10]. Studies with younger children have yielded more mixed results, which suggest that cognitive control begin as a unitary function that becomes differentiated into distinct components over development. These developmental changes correlate with the maturation of the frontal lobes [9-13]. Cognitive flexibility is dependent on working memory and inhibition, and these three core functions make up the higher-order functions such as planning, reasoning, and problem-solving [9]

Even if the core cognitive control functions of working memory, inhibition, and cognitive flexibility separate from each other during childhood, they are not unitary constructs. The most commonly used theory of working memory is that it is made up of four components [6], central executive, together with its subsidiary systems, the phonological loop, the visuospatial sketchpad, and the episodic buffer. The central executive is an attentional controller and content manipulator that works with the information contained in the other three subsidiary systems. The phonological loop and the visuospatial sketchpad retained auditory and visuospatial information, respectively. In the episodic buffer, information from long-term memory is retained [6].

Inhibition is commonly thought of as divided into; cognitive inhibition (the process of reducing the interference in working memory), behavioral inhibition (suppression of prepotent responses that are either automatic or prepared), interference control (preventing interference due to resources or stimulus competition) and delay of gratification [9, 13, 14]. These different inhibitory functions depend differently on the central executive [9].

1.2 Cognitive control and the brain

Cognitive control is associated at the neuroanatomical level with the frontoparietal network [15], also denoted as the cognitive control network [16]. It consists of the dorsolateral prefrontal cortex (DLPFC), posterior parietal cortex (PPC) and the anterior cingulate cortex (ACC) [16]. While functional synchronicity of these brain areas seems to make cognitive control possible, they still play different roles in adjusting processes and behavior to solve a task. DLPFC maintains

information and imposes an attentional set to select the relevant response in a given context [17, 18]. The PPC, especially the left PPC, is involved in response processing and response selection [17, 18]. For the ACC it was proposed to be involved in monitoring and detecting conflicts of information [19], whereas other theories propose that the ACC's involvement reflects arousal [20, 21]. Notable is that individuals with lesions in the ACC show typical performance on cognitive control tasks such as the Stroop test. Other brain areas are also associated with cognitive control tasks, in particular the anterior insula, supplementary motor area and ventrolateral prefrontal cortex (VLPFC) [15], but also different forms of cortico-striatal-thalamic loops that play an essential part in saliency and motivation [22].

Some definitions of different cognitive control functions, such as working memory with its central executive component, can encapsulate most cognitive phenomena besides long term memory. Furthermore, since cognitive control is such a critical part of our cognition, it is not surprising that in an overview of the neural underpinning of working memory Eriksson and colleagues stated that "[a]t the systems level, working memory has been linked to most areas of the brain […]. For working-memory maintenance *per se*, frontoparietal cortical regions make up a core circuit…" (page 42 [23]). In Table 1, a summary of brain regions associated with the core cognitive control functions is presented [15, 24-27].

Table 1. Executive functions and brain regions.

Core function	Subfunctions	Brain regions
Working Memory	Central Executive	Medial PFC, PPC, medial temporal lobe
	Episodic Buffer	PFC, medial temporal lobe, parietal lobe
	Phonological Loop	Left frontal cortex, inferior parietal lobe
	Visuospatial Sketchpad	Parieto-occipital regions, PFC
Inhibition	Cognitive Inhibition	LPFC, ACC
	Behavioral Inhibition	LPFC and motor cortex
	Interference Control	DLPFC, ACC, PPC, motor cortex, basal ganglia, striatum
Cognitive flexibility		Lateral PFC, PPC, ACC, striatum

1.3 Mental fatigue

Fatigue is a common problem estimated to impact 10 to 25% of the general population [28-32]. Fatigue is a phenomenon studied in different research fields, *e.g.*, medical science, exercise physiology, psychology, and cognitive neuroscience, and has been the subject of scientific investigation since the 19th century [33]. It was in the aftermath of the industrial revolution, around the 1870, the term fatigue came in to the medical textbooks under the diagnoses of neurasthenia, even thought it had its precursor in the more general melancholia.

It was also during this time when fatigue received its negative connotation and metaphorical interpretation as "lack of energy" and "running out of steam." Before that, fatigue was viewed as a natural state associated with the temporal "loss of spirit"[34]. Common for all forms of fatigue, cognitive, emotional, or physiological, is that all have a mental fatigue component. Mental fatigue is the persistent, subjective state of cognitive exhaustion that can affect cognitive performance [35]. Despite a large amount of work and its effect on patients and everyday life, its multiple expressions, the subjective nature, and the engrained metaphorical language have made the scientific understanding of mental fatigue hard to pin down [35].

Much like the study of cognitive control, the research on fatigue in general, and mental fatigue in particular, has led to a plethora of related terms and concepts. For the purpose of this thesis I define the terms used in table 2.

Table 2. Definitions of terms for studying mental fatigue.

Term	Definitions and operationalizations
Perceived fatigue	The introspected feeling of fatigue
State mental fatigue	The transient condition or feeling of fatigue that can change relatively fast within minutes or hours [36]
Trait mental fatigue	The stable and enduring fatigue that does not change rapidly, but over weeks and months [36]
Fatigability	The decrement in performance between two timepoints [36]
Active fatigability	The decrement in performance due to "overload" or actively doing something such as physical activity, vigilance test, sleep deprivation, or cognitive activity [35]
Passive fatigability	The decrement in performance due to "underload", not doing something actively, under stimulation, boredom, or performing monotonous activity over a prolonged time [35]
Pathological mental fatigue	Pathological mental fatigue is the trait mental fatigue at a level that makes work/activities of daily living very difficult, requiring attention/diagnosis by a medical/psychological professional. It is characterized by fast and drastic change in state mental fatigue, with a high level of perceived fatigue and a fast and strong active fatigability. The fatigability could be due to shorter periods of cognitive or physical activity or sensory stimulation. Characteristic is also a disproportionally long recovery time to get the state mental fatigue to back baseline.

Pathological mental fatigue is a sequel to a trauma to, or disturbance in, the central nervous system [37, 38]. The prevalence of pathological mental fatigue is estimated to be between 38-83% in multiple sclerosis (MS), 28-58% in Parkinson's disease, 36-77% after stroke and 45-73 % after TBI [36]. It is also associated with conditions, such as ED [39, 40], infection of the central nervous system [41] or hormonal imbalance [42]. Additional symptoms of pathological mental fatigue are increased irritability and tearfulness, concentration difficulties, procrastination and difficulty to make decision, sensitivity to sensory stimulation such as light and sound, sensitivity to stress, and sleeplessness [43].

Pathological mental fatigue is often regarded as secondary to the primary symptoms of the disease, disorder, or trauma. Consequently, these symptoms are often overlooked and untreated. However, pathological mental fatigue is often reported to be among the most disabling long-term consequence to a patient's everyday life post-treatment/rehabilitation.

Patients with pathological mental fatigue report having problems with cognitive control or cognition in general. They cannot perform cognitively demanding tasks over an extended time, for example, cooking a meal or having a longer conversation with more than one person [44]. Mental fatigue as a result of TBI or stroke is associated with problems of processing speed and attention [45-53], while stress-related exhaustion disorder is associated with long-term memory [40, 54-58] and working memory difficulties [40, 54, 55, 59, 60]. The underlying neural mechanism of mental fatigue is still unclear. However, the cortico-striatal-thalamic loops seem to be affected when pathological mental fatigue is present after TBI [61-65], in MS [66-70] or chronic fatigue syndrome [71].

1.4 functional Near-Infrared Spectroscopy

fNIRS takes advantage of the fact that light in the near-infrared spectrum (between 650 to 1300nm, called the near-infrared window) can penetrate tissue and that the absorption rates of different chromophores depend on the wavelength [72]. There are three kinds of fNIRS techniques; continuous wave [73], frequency depended [74] and time-domain [75]. The most frequently used type of fNIRS is the continuous wave technique, and henceforth I will use the term fNIRS synonymously for this type.

Oxygenated hemoglobin and deoxygenated hemoglobin (oxy-Hb/deoxy-Hb) have the same absorption rate only at around the wavelength 800nm and differ at other wavelengths (Figure 1) [76]. By continuously sending two or more beams of near-infrared light with wavelengths on different sides of 800nm into the brain and by measuring the intensity of the re-emerging (i.e., diffusely reflected) light, it is possible to determine the relative change from a set timepoint in the concentration of oxy-Hb and deoxy-Hb [77, 78]. This is of interest to neuroscientists since it enables us to measure the hemodynamic response as an indirect measure of brain activity. Hemoglobin supplies neurons with oxygen. When neurons produce action potentials, it is very energy-consuming and causes a need for more energy and oxygen supply. As a response, due to the neuro-vascular-coupling, there is a dilatation of the arteries to increase the blood flow, which produces the localized hemodynamic response along with changes in oxy-Hb and deoxy-Hb concentrations.

The change in oxy-Hb and deoxy-Hb concentration has several phases (Supplementary Figure 1, **paper I**). First, there is a decrease in oxy-Hb, together with an

increase of deoxy-Hb, since the hemoglobin has released its oxygen to supply the activated neurons, which is referred to as the initial dip [79]. The hemodynamic response starts after the initial dip with a rise in the oxy-Hb concentration, together with a decrease of deoxy-Hb beyond baseline levels. In adults, this takes place around one second after stimulus onset, around two seconds after stimulus onset for the elderly (age 70 and above) and around three seconds after stimulus onset for children [80]. The peak oxy- Hb concentration is reached after six seconds and returns to baseline after twelve seconds for adults and the elderly. For children, the peak is reached at around eight seconds, but it also returns to baseline after twelve seconds [79-81].
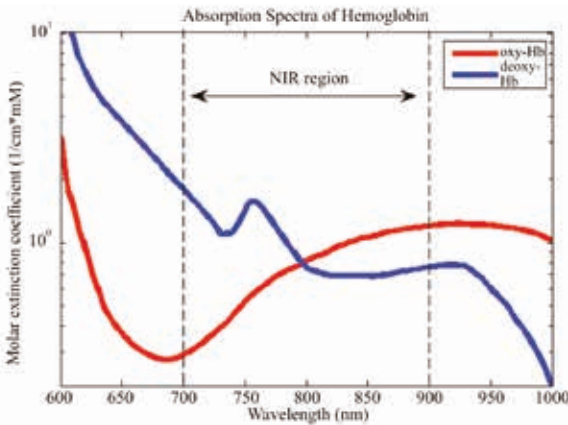

Figure 1. *Absorption spectra of hemoglobin. Image obtained under CC BY-SA 3.0 license from https://en.wikipedia.org/wiki/Functional_near-infrared_spectroscopy#/media/File:Oxy_and_Deoxy_Hemoglobin_Near-Infrared_absorption_spectra.png. Legend and font modified from original.*

An optode that sends light is typically called a *source*, and the light sensor is called a *detector*. Each source sends specific wavelengths of light, which allows a single detector to register light sent from several different sources at the same time. A source-detector pair is called a *channel*. When light is emitted to the skull, it scatters. It has been shown that if one places a detector around three centimeters from the source, then about 80 % of the detected light will have traveled in a "U-shape" a few centimeters down below the skull and back up to the detector [82]. The spatial resolution is approximately 1 cm^3. The sampling rate of different machines varies, but the most common temporal resolution is 10 Hz. Reliability studies with fNIRS show that, as long as the analysis is on a group level and with regions of interest (ROI) instead of individuals and channels, the reliability is very high, with an intraclass correlation coefficient between 80-96 % [83, 84].

1.4.1. Advantages with fNIRS

The advantage of fNIRS is usually highlighted by the limitations that other imaging techniques have. 1) fNIRS is comparatively more robust against motion artifacts, i.e., movements of the eyes, the head, or other body parts, and does not interfere with the recording to the same extent as with other imaging techniques, such as functional magnetic resonance imaging (fMRI); 2) The recording can only be affected by other light sources, which is easily handled by dimming the ambient light or an additional cap; 3) The hardware is portable; 4) The hardware is relatively inexpensive; 5) fNIRS generates information about several chromophores oxy-Hb, deoxy-Hb, and their sum denoted total hemoglobin (tot-Hb), which can be used to calculate cerebral blood volume change [85]. When using three or more wavelengths, it is also possible to measure the concentration of cytochrome-oxidase redox state [86]; 6) The relatively high temporal resolution gives a good specificity about different properties of the hemodynamic response; 7) Because we can estimate how light travels in the tissue, we can identify where the signal originated from; 8) fNIRS is noninvasive; 9) The preparation time before recording is short, from only a few seconds to a few minutes; 10) fNIRS is a noiseless functional imaging technique.

Altogether, this has made fNIRS a suitable alternative for studies with populations that might find other imaging technique problematic due to claustrophobia, sound sensitivity, having metal in or on their body such as implants, braces or piercings, havening problems sitting still or having to restrict movements. Also, if one uses a design that requires longer test intervals (**paper I** and **paper II**), using ways of answering that require movements, such as paper and pen tasks (**paper I, paper II** and **paper IV**), then fNIRS is preferable. As such, fNIRS is a suitable imaging tool for studying infants [73], children [87], individuals with developmental or psychiatric disorders [88], and using study design with higher ecological validity [89, 90].

1.4.2. Disadvantages with fNIRS

A problem with fNIRS is that hair, especially dark hair, absorbs light [91], but this can be overcome by brushing/moving the hair aside. More important is generally the volume and elasticity of the hair, which can make it challenging to keep the optodes close to the scalp. Another disadvantage is the problem of determining where in the brain measurements were taken. In order to compensate for this, optodes are placed according to the 10/20 system developed for EEG recordings [92]. The 10/20 system is a standardized map of landmarks on the head that correspond to specific brain regions. The use of the 10/20 system can be combined with digitized 3D-markers and structural magnetic resonance imaging (MRI) or standardized atlases. Since the fNIRS measures light absorption, other light sources such as daylight or a lamp can potentially affect the measurement,

which one can avoid by eliminating other nonessential ambient light sources during the recording or using a shielding cap.

Due to the scattering properties of near-infrared light, the fNIRS is only able to measure the hemodynamic change in the superficial portions of the neocortex. The superficial measurement is a disadvantage when one is interested in studying cognitive control, which, besides involvement of the frontal and parietal cortex, is known to involve deeper brain and subcortical structures such as ACC and striatum [22].

Most commercial fNIRS systems to date, like the one used in this thesis, do not have enough optodes to allow complete head coverage. Therefore, when studying cognitive control, a choice in the design of the array (i.e., the layout of the optodes) needs to be done in order to pre-determine the cortical areas of interest. Even though fNIRS systems have a relatively high temporal resolution compared to positron emission tomography (PET) and fMRI, the hemodynamic response is a rather slow physiological process. Consequently, if one wants to take advantage of the good resolution, a relatively long time between trials is needed in order for each hemodynamic response to subside, which can make the test situations long and monotonous for the participants, increasing the risk for passive fatigability.

1.5 Behavioral measurements of cognitive control

Due to the limitations of the extent to which fNIRS can shed light on the mechanism of cognitive control, it is advantageous to include behavioral measurements. The most common task to measure cognitive control is by examining interference through congruency tests such as the Stroop [93, 94], the Eriksen Flanker [95], and the Simon test [96]. The primary behavioral variable in congruency tests is response time, i.e., the time it takes from the presentation of a stimulus to the participant's response, usually by pressing a key or a button. In this section, I will present the basics tools and concepts of response time measurements of congruency test and how these tests can generate new and complementary information to the imaging results about cognitive control.

1.5.1. Interference and congruency

By determining the response time, we can establish the baseline from which negative and positive divergence can occur, which we can also refer to as cost and benefit [97]. Cost is the decrement, and benefit is the increment relative to baseline. Interference is then a theoretical explanation of this cost, and I will define it as:

Interference is the phenomenon that occurs due to multiple sources or dimensions of information competing to enter, or within, the central executive. The effect of this competition is that process efficiency or effectiveness is stopped, slower, or worse compared to if there were not multiple sources or dimensions of information present viz. cost relative to baseline.

In the Stroop test, developed by J.R. Stroop in the 1930s [93], the participant reports the ink color of a color word, e.g., the word RED in blue ink. The interference is created when a non-overlap of the stimulus-relevant dimension, i.e., the ink color, and the irrelevant dimension, i.e., the semantic meaning, exists. Overlapping trials are called congruent, and non-overlapping trials are called incongruent. The cost difference, i.e., when response time is slower, or the brain activity is increased, between incongruent and congruent trials, is defined as a congruency effect. For the Stroop test, it is called the Stroop effect (figure 2A).
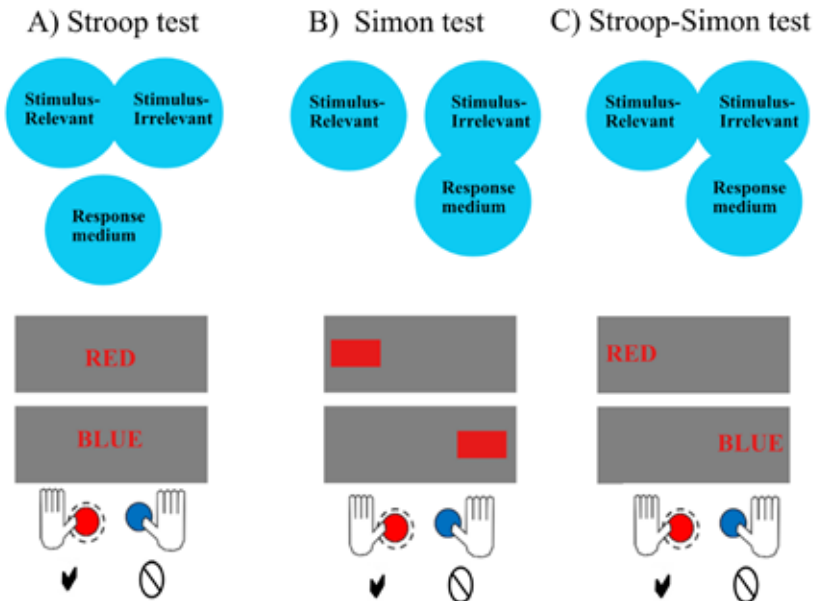
Figure 2. *Congruency tests*
The upper row with the blue circles illustrates where the overlap and non-overlap between the stimulus relevant and irrelevant dimensions and response medium for the three test A) Stroop test, B) Simon test and C) Stroop-Simon test. The two grey rectangles, in the middle, illustrates congruent and incongruent stimuli. For C) the upper stimulus is a Stroop congruent Simon congruent stimuli, and the lower is a Stroop incongruent Simon incongruent stimuli. The lower row illustrates what is the correct answer for the example stimuli. See text for explanation.

There are also congruency effects that do not depend on the overlap of the stimulus dimensions. In the Simon test, developed by J.R. Simon in the 1960s [98], the interference arises from a non-overlap between the irrelevant stimulus dimension and the response medium. Here, the participant is assigned to respond to one color with the left hand and to the other with the right. The figures are presented on either side of a screen, and therefore, the color of the figure represent the stimulus-relevant and its location the irrelevant dimension. For congruent trials, the figure is on the same side as the response hand, and incongruent when they are not. The congruency effect of the Simon test is called the Simon effect (Figure 2B).

1.5.2. Congruency Sequence Effect

Part of our cognitive control is the ability to quickly adapt our behavior or information processing to handle upcoming events or conflicts better. In the research lab, we can see this conflict adaptation in the CSE or Gratton effect [7]. The CSE is the phenomenon where processing a previous stimulus affects the performance of the current. More specifically, the subject will answer faster on incongruent trials if the previous trial was also incongruent compared to a congruent trial (see figure 3). Another way of describing this is that the cost, i.e., the interference, is reduced in the incongruent trial if it directly follows an incongruent trial. This conflict adaptation is present in several different congruency tests. The longer interval between response to the next stimuli (RSI), the smaller the CSE will be, and it has previously been shown to have a decaying lifespan of up to six seconds [99].

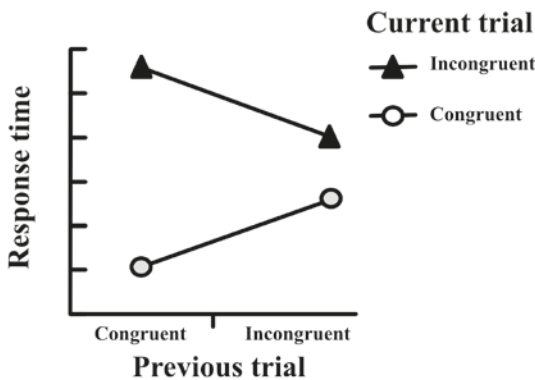**Figure 3.** *Model the Congruency sequence effect (CSE). See text for explanation.*

The conflict adaptation, or CSE, is thought to occur because the neural system enhances task-specific processes [100-102]. Since the CSE is stable over several different congruency tasks, it raises the question, whether this adaptation mechanism and also the information processing system, is domain-general or domain-

specific. For the information processing system to be domain-general would mean that it processes and solves all conflicts the same way. If it were domain-specific, this would indicate that there are several different information processing systems specialized in solving one type of conflict.

To measure this, one can use a factorial task-crossing design, where the congruency conditions from two tests, e.g., the Stroop-Simon task, are combined (see Figure 2C). In this test, the subject performs a Stroop test with the words on different sides of the screen, incorporates the stimulus-response hand conflict of the Simon test into the Stroop trial. Each trial will thus have a Stroop component (semantic meaning and ink color) and a Simon component (stimulus location in relation to the response hand). We can thus analyze how each component affects the other. If the information processing and adaptation mechanism are domain-specific, then we should find a Stroop CSE and a Simon CSE but not a transfer effect between them, i.e., that the previous Simon dimension should not affect the current Stroop dimension or *vice versa*. In a recent review, Braem *et al.* [102] concluded that eight out of the nine studies, which used a factorial design, did not detect a transfer [103-110], except one [111]. All these studies used healthy adults in the age span of 18 to 30 years. The evidence thus suggests that in normal healthy adults, the congruency adaptation is a domain-specific process. The fact that it is domain-specific suggests that multiple conflict-control loops can process conflicting information and these can probably run in parallel [101]. That the factorial design has only been used with healthy adults begs the question of whether it is possible that this parallel processing can be affected in some clinical population.

1.5.3. Proactive and reactive cognitive control
Strategy and previous information do also impact the congruency effects [112]. If a participant in a study is informed that the next trial will probably be incongruent, then she can proactively prepare for the upcoming trial and would thus perform better (faster and/or with higher accuracy) than if she acted reactively to the stimulus [113]. However, if a proactively acting subject prepares for an incongruent trial, while a congruent trial is presented, then she would perform worse compared to if she acted reactively.

The dual mechanism of control theory (DMC) [8] postulates that we can use our cognitive control in either a proactive or a reactive way. When utilizing the proactive mode, we prepare how to think or act for an upcoming event by using context-relevant clues. Whereas when we use our cognitive control in reactive mode, we rely on (and wait for) the upcoming event to triggers our decision on how to think and act. The ability and tendency to engage in proactive control follows an inverted U-shape across the lifespan [114] and is related to working memory capacity [115]. The congruency effect, in tests like the Stroop test, is affected by both age and working memory, possibly since younger adults with higher working memory engage more in proactive control [116]. The CSE has

also been shown to be related to the reactive mode and decreased or disappeared in the proactive mode [117, 118]. A more in-depth discussion of the DMC and how to study proactive cognitive control is presented in **paper III** and **V**.

2. Aims

Paper I – To investigate how prolonged mental activity affects cognitive performance and functional activity in the frontal cortex in individuals suffering from pathological mental fatigue after TBI.

Paper II – To investigate how prolonged mental activity affects cognitive performance and functional activity in the frontal cortex in patients with exhaustion disorder.

Paper III – To investigate the relationship between trait mental fatigue, proactive cognitive control and the hemodynamic response in the frontal and parietal cortex in healthy adults.

Paper IV – To explore possible differences in functional brain activity between different mathematical situations in a natural school setting, as well as investigating any possible associations between hemodynamic activity during mathematical cognition and children's tendency to use proactive control and their processing speed.

Paper V – To investigate the functional activity of proactive control in the frontal and parietal cortex of 8- to 9-year-old school children.

3. Patients and Methods

3.1 Ethical approval

All studies were conducted in accordance with the declaration of Helsinki. Ethical approval was obtained for all studies by the local Ethics Committee in Gothenburg. All participants in **papers I, II**, and **III** signed informed consent before participating in the study. Informed written consent was obtained from the legal guardian for the participating children before the study was conducted in **paper IV** and **paper V**.

3.2 Participants and recruitment

Paper I: Twenty-one individuals suffering from long-term mental fatigue after TBI (TBI-MF), at least five months after injury, were recruited from the Department of Neurology, Sahlgrenska University Hospital, Gothenburg. Inclusion criteria were as follows: diagnosed with mild TBI according to the definition proposed by The World Health Organization Collaborating Centre for Neurotrauma Task Force[119]; scoring above the cut-off score of 10.5 on the Mental Fatigue Scale (MFS) [43]; aged 20–65 years and not suffering from any other psychiatric or neurological disorders. One individual was excluded due to the inability to follow the instructions. Of the included 20 participants, 7 were males, and 13 were females with a mean of 42.1 ($\pm$10.2) years.

Twenty-one healthy controls who neither suffered from pathological mental fatigue (below 10.5 points on MFS) nor any psychiatric or neurological disorders, were recruited at the request from the general community. One was excluded due to the inability to follow the instructions. Of the included 20 participants, 8 were males, and 12 were females with a mean of 39.3 years with an SD of 11.9 years.

Paper II: Twenty-one patients diagnosed with exhaustion disorder (ED), code F43.8A, ICD-10, were recruited from the Institute of Stress Medicine, Gothenburg. All patients had received 12–18 months of multimodal treatment for ED. This treatment has previously been described in detail [120]. Exclusion criteria for the treatment program were a body mass index less than 18.5 kg/m^2 or over 30 kg/m2, high blood pressure, infection, menopause, pregnancy, nursing, vitamin B-deficiency (high homocysteine), known systemic diseases such as diabetes or thyroid disease or known psychiatric disease. One patient was excluded from the analyses since she did not perform the second test session, stating that

she was too fatigued to continue. Of the included 20 participants, 4 were males, and 16 were females with a mean of 47.5 years with an SD of 10.0 years. The same group as in **paper I** served as control subjects for this study.

Paper III: Thirty-one healthy adults were recruited in a convenience sampling by asking among an extended group of students, colleagues, and acquaintances for voluntary participation. Exclusion criteria were a score below 26 on the Montreal Cognitive Assessment (MoCA) and an inability to follow instructions. One was excluded due to the inability to follow the instructions. Of the included 30 participants, 15 (50%) were males with a mean age of 34.3 (±8.1) years, and 15 (50%) were females with a mean age of 31.1 (±6.0) years.

Paper IV and Paper V: The children were recruited from two Swedish primary schools, one in the Västra Götaland County and one in the Uppsala County. The cohort consisted of 30 boys, and 23 girls, mean age of 8.5 years with an SD of 4 months. Based on self-report, 46 of the children were right-handed, and seven were left-handed.

3.3 Summary of protocols

3.3.1 Paper I and II

The study had a test-retest design. Six neuropsychological tests were performed in the same order and were repeated after an intermission with the mental fatigue scale (MFS) [43] and a sustained attention test OPATUS-CPT. The order of the test was: Stroop-Simon test [101, 121], Symbol Search (SS) from Wechsler Adults Intelligence Scale 4th (WAIS-IV) [122], Digit Span (DS) from WAIS-IV [122], the *parallel serial mental operation* test (PaSMO) [123], the simultaneous assessment of Speed, divided Attention and Working Memory test (SAWM) [124] and Digit Symbol Coding (DSC) from WAIS-IV [122]. The whole test session took around 2.5 hours, and before and after the test session, a visual analog scale (VAS) asking about perceived fatigue was used to determine state mental fatigue. fNIRS data were recorded during all tests.

3.3.2 Paper III
All participants did the test in the same order. It started with the MoCA [125], SS [122], DSC [122], and the MFS questionnaire. Thereafter, they performed an on-screen spatial navigation task lasting 20-25 minutes, followed by the proactive control task AX-Continues performance task (AX-CPT) [126]. fNIRS recording was performed for the spatial navigation task and the AX-CPT.

3.3.3 Paper IV and V

The individual test session consisted of SS and DSC from Wechsler Intelligence Scale for Children fourth edition (WISC-IV) [127], a reaction time test, a child-friendly version of the AX-CPT, a test of additive situations (AS), and one of additive reasoning text-based or with geometric (visual) support (AR-T, AR-G). The fNIRS data were recorded during the AX-CPT and the two mathematics tests. All these tests were conducted at two Swedish schools. Two weeks after the fNIRS recordings, the children undertook four whole-class tests conducted by the teacher; *Basic numeracy and calculations (BANUCA)* [128], Additive and multiplicative reasoning (AMR) [129], Test of Visual Perceptual Skills-III (TVPS-III [130] and the working memory subtest from *Lilla Duvan (LD)* [131].

3.4 Methodological considerations fNIRS

The fNIRS machine used in these studies is a continuous wave system (NTS, Optical Imaging System, Gowerlabs Ltd., UK) [132] operating with light at two wavelengths around 780 and 850nm. This system uses 16 sources and 16 detectors. Since each source uses a pair of specific wavelengths e.g., 780 and 850nm for one source, for the next 779 and 849nm, 778 and 848nm, etc., up to 8 pairs of wavelengths, it is possible for the detectors to identify the origin of the light source and allows approximating through which part of the tissue the light has traveled. The setup, therefore, requires that a detector should not receive light from two sources with identical wavelengths since it would not be able to separate these.

To design a source/detector layout, or array, for each specific experiment, we first created an array in the MATLAB-based open-source program Atlasviewer [133]. This program helps inform which brain areas the designed array is sensitive to, and how each source and detector is related to the 10/20 landmarks (Figure 4). Based on this information, the array is transferred to elastic fabric caps suitable for different shaped heads (Easycap GmbH, Hersching, Germany). Sources and detectors are attached at the prespecified locations on the cap before the cap is placed onto the head of a subject. To validate the resulting locations of the caps, we used a digitizer Polhemus PATRIOT (Polhemus, Colchester, Vermont, USA), on a head model. We also used the digitizer on each participant on the adults in **papers I**, **II**, and **III**.
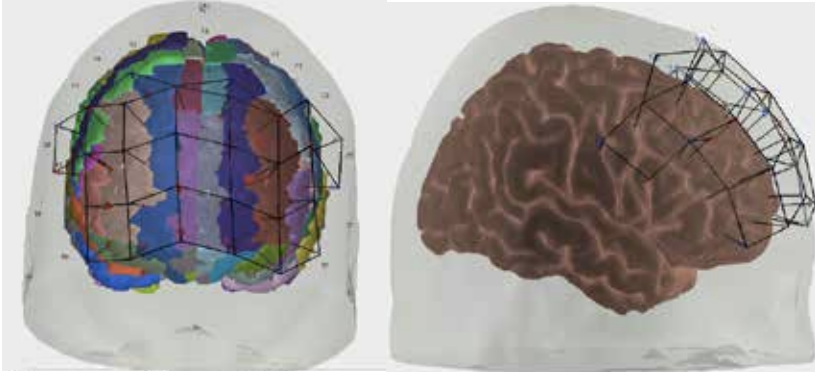
Figure 4. Visualization of array creation in Atlasviewer.

For **paper, I**, **II**, and **III**, caps with the head size 54, 56, and 58 were used. For **paper IV and V,** the capsize was 50, 52, and 54. To make the optodes attach more stably to the cap, a rubber spinnerette was placed on the inside of the cap (Figure 5A). If the signal was too weak i.e. if too little light was detected, the optode was removed from the holder, and the hair was brushed aside with a hair-pin (Figure 5B).
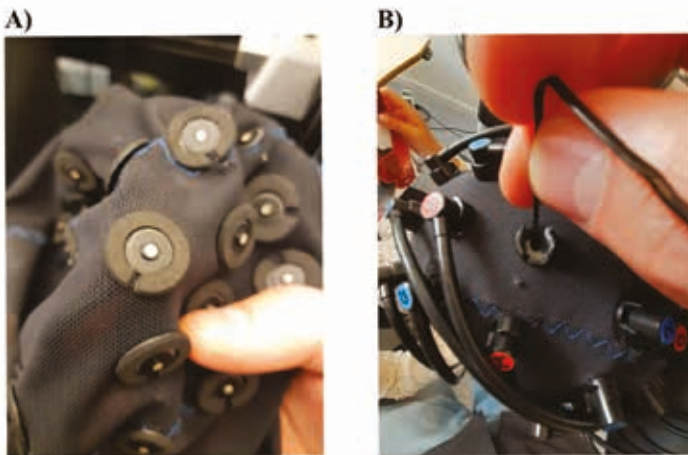
Figure 5. *A) rubber spinnerette was placed on the inside of the cap. B) hair being brushed aside with a hairpin to optimize signal*

The cap was fastened by a velcro strap under the chin and the tighter the strap (Figure 2 in **paper IV**), the easier it was to keep or brush the hair away. The participants were asked to tighten the strap but only to the point that they could still endure wearing the cap during the whole test session. For the long recordings in **paper I** and **II**, this meant that some participants were not comfortable wearing

the cap tight for a long period of time, which lead to a reduced signal quality. For the children study, **paper IV** and **V**, only a few minutes were spent to optimize signal quality.

3.5 The Mental Fatigue Scale

In **papers I**, **II**, and **III**, we use the MFS questionnaire to assess the level of trait and pathological mental fatigue. The scale was developed by Johansson *et al.*[53] as an assessment of pathological mental fatigue irrespective of neurological illness. It is made up of 14 questions, with an additional question not included in the sum score. The MFS is not constructed as a Likert scale, i.e., not an agreement/disagreement scale. Instead, it uses descriptions of life situations or symptoms meant to describe: no (0), slight (1), fairly serious (2), or serious (3) problems. It is also possible to answer 0.5, 1.5, and 2.5. The questionnaire has a maximum score of 42 points, with the recommended cutoff value of 10.5 to indicate concern for pathological mental fatigue [43]. The MFS is invariant to age, sex, and education [43, 53].

In the instruction of the questionnaire, the participant is asked to describe how the situation has been for the last months and not just how it is today. Five of the fourteen questions ask how it is now compared to how it was prior to the event/injury/illness. For the healthy controls in **paper I** and **II** and all participants in **paper III**, this is not applicable since they did not have a prior injury. Instead, they are asked to take a reference point some time ago, however not during a particularly difficult time in their life, to which they could compare the present state.

3.6 Statistics

Scientists use statistical tools to reveal information about or based on their data sets, which can be divided into four crucial components; describing, explaining/modeling, analyzing, and decision making. These components roughly correspond to four subfields of statistics; *descriptive statistics*, which is used to quantitatively describe features of a data set such as mean and SD; *probability modeling,* which is about formulating and testing probability models of the data; *data analysis*, which deals with extracting patterns from the data such as principal component analysis; *inferential statistics*, which is about helping the decision making under uncertainty [134].

The research done in this thesis is both confirmative and explorative, with a focus on inferential statistics. Different statistical tools deal with different types of uncertainty. The most common statistical inferential tool is called frequentist sta-

tistics, which makes inference based on p-values, and it quantifies the uncertainty of random variation or chance [135]. This type of statistics is used in **paper I**, **II**, and **III**. Another statistical inferential tool, Bayesian statistics, quantifies degrees of beliefs about a fixed reality as probabilities and indicates how much or to what degree we should believe in a hypothesis [136]. This type of statistics is used in **paper IV** and **V.**

3.6.1 Frequentist statistics

In this statistical tradition, a "p-value" is calculated to help make inferences. P-values are defined as the probability under the null-hypothesis of obtaining a result equal to or more extreme than what was actually observed. For the frequentist tradition, the null-hypothesis (H_0) is the hypothesis that is meant to be nullified by the statistical test. In the frequentist tradition, there are two different school of thought and procedures, Fisher and Neyman-Pearson [137]. There is also the amalgam of the two i.e. the null hypothesis significant testing (NHST). However, since the NHST blends the assumptions from both Fisher and Neyman-Pearson it often results in an epistemologically inconsistent view or are reduced to either the Fisher or Neyman-Pearson approach [138].

In short, the Fisher approach to data testing has few a priori assumptions making it more flexible, and it can be used when data are already gathered. It only uses the H_0, and the p-value is used as gradience of evidence against the H_0, meaning that a p-value of 0.049 or 0.051 gives almost the same amount of evidence against H_0, on this view. Fisher did also adopt the practice of using one or several levels of significance, gradating the amount of significance, to help the researcher or the reader make decisions. The level of significance needed not be decided a priori and could change depending on the test and research question. Fisher urged the use of significance testing only when there is no prior knowledge. This means both that in Fisher's view it is important to report the exact p-value to allow the reader to evaluate the evidence for themselves, and that this approach to decision making is inferential in nature and not deductive.

Newman-Pearson's approach on the other hand, is less flexible since it involves several decisions about the data analysis to be known or made a priori, e.g. estimated effect size in the population, power, α and β values. In contrast to Fisher's level of significance, the use of an αvalue is making the data analysis a test of acceptance and not of significance and it does not allow gradience of evidence. As a result of involving more decisions and estimations before data collection, the Newman-Pearson approach is deductive and increases reproducibility. The innovation by the Newman-Pearson approach is the addition of the alternative hypothesis. In the formulation of the alternative hypothesis, the estimation of ef-

fect size and β is incorporated, since without these parameters there are no a priori criteria for acceptance, making the alternative hypotheses obsolete, and the Newman-Pearson approach defaults to the Fisher approach [137].

There was no power calculation, estimation of effect size in population and β, prior to the collection of data in any of the studies in this thesis, making my attempt in **paper I**, **II** and **III** to follow a NHST approach, half reflecting the Newman-Pearson approach to *de facto* default into a Fisher approach.

The computation of a p-value for any specific situation is based on a defined space of possible outcomes. This defined space of possibilities is changed depending on the reason for stopping the collection of data (due to fixed number of participants, due to time or due to results) and how many tests are meant to be performed on the data set [139]. This means that an accurate interpretation of the p-value cannot be done if one does not know what the defined space of possible outcomes is, and thus decisions based on the p-value become problematic. One way to handle this is to adjust the p-value for multiple testing. In **paper I** and **II**, we use the false discovery rate (FDR) to correct for multiple testing. In contrast to other correction methods such as the Bonferroni method, where one multiplies the p-value with the number of tests done, the FDR controls the proportion of expected type I errors (false alarms or false discoveries). The FDR adjusts the p-value, first by ranking original p-values. Then, going down the ranking order from the highest to the lowest p-value, the following rules are applied: i) The highest p-value and the highest adjusted p-value are the same. ii) The next adjusted p-value is the smaller of two options, either previously adjusted p-value or the p-value multiplied by the total number of p-values divided by the rank number of the current p-value.

In **paper III**, which primarily used correlations, we choose not to use FDR. Instead, we used a leave-one-out-cross-validation method, where we eliminated one data point at a time and recalculated the correlations. If all these correlations had a p-value <0.05, then we concluded that the original correlation was stable, i.e., not affected by an outlying data point.

3.6.2 Bayesian statistics

Another statistical inference tool, Bayesian statistics, quantifies the degree of beliefs about a fixed reality and shows how much or to what degree we should believe in a hypothesis [136]. The heart of Bayesian analysis is the "reallocation of credibility across possibilities" [140]. To illustrate the meaning of the above statement, I will use an example of two groups performing the backward digit span test, where the participant is asked to repeat a string of digits in the reverse order it was presented. The possibilities that are denoted here are the possibilities that the parameters take on different values in the descriptive model of our

data. For example, one possibility is that the average correct answer for one group will be five digits; another is three digits, nine digits, 4.5 digits, and so on. There are many different possibilities for the parameter values; mean and SD. However, we usually do not believe that each possibility is equally probable. We might, for example, believe that it is more credible that the mean of group one will be five digits and not nine digits. This credibility of the different possibilities might be informed by previous knowledge. However, it might also be the case that we think that all possibilities have the same credibility. What Bayesian analysis does is to reallocate the credibility of the different possibilities in light of the new data. The reallocation presupposes a prior estimation of the possible values that later can be reallocated, given the data to what we call our posterior. The posterior is calculated with the Bayes rule that provides a mathematical way of reallocating of credibility across the parameter values. The result will thus show how strong we should believe in each parameter value given the data and our prior beliefs. Our hypothesis can be summed up as the sum of our parameter values in this model or the credibility of a specific possibility compared to other possibilities. If we denote hypothesis with H, and the data with D we can formulate the Bayes rule:

$$p(\text{H}|\text{D}) = \frac{p(D|H) \times p(H)}{p(D)}$$

where the posterior, p(H|D), is verbalized as the probability of the hypothesis H give the data D. So, the type of uncertainty that Bayesian statistic works with is epistemic uncertainty, i.e., how much should we believe in one scenario compared to another.

In paper **IV** and **V,** and the Stroop-Simon data in 4.1.3, the Bayes factor (BF) analysis is used [141]. We applied BF_{10} as the main criterion, and the interpretation of $BF_{10}=3$ would be that, given the data, the alternative hypothesis (H_1) is three times more likely than the null hypothesis (H_0), while $BF_{10}=0.3$ can be interpreted that, given the data, the H_0 is three times more likely than H_1. Even in the Bayesian tradition there have evolved conventional decision criteria, which are $BF_{10} \geq 3$ to accept H_1, or $BF_{10} \leq 0.33$ to accept H_0. A $BF_{10} > 3$ can also be interpreted as the equivalent to a p-value < 0.01[135]. Following the praxis of Wagenmakers and colleagues [136], a BF_{10} in one of the four categories between 3-10, 10-30, 30-100, or above 100 is interpreted as *substantial, strong, very strong* or *extreme* evidence for H_1, respectively. We used a default Cauchy prior of 0.707.

3.6.3 Analyzing the Congruence Sequence Effect

In **paper I** and **II**, we used the Stroop-Simon task as described in section 1.5.2. For the fNIRS result, we focused only on the Stroop Effect. However, for the response time, we asked two additional questions. i) Is it possible to have a CSE

for the Stroop and Simon effect over six seconds, which has previously been reported? In our study, we used nine seconds between responses and the next trial. ii) Is it possible that domain-specific processing can be affected in individuals suffering from TBI-MF or ED?

The CSE is calculated as follows:

$$CSE = \left(Con_p In_c - Con_p Con_c \right) - \left(In_p In_c - In_p Con_c \right),$$

where $Con_p In_c$ is the reaction time after a previous congruent & current incongruent stimulus. $Con_p Con_c$ represents previous congruent & current congruent, $In_p In_c$ represents previous incongruent & current incongruent, and $In_p Con_c$ represents previous incongruent & current congruent. With this formula one can thus calculate, in milliseconds, how much the Stroop or Simon effect is changed, *i.e.* the cost or benefit of the current trial depending on the (non-)overlap of the stimulus-relevant/irrelevant dimension and (non-)overlap of the stimulus-relevant/irrelevant dimension and response hand.

To evaluate this, we used a Bayes factor version of a one-sample t-test, comparing it to zero, i.e., the null hypothesis assuming that there is no change in milliseconds of the Stroop or Simon effect depending on the nature of the previous trial.

4. Results

4.1 Summary result paper I and paper II

The main objective of the study was to investigate if the functional activity during cognitive control in the frontal cortex changed for TBI-MF (**paper I**) and ED patients (**paper II**) when their state mental fatigue increase. To ensure that the state mental fatigued would increase, the participants performed cognitive tasks for about 2.5 hours, made up of six neuropsychological tests, which they repeated one time after an intermission with questionnaires and a sustained attention test. An additional reason for the prolonged study design was to simulate a situation that was more corresponding to a working day since participants suffering from mental fatigue, and ED can often perform well on neuropsychological tests while they are still not able to work.

4.1.1 Result Paper I

For the VAS, the interaction between Time (before, after) and Group (TBI-MF, control) showed that prolonged mental activity effects the state mental fatigue more among individuals with TBI-MF as compared to controls. There was also an interaction between Time (test, retest) and Group for the DSC test, indicating that the controls improved their performance on a processing speed task, whereas the TBI-MF did not, i.e. no fatigability was detectable for the TBI-MF group. The TBI-MF group also showed lower performance on the Stroop-Simon task, the mental flexibility task PaSMO, and the dual-task SAWM (Figure 3 in **paper I**).

The TBI-MF group had a smaller increase of oxy-Hb in bilateral FPA and VMC in the Stroop-Simon test compared to controls. There was also an interaction between Stroop effect (congruent, incongruent) and Group (TBI-MF, controls) in the left VLPFC, showing that the TBI-MF group utilized the left VLPFC as much for congruent as for incongruent trials. In contrast, controls had a higher increase of oxy-Hb in the incongruent trials than in the congruent. We could not detect any effect of the prolonged mental activity (test, retest) in the fNIRS recordings (Figure 4 in **paper I**).

4.1.2 Result Paper II

For the VAS, the interaction between Time (before, after) and Group (ED, control) showed that prolonged mental activity affected the ED groups' state mental fatigued more than the controls. There was also an interaction between Time (test, retest) and Group for the Stroop-Simon task. However, we could not conclude any difference (fatigability) between the test and retest when we analyzed the groups separately, which makes it less likely that the ED group response time was affected by the prolonged mental activity in a different way than the controls. The patients with ED also perform worse on the PaSMO and SAWM during the retest (Figure 2 in **paper II**).

Patients with ED had a higher increase of oxy-Hb in the DLPFC compared to controls during the first SS and DSC test (Figures 4 and 5 in **paper II**). The ED group also had a lower increase in oxy-Hb in bilateral FPA, VMC, DLPFC as well as right VLPFC and left DMC in the Stroop-Simon test. Moreover, there was an interaction between the Stroop effect (congruent, incongruent) and Group (TBI-MF, controls) in the left VLPFC, indicating that the patients with ED utilized the left VLPFC as much for congruent as for incongruent trials. Furthermore, we could not detect any Stroop effect in any of the ROIs for the ED group. (Figure 3 in **paper II**).

4.1.3 Result Congruency Sequence Effect

Our data suggest that there is a possible Simon CSE (or Simon-Simon effect) even after nine seconds. When pooling all patients with a MFS score above the cutoff of 10.5 there is a medium effect size (table 3 and the upper row of Figure 6). Another question was whether it is possible that domain-specific processing can be affected in individuals suffering from TBI-MF and ED? The evidence suggests that with a nine-second response to stimulus interval, there is no transfer effect from previous Stroop to current Simon dimensions or previous Simon to current Stroop dimensions, suggesting that the domain-specific processing is intact in patients and individuals suffering from pathological mental fatigue (table 3, and the lower row of Figure 6).

Table 3. Result of the congruency sequence effect analysis.

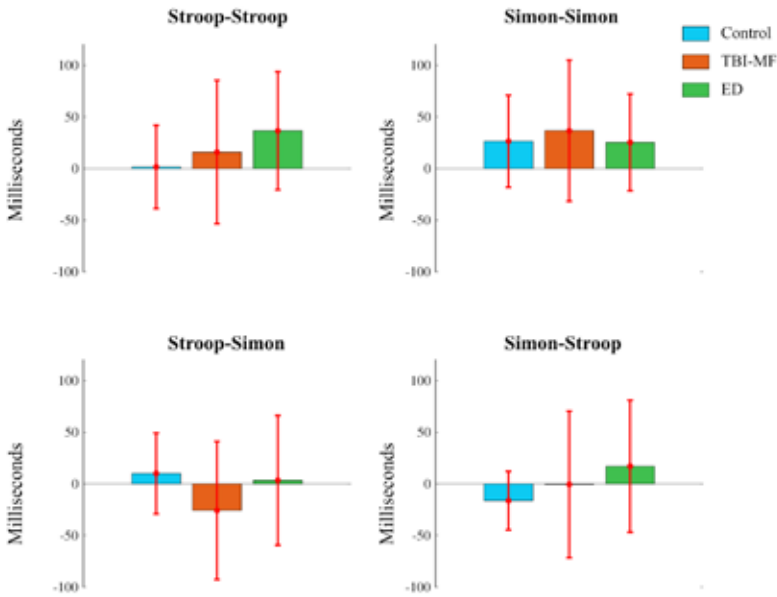| Previous-Current	Control (df*=19)			TBI-MF (df=18)			ED (df=16)			MFS >10.5 (df=35)		
	t	BF_{10}	d	t	BF_{10}	d	t	BF_{10}	d	t	BF_{10}	d
Stroop-Stroop	0.17	0.40	0.03	1.00	0.37	0.23	2.63	3.33	0.640	2.41	2.25	0.40
Simon-Simon	2.66	2.02	0.59	2.33	2.06	0.53	2.23	1.73	0.541	3.20	12.39	0.53
Stroop-Simon	1.16	0.90	0.25	-1.67	0.77	-0.38	0.23	0.25	0.056	-1.08	0.30	-0.18
Simon-Stroop	-2.55	0.23	-0.57	-0.02	0.23	-0.00	1.10	0.42	0.267	0.69	0.22	0.11

* = degree of freedom

Figure 6. *Result CSE Stroop-Simon test.*
The upper left is how previous Stroop dimension effects performance on current Stroop. The upper right is how dimension previous Simon effects performance on current Simon. The lower left is how previous Stroop dimension effects performance on current Simon. The lower right is how previous Simon dimension effects performance on current Stroop. Error bars are SD.

4.2 Summary results paper III

The objective of the study was to investigate the relation between trait mental fatigue, proactive cognitive control, and functional activity in the frontal and parietal cortex of healthy adults. The trait fatigue was evaluated by the MFS, and the proactive cognitive control with the proactive behavioral index (PBI), which is generated from the AX-CPT. The functional activity was evaluated by focusing on the difference in oxy-Hb increases between reactive and proactive trials.

We detected a negative association between trait MFS and the PBI, indicating that the more mentally fatigued, the less proactive or more reactive an individual is. There was a positive association between the MFS and the oxy-Hb difference in left medial PPC and right DLPFC, showing that the more mentally fatigued an

individual is, the higher the increase in oxy-Hb is observed in reactive trials relative to proactive trials. We were not able to detect any association between the PBI and the difference in oxy-Hb difference.

4.3 Summary results paper IV

The main objective of **paper IV** was to study functional activity for mathematical cognition both in an ecological environment, i.e., at school, and with tasks closer to what children in grade two usually do, i.e., with pen and paper question that are similar to those students usually encounter. We developed three different tasks of mathematical reasoning for numerical addition and performed the fNIRS at two schools.

We found a transitive relation for the involvement of the right DLPFC when solving the mathematical tasks, associated with the cognitive load of the task (Figure 3, **paper IV**) from AS to AR-G to AR-T, where the increase in oxy-Hb was largest during AR-T. There was also an association between the performance on additive situations and the general cognitive ability evaluated with the modified AX-CPT and the DSC (Figure 5, **paper IV**).

4.4 Summary results paper V

The main objective for **paper V** was to investigate the functional activity of proactive and reactive cognitive control in the frontal and parietal cortex of 8- to 9-year-old children. We used a modified version of the AX-CPT to study proactive and reactive cognitive control. We found an association between AX-CPT performance and functional brain activation. The more proactive, or less reactive, the children were, the more they involved the right LPPC in reactive situations compared to proactive ones.

5. Discussion

Paper I, **II**, and **III** focused on how trait (or pathological) mental fatigue affects cognitive control. To rate the extent of trait mental fatigue, we used the MFS, and to study cognitive control, we applied different behavioral measurements and fNIRS. In **paper IV** and **V**, we investigated proactive cognitive control in 8- to 9- year old children and its relation to mathematical cognition.

5.1 Mental fatigue and cognitive control

In the two first papers, we focused on how cognitive control was affected by pathological mental fatigue after TBI and in ED. In both studies, we failed to detect a change in functional activity between the test and retest. Other studies have seen change over time, e.g. Berginström *et al*. detected decrease, from the start of the test to the end of the test, in the blood oxygen level dependent signal during a sustained attention task for healthy controls but not TBI with pathological mental fatigue in subcortical and deeper brain structures that cannot be measured with the fNIRS such as thalamus, caudate and left hippocampus [62]. They did also see a change in the right SMA and frontal middle gyrus, which we did measure. However. the sustained attention test was relatively short, up to 27 minutes, where the Stroop-Simon test took 25 minutes. Such a difference could have occurred between the beginning and the end of the first Stroop-Simon test, but this was not analyzed. Due to a coding error, we were only able to analyze the Stroop effect in the fNIRS data.

The role of the DLPFC in cognitive control is to impose an attentional set, to bias features of sensory input and responses, to select the relevant response in a given context [17, 18]. Several fNIRS studies with healthy adults performing the Stroop test have reported increased activity in the DLPFC [81, 142-148]. Previous fNIRS studies had shown a lower functional activity in DLPFC for patients with TBI compared to healthy controls for cognitive performance [149-154]. In **paper I**, we wanted to test if the cognitive control problems associated with TBI-MF were related to a problem with imposing an attentional set when selecting the correct response. This could not be confirmed; however, we found an interaction between the Stroop effect (congruent, incongruent) and Group (TBI-MF, controls) in the left VLPFC, suggesting that the TBI-MF have difficulties utilizing the left VLPFC during the Stroop task. The VLPFC is involved in semantic conflict processing [148, 155, 156]. The same interaction was also

found between controls and patients with ED, suggesting that the problem of utilizing the VLPFC is related to the pathological mental fatigue.

Both patients with TBI-MF and ED showed generally a smaller increase of oxy-Hb during the Stroop-Simon test compared to the controls. In **paper II**, we analyzed the Stroop effect for the ED group and controls separately, showing that while the controls had a larger increase in oxy-Hb for incongruent trials than congruent trials in left FPA, left VLPFC and right DMC, the ED group did not show differences in any of the ROIs (this analysis was not done for the TBI-MF in **paper I**). This demonstrates some of the limitations with the fNIRS investigation since the ED patients showed a Stroop effect in the response time measurements (Figure 2, **paper II**) suggesting that they utilized other brain regions to solve the conflict, such as the PPC, which we decided during the planning phase not measure due to the limited number of optodes, or the ACC, which is not detectable using the fNIRS.

We also wanted to view the effects of mental fatigue on cognitive control through the lens of the attentional control theory from Eysenck and colleagues [157]. It postulates that there is within our cognitive control system a trade-off relation between *efficiency* (how fast something is done) and *effectiveness* (how accurate something is done). Different problems with cognitive control generate different compensations in efficiency or effectiveness. Both the TBI-MF and the ED group showed a reduced efficiency (slower response time). There might be several reasons for the decrease in efficiency. One is that it could be due to prioritizing of effectiveness[157]; however, our data do not support this view. After FDR correction, we could not conclude any difference in accuracy for the Stroop-Simon in **paper I** or **II**. However, the F- and the Z- values (table 2 **paper I** and supplementary table 3 **paper II)** suggest that if anything, both patient groups had also more errors than the controls.

Another possibility is that, due to their pathological mental fatigue, patients process information differently. For example, the domain-specific parallel processing could be affected, putting a higher demand on domain-general processing. If that had been the case, then the efficiency of processing two different conflicts in parallel should have been reduced, leading to a slower response in the Stroop-Simon test. This was tested with the CSE in section 4.1.3, but we found no evidence for any transfer effect of the previous Stroop to the current Simon effect or the previous Simon to the current Stroop effect. That we did not detect a transfer effect could, of course, be attributed to the long response-stimulus interval (RSI) of nine seconds. With a shorter RSI, the possibility to detect such an effect would increase. However, turning this argument around seems more plausible i.e., since there was such a long RSI, a transfer effect should not be present. However, since we still observed a difference in efficiency, it is possible that at least in our sample, there is a general decrease in efficiency of the cognitive control system associated with pathological mental

fatigue, which is not due to any change in how the individuals process information.

As shown in table 3 in 4.1.3, there was strong evidence for a regular Simon CSE despite the longer RSI, but not for the controls. A conjecture is that the controls lack a CSE since they are more proactive, while the TBI-MF and ED groups have a CSE since they respond more reactively. Gonthier *et al*. showed that the CSE is only present in the reactive mode and is affected or disperses when one is proactive [112]. They also argued that the longer the RSI, the higher the probability of being proactive. This is fitting with the results in **paper III** where we showed that in healthy adults, the higher their trait mental fatigue was, the more they tended to be reactive.

The fNIRS analysis in **paper III** showed an association between higher trait mental fatigue and a larger increase in oxy-Hb during reactive compared to proactive trials in the left medial PPC and the right DLPFC. If this represents a general pattern, it will provide some insight into why the ED group and possibly the TBI-MF did not show any Stroop effect in the fNIRS data. Since the design of tests like the Stroop-Simon test emphasizes the reactive mode [25], and higher mental fatigue is associated with a larger increase in oxy-Hb when reactive, the difference between congruent and incongruent trials should be more challenging to detect [150]. However, this does not explain our results in **paper I** and **II**, where both TBI-MF and ED groups had a smaller increase of oxy-Hb for congruent trials compared to controls.

Even though we use the MFS to measure both, trait mental fatigue in healthy adults and pathological mental fatigue in TBI-MF and ED patients, it is not clear that trait mental fatigue in healthy adults and pathological mental fatigue are comparable. It might be the case that mental fatigue is a continuum, just like the scale, and then pathological mental fatigue is just a more severe version of trait mental fatigue. Nevertheless, even if it were a continuum, it is an open question whether the effects on the cognitive control system are linear in that way. Alternatively, it could not form a continuum, and pathological mental fatigue is a different construct from high trait mental fatigue, making the comparison between high trait and pathological mental fatigue less fruitful.

5.2 Internal vs. external validity

Internal validity is about how well the results can be explained by the experimental manipulation and not by other explanations (confounders). External validation, or ecological validity, is about how well the results can be generalized to other situations or more real-life situations. Over the years, the internal validity for a test of cognitive control, such as the Stroop test, has been increased. Interestingly, what has previously been thought of as possible confounders are now

integrated part of theories about cognitive control such as the state or trait mental fatigue and the CSE.

The strength of fNIRS, as a functional imaging tool, is that it allows for more liberal study designs e.g., at schools, more extended tests, verbal response, and test with pen and paper [90]. This increases the ecological or external validity of the results, features that studies with other imaging techniques have been criticized for [158]. However, it is also important to keep in mind that by focusing on the external validity, as we have done in **paper I**, **II**, **IV**, and **V**, it also adds noise and possible confounders, which decreases its internal validity. Whereas in **paper III**, which is a classic research lab experiment that has a higher internal validity, might beg the question of why this study was done with fNIRS when it could have been done with other imaging techniques such as fMRI (that have better spatial resolution) or EEG (better temporal resolution). The answer is, of course, that we wanted to use the test in such a strict environment first so we could compare future studies in more liberal settings in order to evaluate its internal validity.

It is also essential to reflect on the external and internal validity of the test themselves and not just the functional imaging. The Stroop-Simon test, for example, has a very high internal validity, with the contrast between congruent and incongruent, the controlled RSI, the response medium, and the CSE. However, spending 25 minutes ignoring the semantic meaning of the word RED and BLUE is not something that often happens in everyday life. The different mathematical situations in **paper IV**, did not have any control condition making the internal validity not as high. However, since it is a task a child is likely to encounter in math classes, it has a very high external validity.

5.3 Proactive cognitive control and mathematical cognition in children

The data for **paper IV** and **V** were collected at the same time, and while **paper IV** focused on the functional differences in mathematical cognition during three different mathematical tests, **paper V** analyzed the functional brain activity during proactive cognitive control. In both studies, the behavioral measurement of AX-CPT, especially the PBI, was used.

Typically, when it comes to functional brain imaging of different cognitive control functions in children in the early school years, the result is that they have a more diffuse pattern of activation compared to adults, and that the activity becomes more localized with time [159]. This pattern appears not to match our

finding for proactive cognitive control. In adults, the activity of proactive cognitive control is associated with a functional change in both the frontal and parietal cortex [8, 25, 160]. In contrast, in children, it is mostly the parietal cortex [161-163]. Why this is the case is still an open question. One reason could be that when children learn to engage more in proactive control through development, they also involve the frontal cortex more. However, this might suggest that children do not engage in proactive cognitive control *properly* until late adolescents, which would imply that there are several different proactive modes [164], one involving the whole frontoparietal network and others that do not. Another possibility is that, since it is a mode, i.e. a way to implement a cognitive control function and not a function *per se*, the rule of more diffuse activity during development might not hold. There is evidence from the literature with adults that the reactive and proactive mode utilize similar networks, the frontoparietal network, but that there is a difference in temporal dynamics [25, 160]. Whether this is the case during development or whether possibly different types of proactive control exist for children needs further investigation.

In **paper V** we detected an association between increased activity in right PPC during reactive trials and higher PBI. Without following the same setup as other imaging studies with children of similar age, we could thus replicate the effect, this time with a new imaging modality and in a school environment. That we could reproduce such a relatively complex or subtle effect with fNIRS in a school environment, is important for further research in several ways. Firstly, in a scientific climate where the validity of many psychological effects and theories is brought into question [165], this increases the credence to the construct of proactive and reactive cognitive control. Secondly, the effect is still observable when the external validity is increased.

Figure 5A in **paper IV** shows the possible association between increased oxy-Hb during the *additive situations* task (Figure 1B **paper IV**) and the PBI in the medial parietal cortex, indicating that there is an association between context processing and functional activity during mathematical cognition. Even though imaging techniques such as fMRI propose several challenges for studying mathematical cognition with children, it is not impossible. A meta-analysis of 32 fMRI studies with children investigated the functional activity for number processing, i.e., no formal calculation, only viewing different digits or quantities of small and vast arrays of dots, and calculation applied to numbers usually addition, subtraction or multiplication[166]. They found that both number processing and calculation involved the right inferior parietal lobe, inferior parietal sulcus, insula, and claustrum.

A major supplement that fNIRS studies can bring to the field of mathematical cognition is the increased ecological validity. The research field is still in an early state, for which **paper IV** is an example. A recent review of fNIRS and

mathematical cognition in children (age 9 to 16 year of age) found only six stud-
ies and some had few participants (n=8 and n=14) [90]. Based on the result
in **paper IV**, we propose that the difference between the three mathematical
tasks could be possibly explained by a difference in the cognitive load. This in-
terpretation is in line with previous fNIRS studies [167, 168]. That children uti-
lize the frontal and parietal cortex less when there is a visual aid compared to the
equivalent mathematical task, that does not have a visual aid, might support the
idea that when children are learning a specific mathematical skill, it is useful to
unburden the overall cognitive control functions, with for example visual sup-
port.

5.4 Epistemological reflections

Depending on the object or phenomenon of interest, a researcher can either use
direct or indirect observation (Figure 7). If one is interested in the properties of a
tree, say length and width, one can measure this directly. For direct observation
each discovered object is also the validation of that object's existence i.e. the ob-
servation of a tree makes it certain that there is a tree. Indirect observation takes
place when the object or phenomenon of interest is measured by the effects it has
on something else, e.g. studying the properties of a tree by observing its reflec-
tion in a pond. Indirect measurements rely on the entity measured (the reflection
in the pond) to be a consequence of the object or phenomenon of interest (the
tree). This means that there needs to be an inference from the entity measured to
the existence of its cause or underlying structure (or in some cases at least that
the measurement is predictive). Since inferences like these are probabilistic, the
discovery and validation become separated from each other in indirect observa-
tions, and cannot happen at the same time, i.e. the observation of the reflection in
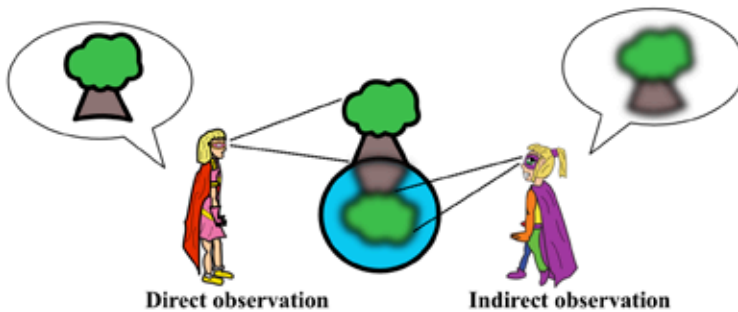the pond does not make it certain that there is a tree.

Figure 7. *Direct vs. indirect observation. See text for explanation*

The study of cognitive control is one of only looking at the pond without the possibility to look up. The indirect measures used in this thesis are neuropsychological test and functional brain imaging. Cognitive control is thus one, of the possible myriad of the hidden causes and structures, that could explain the observed change in behavioral data (from neuropsychological tests) and functional data (from fNIRS). In section 1.5.1. I stated that interference is a theoretical explanation of the phenomenon of increment in response time, making the increment in response time the observed variable and the interference the proposed underlying cause for the change in response time. The solution of the interference is due to the capacity of cognitive control.

It is important to note is that any type of fNIRS recording, just like any type of response time observation, is not a measure of cognitive control. But in the right circumstance, such as when one compares the oxy-Hb increased over the DLPFC for congruent and incongruent trials of a Stroop task then it becomes a measure of cognitive control just like response time.
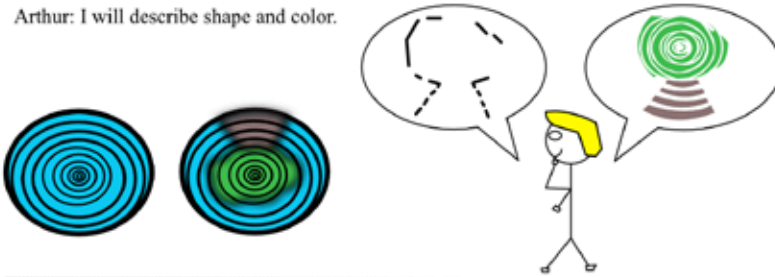
5.4.1. Exploratory vs. confirmatory research

Staying with the pond example and keeping in mind that such an example can only go so far, I will give some examples to illustrate some of the epistemological fundaments underlying the work in this thesis. In Figure 8, Arthur cannot look up past the shore but wants to learn more about what he sees in the pond. However, there are water rings in the pond and other noise obscuring the observation. What he can do is to compare this pond with other ponds where he does not see the same reflection. He can also choose to describe different properties e.g. the shape or the colors. The description of these phenomena does not explain why he observes what he observes, meaning that Arthur does not know more about the possible existence of any tree on the shore, but he knows more about the reflection in this pond.

Bruce, in Figure 8, on the other hand observes both shape and colors at the same time. Based on these observations he tries to "connect the dots" by extrapolating both shape and color. The result is a hypothesis of the existence of a tree. He is not really sure what a tree looks like, but something similar to what his theory describes could be the reason for the reflection in this pond. Bruce has not confirmed that there certainly is a tree, he has only generated a possible explanation to why he observes what he observes.

Clark, in Figure 8, has talked to both Arthur and Bruce and other pond watchers. He is interested in confirming the existence of an apple tree on the shore of his pond. Since he knows apples are red and he cannot see anything red in the reflection of the pond, he confirms that there is no apple tree on the shore. However, he wants to confirm that there is some kind of tree on the shore and he knows the tree shape. He observes the pond again and based on the shape he concludes that there is some kind of tree.
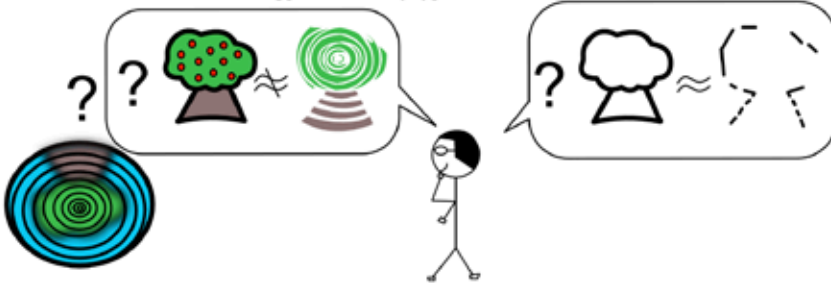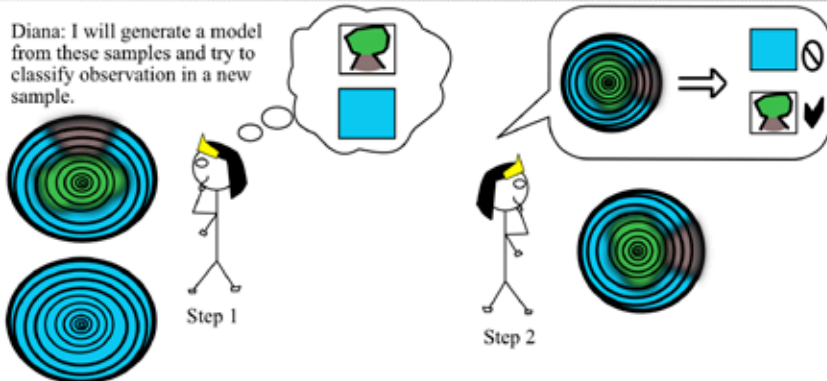
Figure 8. Research of the pond. See text for explanation.

Lastly in Figure 8, we have Diana. She observes the colors in different ponds and creates a model that distinguishes them. She then continues to categorize other ponds according to the model. In contrast to Clark, Diana does not focus on the reason behind the observed colors, only that these phenomena can be generalized on an observational level.

The research done by both Arthur and Bruce is called explorative, Clark's is called confirmatory and Diana's predictive research. The research done in this thesis is a combination of both exploratory and confirmatory. Both exploratory and confirmatory research are essential for the scientific enterprise. In confirmatory research it is important to falsify or give credibility to theories and explanations. However, without exploratory research, theory development and refinements would be based on a whim, which in the end makes the confirmatory research problematic [169].

In the last decade there have been vivid discussions about the use and misuse of exploratory and confirmatory research in the realization that a relatively high proportion of the published results in psychology, cognitive neuroscience and medicine [170] cannot be replicated [165]. The argument is that much research that has been presented as confirmatory, but was in reality done exploratory i.e. exploratory findings with confirmatory conclusions [171]. This is exemplified with Clark in Figure 8. He first rejected the apple tree hypothesis and then tested the any-type-of-tree hypothesis. The problem is that the presupposition of a defined space of possible outcomes often needed in statistical testing implies that data can only be used once [139, 171]. So, Clark might think he has confirmed the existence of a tree, but in reality, the repeated testing has transformed his investigation to be one of finding the best description of the dataset and would thus be exploratory.

Different remedies have been proposed e.g. that we should only view studies with preregistered protocols as confirmatory and the rest as exploratory [171]. None of the papers in this thesis are preregistered and would not meet this criterion. However, I would still argue that the research in this thesis which is grounded in the theories of proactive cognitive control, the DMC [8], and the multiple conflict-control loops about conflict processing and the Stroop effect [101] are confirmatory in nature, since they started out with a clear theory that could be confirmed or disconfirmed.

The confirmatory approach in this thesis varied in success. Even though the design of the fNIRS measurements in **paper I** was to test the difference in the Stroop effect between the groups in DLPFC as discussed in 5.1, an argument can be made like the one in 3.6.1 that the lack of any prior criteria of effect size for acceptance makes the confirmatory part problematic. The same is true for the functional activity associated with proactive cognitive control in **paper III** and **V**, however in **paper V** we used another statistical tool not susceptible to the

same problem**.** In these studies, we aimed to replicate with fNIRS previous findings with adults and children done with other imaging techniques. Important to note is that it was not a straight forward replication studies since the modified version of AX-CPT that we used was not the same as in previous studies. Lastly, we have the CSE. Here again, Clark in figure 8 serves as a good example for the problems with the confirmatory approach done in this thesis. The CSE framework is like the apple tree hypotheses, very detailed but perhaps too specific for this situation.

The part of the research that is exploratory in nature takes place when the research territory is unknown e.g. when we use a neuropsychological test that has not been combined with brain imaging before or when we investigate association between different neuropsychological test and mental fatigue together with fNIRS. Sometimes we extrapolate to give possible explanations, like Bruce, and sometimes we stay at the descriptive level like Arthur. It is important to highlight that even though we utilize the discrimination power of confirmatory techniques such as NHST, for example functional difference during processing speed tests and changes in functional activity over time (**paper I** and **II**) or difference of functional differences in different mathematical situations (**paper IV**), this should be seen as exploratory research.

6. Conclusions

The current thesis has added new knowledge to and expanded the study of cognitive control. In it, theories (such as the DMC and the multiple conflict-control loops), and tests (such as the Stroop-Simon and AX-CPT) have been applied to patient groups and children in research situations (prolonged test designs and experiments in a school environment) that have not been studied before to further our knowledge about the different patient groups, children's cognitive development and cognitive control in general. Due to the novelty of the research done, many of the conclusions in this thesis are tentative.

First, it was shown that patients suffering from pathological mental fatigue after TBI or exhaustion disorder have reduced functional capacity in the frontal cortex during cognitive control, especially in the left VLPFC and that this was related to the severity of their pathological mental fatigue. Even though both patient groups state mental fatigue was affected by prolonged mental activity, surprisingly, the functional activity in the frontal cortex was not. The general decrease in cognitive control efficacy for both patient groups was neither related to increased effectiveness nor a dysfunction in the domain-specific processing.

Secondly, in a non-clinical sample of healthy adults, it was shown that higher trait mental fatigue was associated with a tendency to use cognitive control in a reactive mode. It was also shown that being more mentally fatigued was associated with increased functional activity in the left medial PPC and right DLPFC during reactive situations relative to proactive ones.

Thirdly, it was shown that children between the age of 8- to 9-years utilized the right DLPFC and medial PPC less when there was visual aid during mathematical problem solving compared to when there was no visual aid. Fourthly, children who tend to be less reactive or more proactive involve the right lateral PPC more during reactive situations than proactive ones.

Lastly, the work in this thesis confirmed the possibility to bring neuroscience into the classroom or workplace, which will open up many new and exciting directions in the study of cognitive control and its relevance to everyday life.

Acknowledgement

I would like to express my gratitude to all who have made this PhD possible.

To my main supervisor, **Hans-Georg Kuhn**. More times than I can count have I found the fault in my reasoning and realized that this is what you guided me towards in a previous conversation. Thank you for all the support, constructive criticism and forming me as a researcher, and for making science fun.

To my co-supervisors, **Lina Bunketorp-Käll**, for getting things done and taking a chance on me as a researcher, **Birgitta Johansson**, for your patience and teaching me the importance of being involved in all aspects of data collection, **Helena Filipsson** for your structure and giving me the opportunity to be involved in your projects. Thank you all.

Thanks also to my coauthors **Ingibjörk Jonsdottir**, **Anna Sjörs Dahlman** and **Ola Helenius**, for inspiring discussions and helping me develop as a researcher.

Thanks to everyone in the AMBLE group. Doing interdisciplinary research really is frustrating and delightful – working with you all have truly increased the latter.

Thanks to my coworkers (past and present) at MedTech West, with a special thanks to **Henrik Mindedal** and **Helene Lindström** for all your help with the fNIRS lab.

To my coworkers (past and present) at the wet lab. **Jenny Nyberg** thank you for the discussions and the art. **Reza Motalleb Zadeh** and **Lars Karlsson** thank you for the brief but fun time together.

To **Helge Malmgren** who introduced me to medical science. I am forever grateful, and I hope we can soon meet again in Håland for tea and philosophy.

To **Robert Cooper**, who I learned fNIRS analysis from, thank you for all your feedback and always helping with anything fNIRS related, and **Daniel Ruhe** for friendship, always having an interesting story and tech support.

To **William Hedley Thompson,** thank you for all your help, support and friendship. You are an endless source of possibilities and solutions. You are a true inspiration.

To **Kristoffer Sundberg**, thank you for your support and friendship and keeping my philosophical interests alive.

To **Anton Svanqvist**, thank you for a long and wonderful friendship and for always reminding me how unexamined my assumptions are.

To **Niklas Klasson**, thank you for all the help. To have a friend that never agrees with you and always pushes back, is truly a privilege.

To **Sara Sjödin**, thank you for friendship and sharing fine art with me.

To **Matilda Skau**, thank you for your support all these years.

To **Jesper Lögdahl**, thank you for friendship, support and for making the greyest of days fun.

To **Filip Frumerie**, **Aleksander Lazarevic**, **Per Stefansson**, and **Steffen Fricke** thank you for all the good times.

A special thanks to all participants, teachers and children that made this thesis possible.

Lastly, to my mother, father and brother. For your questions, your support, your worry and your love. Thank you!

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