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FATIGUE AND COGNITION
- HORMONAL PERSPECTIVES

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Destitutus ventis, remos adhibe.

Till Isabella och Cornelia

"Och jag såg att intet är bättre för människan än att hon är glad under sitt arbete, ty detta är den del hon får."
Predikaren 3:22

ABSTRACT

Fatigue is a common complaint and considered a very challenging symptom to cope with in many different medical diseases. The assessment of fatigue is bound up with the problems of both conceptualization and definition. In addition, few studies have investigated suitable neuropsychological tests to examine fatigue and its consequences.

This thesis evaluates whether neuropsychological tests can elicit cognitive fatigue. It also investigates whether specific hormones and hormone replacement therapy influence fatigue as well as cognitive performance.

Study I examined and compared neuropsychological measures of cognitive fatigue with self-rated fatigue in patients with mild traumatic brain injury (mTBI). These patients scored significantly higher than controls on both self-rated and on test-derived measures of cognitive fatigue. Cognitive fatigue was best captured with a score derived from the WAIS Digit Symbol. From our findings we concluded that cognitive fatigue was independent of depression and sleep disorder. Self-rated fatigue, on the other hand, was highly correlated to depression.

Study II compared the effect of combined testosterone and estrogen replacement with estrogen treatment alone on subjective and objective measures of memory in oophorectomized women. Treatment with testosterone undecanoate 40 mg and estradiol 2 mg was associated with lower performance on immediate verbal memory compared to treatment with estrogen plus placebo. All other memory functions were unaffected.

Study III explored cognitive fatigue in oophorectomized women, and whether hormonal treatment regimens, as described in study II, were related to self perceived well-being, estrogen or testosterone serum levels. We found that cognitive fatigue was frequent in oophorectomized women and negatively associated to self-perceived health and positively associated to BMI. However, treatment with testosterone + estrogen or estrogen alone had no significant effect on cognitive fatigue.

Study IV investigated fatigue and cognitive performance in patients with Graves' disease (GD). As compared to controls, patients with GD scored significantly higher on self-rated fatigue and had a higher frequency on the cognitive fatigue. They also demonstrated lower performance on learning, memory, and various tests of executive functioning. Depression was associated with self-rated fatigue but not with the cognitive fatigue measure. High-free triiodothyronine (T3) levels were positively associated to better cognitive functions but negatively to self-rated everyday consequences of fatigue among the patients.

In conclusion: Cognitive fatigue measure, derived from Digit Symbol, could be a useful instrument to capture fatigue. It enables us to calculate an index of cognitive fatigue where neither depression nor sleep disturbance interfere with the result. Cognitive fatigue seems to be related to BMI and self-rated health but not directly related to hormonal levels. A curvilinear relation to sex hormones and the estrogen/testosterone ratio seem more likely. Indirect hormonal imbalances could influence subtle neuronal mechanisms leading to discrete neuropsychological dysfunctions.

LIST OF PUBLICATIONS

I. Möller, M.C., Nygren de Boussard C., Oldenburg, C., & Bartfai, A. An attempt to capture cognitive fatigue with neuropsychological tests. Submitted to the Journal of the International Neuropsychological Society

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IV. Möller, M.C., Bartfai, A., Flöter Rådestad, A., Nygren de Boussard C., & Calissendorff, J. Fatigue and Cognitive Functions in Newly Diagnosed Graves' Disease. Submitted to Psychoneuroendocrinology

CONTENTS

LIST OF ABBREVIATIONS

AD	Alzheimer disease
ADS-f	Ruff 2 & 7 SAT attention detection speed - fatigue measure
BSRT	Buschke Selective Reminding Test
BMI	body mass index
CNS	central nervous system
CSS-f	Ruff 2&7 SAT controlled search speed - fatigue measure
CWT-f	Color Word Test, fatigue measure
DHEA	dihydroepiandrosterone
DST	Digit Symbol Test
DST-f	Digit Symbol Test, fatigue measure
DTI	diffusion tensor imaging
E	estrogen
ER	estrogen receptor
ECF	Everyday Consequences of Fatigue questionnaire
E/T ratio	estrogen/testosterone ratio
FAS/COWAT	Controlled Oral Word Association Test
fMRI	functional magnetic resonance imaging
Free T	free testosterone
Free T4	free thyroxine
FSS	Fatigue Severity Scale
GCS	Glasgow Coma Scale
GD	Graves' disease
HADS	Hospital Anxiety and Depression Scale
HT	hormone therapy
LOC	loss of consciousness
MRI	magnetic resonance imaging
MS	multiple sclerosis
mTBI	mild traumatic brain injury
P	placebo
PGWB	Psychological General Well Being Questionnaire
PSQI	Pittsburgh Sleep Quality Index
PTA	post traumatic amnesia
QSMP	Questionnaire of Subjective Memory Problems
RMBT	Rivermead Behavioural Memory Test
Ruff 2 & 7 SAT	Ruff 2 & 7 Selective Attention Test
T	testosterone
T3	triiodothyronine
T4	thyroxine
TBI	traumatic brain injury
TH	thyroid hormone
Total T	total testosterone
TPO	thyroid peroxidase
TR	thyroid receptor
TMT	Trail Making Test
TSH	thyroid stimulating hormone
TRAb	thyroid stimulating hormone receptor anti body
WAIS-R	Wechsler Adult Intelligence Scale – revised
WAIS-III	Wechsler Adult Intelligence Scale – III
WAIS-III NI	WAIS – III as a neuropsychological instrument

1 INTRODUCTION

1.1 FATIGUE

Fatigue is a frequent and challenging presenting symptom for a wide range of medical conditions, including neurological conditions [1-3], traumatic brain injuries [4-8] stroke [9-11], and psychiatric disturbances [12,13]. Complaints of fatigue have also been documented in cases in which hormonal changes are associated with menopause [14] and hyperthyroidism [15-17]. However, fatigue is not restricted to medical diagnoses – as it is common also in the general population [18].

Fatigue is associated with reduced social and physical functioning [19,20] and an important predictor of failure to return to work after sickness leave [21]. The prevalence of depression is however high among patients with neurological disorders [22] and as fatigue is a common complaint in depressive disorders, it is an open question if there are shared underlying mechanisms of fatigue between different, e.g. depression and medical, disorders [12].

Although fatigue is such a common symptom the assessment of fatigue is still bound up with the problems of both conceptualization and definition [23-25]. Suitable clinical applicable neuropsychological tests to measure fatigue are lacking [26].

It is, therefore, of interest among clinical neuropsychologists to identify methods to capture fatigue and in order to investigate its relationship with other states, such as depression, sleep disturbances and hormonal changes.

1.1.1 Definitions of fatigue

Fatigue is a multidimensional concept involving both physiological and psychological aspects. The experience of fatigue is subjective [27]and can be described in physical, cognitive, and emotional dimensions. Common symptoms described in literature [12,28,29] are presented in Table 1.

Table 1. Different dimensions of fatigue and examples of descriptions

Physical	**Cognitive**	**Emotional**
- Loss of voluntary force-producing capacity - Low/lack of energy - Tiredness - Decreased endurance - Increased effort with physical tasks - General weakness - Heaviness - Slowness - Sluggishness - Non-restorative sleep - Sleepiness	- Decreased concentration - Decreases attention - Decreased mental endurance - Slowed thinking	- Decrease/lack of motivation - Decrease/lack of initiative - Decreased interest - Feeling overwhelmed - Feeling bored - Aversion to effort - Feeling low

In physiology, fatigue is usually defined as "*loss of voluntary force-producing capacity during exercise*" (Zwarts et al., 2008, page 3) and its origin can both be central or peripheral [29]. Peripheral fatigue or muscle fatigability is more easily defined and involves the peripheral nervous system, motor neurons and neuromuscular junctions [1,30,31], while the subjective sense of fatigue is fundamentally perceived in the central nervous system (CNS), which makes it more complex [1,29,31]. The subjective experience of fatigue may be concomitant with physiological fatigue or with deteriorating performance, but may also be a sole complaint [6,23,29,32,33]. For example, some post-polio survivors differentiate between physical fatigue due to muscle weakness and a "brain fatigue" related to cognition problems [34].

Zwarts et al. [29] separate physiological fatigue from psychological fatigue. The former includes both peripheral and central fatigue, while psychological fatigue refers to the subjective experience of fatigue, including concerns about impaired ability to concentrate, lowering of daily functioning, making attributions about fatigue, changes in social functioning and diminished psychological well-being. These are considered best measured with questionnaires [29].

Mental fatigue is a concept found in the literature on fatigue that Ashman (2008, page 34) described as a result from "*an imbalance between the amount of mental effort or activity required to perform a task and the internal resources that person has available to perform it*". The mechanisms contributing to insufficient resources are, however, likely to be multi-dimensional [33]. Some years ago the concept of cognitive fatigue was introduced and is associated with decrements in cognitive performance [32,35]. In this thesis, mental fatigue is a general concept including motivational, cognitive and subjective fatigue; cognitive fatigue is fatigue that can be measured as performance decrements over time of sustained mental effort [36]; and subjective fatigue is considered the inner experience of fatigue measured with self-rating instruments [29]. This thesis will focus on different aspects of cognitive fatigue.

1.1.2 Neural correlates

The basal ganglia are considered exquisitely vulnerable to neurodegenerative processes such as injuries due to hypoxia, invasion of viruses and pro-inflammatory cytokines. Also, many neurological diseases involve these structures. Parkinson disease, multiple sclerosis (MS), and chronic fatigue syndrome include fatigue as a common and disabling symptom. Therefore, these structures could be related to fatigue [37]. Possible mechanisms behind fatigue's involvement with the basal ganglia include interrupted connectivity between the prefrontal cortex and thalamus, but also potential disturbances in limbic integration of cortically driven, voluntary activities [1]. Fatigue related symptoms reported by post-polio patients led Bruno et al. [34] to propose that fatigue results from viral damage to the reticular formation, hypothalamic and thalamic nuclei, cortical motor areas, and dopaminergic neurons in the basal ganglia. Injuries in these regions could lead to decreased cortical activation, impaired attention and slowing of processing speed, which consequently generate the feeling of fatigue [34]. Few studies have, however, found associations between self-rated fatigue and lesion load [31]. Pellicano et al. [38] found that the posterior parietal cortex was the only area significantly associated self-rated fatigue in MS patients. Some functional MRI (fMRI) studies have found higher self rated fatigue among patients with hypometabolism in frontal regions and the basal ganglia [31,39,40]. In stroke patients self-rated fatigue has mostly been related to the state of mood at the time of assessment [41] but some studies have found a relationship between an increased risk for post-stroke fatigue and

infratentorial infarctions [42] and infarctions in basal ganglia [43]. One other study identified a gradient for complaints of fatigue, noting their low frequency in cortical lesions, intermediate frequency in thalamic lesions, and high frequency in brainstem lesions [44].

Results are inconclusive about the association between severity of injury and fatigue in traumatic brain injury (TBI) [4,45,46] However, a prospective longitudinal study found that those patients with significant increases in subjective fatigue over a 2-year period demonstrated poorer outcomes compared to those with decreased or stable fatigue [47]. In a small imaging study on non-depressed mild traumatic brain injury (mTBI) patients with persisting fatigue at least 6 months from injury, Hattory et al. [48] found that mTBI patients demonstrated a different pattern of activation while performing the Paced Auditory Serial Addition Test compared to healthy controls. The authors concluded that frontocerebellar dissociation may explain cognitive fatigue in the chronic recovery phase of mTBI [48].

1.1.3 Comorbid factors

In disorders affecting the CNS investigators are unlikely to identify a single explanatory mechanism for fatigue [4,28]. Fatigue may arise from a primary disease process due to dysfunctions in certain brain areas or from secondary processes due to e.g. medication, depression and sleep disturbance [31,39].

1.1.3.1 Sleep disorders

Various kinds of sleep disturbances give rise to self-rated fatigue [49]; and pain, depression, restless legs syndrome, and medication effects contribute to sleep disturbances [50]. These symptoms are commonly experienced in patients with diseases affecting the CNS. From a sample of 452 TBI patients Ouellet and Morin (2006) found that 50.2% reported insomnia symptoms and 29.4% fulfilled the diagnostic criteria for an insomnia syndrome, which was three times greater than reported in the general population [4].

Sleep disturbances may also be accompanied by performance decrement. A meta analytic study showed that mood seems most affected by partial sleep deprivation followed by cognition, while motor performance seems to be most robust in conditions of disturbed sleep [51]. Vigilance, measured by the frequency and duration of lapses, is also negatively affected by disturbed sleep [52].

1.1.3.2 Depression

The prevalence of depression is high among patients with medical or neurological disorders, which can influence symptom ratings [53] , though symptoms that are associated with neurological disease might also mimic those of depression [22,54].

Results are inconsistent showing an association between depression and cognitive impairment, and not all individuals with major depression show cognitive deficits. Discrepancies among results may be due to factors such as population characteristics (e.g. degree or subtype of depression, age, and comorbid illnesses) or differences in test properties. Cognitive deficits are however frequently observed among depressed on tasks requiring attention, mental flexibility/control, visual-spatial abilities, visual scanning/visuo-motor tracking, executive functions such as verbal fluency (especially phonemic fluency), and verbal and nonverbal learning and retention [55,56].

Depression is a contributing factor to self-rated fatigue [57,58] and in cases of patients suffering from diseases affecting CNS there can be overlap in symptomatology between fatigue and depression making it difficult to disentangle the comorbidity between depressive syndromes and fatigue syndromes. Fatigue may develop in connection with activities demanding sustained effort, or be present independently as a state close to a lack of initiative. When fatigue is associated with loss of interest, it might be more related to a depressive state [44], which also includes lack of self-esteem, despair, or feeling of hopelessness. These feelings are not prominent in fatigue not related to depression. The ability to distinguish depression from fatigue is, however, complicated by the fact that atypical depression is more difficult to detect and fatigue is significantly more reported among patients with atypical depression compared to other depressed groups [12].

1.1.3.3 Medication

Medications affecting the CNS can modulate both cognition and subjective ratings of fatigue. A number of medical conditions as well as their medications, including antihistamines, antibiotics, beta-blockers, and medications for high blood pressure, have been associated to reports of fatigue [29,59] but evaluation of cognitive effects is not easily achieved due for example, to a lack of test sensitivity, practice effects with repeated neuropsychological assessments, and other confounding factors [60]. Moreover, subjective reports of fatigue need not be consistent with objective measures. In a small treatment study on the neuropsychological effects of beta-blockers on 35 hypertensive patients, beta-blocker treatment was not associated poorer neuropsychological functioning; and, although these patients made substantial complaints of fatigue, complaints were equivalent in beta-blocker and placebo conditions [61]. In a study of MS patients, those patients with medication that was considered to contribute to CNS effects demonstrated lower performance on tests of processing speed, attention and self rated fatigue; however, no causal relation could be drawn from this study [62]. Opioids have also been associated with fatigue. In a double-blind study by Allen et al. [63] on healthy, male college students administered a combination of opioid (7.5 mg hydrocodone bitartrate) plus ibuprofen (200 mg) performed significantly less well on a simple tracking task and made significantly more errors on a simple reaction-time task than subjects using ibuprofen alone or a placebo. However, the deficits were highly transitory and did not correlate with confusion or fatigue [63]. Antidepressant therapies have been associated with both physical and cognitive side effects [56]. Fava et al. [64] studied patients who were treated using antidepressant medication during partial or full remission from depression and they reported more than 30% of exhibited cognitive symptoms (all responders to antidepressants). Physical symptoms of fatigue and sleepiness/sedation were reported by over 40%[64]. These were, however, self-reported symptoms, and no neuropsychological assessments were performed, and no control group was used for comparison. Further, questions regarding fatigue were not included in the instrument used for evaluation of remission from depression [65]; therefore, some of the fatigue symptoms could have been due to incomplete resolution of depressive symptoms.

1.1.3.4 Gender

Generally [49] but also specifically in stroke [9] and trauma [57] populations gender predicts women are more likely to self-rate greater fatigue. Women also seem to be at a greater risk for developing fatigue in depression, especially in the atypical-depressed group there seems to be a significantly higher percentage of women. The reasons for this sex difference are not known but atypical depression might be associated with endocrine abnormalities that differ from the classic melancholic depression [12].

1.1.4 Fatigue a symptom or a dysfunction?

Fatigue can, to some extent, be objectively measured by quantifying performance over time, but this does not capture the subjective experience of fatigue. Research has shown little to no relationship between self-reported fatigue and neuropsychological performance in a variety of clinical populations. When self-rating instruments are used, other inner states such as depression, are highly connected with the results. For example, depressed patients tend to score higher than non-depressed patients on generally all symptom rating measures [66]. When assessing patients with mild brain dysfunction, neuropsychological instruments may lack sensitivity to detect cognitive fatigue, while other psychological reactions, such as anxiety and depression, might account for results on the self-rating measures.

Leavitt and DeLuca (2010) argue that instead of striving for associations between subjective and objective measures of fatigue, future research needs to separate primary fatigue, that is, the factors that initiate fatigue (e.g., systemic disease), from secondary fatigue, which are factors that perpetuate or exacerbate it (e.g., sleep disturbances and depression). Making this distinction would take better account of the multidimensional features of fatigue [67].

The investigation of fatigue becomes further entangled by the lack of neuropsychological instruments that can capture fatigue. In cases that incorporate diffuse symptoms, such as fatigue, symptoms may, unwittingly, be attributed to psychiatric disorders. As self-rating instruments are influenced by depression these instruments have limitations in purposes of measuring primary fatigue. Therefore, it may not be sufficient to recognize that the patient suffers from fatigue just on the basis of a questionnaire. To be able to capture fatigue and also to be able to evaluate treatment effects it may therefore be worthwhile to find additional methods, not influenced by depression or sleep disorders [1].

1.1.4.1 Neuropsychological findings and fatigue

In most studies questionnaires measures of fatigue are compared to indices of neuropsychological performance, searching for any association between subjective fatigue and neuropsychological impairment. Few studies have been designed to investigate cognitive performance decline over time as a measure of fatigue.

In studies on TBI patients, subjective fatigue has mainly been associated with decreased performance on measures of sustained or dual attention and reduced processing speed [6,33,68-70]. In a study, Ziino and Ponsford [71] reported associations between self-reported fatigue on the Fatigue Severity Scale (FSS) and lower performance on a task of higher order attention [71]. In another study, the same group found a relationship between self-rated fatigue on visual analog scale of fatigue and a greater number of omission errors on a vigilance task. A subgroup of TBI patients also showed performance decline on a vigilance task and along with a disproportionate increase in subjective fatigue[72]. Ashman and collaborators [33] assessed the relationship between performance and both situational and day-to-day fatigue in their study on TBI patients. In addition, the study examined the relationship between objectively measured fatigue and self-reported situational and day-to-day fatigue. Patients with diagnosed TBI scored significantly higher than controls on the fatigue measures and higher subjective day-to-day fatigue scores were associated with slower performance speed at the end of the tests. The TBI patients also showed significant decline in performance accuracy. This was, however, not associated with subjective fatigue [33]. Fatigue in TBI

has also been associated to day-time sleepiness and reduced alertness, as well as to poorer performance on tests assessing driving capacity [73].

A robust measure of cognitive fatigue, which supports a model of decreased performance over time, employs tasks demanding sustained mental effort [26]. In a study by Chapelle and Finlayson (1989) on brain injury patients with variable etiology (trauma, stroke or encephalitis), fatigue was operationalized as the inability to sustain the speed of finger tapping. On this simple task no group differences emerged between patients and healthy controls [74], while in a study of TBI patients with mixed severity, Melamed et al (1985) found, in a task demanding divided attention, that patients made more errors at the end of the test, suggesting that fatigue was a factor in decreased performance [75].

Studies on cognitive fatigue after mTBI are lacking. Most studies have included patients with TBI of mixed severity levels. In one of the few studies performed on fatigue and mTBI, Cicerone (1996) used a modified version of Ruff 2 & 7 Selective Attention Test (Ruff 2 & 7 SAT) as a measure of fatigue. Cicerone found each mTBI and control group displayed lower processing speed over time but the mTBI patients did so to a significantly greater extent when they were challenged to perform another task simultaneously. This discrepancy between patients and controls was not found when the patients were exposed to irrelevant stimuli while performing. These findings indicate subtle cognitive deficits in mTBI patients may become apparent under conditions that require highly demanding, controlled cognitive processing [68].

Individuals suffering from post TBI fatigue often describe thinking as effortful and ineffective [33] , though performance is not necessarily lowered when the subject experiences the test as effortful. Ziino and Ponsford [72] reported finding that TBI patients generally performed at a lower but at a similar level across the duration of a vigilance test compared to the controls However, the TBI patients showed greater elevation in diastolic blood pressure, which was associated with greater increase in subjective fatigue ratings. This could indicate that some patients are able to compensate for cognitive task demand but at the cost of increased stress [72]. The theory of compensatory mechanisms received some support from an imaging study by McAllister et al. on mTBI patients. They did not obtain significant findings of performance differences between mTBI patients and healthy controls when performing working memory tasks. However, mTBI patients needed greater activation of neural networks [76].

1.1.5 Operationalization of cognitive fatigue

Operational definitions of the construct of fatigue run the risk of confusion owing to several factors, including: many different types of fatigue, the many multifaceted mechanisms behind different types of fatigue, relative lack of previous robust operational definitions, and lack of instruments capable of capturing often subtle cognitive effects of fatigue. This underscores the need to describe different aspects of fatigue when comparing studies [26,33].

As noted above, theoretically, cognitive fatigue is defined as performance deteriorations over time. It has also been proposed in the literature that tasks used to investigate performance should demand sustained mental effort in order to provoke fatigue-related deficits [26,32,77]. Task that demand processing of novel or inconsistent information [32] or sustained attention [26,37] have been proposed to be more likely to show

fatigue-related decrements. Despite this, few studies have been reported that explore which existing neuropsychological tests have appropriate test characteristics to capture cognitive fatigue in clinical populations. Furthermore, little is known about underlying components, including executive or motor functioning, which are necessary to assess in order to identify fatigue in mild and diffuse brain dysfunctions.

Edith Kaplan defined fatigue as an inability to maintain consistent speed of performance over the period of the test [78] and she advocated that using the subtest Digit Symbol from Wechsler Adult Intelligence Scale (WAIS) to measure fatigue in clinical settings. The Digit Symbol Test (DST) demands interaction of cognitive fatigue, psychomotor speed and incidental learning capacity - functions that are vulnerable to different brain influences [69,70]. Generally, performance quickens toward the end of the test as learning of digits normally occurs. If performance speed does not improve over time, the reason could be an inability to maintain a stable performance over time or to a low learning capacity [79]. Therefore, the DST is suitable as at least a partial measure of complex psychomotor aspects of cognitive fatigue. Similarly,– the Symbol Digit Modalities Test, has been used to capture fatigue in patients with mTBI [77], and a modified version has been used in an fMRI study on central fatigue in MS patients [40]. Still, the DST, as a fatigue measure, has not been widely used in fatigue research and comparisons with other tests have not been made that lead to finding suitable tests to measure fatigue among patients with mild cognitive dysfunction.

Speed and executive functioning are useful qualities for detecting cognitive fatigue. Inhibition and working memory are both examples of executive functions. It is, however, not clear if working memory exclusively is important when measuring cognitive fatigue. The Stroop Color-Word Test is a speed and accuracy test that taps inhibition but not working memory. If working memory is not important for fatigue-related performance decrement this test might also have properties that tap executive aspects of cognitive fatigue.

Complex attention factors have been associated to fatigue [35,71]. To investigate if fatigue could be tapped by pure attention tests, the Ruff 2 & 7 Selective Attention Test could be used as a measure of attentional aspects of cognitive fatigue. The Ruff 2 & 7 SAT has been used in research on fatigue, but with a non-standardized procedure [68]. The test is purported to measure both simple and controlled perceptual functions. It demands speed but does not carry a large demand for motor functioning or for working memory [80]. Theoretically, the Ruff 2 & 7 SAT- controlled search speed measure should be more vulnerable to fatigue effect over time compared to functions related more to automated attention measured by the Ruff 2 & 7 SAT - attention detection speed measure. Also the Ruff 2 & 7 SAT permits intermediate performance registrations.

By matching different tests with different fatigue-related properties a battery of suitable tests for assessing fatigue could be developed (Figure 1).

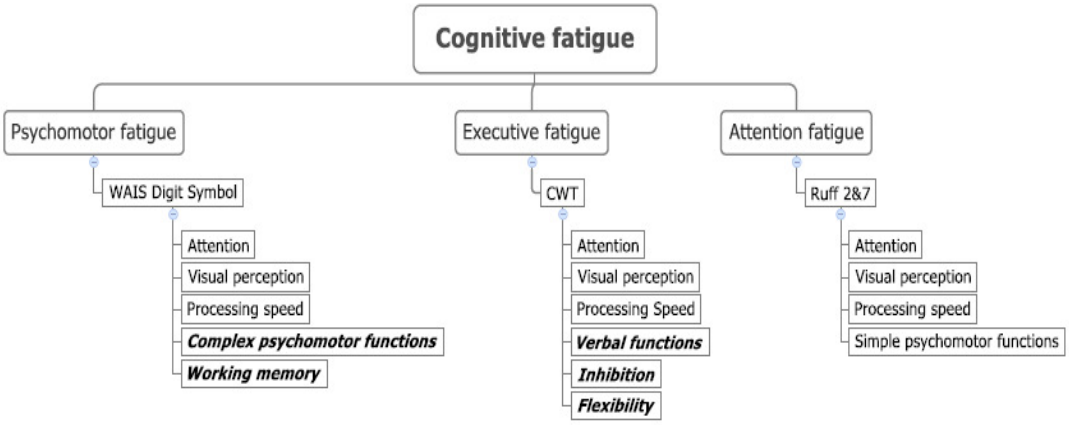

Figure 1. Possible underlying components comprising the different fatigue measures. Italics highlight the specific features of the tests.

1.2 HORMONES AND COGNITIVE FUNCTIONS

Hormones are signaling molecules, released by a cell or a gland to the bloodstream, with a specific regulatory effect on the activity of a distant tissues and organs, where they can bind to specific receptors - acting as the postmen of endocrine machinery [81].

1.2.1 Sex steroid hormones

Sex steroid hormones affect not only sexual functions but also mood, behavior and cognitive functions [82-84]. They are synthesized from cholesterol by enzymatic cleavage into precursors for estrogen and testosterone (Figure 2) and act on a genomic level through specific nuclear receptors to regulate the transcription of specific genes. However, these also act via non genomic action involving membrane-associated receptors [85-88]. Therefore, sex steroid hormones can have both organizational effects engendering permanent structural change but also demonstrate rapid activating effects on the tissue. The organizational effects are most critical during specific periods of development while the activating effects are considered to be relatively transient [83,89].

A small amount of these steroids are synthesized in the CNS and their activity is mediated by various neurotransmitters [88].

Sex hormone receptors in the CNS are widely distributed but are mainly found in the hypothalamic and limbic areas [82]. Postmortem examination of female brains show that the highest concentrations of estradiol and testosterone are in the hypothalamus, preoptic area and substantia nigra [90]. Very few studies have however been able to find correlation between the concentration of steroid receptors in a particular brain area and behavior [91].

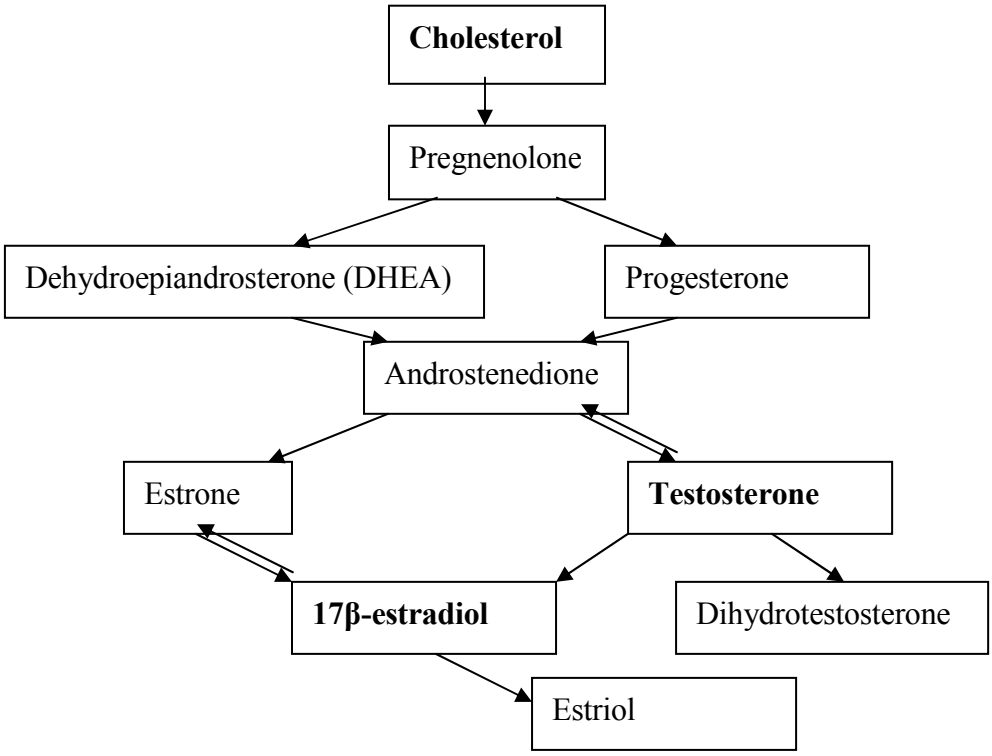

Figure 2. Schematic view of sex steroid hormone synthesized from cholesterol.

Testosterone and estrogens are considered to be potentially neuroprotective hormones [83,92-95]. However, studies investigating associations between sex steroid levels and human cognition have shown inconclusive results [46,96-99]. Some studies indicate that the association between neuropsychological function and sex steroid levels might not be a straightforward dose dependent one, rather, a curvilinear model is more plausible for cognitive functions [100,101]. Also the balance between estrogen and testosterone, and thus the estradiol/testosterone ratio, has been suggested to be more important than the absolute hormone levels [102].

1.2.1.1 Estrogen

Estrogen consists principally of three forms: 17β-estradiol, estrone, and estriol. Estrogen receptors (ER) are recognized in brain regions such as the hippocampus, cerebral cortex, hypothalamus, and brainstem [82,85,103,104].

Of the estrogen produced, 90 % is generated in the ovaries; but brain-derived estrogen also seems to play an important role in brain protection, as in response to ischemia or amyloid-induced cell death [105].

Estrogen is one of the most studied steroid hormones [105] and is considered to be a psychoprotective hormone for diseases such as Alzheimer disease (AD) [106], and Parkinson disease, as well as depression since it interacts with dopaminergic neurons and involves dopaminergic brain structures in the basal ganglia that affect motor activity [84]. Estrogen has also been linked to mood disorders, as the risk of developing depression is two times grater for women compared to men [107].

Estrogen and memory functions

Some studies have found that performance in certain cognitive domains fluctuates during the normal menstrual cycle due to variability in hormonal levels [108]. In both men and women estrogens are involved in memory processing [109-111]. The estrogenic impact on memory seems to involve activity of cholinergic neurons in the hippocampus and basal forebrain [83,112]. Thilers and coworkers conducted a longitudinal investigation of cognitive changes associated with menopausal transition in 193 women. They found that women within the normal range of BMI displayed more rapid decline of episodic memory than women with BMI > 25 [113].

Data is inconclusive concerning the role of hormone therapy (HT) on memory function. A systematic review of randomized controlled trials showed no consistent short-term benefit when HT was given during perimenopause or early postmenopause. When HT was initiated in the late postmenopause they found no evidence of benefit on episodic memory or other cognitive skills [114]. A meta analytic review of randomized controlled trials and cohort studies showed that only women with menopausal symptoms improve their verbal memory, vigilance, reasoning, and motor speed with HT treatment. No benefits were observed in asymptomatic women [97].

Estrogen has also been suggested to have a neuroprotective effect on AD [106] but studies on humans have shown inconclusive results. Some randomized, double-blind, placebo-controlled clinical trials have found that late onset of HT after natural menopause seems to increase the risk of dementia in women over 65 years of age [96,99]. However population-based studies have shown a possible "window of opportunity" when HT was administered close to a natural or surgical menopause [108]. In a recent population-based study where 1,768 women were followed, women who used any type of HT within 5 years of menopause had 30% less risk of AD especially if use was used for > 10 years. By contrast, the risk of AD was not reduced for those who had initiated HT > 5 years after menopause. The authors conclude that association of HT use and risk of AD may depend on timing. It might be beneficial if taken during a critical window near menopause, while initiated in later life may be associated with increased risk [115].

1.2.1.2 Testosterone

Androgens, such as testosterone, are vital sex hormones for both men and women. They act via androgen receptors located in different tissues in the body, including the CNS. In women, half of the testosterone arises from production in the ovaries and the remainder from the adrenals [116]. In women the testosterone level is low with serum levels ranging from 0.7 – 3 nmol/l [117], while total testosterone in men ranges from 10 – 30 nmol/l [118]. Of the total circulating testosterone only 1-2% is free. Approximately 25% is weakly bound to albumin and the remainder is strongly bound to sex hormone-binding globuline (SHBG). Only the free and albumin fractions are biologically active[119].

Testosterone in both men and women can be aromatized to estrogen [84]. Thus, a change in testosterone level during treatment also affects the level of serum estrogen. Furthermore, the balance and ratio between estradiol and testosterone may modulate cognitive functioning in women [120].

Symptoms of androgen deficiency in women include a diminished sense of psychological well-being, fatigue, sexual function, and negative metabolic

consequences such as reduced bone density and muscle mass [14,121-124]. Several testosterone treatment studies in women have found positive effects on psychosexual function and on both physiological and psychological well-being in women [125-130].

While the effects of estrogen on memory functions in women are rather well known much less is known about the testosterone effect on the female brain [131]. In men with androgen deficiency, testosterone treatment has been beneficial to verbal memory [109,131]; and in a small study on healthy volunteers, improvement in working memory was evident with testosterone treatment in older men but not in women [132]. Few studies have investigated testosterone effect on cognition in women, and results have not been conclusive [133]. A single supraphysiologic dose of testosterone in healthy women has resulted in increased visuospatial memory [134] and memory for location [135,136]. In a study on women with polycystic ovary syndrome, which is associated with elevated testosterone levels, women performed worse on tests tapping abilities with which are associated female advantage, such as verbal fluency [137]. Verbal fluency improved while other cognitive and memory functions remained unchanged when free testosterone was reduced pharmacologically [138]. A study on healthy naturally post-menopausal women reported no support for beneficial effects on verbal fluency, verbal memory, or spatial ability with testosterone or estrogen treatment [139].

1.2.2 Thyroid hormones

Thyroid hormones (TH) are released by the thyroid gland and play a critical role in cellular metabolism in the brain and other organ systems [140]. In the fetus TH are involved in the growth and development of the CNS and in adults thyroid dysfunction is associated with somatic, neurological and psychiatric abnormality [141,142]. Deficiency of TH affects the migration, proliferation, survival, and differentiation of distinct neuronal cell populations in the fetus [140].

Production of triiodothyronine (T_3) and its prohormone thyroxine (T_4) are activated by thyroid-stimulating hormone (TSH), of which the latter is synthesized from the anterior pituitary gland in response to TSH-releasing hormone. In serum, more than 99% of thyroid hormones are bound to specific proteins, such as T4 binding globulin and albumin [142]. Only the free hormones are active in cells [143].

TH are members of the nuclear receptor superfamily [144] . These mainly act on genomic level [141]. A close relationship exists between THs and cholinergic system functions, especially in the basal forebrain and hippocampus [141].

Few neuropsychological studies have examined the relationship of cognition to alternation in thyroid functions [143,145]. However, T4 levels are associated with cognitive functioning. In a double-blind, randomized, cross-over study reported by Samuels and coworkers [146], hypothyroid patients were treated with two doses of T4, the larger of which corresponded to subclinical thyrotoxicosis while the smaller dose corresponded to euthyroidism. The larger dose was related to an increase in free T3 level and improvement in mood and motor learning, but not to other cognitive functions, such as working memory, or verbal or nonverbal declarative memory [146].

1.3 CLINICAL ASPECTS OF FATIGUE

1.3.1 Mild Traumatic Brain Injury

The incidence of mTBI in the industrialized world is estimated at 100 to 300 cases per 100,000 in the population [147]. How to define mTBI is though debated[148]. The American Congress of Rehabilitation Medicine established diagnostic criteria for mTBI: A traumatically induced physiological disruption of brain function, as manifested by at least one of the following: Any period of loss of consciousness (LOC) for up to 30 minutes; any loss of memory for events immediately before or after the accident but less than 24 hours; any alternation of mental state at the time of accident (e.g., feeling dazed, disoriented, or confused), but including that after 30 min the patient should score between 13–15 at Glasgow Coma Scale (GCS); and, focal neurological deficit that may or may not be transient [149].

In mTBI the prognosis may be considered good even though symptoms of headache, fatigue, poor concentration, and memory difficulty persist well beyond the first days to weeks after a concussion, and for most patients full recovery is reached before 3-6 months after the trauma [150]. However, some patients report residual intellectual, emotional and behavioral symptoms [151,152] in addition to significant fatigue [4,5,7,20]. The incidence of persistent cognitive disability after mTBI is debated. Meta-analytical studies have identified only minor disabilities occurring directly after the trauma and up to three months later [153].

Among mTBI patients the amount of reported symptoms have been associated with insurance claims [147,150], low educational level, emotional distress, self reported fatigue [154,155] ,depression [156] and psychiatric disorders [157]. The report of symptoms may not correspond to cognitive deficits since data are apparently subjected to patterns of both under and over reporting [158,159]. Fatigue is, however, a major risk factor for a poorer prognosis when it comes to sick leave from work and poor quality of life [20]. Investigating fatigue further might optimize rehabilitation in patients with persisting symptoms after mTBI.

1.3.2 Oophorectomy

Oophorectomy is the surgical removal of an ovary or ovaries. A consequence of bilateral oophorectomy is the abrupt decline of estrogen levels, as compared to a gradual decline after natural menopause. Post-surgical-menopause serum estrogen is decreased by about 90 % [160] and testosterone by half [161,162]. The production of ovarian testosterone remains largely unchanged after natural menopause [161,163]. This abrupt decline of sex steroid hormones often gives rise to menopausal symptoms [164]. Guidelines recommend postmenopausal women younger than 45 years of age to take estrogen supplements until their natural age of menopause in order to preserve bone density [165]. Testosterone supplementation, on the other hand, is seldom given. Little is known about the effects of androgen insufficiency on women's health [14,117]

Different hormone profiles in oophorectomy versus natural menopause suggest that different treatments may be warranted to address symptomatology [165]. The risk of cognitive impairment is higher among oophorectomized women who who did not receive estrogen until their predicted age of natural menopause [166].

Even though testosterone levels do not decline as much as estrogen levels after oophorectomy, androgen insufficiency is a risk in these women. Complaints of

subjective fatigue have been reported, as well as a sense of diminished well-being, dysphoric mood, reduced sexual pleasure and negative vitality [14,121-124]. In one study of the effects of testosterone on memory and cognition in younger recently oophorectomized women, Sherwin [167] compared treatment with estrogen-alone, estrogen-plus-androgen and androgen-alone. She found that estrogen-alone and estrogen-plus-testosterone had the same effect on memory functions.

1.3.3 Graves' disease

Graves' disease (GD) is one of the major autoimmune diseases with an estimated incidence in Sweden of 21/100,000 individuals [168]. In GD, antibodies to the thyroid stimulating hormone receptor (TRAb) stimulate the thyroid stimulating hormone (TSH)-receptor, thereby increasing thyroid hormone synthesis and secretion. TRAb is a marker for the disease, which is also characterized by low levels of TSH, elevated thyroid hormones, free T4 and/or free T3 [169]. Female to male ratio in GD is 3.9:1 and the peak incidence occurs during the age span of 40-59 years of age [168]. Both a genetic predisposition and environmental factors, such as moving from iodine deficiency areas to iodine sufficiency, have been proposed to increase the risk for the disease, but what actually triggers the onset is still unknown [169]. Also, life style factors contribute to the onset of disease. Smoking has been associated with higher risk of GD and obesity with a relative lower risk of incidence [170].

Physical and psychiatric symptoms may present early in GD, including weight loss, tachycardia, tremor, ophthalmopathy, poor vitality, sleep disorders, sensitivity to stress, anxiety, depression and irritability [171]. Several studies have suggested a high prevalence of psychiatric symptoms in GD [172-174].

Patients with GD are often initially treated with methimazole, which blocks thyroxine synthesis, and after two weeks thyroxin may be added or methimazole may be used as a single therapy. With 18 months of this treatment the chance of complete remission is about 50 %. Despite that somewhat positive outlook, the patient is in a euthyroid state during the ensuing 16-17 months and some patients do not feel recovered. Some studies report diminished vitality and quality of life and residual cognitive problems many years after treatment [15,16,175-177]. Depression and complaints of lacking energy are common and in some cases patients despite having full-time jobs are not able to return previous their work level as before onset [16]. According to a Swedish long term follow up study, the feeling of not being fully recovered can persist several years, though it does not seem to be related to levels of thyroid hormones or TSH [177].

Neuropsychological investigation is conspicuously lacking in the literature on GD. A few studies on newly diagnosed (untreated) GD patients show mild deficits in attention [178], memory, and complex problem solving [179], while others have found no cognitive effects [173]. There is a lack of correspondence between thyroid hormone levels and symptoms [180] and with neuropsychological findings [173,178]. Clinically, high free T3 and free T4 levels have been associated to severity of disease [169]. No study has focused on fatigue in patients with untreated GD although complaints of fatigue, tiredness and unstable energy are common in treated GD patients [15,16].

2 AIMS OF THE THESIS

This thesis aims to examine the possibilities to capture cognitive fatigue with established neuropsychological methodology. Furthermore to explore whether specific hormones and hormone replacement therapy may influence cognitive fatigue and neuropsychological performance.

Aims of each study were as follows:

- To investigate if cognitive fatigue is possible to capture using neuropsychological tests on patients with persisting symptoms after a mTBI. Further to investigate if cognitive fatigue is independent from depression and sleep disorders in this patient group.

- To study if additional testosterone treatment, in combination with estrogen replacement, improves subjective and objective measures of memory compared to estrogen treatment alone in oophorectomized women.

- To explore if cognitive fatigue is present in oophorectomized women and if this treatment regimen is related to self perceived physical and psychological well-being, as well as estrogen and testosterone serum levels.

- To investigate if subjective as well as cognitive fatigue are present among patients with untreated Graves' disease. Further to study if this is related to depression, sleep disturbances, hormonal changes or other neuropsychological dysfunctions.

3 METHODS

3.1 PARTICIPANTS

3.1.1 Patients in Study I

The sample consisted of 24 consecutively enrolled patients (12 women and 12 men), aged between 18 and 51 years (mean 35.7 ± 9.8 years) each referred for a neuropsychological investigation due to persistent cognitive complaints associated with their mTBI. Nine patients were recruited from the Department of Rehabilitation Medicine, Danderyd Hospital, Stockholm: 9 patients from Kullbergska Hospital, Katrineholm; 5 from Nyköping Hospital; and 1 patient from Mälarsjukhuset Hospital, Eskilstuna. Age was stratified (18-50 years) to reduce variance due to the risk of cognitive decline due to preclinical dementia and stroke in the older participants and the risk of developmental differences in the younger participants. As one of the patients was 50 years during enrolment but became 51 before assessment, the range was adjusted to 18-51 years of age. The mean length of formal education was 12.0 ± 1.5 (range 9 – 16 years) and mean time from trauma to the neuropsychological assessment was 21 ± 19 months with a range of 4 – 70 months.

All patients had post-concussional symptoms of at least 3 months but less than 6 years in duration since the time of trauma. All fulfilled the criteria of mTBI according to the American Congress of Rehabilitation Medicine; traumatically induced physiological disruption of brain function, as manifested by at least one of the following:

- a period of loss of consciousness (LOC) of up to 30 minutes;
- any loss of memory for events immediately before or after the accident but with a duration of less than 24 hours;
- any alternation of mental state at the time of accident; score on the Glasgow Coma Scale (GCS) administered after 30 min from trauma between 13 and15;
- presence of focal neurological deficit that may or may not have been transient.

Clinical characteristics of the patients are presented in Table 2.

Table 2. Injury related information for the mTBI patients (n = 24).

Characteristics	**count**	**Characteristics**	**count**
Type of accident	n (%)	*Anterograd amnesia*	n (%)
Fall	8 (33)	None	4 (17)
Car accident	9 (38)	1-5 min	2 (8)
Assault	2 (8)	6-45 min	7 (29)
Bi- or motorcycle accident	2 (8)	> 45 min	4 (17)
Other	3 (12)	uncertain but <60 min	7 (29)
Retrograde amnesia		*Loss of consciousness*	
None	16 (67)	None	7 (29)
< 1 min	2 (8)	< 1 min	1 (4)
1-5 min	3 (12)	1-5 min	6 (25)
> 5 min	2 (8)	6-30 min	5 (21)
Missing	1 (4)	uncertain but <30 min	5 (21)

Patients were excluded from participation if one was uncertain of the time of LOC (as may occur with comorbid alcohol intoxication), had taken medication that could interfere with neuropsychological test results, suffered from dementia evidenced from

CT-scans, diagnosed with hydrocephalus or subdural heamatoma after the trauma, or was known to have had seizures or severe psychiatric disease prior to the head injury. Also, patients who did not fully comprehend or speak Swedish were excluded as several tests demanded verbal comprehension. Information about current medication was obtained from interview data and hospital records. At the inclusion none of the participants abused alcohol or illicit drugs.

Six patients showed imaging abnormalities. One patient had a small bleed in the cisterna magna, one had a small contusion hemorrhage in the right side of the basal ganglia, one had bilateral hemorrhages in the temporal lobe, and one showed a skull fracture but with no injuries in the brain parenchyma. Two additional patients had abnormalities that were less likely to be injury related: One had diffuse, periventricular white-matter lesions and a one had diffuse white-matter lesions at the back horn of the left lateral ventricle. In the last case, abnormalities were not present during ordinary MR sequences but were visible on diffuse tensor imaging (DTI) sequence.

3.1.2 Patients in Study II and III

From the patient discharge register of Stockholm county, women aged from 45 to 60 years of age, who had undergone hysterectomy plus bilateral salphingo-oophorectomy for benign disease, were invited to participate in the study.

Inclusion criteria were: Age between 45-60 years; BMI between 18-29 kg/m²; blood pressure below 170/105 mm Hg; normal liver enzymes; and a normal mammogram within the last 12 months. Sexual dysfunction or decreased psychological well-being was not mandatory for inclusion.

The exclusion criteria comprised of the use of HT within the last two months; concomitant medication (e.g. lipid lowering agents, other sex hormones, calcium-antagonists, beta-blockers, tranquillizers barbiturates, and antihistamines); history of premalignancy/malignancy, liver disease, lipid disorder, a cardiovascular, cerebrovascular or trombo-embolic event; and current psychiatric disease, alcohol abuse or smoking $\geq$10 cigarettes/day [181,182].

A total of 65 women were assessed for eligibility during a recruitment period of 6 months. Of these women, 15 did not fulfill the inclusion criteria. Fifty consecutive women were recruited. At time of inclusion the mean age was 54.0 ± 2.9 years (range 46-60 years), mean body mass index 25.7 ± 2.8 kg/m² and mean time since oophorectomy 4.6 ± 2.4 years. Six women (three from each group) discontinued the study, five due to poor drug compliance and one due to migraine during the estrogen treatment. Forty-four women were included in the analyses.

3.1.3 Patients in Study IV

The sample consisted of 44 consecutive patients (35 women and 9 men), each newly diagnosed with a first time incidence of GD, and who were recruited from the three endocrinology departments in the county council of Sörmland. Patients with severe dyslexia (n=4) and/or history of mild traumatic brain injury (n=6) were excluded from further analyses in this study. Subsequent analyses were carried out on the 34 remaining patients (28 women and 6 men). Failure analyses showed that the excluded patients scored higher on fatigue severity scale (p = .045) but revealed no significant differences on neuropsychological tests. The mean age among the remaining patients

(n=34) was 39.2 ± 9.8 years (range: 18 – 51 years) and mean length of formal education was 12.2 ± 2.2 years (range 9 – 17 years). All participants had elevated peripheral thyroid hormones and suppressed TSH. All but one of the 34 patients had elevated TRAb. This patient had an increased even diffuse distribution on a radionuclide scan.

Exclusion criteria were: medication that could interfere with neuropsychological test results, patients suffering from dementia, seizures or severe psychiatric disease. Also patients who did not fully comprehend or speak Swedish were excluded as several tests demanded verbal comprehension. Information about current medication was obtained from an interview and hospital records. Beyond the 44 included patients eight patients declined to participate, one patient had indication for operation and one patient was missed due to administrational misses, although the patients otherwise met the inclusion criteria.

Treatment with anti-thyroid medication was not allowed prior to neuropsychological assessment. However, in cases of tachycardia and/or tremor beta-blockers were allowed (16 patients used beta-blockers at the neuropsychological assessment). One patient had hypertension and used an angiotensin-converting-enzyme inhibitor; three were on anti-depressant pharmacotherapy.

Eleven patients were smokers while 23 were non-smokers. Two patients were smokers until 1 week before the neuropsychological assessment and were scored as smokers. At inclusion none of the participants abused alcohol or illicit drugs.

3.1.4 Controls in Study I and IV

A control group (n=34) was recruited via advertisement and friends to hospital staff. Age was stratified between 18-50 years. Three of the controls were excluded; two due to a mild head injury and one due to encephalitis not reported prior to the assessment. Thirty one controls remained for further analyses. The mean age for the remaining controls (n = 31, 18 women and 13 men) was 36.7 ± 8.8 years (range 20 - 49 years) and the mean length of formal education was 13.1 ± 1.9 years (range 11 – 17.5 years). Twenty-nine of the 31 controls were right handed.

Three controls with asthma used inhalation therapy and one used antidepressant pharmacotherapy, all the other controls were free of medication. Four of the controls smoked and 22 were non smokers. One control smoked less than 20 cigarettes yearly and was scored as non-smoker. Information regarding smoking was missing for five of the controls. At inclusion none of the controls were addicted to alcohol or illicit drugs.

The controls were offered a gift certificate (500 Swedish kronor) and an optional feedback session of individual test performance profile after full participation. All controls were required to be fluent in Swedish.

3.2 PROCEDURES AND MEASURES

3.2.1 Assessment

3.2.1.1 Study I and IV

The neuropsychological tests were administered in an outpatient setting. The patients and controls were assessed on at least two occasions by individual neuropsychologists competent to administer the test battery in a consistent manner. For the patients in

Study IV the neuropsychological assessment took place before a maximum span of 7 days lapsed from diagnosis to assessment.

3.2.1.2 Study II and III

A randomized, double-blind, crossover and placebo controlled study. Fortyfour oophorectomized women were treated with either estrogen + placebo or estrogen + testosterone for 24 weeks; and then the treatments were switched. Only testosterone and placebo were randomized. Estrogen was administered to every woman.The medication used in the study was individually numbered for each subject. No one monitoring the study had access to the randomization list. Both testosterone undecanoate and placebo tablets were manufactured by the same pharmaceutical company and had identical appearances and packages.

Blinding was maintained until completion of the study. After inclusion and a washout period of two months the women were randomly assigned to receive oral treatment with either estradiol valerate 2 mg + testosterone undecanoate 40 mg (E/T) daily or estradiol valerate 2 mg + placebo (E/P) daily. The women were monitored and assessed with neuropsychological tests by trained research nurses before treatment, after 24 weeks (at crossover) and after 48 weeks (at end of study). The assessment was supervised by a neuropsychologist.

3.2.2 Measurements and definitions

In Studies I and IV patients and controls were assessed using a comprehensive battery of neuropsychological tests (Table 3). Tests relevant to this thesis are described here.

Table 3. Tests, subtests and questionnaires used in the comprehensive mTBI study.

Tests	**Questionnaires**
- WAIS-III Information (1a/1a)*	- Rivermead Post Concussion
- WAIS-III Digit Span (2a/2a)*	Questionnaire (expanded version)
- WAIS-III NI Block Span (3a/3a)*	- Hospital Anxiety and Depression
- WAIS-III NI Digit Symbol (4a/4a)*	Scale (HADS)
- WAIS III: Letter-Number Sequencing (5a/5a)*	- Impact of Event Scale (H)
- WAIS III: Matrix Reasoning (6a/6a)*	- Fatigue severity scale (FSS) (H)
- Buschke Selective Reminding Test (1b/1b)*	- Everyday Consequences of Fatigue
- Rey-Osterrieth Complex Figure Test	(ECF) (H)
(BQSS) (2b/2b)*	- Pittsburgh Sleep Index
- FAS (Controlled Word Association Test (3b/3b)*	Questionnaire (PSIQ)(H)
- Design Fluency Test (fixed, 4 min.) (4b/4b)*	- Örebro Musculoskeletal Pain
- Trail Making Test (TMT) (5b/5b)*	Screening Questionnaire (H)
- Ruff 2 & 7 Selective Attention Test (6b/6b)*	- Swedish Universities Scales of
- Motor functions from Luria battery (1c/7a)*	Personality (SSP) (H)
- Grooved Pegboard Test (2c/8a)*	- State-Trait Anxiety Inventory
- Color-Word Test (Stroop test) (3c/8b)*	(STAI) (H)
- Iowa Gambling Test (4c/7b)*#	
- Rey 15 Item (5c/10a)*	
- Levels of Emotional Awareness Scale (LEAS)(6c/9a)*#	
- Sniffn' Sticks (screening 12 version) (7c/9b)*	

* = test order numbered and occasion in letters for patients/controls respectively
# = not in study IV
H= completed at home before assessment

3.2.2.1 Neuropsychological tests reported in this thesis

Buschke Selective Reminding Test (BSRT) measures verbal learning and memory [183]. Scores for number of immediately recalled words and recalled after a 30-minute delay are obtained. Low scores for the former indicate poor immediate retention, while the latter indicate poor verbal learning. To accommodate the treatment feature of Study IV the parallel version of SRT test was used for half of the patients. There was no significant difference in difficulty level between the parallel versions (Study IV).

Color-Word Test (CWT) / Stroop Test taps executive functions and measures inhibition[184]. A Swedish version of the CWT test was used [185]. The pretest consists of ten rows of ten blue, red, green or yellow colored "XXX" letters and the main test consists of ten color words in contradictory colors per row, e.g. the word "red" is written in green letters and the subject has to say "green" and not "red. The discrepancy between the total time required to perform the pretest and the total time required to perform the main test is presented as the "Stroop effect" (Studies I and IV).

Dynamic Motor Functions (from Luria battery) screens for several types of motor functions such as simple coordination, kinesthetic and dynamic motor functions and inhibition. This test is a short version of tasks included in the Luria battery [186,187] (Appendix 10.1). A high score indicates good dynamic motor functioning (Study IV).

FAS/COWAT evaluates phonemic fluency evidenced by the spontaneous production of words under restricted conditions. One minute each for words beginning with F, A and S, respectively. Participants are instructed not to use proper nouns and numbers, which are not tallied in the total number of accurate words produced [79,188]. As Study IV is part of a larger treatment study a parallel version was used for half of the patients. In this version the letters K, O, and R were used. There was no significant difference in difficulty level between the two versions (Study IV).

Grooved Pegboard Test measures motor precision and motor speed [184]. The participants are asked to place 25 grooved metal pegs into matching holes on a board as fast as they can. In this study a mean score each for the right and left hand is presented. Low scores indicate faster performance (Study IV).

Rey 15-item [79] is used as a test of effort on memory testing during assessment. Patients and controls with a score less than 9 were excluded (Studies I and IV).

Rivermead Behavioural Memory Test (RBMT) a practical measure of memory. Verbal learning was measured by reproduction of a logical story - immediate recall, and episodic memory - delayed recall after about 15 - 20 min. Three parallel versions of the stories were used [189]. There was no significant difference in difficulty level between the parallel versions (Study II)

Ruff 2 & 7 Selective Attention Test (Ruff 2 & 7 SAT) measures visual automatic detection speed and accuracy and controlled search speed and accuracy [80]. The subject has to cancel the numbers 2 and 7 in a row of letters (Automatic Detection Speed) or among other numbers (Controlled Search Speed) 15 sec/section under a period of 5 minutes. The number of correct cancellations (speed) was counted (Studies I and IV).

Trail Making Test – Trails A and B. Trails A measures attention, perceptual organization and speed. The test requires the subject to connect 25 numbered randomly arranged circles by pencil lines in proper order. *Trails - B* measures attention,

perceptual organization, speed, and mental flexibility. The test requires the subject to connect 25 encircled numbers and letters, by a pencil, in alternating order The time to perform the test is measured [79,188]. Low score means fast performance (Study IV).

WAIS-III and WAIS-R Digit Span - repetition of digits-forward is considered to assess verbal attention span and backward repetition of digits (digits-backward) is considered to assess working memory [79,190,191]. In this study the standard procedure from the WAIS-III and WAIS-R manual was used, i.e. the length of number series is successively increased until the subject fails two attempts at accurate repetition of a series of numbers. The scores are obtained for total sum forward and backward, respectively. In Study IV a discrepancy score between maximum forward and backward span length was calculated since the working memory component is related to the ability to recall the digits forward [79], the more negative score the poorer working memory (Studies II and IV).

WAIS-III Digit Symbol is a multi-factorial subtest, originally used for measuring psychomotor processing speed [191]. The test consists of rows containing small blank frames, each paired with randomly assigned number from one to nine. Above these frames is a printed key that pairs each number with a symbol. This 120-second, timed task requires one to fill in blank spaces with a symbol that is paired to the number. The score is the numbers of squares correctly filled in. Digit Symbol demands visual detection ability and learning capacity [79]. Since psychomotor speed is also influenced by incidental learning capacity, memory function was investigated by measuring incidental memory after four completed rows by requesting the test subjects to fill out the correct symbol under each digit twice/digit [78] (Studies I and IV).

WAIS-III Information is a subtest measuring premorbid educational and intellectual level, and is also a test of declarative memory [79,188,191] (Study I).

WAIS-III NI Block Span as a nonverbal subtest corresponds to the Digit Span. The participants are instructed to tap fixed blocks in a given order indicated by the test leader. Two trials for each span are allowed. The test is terminated when the patient makes two errors at the same length of span [78,192]. In this study the standard procedure from the WAIS-R and WAIS-III manual was used, i.e. the length of block series is successively increased until the subject fails two attempts at accurate repetition of a series of blocks. The scores obtained are the total sums, forward and backward, respectively. In Study IV a discrepancy score between maximum forward and backward span length was calculated as the working memory component is related to the ability to recall the forward order of the blocks [79]. The more negative score the poorer working memory (Study IV (Study IV).

WAIS-R Digit Symbol Test is an older version to the WAIS-III Digit Symbol. The procedure is as in WAIS-III but the requested time is 90 seconds instead of 120 seconds [190]. Two parallel versions of the test were used. There were no significant differences between the two versions. Incidental memory was measured after three completed rows. *Paired recall* was measured in a string of 25 digits in random order, by memory after three completed lines and at *free recall*, the participants were asked to write down the symbols without connecting them to a given digit [79]. *Spatial errors* were considered to occur when subjects rotate a symbol but otherwise correctly place it; these errors were recorded as well. The percent of possible rotations had to be calculated, due to the fact that the symbols O and X cannot be rotated (Studies II and III).

The cognitive fatigue measures were operationalized as follows:
A measure of *psychomotor fatigue* (DST-f) was derived from WAIS-NI procedure [78] of performance on the Digit Symbol Test by subtracting the number of digits produced in the first 30 seconds from the number of digits produced in the last 30 seconds, while still within the time interval of 120 seconds for WAIS III and 90 seconds for WAIS-R [78,190-192]. A DST-f (difference) less than or equal to "0", indicated cognitive fatigue [78]. Since the fatigue measure also could be affected by decreased incidental learning capacity, this was controlled for by measuring incidental memory [78,192].

Executive fatigue (CWT-f) is derived from a Swedish version of the Color Word Test [185]. Speed was recorded for every second row. Total time (in seconds) to name the color words in the first two rows is subtracted from total time to name color words in two last rows of the test. A positive score indicates slower performance during the end of the test and, thereby, fatigue.

Attention fatigue was measured by the Ruff 2 & 7 SAT as follows: Results from the first two sections of detection speed (number of correct cancelled 2 and 7) subtracted from the two last sections would measure automatic detection fatigue (ADS-f). Subtracting the first two rows of controlled search speed from the two last rows gave a measure of controlled search fatigue (CSS-f). A negative score would indicate a slower performance speed at the end of the test defined as fatigue.

3.2.2.2 Questionnaires reported in this thesis

Everyday Consequences of Fatigue (ECF) is a questionnaire designed for these studies, covering five everyday consequences of fatigue (Appendix 10.2). The participants rate how often fatigue made them fall asleep during daytime or early evening while they were inactive, caused them to take naps or yawn excessively, and prohibited them from doing mentally or physically demanding tasks. The scale ranges from "not during the last month" (0 points) to "at least three times a week" (5 points). The maximum score of 25 indicates a high fatigue impact on everyday activities (Studies I and IV).

Fatigue Severity Scale (FSS) measures subjective symptoms of fatigue [27,193] and comprises nine questions covering the behavioral consequences of fatigue. It has been proven to be a sensitive measure of fatigue among TBI patients [46]. Each item is scored on a 7-point Likert scale. A high mean score is equivalent to a high level of fatigue (Studies I and IV).

Hospital Anxiety and Depression Scale (HADS) is used to indicate depression and anxiety. A score > 10 points on the HADS depression subscale indicates that the participant suffers from depression [194] (Studies I and IV).

Pittsburgh Sleep Quality Index (PSQI) is a questionnaire used to assess different sleep disorders such as subjective sleep quality, insomnia, sleep distractors etc. There are seven items with ratings from 1-3, with a maximum summed score of 21. A high score indicates poor sleep quality [195] (Studies I and IV).

Self reported memory was assessed with a questionnaire of subjective memory problems (QSMP), which is a self-administered questionnaire covering everyday memory problems (Appendix 10.3). A maximum score of 36 indicates severe memory problems. The questions were derived from the more comprehensive Cognitive Failure

Questionnaire - used in clinical practice at Danderyd Hospital and not validated in other research studies (Study II).

The Psychological General Well-Being Index (PGWB) was used to assess affective or emotional states reflecting subjective well-being or distress. The questionnaire consists of 22 items forming six subscales (anxiety, mood, well-being, self-control, general health, and vitality) and a total index score [196] (Study III).

3.2.2.3 Hormone assays

3.2.2.3.1 Study II and III

The serum concentrations of total testosterone (T) were determined with radioimmunoassay (RIA) in untreated serum. The serum concentrations of SHBG and estradiol (E2) were determined by chemiluminescence. The apparent concentrations of free T were calculated from values for total T, SHBG and a fixed albumin concentration of 40 g/l by successive approximation, using a computer program based on an equation system derived from the law of mass action [197].

3.2.2.3.2 Study IV

Venous blood samples were collected at baseline before the neuropsychological assessment took place. Serum concentrations of free T3, free T4, TRAb, TSH, tyreoperoxidas autoantibodies (TPO), were collected as were hemoglobin, calcium, albumin, and creatinin. Concentrations of TSH, free T3 and free T4 and anti-TPO antibodies were measured by chemiluminescent methods. Thyrotropin receptor antibodies were measured by radioimmunoassay. Remaining samples were analyzed by routine laboratory work.

No hormonal samples were collected from the controls.

3.2.3 Power calculations and statistical analyses

3.2.3.1 Study I

A power calculation on the DST fatigue measure was performed. For a mean score difference between patients and controls of 2.5, a SD of 3.0, an alpha level of 0.05, and a power of 0.80 a sample of 24 patients and 24 controls was sufficient.

Mann-Whitney U-test was used for comparison between patients and controls. Spearman's rank correlation were used even when the variables were normally distributed. In order to avoid the risk of obtaining false positives due to the number of variables entered in analysis, Bonferroni correction was applied. Binary logistic regression analyses were used to analyze factors potentially contributing to psychomotor fatigue. Medications were classified in two groups:

1. No medications
2. Medications (e.g., acetylsalicylic acid, paracetamol, ibuprofen, terbutaline, vitamins, pregabalin, codeine, tramadol, zopiclone, amitriptyline, citalopram, hydroxyzine).

Both forward and backward, stepwise logistic regression were used to check for multicollinearity.

3.2.3.2 Studies II and III

A power calculation on cognitive fatigue (WAIS-III digit symbol test) was based on an assumption of a treatment effect of 1.0 score, SD of 2.04, an alpha level of 0.05, and a power of 80. This would demand a sample size of 35 individuals.

Parametric methods were used for normally distributed variables with interval-level data (Student's t-test for paired samples and Pearson's product-moment correlation), and non-parametric methods were used when the ordinal data was skewed (Wilcoxon matched-pairs ranks test and Spearman's rank correlation test). In Study III, post hoc analyses of comparisons between subgroups. Student's t-test for independent samples was used. For comparison between dichotomized variables (> the 75:e percentile and $\leq$ the 75 percentile) Fisher's exact test was used. The possible effects of randomization bias were investigated using a linear mixed-model analysis including one within-group factor treatment and one between-group factor.

3.2.3.3 Study IV

Power calculations were the same as in Study I above.

Parametric methods were used for normally distributed variables with interval-level data, and non-parametric methods were used for skewed and for ordinal data. For categorical data χ^2 and Fisher's exact test were used. To correct for gender influences on the neuropsychological measures a one-way ANOVA, with gender as a covariate, was performed: and to correct for false positives due to the number of analyses, a Bonferroni correction was applied. For ad hoc analysis to examine contribution of factors to cognitive fatigue, binary logistic regression analysis was used. Both forward and backward stepwise logistic regression was used. Both methods revealed the same results indicating that there were no problems with multicollinearity. The results from backward logistic regression will be presented.

In all studies two-tailed p-values were used with a critical significance level of 0.05. SPSS statistics 19 was used for the analyses.

3.3 ETHICAL CONSIDERATIONS

All participants gave informed consent to take part in the studies. The research was carried out in accordance with the Declaration of Helsinki (2000) and was approved by the Regional Ethical Board in Stockholm.

4 RESULTS

4.1 STUDY I

The mTBI patients performed significantly poorer on the complex neuropsychological fatigue measures (DST-f and CWT-f) compared to the healthy controls (Figure 3).

Neither age, years of formal education, nor depression correlated with any of the cognitive fatigue measures. However self-rated sleep disturbances (PSQI) correlated with executive fatigue (CWT-f) (r_s(21) .503, p = .020) among patients but not among controls.

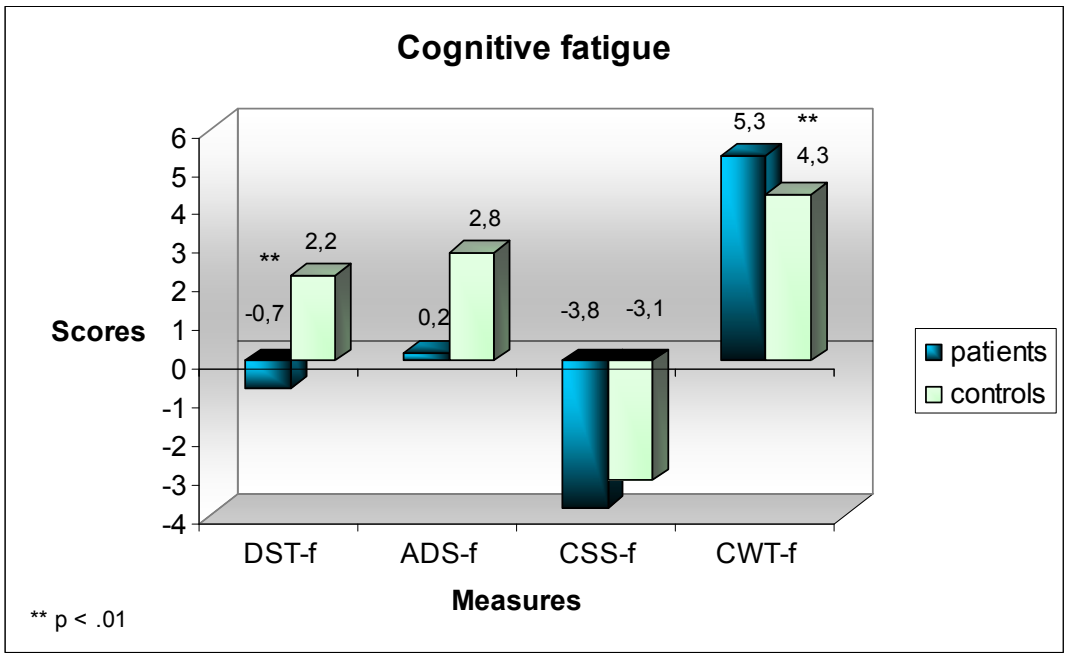

Figure 3. Results on the different cognitive fatigue measures for mTBI patients (n = 24) and controls (n = 31). Abbreviations: DST-f (Digit Symbol-derived fatigue score), ADS-f (Ruff 2 & 7 - attention detection speed, derived fatigue score), CSS-f (Ruff 2 & 7 - controlled search speed, derived fatigue score), CWT-f (Color Word, derived fatigue score).

Compared with controls, mTBI patients self-rated fatigue significantly higher (p = .001) on both FSS and ECF; but they also scored sleep quality and depression each poorer (Figure 4).

Among the patients depression (HADS) correlated positively with self-rated fatigue (FSS) (r(23) .568, p = .005) and sleep symptom ratings (PSQI) (r(24) .584, p = .003) but not with everyday consequences of fatigue (ECF) r(24) .285, p = .177). Five of the patients scored $\geq$ 10 on the HADS depression subscale.

The only correlation found between the self-rated fatigue measures and cognitive fatigue measures was between FSS and executive fatigue (CWT-f) among the patients (r(21) .539, p = .012).

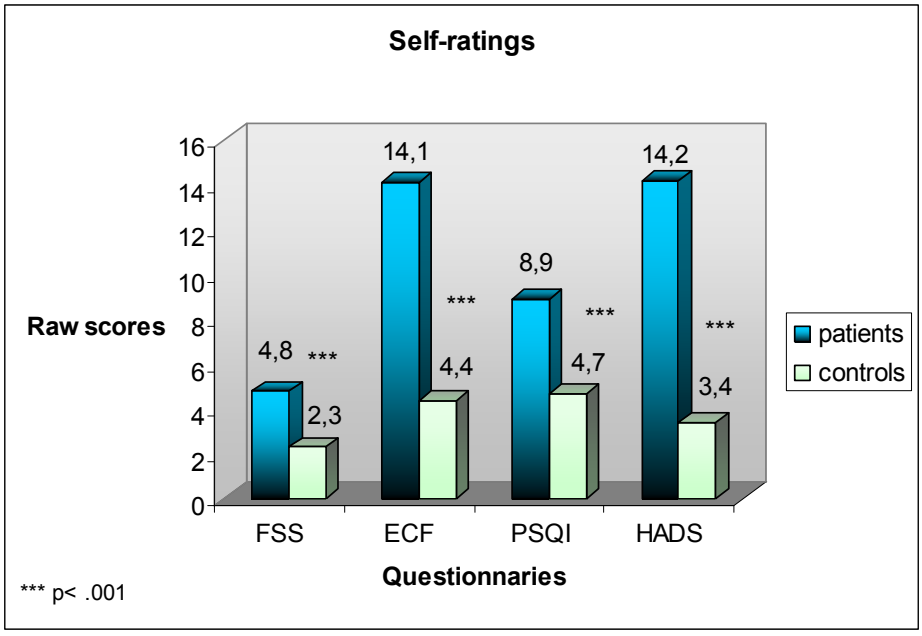

Figure 4. Results on self-rated measures for mTBI patients (n = 24) and controls (n = 31). Abbreviations: FSS (Fatigue Severity Scale), ECF (Everyday Consequences of Fatigue), PSQI (Pittsburgh Sleep Quality Index), HADS (Hospital Anxiety and Depression Scale).

The mTBI patients exhibited descending performance speed, between the first and last 30 seconds on the DST-f measure while the controls accelerated their performance speed (Figure 5). Fifteen (62 %) of the 24 patients and 6 (19 %) of the 31 controls showed a non-ascending speed on the DST. Logistic regression analyses showed that neither educational level nor memory for symbols contributed to the results.

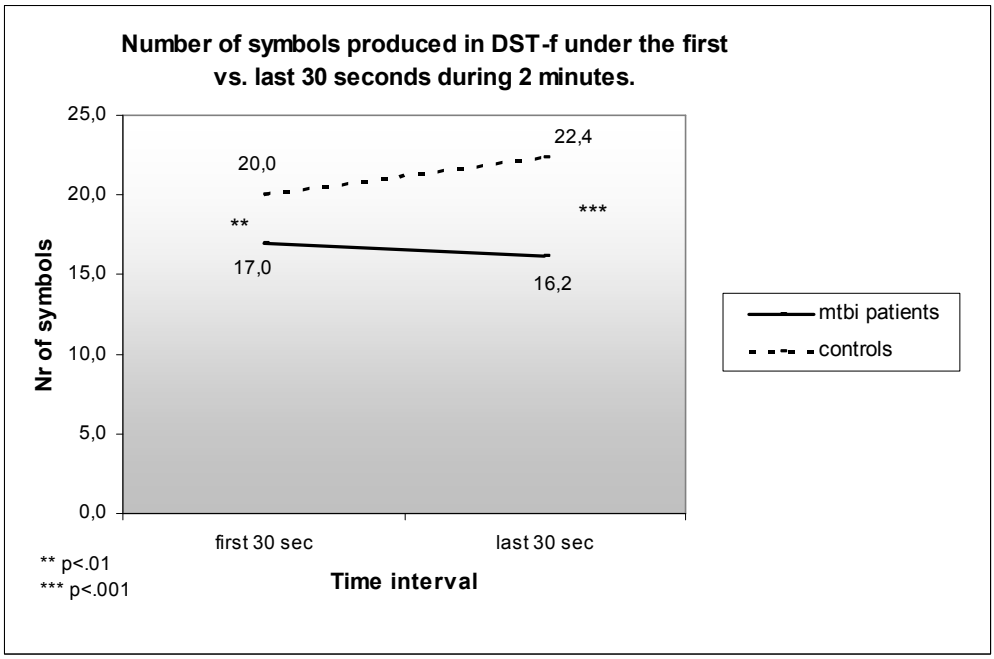

Figure 5. Numbers of symbols produced in the first 30 seconds compared to in the last 30 seconds on the WAIS-III Digit Symbol Test for mTBI patients (n = 24) and controls (n = 31) respectively.

As five patients scored high on the HADS depression subscale, the analyses were rerun without these patients (n = 19). The results on psychomotor fatigue were the same as before (p = .002); but with their omission executive fatigue was no longer significant (p = .051). The attention measures were not significant on ADS-f (p = .099) and CSS-f (p = .415).

4.2 STUDY II

The memory improved from baseline with both treatment regimens. Immediate recall performance, measured by the RBMT, significantly improved with estrogen+ placebo treatment as well as with estrogen+ testosterone (Figure 6).

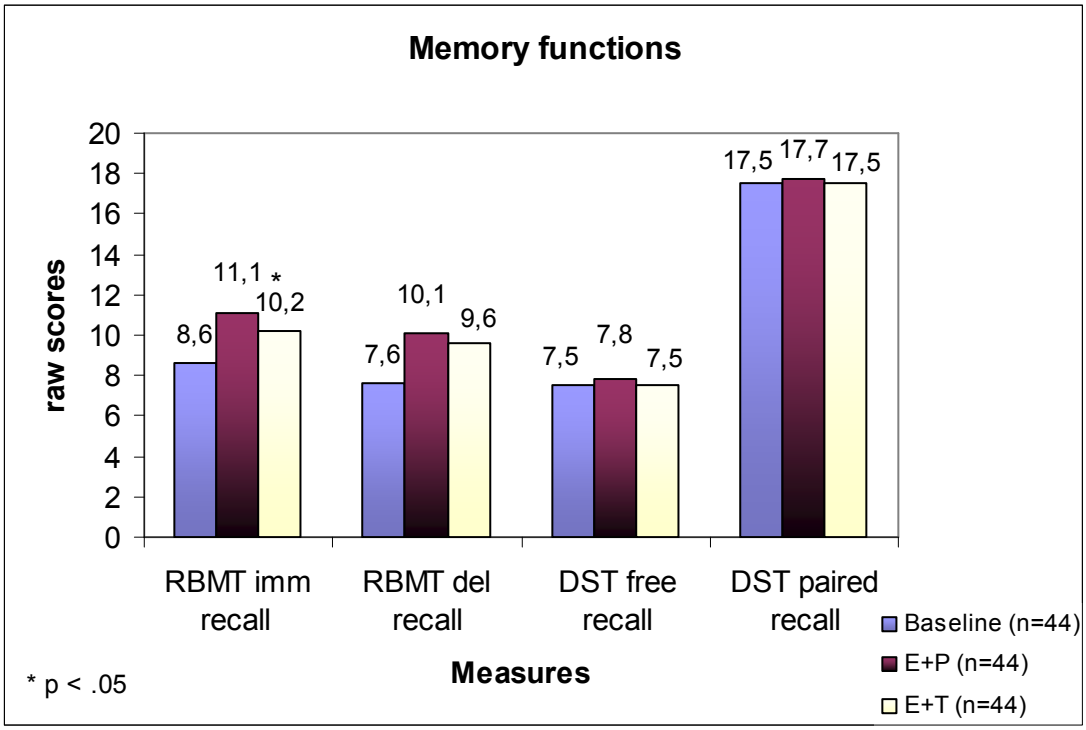

Figure 6. Memory functions for baseline and the two treatment regimens.
B = baseline, E/P = estrogen + placebo regimen, E/T = estrogen + testosterone regimen.

At baseline estrogen levels did not correlate to any of the cognitive measures while total testosterone showed a negative correlation to immediate recall on RBMT (r_s(44) = - .350, p = .020).

During the estrogen + placebo regimen the estrogen level correlated positively with free recall of digits (r_s(44) = .358, p = .035). Total testosterone did not correlate with any of the cognitive measures while free testosterone showed a negative correlation with immediate recall on the RBMT (r_s(42) = - .349, p = .023) and working memory (WAIS- R Digit Span backwards) (r_s(39) = - .316, p = .050).

During the estrogen + testosterone regimen hormonal levels did not correlate with memory functioning.

4.3 STUDY III

At baseline, when the hormone levels were very low, 20 of 43 women (46 %, one missing case) showed cognitive fatigue – defined as a non-ascending result on the test. Incidental memory did not explain the psychomotor fatigue as the DST-f measure did not correlate with recall of digits.

Performance on the DST-f did not correlate with sex hormone levels at baseline. However, DST-f correlated with PGWB - general health ($r_s(43) = .35$; $p = .02$) and with self-control (r_s (43) = .32, p = .04); and correlated negatively to BMI ($r_s(43) = -.32$, $p = .04$). This pattern in PGWB subscales were also present when the women were divided into fatigue (n = 20) or non-fatigue (n = 23) groups (Figure 7).

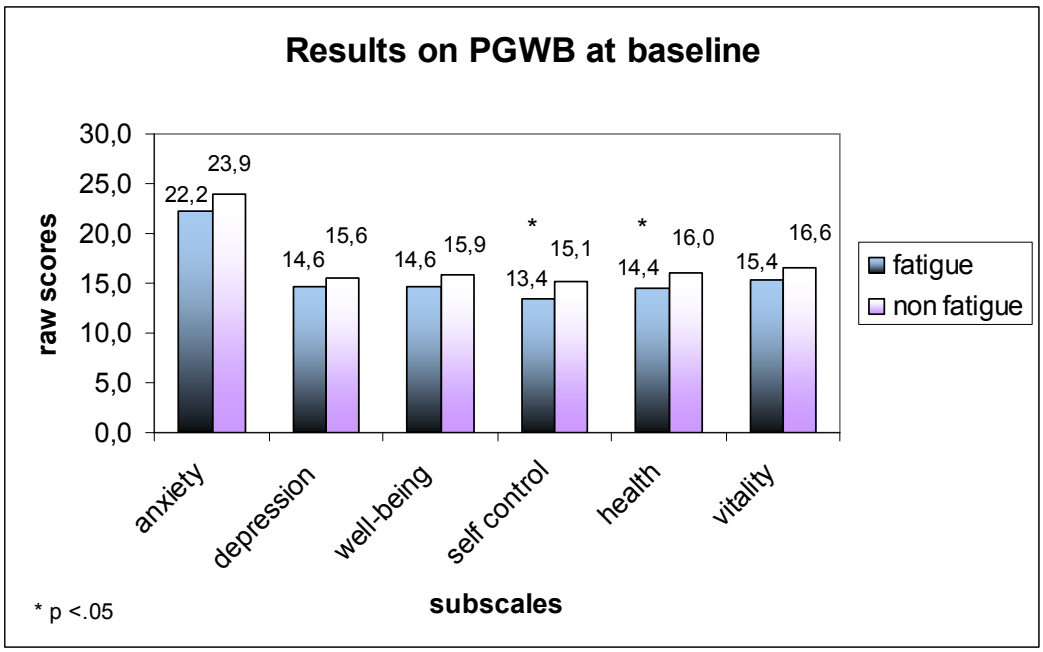

Figure 7. Results on the PGWB subscales at baseline for fatigue (n = 20) vs. non fatigue (n = 23) women at baseline

We found no treatment effects after 24 weeks of treatment with estrogen plus testosterone, compared to estrogen plus placebo. No significant correlation resulted from comparison of hormonal level with DST-f.

During the estrogen plus testosterone treatment, 8 of 9 women with the highest E/T ratio (> 75 percentile) tended to show cognitive fatigue (Fisher's exact test, $p = .06$,). During the estrogen plus placebo treatment 20 of 29 women with an E/T ratio <75 showed cognitive fatigue (Fisher's exact test, $p = .04$).

4.4 STUDY IV

Seventeen GD patients showed cognitive fatigue (non ascending speed on the DST-f) compared to six of the controls ($p = 0.01$).

Significant findings were obtained on several self-report fatigue, sleep quality and depression measures. Patient status elicited significantly more severe fatigue, greater consequence in everyday life due to fatigue, poor sleep quality, and elevated depression (Table 4).

Table 4. Results obtained from on questionnaires. Means ± standard deviations are presented.

Questionnaires	patients (n=34)	controls (n=31)	p-level
FSS - mean score	4.4 ± 1.4	2.3 ± 0.8	p <.001
ECF - total score	9.8 ± 5.8	4.4 ± 3.5	p <.001
PSQI - total score	8.2 ± 3.4	4.7 ± 3.1	p <.001
HADS - total score	13.2 ± 8.7	3.4 ± 2.7	p <.001
- anxiety score	8.2 ± 5.4	2.6 ± 2.4	p <.001
- depression score	5.0 ± 4.0	.8 ± .8	p <.001

Mann-Whitney U test is used for comparison.
Abbreviations: HADS (Hospital Anxiety and Depression Scale), FSS (Fatigue Severity Scale), ECF (Every day Consequences of Fatigue), PSQI (Pittsburgh Sleep Quality Index). Bonferroni corrected significance level is p = .008

Individual patient group HADS scores correlated with FSS ($r_s(34) = .507$, $p = .002$), ECF ($r_s(34) = .498$, $p = .003$), and PSQI ($r_s(34) = .427$, $p = .012$).

No significant differences in HADS scores were obtained between fatigue (n=17) and non-fatigue (n=17) GD patients (5.5 ± 4.4 vs. 4.5 ± 3.6) ($Z = 0.64$, $p = .521$); and neither were significant differences found with age, number of smokers, hormone levels or self-rated measures between the fatigue and non-fatigue patients. However, the fatigue patients had lower educational level than the non fatigue (11.5 ± 1.6 vs. 12.9 ± 2.5) ($Z = -2.06$, $p = .039$) and there fewer users of beta-blockers among the fatigue (n = 5) compared to the non fatigue patients (n = 11) ($p = .039$). Logistic regression analysis disclaimed lower length of educational level as an explanation for cognitive fatigue among GD patients.

The GD patients performed significantly poorer on the test of dynamic motor functions ($p = .006$), perceptual organization ($p = .008$) incidental memory ($p = .010$), verbal learning ($p = .012$), verbal working memory ($p = .006$) and word generation ($p = .002$) compared to the controls, when gender differences were controlled for.

Among the patients free T3 levels correlated positively with faster performance in motor precision (Grooved Pegboard Test) ($p = .013$) and visual organization (Test, Trail Making Test - A) ($p = .007$), better automatic attention speed ($p = .037$), controlled search speed ($p = .043$) (Ruff 2&7), incidental memory on DST ($p = .009$), and better inhibition (Stroop effect on CWT) ($p = .004$). Free T 3 also correlated to high scores of every day consequences of fatigue (ECF) r_s (29) .445, $p = .015$, but not to cognitive fatigue. Also no correlations were found between hormone levels and depression, anxiety or sleep quality.

5 DISCUSSION

5.1 COMMENTS ON MAIN FINDINGS

5.1.1 Capturing fatigue with neuropsychological methods

Study I showed, in line with the hypothesis, that tests demanding a coordination of complex cognitive functions including higher order attention [35] , "executive control" [198] and working memory [199] as well as motor behavior [31,39,200] could be more suitable to measure cognitive fatigue compared to less cognitive challenging tests.

The DST-f score is derived from the WAIS Digit Symbol Test, which is a complex test and sensitive to many different kind of neuropsychological dysfunctions [79]. Compared to performance on a simple graphomotor test, performance on the DST involves bilateral activation in predominantly right side, inferior frontal regions [201]. Theoretically, more "functionally clean" neuropsychological tests, as those measuring attention or working memory solely, might allow the neural system to compensate for diffuse complex dysfunctions in neuronal networks. On the other hand, when a test demands coordinated utilization among many different functions, the vulnerable patient might not be able to perform at an optimal level. The heterogeneity of contributing factors in the DST makes it difficult to determine which, of many components, have the larger effect on the performance [79,202,203]. However, at the same time, such functional heterogeneity makes the test suitable to measure cognitive fatigue in different kind of patient groups with mild cerebral influences. For clinical purposes, this need not to be a problem, as broader test batteries are typically included in assessments in clinical settings.

As self-rating instruments can be influenced by depression there is a risk of relating fatigue among patients to depressive disorders. Psychiatric comorbidity should be respected but it is unknown to what extent fatigue weights on cognitive dysfunction. In neuro-rehabilitation it is important to find the underlying components of different characteristics of fatigue, thus enabling individual rehabilitation plans to be customized. Thus, it is essential to develop neuropsychological tools, not subject to influence by depression or sleep disorder, permit both the ability to measure cognitive fatigue and to evaluate treatment effects [1].

5.1.2 Cognitive fatigue in mTBI

In this study, patients with symptoms after mTBI presented significantly more cognitive fatigue than did controls; which corresponded with scores higher on self-rated fatigue. While self-rated fatigue was correlated with self-rated depression in the patient group, DST-f derived cognitive fatigue was not related to depression nor to poor sleep quality. The lack of correlations between self-rated and cognitive fatigue is noteworthy and its clinical implications should be considered.

The possibility to generalize the results of this study is difficult since patients with residual symptoms after an mTBI are a self selected group. The majority of patients shows full recovery [153] while many underlying reasons may account for that minority of patients with residual symptoms [153].

Cognitive symptoms could persist in some patients due to factors such as psychiatric comorbidity [158]. Some patients might have had a premorbid low-performing cognitive profile while in other cases the dysfunctions might have been primarily injury related.

Even though our study was a study of patients with persistent symptoms, there was high variability of length of time between the incident-accident and subsequent assessment. Theoretically, cognitive fatigue should be more prominent in patients assessed very soon after injury as natural recovery, at least in some degree, is expected [150]. However, in this study the sample size was too small for separate analyses to examine effects of latency between accident and assessment.

As seen in studies included in this thesis and in other previous studies, the underlying cause of self-perceived fatigue could be depression or sleep disorders. Depression or sleep disturbances could be related to the trauma but, nonetheless, contributing factors such as lack of social support, financial concerns, etc. must also be considered.

Our study provides support for an argument that it is important to reflect on the type of instruments used when assessing persisting symptoms among patients with mTBI. Questionnaires used during recurrent assessments run a high probability of measuring depression rather discriminating the true level and quality of injury-related symptoms. Smaller studies may be weak due to inadequate power and, with them, blinding is difficult in studies were neuropsychological assessment is used. Such factors could exclude such studies from being enrolled in meta-analyses. The minority of patients with residual dysfunction may be overlooked in meta-analyses [204].

Furthermore, when evaluating the effects of neuropsychological impairment, interpretation and weighting of scores is often forgotten. In cases where neuropsychological instruments are used it is also of importance to bear in mind the everyday effect of test results. For example, impaired working memory might be much more problematic to cope with in the everyday setting than, say, visuospatial shortcomings.

5.1.3 Effects of hormone replacement on memory and fatigue

In Study II, the main finding was that the addition of testosterone to estrogen therapy carried a greater effect to impair immediate verbal memory compared to estrogen plus placebo treatment. This finding is contrary to a study by Sherwin in 1988, in which she found positive effects of testosterone treatment in oophorectomized women [167]. On the other hand, a population-based study found a negative association between testosterone and verbal fluency, semantic and episodic memory in women. The influence was stronger with increasing age [205]. It is, however, problematic to compare treatment studies with population-based studies since the basis for drawing conclusions are quite unequal for different types of studies.

In Study III, no straight forward relation emerged between testosterone treatment and cognitive fatigue; but the study suggested that the balance between estrogen and testosterone levels is important. During testosterone and estrogen therapy, both testosterone and estrogen levels were generally high. While undergoing testosterone supplementation, several women in the upper quartile of the E/T ratio showed fatigue. In contrast, during estrogen and placebo treatment, in which estrogen levels were relatively high compared to testosterone levels, the women who did not reach the upper quartile suffered significantly more from cognitive fatigue. These results may fit a model with a curvilinear relationship indicating potential influence of hormone levels on cognition [100,206].

Studies regarding sex hormonal levels and cognitive performance seldom show conclusive results [96-99]. The reasons are many, including:

- Methods for measuring low levels of testosterone, as in women, have a large degree of uncertainty [207].
- Testosterone can be aromatized to estradiol and thus testosterone treatment can also increase levels of serum estrogens, complicating the interpretation of the treatment effect [102].
- The association between neuropsychological functions and sex steroid hormone levels might not be strictly dose dependent [100,101] and the balance and ratio between estradiol and testosterone may be an important modulator in cognitive function in women [120].
- Time elapsed between oophorectomy and treatment is important - there might be permanent loss of estrogenic and testosteronic synapses in the human brain after a period of hormone depletion. Toran-Allerand et al. (1992) found that estrogens, along with other growth factors, were crucial for the survival of certain estrogen-responsive neurons. Therefore, estrogen-sensitive neurons may be lost with estrogen depletion; and,
- Type of testosterone preparation with divergent dose and pharmacokinetic properties. Fluctuating pattern and peak levels can result in testosterone levels exceeding the upper limit of the established female norms [208,209].

The mean time between oophorectomy and inclusion in the study exceeded 5 years and no information was available regarding the individual cases for data analyzes. The long latency between surgery and treatment could have had effects on receptor function for both estrogen and testosterone. Unfortunately, there was missing data on the number of oophorectomized women who had received HT before the study recruitment. Therefore, we did not examine correlations between mean time since oophorectomy and cognitive function.

Another reason for the different results might be that tests used in our study might have lacked sensitivity to detect subtle differences. A more sensitive test battery is needed to capture more subtle aspects of memory functions.

5.1.4 Fatigue and cognition in untreated Graves' disease

The patients with newly diagnosed GD gave higher self-ratings of fatigue. Fifty percent of these patients were found to have cognitive fatigue compared to 19 % among the controls. While self-rated fatigue was related to depression among the patients, cognitive fatigue was not.

No correlation was obtained between T3 levels and cognitive fatigue. However, although no correlations were elicited between hormones and cognitive fatigue, high free T3 was positively associated with neuropsychological performance.
The associations were, however, not in the expected direction, that is, high T3 is related to severity of the disease [169]. On the other hand, self-ratings of everyday consequences of fatigue were associated to higher T3 levels. It could be interpreted that patients with high free T3 levels are more hyper-vigilant due to increased metabolism, resulting in high activity level that produces secondary consequences of fatigue. This could also suggest that higher free T3 levels somehow benefit cognition in GD. Data are inconclusive whether high T3 levels directly benefit cognition in GD or if factors such as general health contribute to enhanced T3 levels.

Another interesting related finding was that smokers had lower levels of free T3 and free T4 compared to non-smokers. In studies on GD, smoking has been associated to poor outcome after ophthalmopathy [210,211] and menstrual disturbances [212], probably associated with oxidative stress [213].

Neuropsychological studies on untreated patients with Grave's disease have been sparse and inconsistent. Earlier studies have shown attention and memory difficulties, and problems with complex problem solving [178,179]. Others have found no neuropsychological dysfunctions in GD patients [173]. Findings concerning the relationship between hormonal levels and cognitive functions have been sparse.

A limitation of this study was too small a sample size that restricted subgroup analyses and that hormonal data was not obtained for the controls. Another limitation in this study was that in order to spare the patients from a prolonged time to treatment the neuropsychological assessment was performed at visit while controls were tested over two visits.

The study, nevertheless, confirms the presence of fatigue and neuropsychological dysfunctions among patients with untreated GD, which also could support previous findings regarding subjective complaints of fatigue and a decreased quality of life in this group [176].

5.1.5 Cognitive fatigue as a dysfunction

Attention, working memory and motor speed are functions vulnerable to mild or diffuse brain influences after mild traumatic brain injury [6,214,215], ischemic vascular lesions [216], sleep apnea [217] but age-related changes also contribute to alternations in white matter integrity [218].

In both Studies I and IV the frequency of cognitive fatigue was higher in the patient groups compared to healthy controls; 62 % of the mTBI patients and 50 % GD patients showed cognitive fatigue compared to 19 % of the healthy controls, but there might have been different underlying mechanisms resulting in the fatigue in two different patient groups respectively.

Medications such as beta-blockers and anti-depressant medications are associated with reports of fatigue [59]. In Study I, no association between type of medication and cognitive fatigue was found. However in Study IV use of beta-blockers were less common in the cognitive fatigue group than in the non-fatigue group. Thus one can not rule out that the use of beta-blockers prior to the assessment would have had an impact on the results.

In Study III, cognitive fatigue was quite frequently elicited within the group of untreated, oophorectomized women at baseline. However, no comparison with a control group was possible. Cognitive fatigue was related to high BMI and low self-rated health and low self control. Women suffering from cognitive fatigue had a BMI corresponding to being overweight but not obese; and, according to the general health items in PGWB they were more likely to complain of physical disorders or pain and general health concerns compared to the women without fatigue at baseline. This was intriguing as the exclusion criteria were rigorous by not allowing cerebrovascular insults, smoking, and medication. On the other hand, the association between

cognitive fatigue and high BMI is in line with a recent study on psychomotor vigilance by Lee et al. [219]. Obesity has also been associated with impaired health-related quality of life and disability as measured by self rating scales [220].

Neither Study III nor IV showed any direct hormonal correlation to fatigue. However in Study III there were indications that cognitive fatigue could be related to an imbalance between E/T levels. Also, in Study IV the T3 levels were associated to neuropsychological functions, such as working memory and psychomotor speed, functions that could be related to the underlying abilities demanded for performance of the DST. This implies that cognitive fatigue is probably not directly linked to hormones, rather, it is a consequence of different kinds of influence, giving rise to imbalance in sensitive cognitive systems.

Furthermore, cognitive fatigue did not correlate to self-rated fatigue in either Study I or IV, while self-rated fatigue was correlated to depression among mTBI and GD patients. Findings of association between self-ratings and performance have been difficult to obtain in studies of different medical illnesses [33,221,222]. This probably reflects that subjective fatigue is not the same as cognitive fatigue. The studies indicate that subjective fatigue is more related to psychological factors such as depression and sleep disturbance, while fatigue measured with neuropsychological tests is more related to cognitive functions such as attention, working memory, executive functions or a complex interaction of these factors. Measuring cognitive fatigue is thus not the same as measuring self-rated subjective fatigue. It is important to keep this in mind when evaluating fatigue in clinical populations as self-rated and cognitive fatigue brings different dimensions to the concept of fatigue.

6 GENERAL CONCLUSION

As fatigue is a diffuse phenomenon with multidimensional features, it is important to distinguish factors that initiate fatigue from factors that perpetuate or exacerbate fatigue[67]. Self-rating instruments are influenced by e.g. depression and sleep disorders therefore neuropsychological tools capable of measuring cognitive fatigue are required. This study, consistent with earlier findings, found that cognitive fatigue could be detected using tests that demand simultaneous, complex cognitive functioning, such as attention, working memory and psychomotor functions. In particular, the Digit Symbol, using a scoring method that isolates a fatigue index, seems to be a valid instrument that can detect cognitive fatigue, despite comorbid features of depression or sleep disturbances. Also, again in line with previous studies, cognitive fatigue related to BMI and general health. Cognitive fatigue did not seem to be directly related to sex hormonal levels or T3 levels; rather, secondary mechanisms, such as hormonal imbalance could influence subtle neuronal mechanism leading to discrete neuropsychological dysfunctions. The lack of coherence between cognitive fatigue and self-perceived fatigue suggest that we measure different aspects of fatigue with neuropsychological tests compared to self-rating instruments.

6.1 FUTURE STUDIES

Although cognitive fatigue was over represented in the patient group we could not know the mechanisms behind the results. In an ongoing fMRI project with Arterial spin labeling technique on mTBI patients suffering from fatigue we will investigate if there are differences in neuronal resting state before, during and after a vigilance challenge. This might provide information about neuronal activity leading to overload under activity, but also on whether the fatigue patient after activation recovers neuronal activity more effectively than a comparative control.

The interaction between BMI, hormones, general health and fatigue would certainly be worth while studying more. From a psychoneuroimmunological perspective factors such as high BMI [223], traumatic brain injury [224] neurological diseases [31] stress and depression have been related to inflammatory processes [225] and could theoretically give secondary negative effects on cognition [226].

Patients suffering from GD, suffered from fatigue and demonstrated lower neuropsychological performance on several tests. The neuropsychological field is open for interesting studies as this is not yet neuropsychologically thoroughly studied. Prior research indicated that some patients do not feel fully recovered after treatment despite having regained normal hormonal levels [176,177]. Questionnaires as well as neuropsychological tests should be employed in studies on treatment recovery. Furthermore we still have insufficient knowledge about the long-term effects on cognition due to prolonged imbalance in hormone levels in humans.

Fatigue is one of the most difficult symptoms to cope with as well as to ascertain and relieve. It deeply impacts social and physical functioning, and it is, therefore, highly important to learn methods to assess different aspects of fatigue, and to find proper treatments. In this thesis, we found that cognitive fatigue was best captured using tasks that demand complex functioning and we also found different factors associated to performance decrements. Adopting a multi-professional approach is important when investigating fatigue, as well as when finding ways to treat it.

7 SAMMANFATTNING PÅ SVENSKA

Trötthet drabbar många patienter efter sjukdomar som påverkar hjärnan men också vid hormonförändringar. Trots att trötthet har intresserat psykologer sedan den moderna psykologins begynnelse saknas det fortfarande en enhetlig definition av begreppet och bra mätmetoder. Trötthet påverkar livskvalitet och arbetsliv och är ett av de vanligaste orsakerna till att sjukskrivna personer inte lyckas komma tillbaka i arbete.

Den självupplevda trötttheten mäts med skattningsskalor. Problemet med att mäta ett symptom med enbart skattningsskalor är att svaren i många fall är förknippade med andra tillstånd som påverkar resultatet då t.ex. deprimerade personer har en benägenhet att skatta mera besvär på skattningsskalor.

För att kunna rehabilitera och behandla patienter optimalt är det viktigt att kunna särskilja trötthet som beror på underliggande neuropsykologiska funktionsnedsättningar från trötthet som är sekundär till följd av depression eller sömnstörningar. Det finns därför ett behov att utveckla instrument som är kliniskt lättanvända och kan skilja funktionsnivå från självupplevda symptom.

Vi har studerat olika neuropsykologiska metoder som kan vara lämpliga för att fånga kognitiv trötthet och att undersöka om specifika hormonförändringar och behandlingar bidrar till kognitiv trötthet.

Tre olika patientgrupper ingick i studien; Patienter som drabbats av en lätt traumatisk hjärnskada, kvinnor som opererat bort äggstockar och som utöver behandling med östrogen erhöll tilläggsbehandling med testosteron, patienter med nydiagnostiserad men obehandlad Graves sjukdom (giftstruma).

Avhandlingen har kunnat visa att kognitiv trötthet, i enlighet med tidigare forskning, är mer framträdande på test som kräver uppmärksamhet, arbetsminne och motoriska funktioner och där man samtidigt måste bearbeta komplex information. Deltestet Kodning från Wechslerskalorna verkar vara ett test som har lämpliga egenskaper för att mäta kognitiv trötthet hos patienter med lätta traumatiska hjärnskador. Självskattad trötthet verkar vara mera relaterad till nedstämdhet och sömnstörningar medan så inte är fallet för kognitiv trötthet.

Hos obehandlade kvinnor som opererat bort äggstockar var könshormonnivåerna generellt mycket låga och man fann inget samband mellan hormonnivåer och trötthet. Trötttheten var kopplad till övervikt och sämre självskattad hälsa. När dessa kvinnor behandlades med antingen östrogen och placebo (sockerpiller) eller östrogen och testosteron visade det sig att det inte var hormonnivåerna i sig som var relaterade till kognitiv trötthet utan snarare tycktes förhållandet mellan östrogen- och testosteronhalten vara viktigare. Man fann också att testosteronbehandling som tillägg till östrogenbehandling hade en negativ effekt på vissa minnesfunktioner.

Patienter med Graves sjukdom upplevde högre grad av självskattad trötthet och hälften av patienterna led av kognitiv trötthet jämfört med endast en femtedel av deltagarna i kontrollgruppen. De presterade också sämre på tester för motorik, inlärning och minne. De hade svårare att generera ord och sämre språkligt arbetsminne. De som hade höga nivåer av tyroideahormonet trijodtyronin (T3) fungerade bättre vad gäller bearbetningshastighet, uppmärksamhet och vissa minnesfunktioner och hade även

bättre impulskontroll men de upplevde större problem med självskattade vardagskonsekvenser av trötthet. Rökare hade generellt lägre nivåer av fritt T3 än icke-rökare.

Sammantaget talar studierna för att det är möjligt att mäta kognitiv trötthet med test som kräver samtidig bearbetning av komplexa kognitiva funktioner. Deltestet Kodning från Wechslerskalorna har egenskaper som är lämpliga för att mäta kognitiv trötthet då depression och sömnstörningar inte påverkade resultatet. Kognitiv trötthet verkar vara relaterat till BMI och självrapporterad hälsa men inte direkt till hormonnivåer. Däremot är det möjligt att sekundära mekanismer såsom hormonell obalans kan påverka känsliga neuronala processer och därmed leda till diskreta neuropsykologiska dysfunktioner.

Bristen på samstämmighet mellan självskattad trötthet och kognitiv trötthet kan bero på att vi mäter olika aspekter av trötthet när vi använder frågeformulär jämfört med neuropsykologiska test.

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10 APPENDICIES

10.1 MOTORISK SCREENING FRÅN LURIABATTERIET

Datum:	Luria – motorisk dynamik	*Namn:*

Föreligger perifer nervskada? Nej ☐ Ja ☐ Var?_____

D1. Händernas motoriska funktion

D1.1 *Enkel rörelse*

D.1.1.1 **Gör som jag. Börja med dominant hand och sätt tummen mot pek, lång, ring och lillfingrarna i tur och ordning. Gör så snabbt du kan!**
Pat får göra så 5 gånger med dominant hand.

Markera misslyckade försök med kryss: ☐ ☐ ☐ ☐ ☐

summa korrekt domin:___

Gör nu samma sak med den andra handen!

Markera misslyckade försök med kryss: ☐ ☐ ☐ ☐ ☐

summa korrekt i-dom:___

D1.1.2 **Gör som jag: Lägg händerna på bordet med handflatan nedåt. Spreta ut med fingrarna och för ihop dem. Använd båda händerna och forstätt till jag säger till:** Pat får göra så fem gånger:

Markera misslyckade försök med kryss: ☐ ☐ ☐ ☐ ☐

summa korrekt bilateralt:___

Noteras lateralisering mellan höger / vänster? _____

D.1. 2 Rörelsens kinestetiska bas

D.1.2.2 Churchill – Manson testet:

Placera dominant hand på bordet (täck över med blocket så att pat inte ser) **och gör likadant som jag gör (gör Churchill tecken) och gör sedan Manson tecknet om pat klarar uppgiften.**
Klarar pat båda uppgifterna? Ja: ☐ Nej: ☐
Om ja (2 poäng/rörelse): max 4 poäng

Om nej: klarar pat då han/hon ser fingrarna Ja: ☐ Nej: ☐
Om ja: 1 poäng/rörelse: max 2 poäng

summa dominant:___

Gör samma sak nu med den icke-dominanta handen:

Klarar pat båda uppgifterna? Ja: ☐ Nej: ☐
Om ja (2 poäng/rörelse): max 4 poäng

Om nej: klarar pat då han/hon ser fingrarna Ja: ☐ Nej: ☐
Om ja: 1 poäng/rörelse: max 2 poäng

summa icke-dom:___

D.1.4 *Rörelsens dynamiska organisation*

D1.4.1.1 **Lägg händerna som jag och låt dem växla ställning samtidigt (fig. 4).**

Låt pat växla 10 ggr:

Markera misslyckade försök med kryss: ☐☐☐☐☐☐☐☐☐☐

summa korrekt:____

D.1.4.2 **Lägg händerna på bordet och knacka två gånger med dominant hand och en gång med icke-dominant hand.** När pat lärt sig be pat byta till icke- dominant hand (två med icke-dominant hand och en med dominant hand). Be sedan pat växla lugnt från ena sidan till den andra med ojämna mellanrum när du säger byt.
Pat får göra 7 växlingar.

Markera misslyckade försök med kryss: ☐ ☐ ☐ ☐ ☐ ☐ ☐

summa korrekt:____

D.1.4.4 **Inta de här ställningarna med dominant hand (**fig. 7). **Säg samtidigt ”knytnäve, sida, handflata”.** Låt pat göra rörelsen 5 ggr med dominant hand efter några gångers övning tillsammans med tl:

Markera misslyckade försök med kryss: ☐ ☐ ☐ ☐ ☐

summa korrekt domin:____

Gör nu samma sak med icke-dominant hand:

Markera misslyckade försök med kryss: ☐ ☐ ☐ ☐ ☐

summa korrekt i-dom:____

D.3.2.3.1 *Konfliktreaktioner*

Om jag sträcker fram mitt finger ska du visa din knutna hand
och om jag sträcker fram min knutna hand ska du visa ditt finger.

Markera misslyckade försök med kryss:

F	KH	KH	F	F	KH	F	KH	F	KH
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

summa:_____

Total summa samtliga uppgifter: ___/60

10.2 VARDAGSKONSEKVENSER AV TRÖTTHET

Följande frågor gäller din upplevelse av trötthet den senaste månaden.
Dina svar gäller det mest riktiga svaret för flesta av dagar under senaste månaden.
Var snäll och besvara alla frågor.

Hur ofta har trötttheten gjort att Du ...

(a) somnat dagtid eller tidig kvällstid under fysisk inaktivitet (t.ex. vid teven eller på möte)?

Inte under den senaste månaden ____ Mindre än en gång i veckan ____ En eller två gånger i veckan ____ Minst tre gånger i veckan ____

(b) varit tvungen att sova middag?

Inte under den senaste månaden ____ Mindre än en gång i veckan ____ En eller två gånger i veckan ____ Minst tre gånger i veckan ____

(c) gäspat flera gånger under dagen?

Inte under den senaste månaden ____ Mindre än en gång i veckan ____ En eller två gånger i veckan ____ Minst tre gånger i veckan ____

(d) avstått att göra uppgifter som är tankekrävande?

Inte under den senaste månaden ____ Mindre än en gång i veckan ____ En eller två gånger i veckan ____ Minst tre ånger i veckan ____

(e) avstått från fysiskt krävande uppgifter?

Inte under den senaste månaden ____ Mindre än en gång i veckan ____ En eller två gånger i veckan ____ Minst tre gånger i veckan____

10.3 FRÅGEFORMULÄR OM MINNET

Namn:_____

Datum:_____

INSTRUKTION: Kryssa för det alternativet som bäst motsvarar Ditt sätt att vara under den senaste månaden.

	Stämmer inte alls	Stämmer ibland	Stämmer ofta	Stämmer helt
1. Mitt minne är inte vad det varit.	☐	☐	☐	☐
2. Jag glömmer uträtta det jag har planerat	☐	☐	☐	☐
3. Jag kommer ihåg att lämna meddelanden till andra.	☐	☐	☐	☐
4. Jag glömmer var jag lagt viktiga saker.	☐	☐	☐	☐
5. Jag glömmer vad man har sagt mig någon dag tidigare.	☐	☐	☐	☐
6. Jag påbörjar något och glömmer sedan vad det var jag ville göra.	☐	☐	☐	☐
7. Jag har lätt för nya rutiner.	☐	☐	☐	☐
8. Jag glömmer lätt folks namn.	☐	☐	☐	☐
9. Jag har svårt att samla tankarna.	☐	☐	☐	☐

TACK FÖR DIN MEDVERKAN