RECOVERY TIME-COURSE OF BIOMARKERS AND PHYSICAL PERFORMANCE AFTER STRENUOUS MILITARY TRAINING IN MALE SOLDIERS

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ABSTRACT

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Balancing between training induced stress and recovery is important in a military population. If operational capacity is compromised during high-risk operations, consequences may be serious. Recovery has been studied extensively in athletes, but not in military populations. Physiological demands and methods of training are vastly different in these populations. In certain tough military training courses, the training load is very high, with limited capacity to operate in optimal conditions. Thus, it is important to understand recovery in the context of military training courses and populations to optimize the adaptation and training strategies used. This review provides information about the required recovery times from some of the toughest military training courses that have been measured.

The objective of this systematic review was to evaluate the time-course of recovery of biochemical markers and physical performance after strenuous military training and identify which biomarkers have been researched and how they are affected.

A systematic literature search was conducted using the databases MedLine (Ovid) and Web of Science to identify studies up to July 2021. Varying, relevant search terms were used, related to military training, special forces, physical performance, and biomarkers. Records were included according to the strict inclusion and exclusion criteria.

A total of 12 studies fit the inclusion criteria and were selected for this review. A variety of physiological and physical performance markers were measured, and military training length varied from 4 to 62 days, with recovery measurement times varying from 24 hours to 6 weeks. Among these studies, two showed full recovery of variables, seven studies showed almost full (79-90%) recovery, and in three studies, 44-63% of markers were recovered after the recovery period. However, in some studies, more markers could also be considered recovered.

In majority of the studies, most of the measured variables recovered during the follow-up, but commonly some variables remained unrecovered, and sometimes only modest recovery was seen. Therefore, according to the results of this review, it seems that majority of the typically measured markers recover in a relatively short time from sustained extreme and intense stress induced by strenuous physical activity, sleep and food deprivation, environmental extremes, and psychological stress, but in some cases only modest recovery seems to occur. Overall, the recovery time seems to vary between the markers, and sometimes recovery might not occur even after longer recovery times. Therefore, it is important to measure recovery after strenuous training courses to maximize operational capability and optimize periodization of training.

Key words: recovery, military training, performance, biomarkers, stress

TIIVISTELMÄ

Granlund, J. 2021. Fyysisen suorituskyvyn ja biomarkkerien palautumisaika erittäin kuormittavan sotilasharjoittelun jälkeen miessotilailla. Jyväskylän yliopisto, liikuntatieteellinen tiedekunta, liikuntafysiologian maisterin tutkielma. 82 s.

Tasapaino sotilasharjoittelun aiheuttaman kuormituksen ja palautumisen välillä on tärkeää. Mikäli operatiivinen toimintakyky on madaltunut korkean riskin operaatioissa, voivat seuraukset olla vakavia. Palautumista on tutkittu kattavasti urheilijoilla, mutta ei sotilailla, ja fysiologiset vasteet ja harjoitusmetodit ovat selvästi erilaisia näissä populaatioissa. Kovimmissa sotilasharjoituksissa harjoituskuorma on erittäin korkealla, ja operointi tapahtuu hyvin epäoptimaalisissa olosuhteissa palautumisen kannalta. On tärkeää ymmärtää palautumisaikoja sotilasharjoituksista, jotta voidaan optimoida harjoittelun ohjelmointi ja operaatioiden rytmitys. Tämä katsaus tarjoaa tietoa palautumisajoista kovimmista mahdollisista sotilasharjoituksista, joissa sopivia tutkimuksia on tehty.

Tämän systemaattisen kirjallisuuskatsauksen tarkoitus on arvioida eri biomarkkerien sekä fyysisen suorituskyvyn palautumiseen vaadittavia aikoja sekä sitä, mihin tutkittuihin muuttujiin vaikutukset kohdistuvat.

Systemaattinen kirjallisuushaku toteutettiin käyttäen tietokantoja MedLine (Ovid) ja Web Of Science, josta tutkimuksia etsittiin kesäkuuhun 2021 asti. Käytetyt hakusanat liittyivät esimerkiksi sotilasharjoitteluun, erikoisjoukkoihin, fyysiseen suorituskykyyn, ja eri biomarkkereihin. Tutkimukset valittiin tiukkojen sisäänotto- ja poissulkukriteerien perusteella.

Yhteensä 12 tutkimusta valikoitui mukaan katsaukseen. Tutkimuksissa oli mitattu useita eri fysiologisia ja suorituskykyyn liittyviä muuttujia. Harjoitusten kesto vaihteli neljästä päivästä 62 päivään, ja palautumismittausten kesto vaihteli 24 tunnista kuuteen viikkoon. Kaikki mitatut muuttujat palautuivat kahdessa tutkimuksessa. Seitsemässä tutkimuksessa 79–90 % muuttujista palautui, ja kolmessa tutkimuksessa 44–63 % muuttujista palautui. Joitain muuttujia lisää olisi voitu myös tulkita palautuneeksi, riippuen kriteereistä palautumiselle.

Suurimmassa osassa tutkimuksia suurin osa mitatuista muuttujista palautui seurannan aikana, mutta oli yleistä, että jotkin muuttujat eivät palautuneet. Joissain tapauksissa vain noin puolet muuttujista palautui. Katsauksen päätuloksena huomataan, että suurimmassa osassa tutkimuksia palauduttiin erittäin kovasta kuormituksesta suhteellisen lyhyessä ajassa ainakin lähes täysin, mutta joissain tutkimuksissa palautuminen oli selvästi vähäistä. Palautumisaika vaikuttaa olevan melko vaihtelevaa muuttujien välillä, ja joskus palautuminen on vähäistä pidempienkin palautusjaksojen jälkeen. Palautumista olisikin tärkeä arvioida ja mitata erittäin kovien harjoitusten jälkeen, jotta voidaan optimoida harjoittelun jaksotus.

Asiasanat: palautuminen, sotaharjoitus, suorituskyky, biomarkkerit, stressi

ABBREVIATIONS

ANS	autonomic nervous system
PFC	prefrontal cortex
LC	locus coeruleus
SNS	sympathetic nervous system
HPA	hypothalamus-pituitary-adrenal
SAM	sympathetic-adreno-medullar
CRH	corticotropin releasing hormone
SF	special forces
PTSD	post-traumatic stress disorder
SOF	special operations forces
NFOR	non-functional overreaching
FOR	functional overreaching
OT	overtraining
OTS	overtraining syndrome
SERE	survival, evasion, resistance, escape
ACTH	adrenocorticotropin
CNS	central nervous system
NTS	nucleus of the solitary tract
CeA	central nucleus of the amygdala
PL	prelimbic
VTA	ventral tegmental area
NAc	nucleus accumbens
IL	infralimbic
PVN	paraventricular nucleus
DMH	dorsomedial hypothalamus
RVLM	rostral ventrolateral medulla
DMX	dorsal motor nucleus of the vagus nerve
NA	nucleus ambiguus
SFO	subfornical organ

BLA	basolateral nucleus
MeA	medial nucleus
LC-NE	locus coeruleus-norepinephrine system
CBG	corticosteroid-binding-globulin
CRF	corticotropin-releasing factor
AVP	arginine vasopressin
APG	anterior pituitary gland
SCN	suprachiasmatic nucleus
PNMT	phenylethylamine N-methyl transferase
LTP	long-term potentiation
IGF-1	insulin-like growth factor
HRV	heart rate variability
SD	standard deviation
NPY	neuropeptide-y
SF	special forces
DHEA-S	dehydroepiandrosterone-sulfate
BL	baseline
PRISMA	preferred reporting items for systematic reviews and meta-analyses
CK	creatine kinase
T3	triiodothyronine
T4	Thyroxine
TSH	thyroid-stimulating hormone
SHBG	sex-hormone blinding globulin
CRP	c-reactive protein
IGFBP-3	insulin-like growth factor binding protein-3
LH	luteinizing hormone
HGH	human growth hormone
IGFBP-1	insulin-like growth factor binding protein 1
IGFBP-2	insulin-like growth factor binding protein 2
IGFBP-4	insulin-like growth factor binding protein 4
IGFBP-6	insulin-like growth factor binding protein 6

LDH	lactate dehydrogenase
DHEA	dehydroepiandrosterone
BDNF	brain-derived neurotrophic factor
IFN-y	interferon-gamma
IL-1	interleukin-1
IL-4	interleukin-4
IL-6	interleukin-6
IL-8	interleukin-8
IL-10	interleukin-10
TNF-alpha	tumor necrosis factor alpha
TBG	thyroxine-binding globulin
HDL	high-density lipoprotein
PCV	packed cell volume
EPO	erythropoietin
FSH	follicle-stimulating hormone
CMJ	counter-movement jump
FT	free testosterone
CPK	creatine phosphokinase
CK	creatine kinase
MB	myoglobin
AGPA	alpha 1-acid glycoprotein
Hb	hemoglobin
Fe	iron
Hapto	haptoglobin
Cor	cortisol
Dop	dopamine
Ad	adrenaline
PSS	progesterone
AS	androstenedione
PRL	prolactin
ES	estradiol

LA	lactate
GLU	glucose
U	urea
TT	total testosterone
INS	insulin
PV	plasma volume
MBT	medicine ball throw
EVAC	evacuation test
AMPA	alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic- acid
NMDA	n-methyl-D-aspartate
17a-HP	17a-hydroxy-progesterone

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THESIS

For the first part of the thesis, a scientific literature review is presented to examine the physiological theories of human stress reaction, as well as theories regarding adaptation to stress and measuring stress during military field exercises. Understanding the physiological basis of stressors is important for discussing the biomarkers and performance maladaptation during and after strenuous military training. After this, a systematic review concerning recovery time-course of biomarkers and physical performance after strenuous military training is presented, starting from page 31. Understanding recovery time-courses and reactions of variables such as physical performance and biomarkers during and after intense military training is important for optimizing soldiers' preparation for war, and to provide correct time-courses of recovery after strenuous training and operations.

1 LITERATURE REVIEW: INTRODUCTION

During war and sustained high-risk operations, soldiers must be able to keep their performance at a high level while enduring many different physiological and psychological stressors (Szivak 2016). Operational stress is very multi-faceted: it includes cerebral, neuroendocrine, cardiac, and cognitive characteristics (Taylor et al. 2007). Operational tempo can also be high, and special operation forces (SOF) soldiers might be required to deploy 2-3 weeks after a Ranger course (Conkright et al. 2020). Therefore, information about recovery time course after extremely strenuous military training is needed.

When training for extreme and high-risk operations, it is important to take the amount of stress into account and try to train the specific physiological systems that are responsible for enduring stress. For this, militaries around the world have specific training and courses, trying to simulate similar, extreme-stress conditions, with the target of preparing soldiers to operate in real-life conditions (Szivak 2016). In real-life operations stress is extreme due to possible harsh conditions, very demanding sustained operations, lack of sleep and nutrition, and psychological stressors, including the fact human lives and other factors are at stake. The goal is to inoculate the stress response in a controlled training environment, so that positive adaptation occurs in certain physiological systems responsible for such stressors (Szivak 2016). Understanding the physiological responses to this extreme stress, interventions targeting better inoculation can be used and recovery time frames assessed appropriately.

Extremely demanding military training courses, such as the Ranger course and different SERE (Survival, Evasion, Resistance, Escape) courses, aim to train the participants in harsh conditions with high amounts of physical exertion, lack of sleep and nutrition while keeping mission demands high. These training courses are targeted to be analogous to stress imposed by war, captivity, or related events. (Szivak 2016.) To understand and attempt to improve the stress response to extreme psychological and physical stress, it is first needed to understand the physiological demands placed on soldiers during these training courses and real-life operations. This sort of structured nature of training provides a unique way to examine the human stress response and performance in a operational military context (Szivak 2016).

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2   HUMAN STRESS REACTION

"Stress" could be defined in short as: "Stress is the response of the body to any demand" (Fink 2016). A strictly biological definition could be: "Stress is any stimulus that will activate the hypothalamic-pituitary-adrenal (HPA) system, thereby triggering the release of pituitary adrenocorticotropin (ACTH) and adrenal glucocorticoids and the sympathetic-adreno-medullar (SAM) system with the consequent release of adrenaline and noradrenaline" (Fink 2009). Joëls & Baram (2009) call stress the "subjective state of sensing potentially adverse changes in the environment". A "stressor" is defined to be any actual or potential disturbance of an individual's homeostasis and environment (Joëls & Baram. 2009). Today, there is also substantial amount of literature that shows that stress reactions are specific to the type of the stressor (Fink 2016).

Stress influences many physiological and psychological processes (Giles et al. 2014). The response to stressful stimulus is generated by the stress system (Figure 2), which operates through many different brain structures that together interpret events as either an actual, real threat or a threat interpreted potentially. (Dedovic et. al 2009). After the perception of potential or real threats, mediating molecules are released. Interaction of these certain molecules and certain receptors in the brain and periphery activate the stress response, which promotes adaptation and restores homeostasis through physiological and behavioral mechanisms (Godoy et al. 2018).

When the body is under threat, the stress response functions to serve a better chance of survival and activates different hormonal and neural systems to optimize metabolic, cognitive, cardiovascular, and immunological function. (Russell & Lightman. 2019.)   The adaptation to environment must be done continuously, as many different physiological and psychological stressors continually threaten homeostasis (Szivak 2016). Various factors impact the magnitude and pattern of the stress response (Figure 1), which include: duration of exposure (chronic or acute), type of stress (psychological vs. physical), context of the stress, developmental stage (age), sex and genetic background (Joëls & Baram. 2009). This means that stress situations seem to be somewhat unique, and in response to a stressor, many different mediators address stressors specifically. Mediators include, for example, steroid hormones, neuropeptides and

catecholamines. The duration of the stressor is also a main influencer of the magnitude of the stress response. Acute stressors cause a fast action of neurotransmission, activation of neurons and release of hormones, which are followed by a fast return to normal levels. However, temporary activation of certain neurons can lead to modifications in the expression of genes, which could change consecutive neuronal responses. Opposite to this, chronic (longer than 1 week) stress can provoke sustained and/or progressive alterations in certain gene-expression, structural modifications in neurons and alterations in firing patterns of neurons in the brain, which if persistent, can result in alterations that are prolonged from the networks normal functioning. (Joëls & Baram. 2009.)
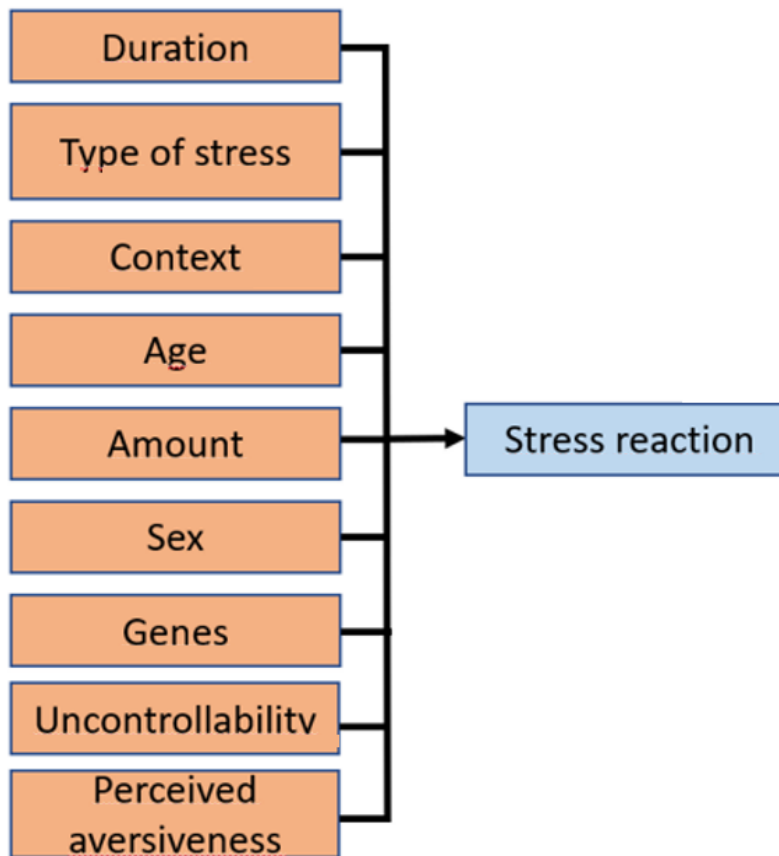

FIGURE 1. Factors affecting the stress response. Adapted from Joëls & Baram. (2009) and Kim & Diamond. (2002).
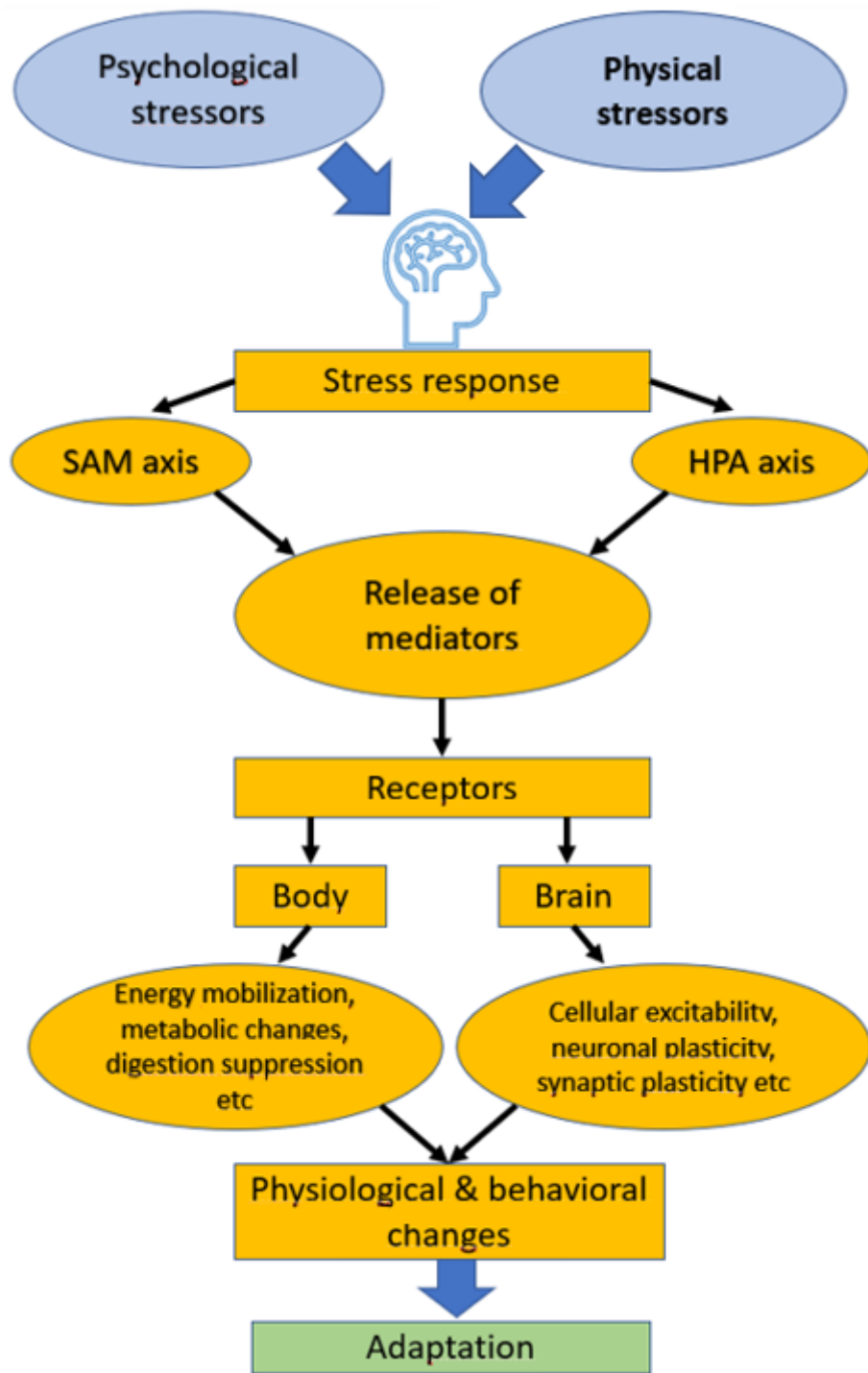
FIGURE 2. The neurobiological stress system. Adapted from Godoy et al. (2018).

As figure 2 shows, the processing of stressful situations involves engagement from different complex mechanisms, integrating brain and body. Various brain structures are also involved. Depending on the type of the stressor, perception of it involves different networks. When a stressor is identified, happens the activation of the two main components of the stress system: SAM axis and HPA axis. The SAM secretes adrenaline and noradrenaline, and the HPA secretes glucocorticoids. Once these systems activate when faced with a stressor, they provoke a response that is coordinated and that starts rapidly within seconds. The response can last for a shorter or a longer time depending on the type of the stressor, and it works to provide a response to restore homeostasis. For the restoration of homeostasis to happen, stress response systematically promotes certain metabolic changes, energy mobilization, activation of the immune system and suppression of the reproductive and digestive systems. In the brain, the response to stress generates shorter and longer-term effects through epigenetic, genomic, and non-genomic mechanisms. The central effects, combined with proinflammatory signals, cause changes in the excitability of cells, and neuronal and synaptic plasticity. With these effects concerning the brain and the whole body, the stress system mediates adjustments in physiology, and also in behavior that enable the situational adaptation and therefore improve chances for the survival of the human body. (Godoy et al. 2018.)

2.1   How the brain processes stress

When facing a stressor, the first step is the perception of it. Neural response to stress involves a system that is complex, and adjustments occur in various grades of the central nervous system (CNS) controlling, for example strategic decision and learning. (Godoy et al. 2018.) When something, for example a situation is considered to be a threat, the brain can recruit different circuits of neurons to maintain physiological composure even when faced with the most unfavorable conditions (Ulrich-Lai & Herman. 2009). Detection of different psychological and physical stressors happens through diverse neuronal networks and cell-level activity. (Godoy et al. 2018.) Stressors that are of a different type activate responses that are also different. For example, physical stressors such as the loss of blood, different kinds of bodily trauma and environmental stress recruit mainly the brainstem and hypothalamic regions of the brain. Differently, psychological stressors, such as examinations and embarrassment socially seem to engage primarily the amygdala, prefrontal cortex (PFC) and hippocampal areas. These are

responsible for subserving emotion, memory, learning and making decisions. These systems are not completely separated, and stressors often have both: physical and psychological aspects. (Joëls & Baram. 2009.)

Physical stressors are stimuli that threaten the actual physiological status of the body, overwhelming the organism, such as infections and hemorrhage (Dayas et al. 2001). Psychological stressors are physical and social circumstances that challenge the organism's capabilities and resources for adaptation. These circumstances can be a wide array of different situations, which possess both specific and common psychological and physical attributes (Monroe & Slavich, 2016). In general, psychological stressors are defined to be stimuli that threaten the homeostatic state and can also be perceived anticipatorily. (Dayas et al. 2001). Psychological stressors are for example, experience of interpersonal loss and social rejection (Monroe & Slavich, 2016), cues related to predators, and failure to satisfy drives that are internal (Dayas et al. 2001). Regarding different situations and desirability of events, there is considerable individual variability when responding to stress – first, what someone might experience as being undesirable, someone else might experience to be desirable. Second, even under conditions that are extremely stressful, not all animals or individuals "break down". Factors such as experience, coping responses, and attributes of the experimental and social context have been found to moderate the effects of psychological stressors. (Monroe & Slavich, 2016.)

Stressors are also specific, as Pacak & Palkovits (2001) found that different stressors, such as cold exposure, hemorrhage, pain, or hypoglycemia had different neurochemical signatures. It also seems that the trace of neural activation that is caused in the brain by stressors could be of use when determining the category of the stressor, at least when determining between physical and psychological stressors (Dayas et al. 2001). Therefore, whether reacting to a physical or psychological stressor, the brain will process these through different circuitries, and also overlap is possible during some instances. In any event of processing, the stress system is activated in a coordinated way as shown in Figure 3. (Godoy et al. 2018.)
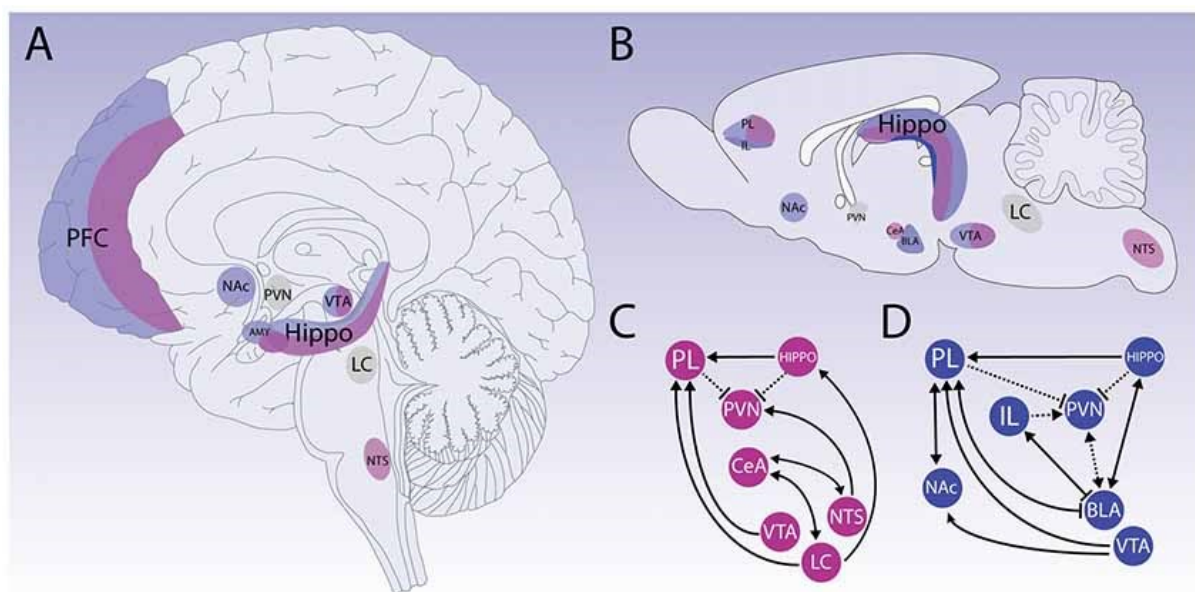
FIGURE 3. (Godoy et al. 2018). The primary neuroanatomical areas that are responsible for psychological (blue) and physical (pink) stressor processing. A, B represent the structures that are engaged to neural processing when different types of stressors are detected. C, D represent how physical and psychological stressors engage different networks. (Godoy et al. 2018.)

Physical stressors mainly activate structures located on brainstem and hypothalamus, that are related to controlling of vital functions. These structures are for example the nucleus of the solitary tract (NTS) and the locus coeruleus (LC), which both have important contributions in the pathways of physical stress responses. Also, certain regions in the forebrain participate in the processing of physical stressors, for example the prelimbic area (PL) in the PFC. The central nucleus of the amygdala (CeA) has a role in autonomous responses and the integration of them, which is important when the perception of psychological stressors happen anticipatorily, because these stressors may rely heavily on structures of the limbic system, and also modulation by the reward system is possible. The PFC works in developing correct responses to environmental alterations and is innervated densely by projections of dopaminergic type from the midbrain's structure ventral tegmental area (VTA), and the nucleus accumbens (NAc), which is in the basal forebrain. Although the PFC is involved in complex way and can integrate varying and different responses to stress, infralimbic (IL) and PL regions coordinate a control that is considered to be top-down. Also, the amygdaloid complex has a role on stress circuitry

of psychological type, and if the PFC is disrupted the amygdala will be more involved, and the circuitry becomes a bottom-up control. An important structure that is relevant for cognitive and memory function is the hippocampus, which is activated in response to both types of stressors, psychological and physical ones. Its CA1 region is important for connections with limbic structures, and the hippocampus itself is an important structure in the negative feedback loop of the HPA axis. Hypothalamus's paraventricular nucleus (PVN) and LC, which are shown in gray in figure 3, picture the main forward-transmitters of the stress response triggering the SAM and HPA axes. Crosstalk between these nuclei allow the processing of the stress response cognitively and enable responses of complex behavioral nature. (Godoy et al. 2018.)

2.1.1 How the brain processes physical stressors

Physical stressors usually require immediate systemic reaction, and their processing happens mainly in the hypothalamic regions and brainstem (Ulrich-Lai & Herman. 2009). Therefore, in the so-called "first phase" of the stress response, the SAM axis is activated by synaptic mechanisms, and it enables a fast physiological adaptation, which results in quick, mainly responses that are short-lasting, such as increased vigilance, alertness, and situational appraisal, therefore enabling the making of a strategic decision in facing the challenge when met with a stressful event (Joëls & Baram. 2009.) After this, the "secondary phase" involves the HPA axis which is responsible for the hormonal mechanism that are both short and long-lasting (Godoy et al. 2018).

Therefore, when the brainstem recognizes or perceives a stressor, neurocircuitry which includes activation of hypophysiotrophic neurons and autonomic neurons of preganglionic sort in the PVN, which can generate quick responses in the autonomous nervous system (ANS) and HPA axis (Godoy et al, 2018).

Along with various nuclei of the brainstem, spinal cord and medullary systems which have a role in the ANS activation through parasympathetic and sympathetic arms, also other brain structures are activated when physical stressor is perceived. These include the dorsomedial hypothalamus (DMH), PVN, and NTS. (Godoy et al. 2018.)

The PVN includes neurons projecting to targets in the spinal cord and brainstem that are autonomic, and to a part of hypothalamus called median eminence. Therefore, PVN also has a role in sympathetic outflow (Godoy et al. 2018). Another important nucleus in the hypothalamus is the DMH, which has a role in regulating autonomic responses and activates or inhibits activity of the HPA axis (Ulrich-Lai & Herman. 2009).

The rostral ventrolateral medulla (RVLM) and LC innervate the intermediolateral cell column, as the nucleus ambiguous (NA) and dorsal motor nucleus of the vagus nerve (DMX) mediate outputs that are descending, for the postganglionic parasympathetic nervous system (Godoy et al. 2018).

The NTS located in the brainstem also plays a major part in the pathways related to stress, as it is directly involved in cardiovascular and respiratory functions control (Zoccal et al. 2014). It also seems to modulate the HPA axis activation mainly by adrenergic and noradrenergic projections to the PVN (Godoy et al. 2018).

Other structures that are important for starting the stress response are the circumventricular organs, such as the subfornical organ (SFO) and median preoptic nucleus that respond to disruptions in for example fluid status and regulation of blood pressure (Goody et al. 2018). For example, when medial parvocellular PVN by SFO is activated, it can have a role in regulating for example drinking behavior (Simpson & Routtenberg. 1975) and increases in blood pressure (Mangiapane & Simpson, 1980).

It might also be possible that certain limbic forebrain areas also contribute to the processing of physical stressors, influencing the HPA-axis activation and other autonomic responses. Stress circuits that are limbic would involve the prefrontal cortex, amygdala, and hippocampus, and they receive information of associational nature from cortical and subcortical areas. (Ulrich-Lai & Herman. 2009.)

2.1.2   How the brain processes psychological stressors

As physical stressors are more likely to elicit stress responses that are autonomic, psychological, for example stressors that are uncontrollable and social-evaluative threatening can cause both cognitive and also physical responses (Skoluda et al. 2015). In this stress response regulation, the prosencephalic nuclei, parts of limbic circuits such as the amygdala, PFC, hippocampus, PVN, VTA and NAc have an essential role (Ulrich-Lai & Herman. 2009).

PFC has an major role also in developing of correct responses to environment changes, and it enables plasticity in behavioral responses (Ridderinkhof et al. 2004). Its involvement is, however, complex, as different anatomic subdivisions have different roles (Godoy et al. 2018). The bilateral lesions of prelimbic cortex portion can increase the levels of ACTH in plasma, corticosterone (Dioro et al. 1993) as well as PVN c-Fos expression (Figueiredo et al. 2003). In contrast, infralimbic cortex lesions can function in the reducing of secretion of corticosterone (Sullivan & Gratton. 1999). Animal studies have shown that dorsal sites of PFC induce effects that are anxiogenic (anxiety-inducing), but ventral sites can induce effects that are anxiolytic (anxiety-relieving) (Sullivan & Gratton. 2002). This could indicate that IL and PL induce contrary effects in psychological stress response, as PVN activity would be stimulated with anxiogenic behaviors and inhibited with anxiolytic effects (Radley et al, 2006). Although the PFC and PVN are functionally connected, the exact pathways between seem to be unclear (Bains et al. 2015).

Also, the PFC can project to the amygdala, which is a complex, important structure in managing emotional information and especially the intensity of emotions (Bonnet et al. 2015). The amygdala has distinct roles when responding to stress (Roozendaal et al. 2009). The amygdala complex can be divided to the CeA, the basolateral nucleus (BLA), and the medial nucleus (MeA) (Godoy et al. 2018). Of these, the BLA is majorly responsible for the processing of psychological stressors (Janak & Tye. 2015), and its role seems to be important in the consolidation of memories that are aversive (Roozendaal et al. 2009). It is mainly activated by stressors that are anticipatory (Cullinan et al. 1995). It does not, however, itself affect corticosterone release (Seggie 1987). The BLA has monosynaptic projections with PFC, which

are crucial, for example, to emotional learning (Laviolette & Grace. 2006), anxiety behaviors and social interactions (Felix-Ortiz et al. 2016). The activity of BLA in context of stress response is also likely to be mediated between amygdala and PVN (Prewitt & Herman, 1998). The BLA also can output to the MeA and CeA, which innervate structures of the brainstem that project to PVN. PVN projections to CeA seem to be activated during long-term fear memory retrieval. (Godoy et al. 2018.) Retrieval of memories that are short-term depends mostly on PFC connections to the BLA, which indicates a shift that is time-dependent in circuits of memories concerning fear (Do-Monte et al. 2015). The CeA also connects to areas that organize the response to threats (LeDoux 2012).

The hippocampal formation is also an important structure for stress processing (McEwen et al, 1968). It has control of inhibitory type to the HPA axis, and acts in a manner of negative feedback (Jacobson & Sapolsky. 1991). Projections from the hippocampus to the PFC and BLA have an important role in regulation of the stress response, as well as in memory (Godsil et al. 2013). Some of the efferents can become disrupted functionally after psychological stress that is severe (Zheng & Zhang. 2015). When experiencing emotional reaction that is strong enough, the hippocampusand BLA activate mechanisms of synaptic plasticity that are memory related while the function of PFC is suppressed, therefore promoting long-lasting and detailed "flashbulb" memories (Diamond et al. 2007).

Therefore, when psychological stressors are present, if the activity of the hippocampus and amygdala increase, the stress system switches to a control considered bottom-up (Arnsten 2009). When psychological stress is prolonged, it can decrease glutamatergic projections to BLA, which can lead to lack of inhibition of BLA by the PFC, leading to BLA hyperexcitability, which is partly responsible for stress-related behavioral abnormalities (Wei et al. 2017).

The PVN, along with some hypothalamic nuclei involved directly in the HPA axis regulation and autonomic responses to stress, seems to be the major integrator of stress signals (Ulrich-Lai & Herman. 2009). Certain neurons of the PVN are connected with various nuclei of the forebrain and brainstem, which makes quick activation of the HPA axis possible. These

connections are important for the integration and processing of both psychological and physical stressors (Senst & Bains. 2014).

Despite the brainstem and forebrain areas having a major role in responsibility for physical and psychological stressors, also some other structures and circuits, for example the reward circuit and its dopaminergic neurons are activated with different types of stressors. Different projections also affect different responses: for example, hippocampus projection to NAc can promote susceptibility to social-defeat stress, and the pathway of BLA-NAc can increase behavior considered reward-seeking and PFC-NAc can promote resilience (Godoy et al. 2018)

For an example of important crosstalk between different structures, the LC-Norepinephrine system (LC-NE) is activated by disparate modalities of stressors that also activate the PVN. For example, restraint, unpredictable shock, audiogenic, and immunological stressors can cause this (Wood & Valentino. 2016). The LC includes most of the neurons expressing norepinephrine in the brain and has innervation to the the whole neuraxis (Swanson & Hartman, 1975). The LC-NE activation occurs coordinated and in line with the activation of PVN, which allows to process the stress response cognitively, with engaging prosencephalic and limbic regions. For example, the cortex and the hippocampus, which are responsible for memory, neuronal excitability, cognition and other complex behaviors (Wood & Valentino, 2016). The LC-NE also seems to have an important role for anxiety-like behavior that is stress-induced (McCall et al. 2015). Between these two systems, it seems that corticotrophin releasing hormone (CRH) is the molecule that coordinates the crosstalk (Valentino & Van Bockstaele. 2008). CRH targets the LC-NE, and during stress, CRH is released to the LC, which increases the firing rate of neurons and release of NE in targets in forebrain areas (Jedema & Grace, 2004). Also, the basal levels of corticosteroids seem to regulate CRH release within LC (Valentino & Van Bockstaele 2008). As the release of CRH in the LC during stress seems to facilitate attention shifting between stimuli that is different (Snyder et al, 2012), the communication between the LC-NE and HPA axis determine the structural basis for emotional arousal, cognitive facilitation, and promotion of behavioral responses to stress that are flexible (Valentino & Van Bockstaele 2008). Therefore, the crosstalk between them enables the tailoring of diverse strategies when coping with environmental challenges that are constantly changing (Godoy et al. 2018).

2.2 The stress systems: the SAM & HPA axes

When the stressor is perceived and organized by the brain, the stressful challenge is compared with previous experienced stress (Fink et al. 2016). When faced with a stressor, various hormones are secreted from the adrenal glands (Sand et al. 2014). When a stressor is detected to challenge the homeostasis, the ANS is activated by the brain, which can trigger the first phase of stress reaction through the SAM system. This leads to release of catecholamines from the adrenal medulla which prepare the human body to take on actions when reacting to the stressor. Simultaneously, responsible for also the longer lasting stress response, also the HPA axis is activated, which releases the adrenal glucocorticoid, cortisol. Increased levels of glucocorticoids can acutely improve the human body's resistance and adaptation to stress. (Fink 2016). In general, the SAM axis is considered to be responsible for effects that are short-term and responses that are rapid, while the HPA axis is responsible for both short and long-term effects (Tank & Lee Wong. 2015). Both of these systems function cooperatively and/or sequentially (Godoy et al, 2018).

2.2.1 Overview of the adrenal glands

Adrenal glands have a major role in physiological stress response, as important steroid hormones and catecholamines are synthesized and secreted from them. The adrenal glands are located above the kidneys (Figure 4). There are two adrenal glands, and they weigh approximately 4 grams each. The whole adrenal glands are surrounded by connective tissue, the renal fascia. Both glands have two parts which are endocrine glands: the cortex and the medulla. Portion of the cortex is approximately 90% of its whole weight. The adrenal cortex is yellowish in color, since the cells inside contain a lot of cholesterol. (Sand et al. 2014.)

The adrenal medulla (Figure 4) is developed from autonomic nervous system cells. Therefore, it is almost like a ganglio of the sympathetic nervous system, but different in that its post-ganglionic cells do not have axons (Sand et al. 2014). It is densely populated by the chromaffin cells, which allow rapid transmission of sympathetic nerve impulses (Kraemer & Rogol 2005;

Szivak 2016). The adrenal medulla is responsible for catecholamine production and secretion (Sand et al. 2014).

Hormones produced by the adrenal cortex are steroids, and they are called corticosteroids, which are vital to life. The adrenal cortex has three different functional levels, which produce different corticosteroids: mineralocorticosteroids from the outermost layer, glucocorticoids from the middle layer, and weak androgens from the innermost layer. All of these are produced from cholesterol. The most relevant corticosteroids in the context of stress are the glucocorticoids. (Sand et al. 2014.)
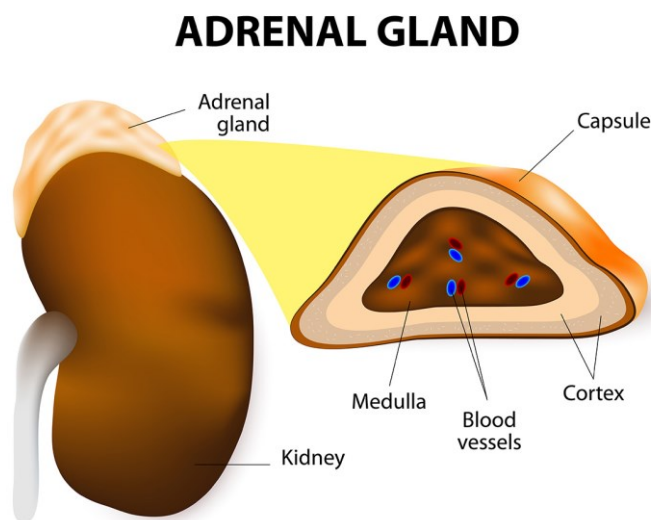
FIGURE 4. Anatomy of the adrenal gland. Picture: Johns Hopkins Medicine.

2.2.2   The SAM axis, release of catecholamines

Catecholamine excretion happens from the adrenal medulla chromaffin cells, and their secretion is low when in normal state. However, stimulation of the preganglionic sympathetic neurons that connect to the adrenal medulla can increase secretion rapidly, which happens when sympathetic nervous system activates when faced with a physical or psychological stressor. (Sand et al. 2014.) Sympathetic branch of the ANS activation dominates during conditions that

are perceived as a stressor, such as fight-or-flight reactions and exercise, and parasympathetic is dominant while under conditions that are considered to be resting (McCorry 2007).

Synthesis of catecholamines (Figure 5) in the adrenal medulla is controlled by the amino acid tyrosine in the serum. Tyrosine is received from nutrition, or it is converted from phenylalanine in the liver (Litwack 2018). Tyrosine is hydroxylated to form dihydroxyphenylalanine, which decarboxylates to dopamine. When forming noradrenaline and adrenaline, dopamine further hydroxylates to noradrenaline, which can be secreted to the bloodstream or further modified by methyltransferase to create adrenaline and then be secreted. Glucocorticoids also upregulate methyltransferase activity, therefore increasing adrenaline production. Catecholamine degradation happens through monoamine oxidase and/or catechol-o-methyltransferase, which both catabolize adrenaline and noradrenaline to vanillylmandelic acid, and dopamine to homovanillic acid. These acids are then broken down by liver and kidneys and excreted in urine. (Paravati et al., 2021.)
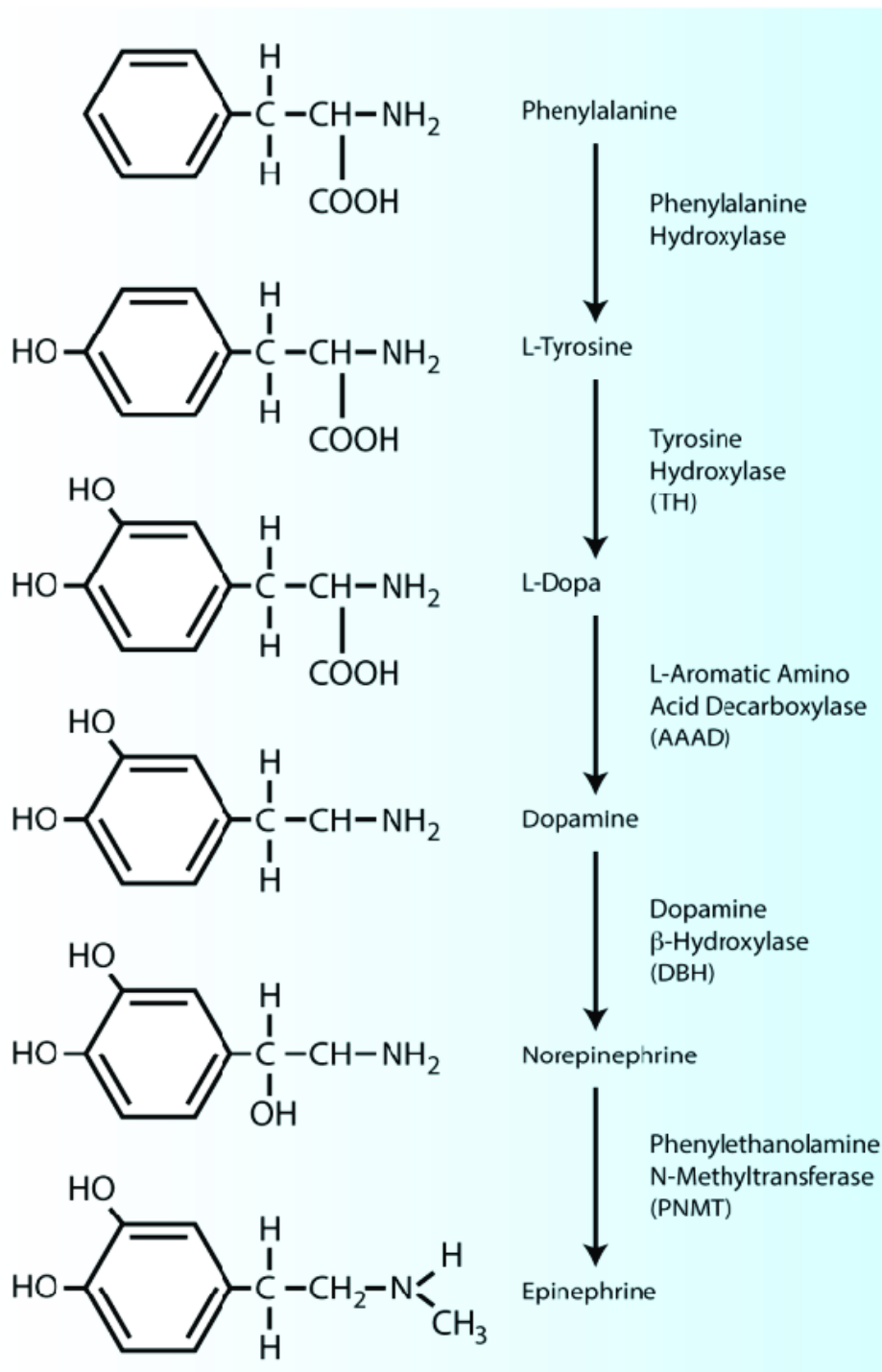
FIGURE 5. Biosynthesis of catecholamines. Végh et al. (2016).

Adrenaline and noradrenaline are the main component mediating the rapid physiological adaptation that occurs in response to physical and psychological stressors (Tank & Lee Wong, 2015). They act as hormones and neurotransmitters that are vital to homeostasis maintenance through the autonomic nervous system (Paravati et al. 2021.) Catecholamines, for example, increase blood pressure and cardiac output, move blood away from the gut and skin to skeletal muscle, split glycogen, and trigger the release of glucose from the liver into the blood stream (Fink, 2016). They are produced in the adrenal gland's adrenal medulla (Figure 4), with 80% of production being adrenaline and 20% noradrenaline (Sand et al. 2014). They circulate freely in the blood for only a few minutes, then they are spliced in the liver and kidneys. Release happens when the sympathetic nervous system is activated. (Sand et al. 2014.)

Dopamine is also technically a catecholamine and present in the adrenal medulla, and it works as an intermediary in adrenaline synthesis. While dopamine is chemically classified as a catecholamine, and it does have synthesis in the adrenal medulla, it is typically not discussed in the same context of adrenal physiology as adrenaline and noradrenaline are. Majority of dopamine is produced in the brain, and considering the dopaminergic pathways, it has major implications on cortical neurophysiology. (Paravati et al. 2021.) Dopamine is released in the PFC during moderate stress, and it is thought to improve decision strategies and assessment of risk. Serotonin seems to have a post-stress anxiety reducing effect (Joëls & Baram. 2009).

The effects of adrenaline and noradrenaline extend to most tissues and cells. They work by binding to adrenoreceptors of the target organs cell membrane. There are two categories of adrenoreceptors: alfa-adrenoreceptors and beta-adrenoreceptors. (Sand et al. 2014.) The rise in circulating adrenaline and noradrenaline cause physiological changes of general sort, so the body is prepared for the so-called "fight-or-flight" reaction (Cannon 1915). Primarily the raise in catecholamines have metabolic effects that are relevant during high stress, arousal, or excitement (Szivak 2016). For example, effects include maintaining alertness, metabolic actions, increased oxygen consumption and cardiovascular actions (Aires 2012; Godoy et al. 2018). Most of the important effects (Figure 6) are caused by the catecholamine adrenaline. (Sand et al. 2014.)
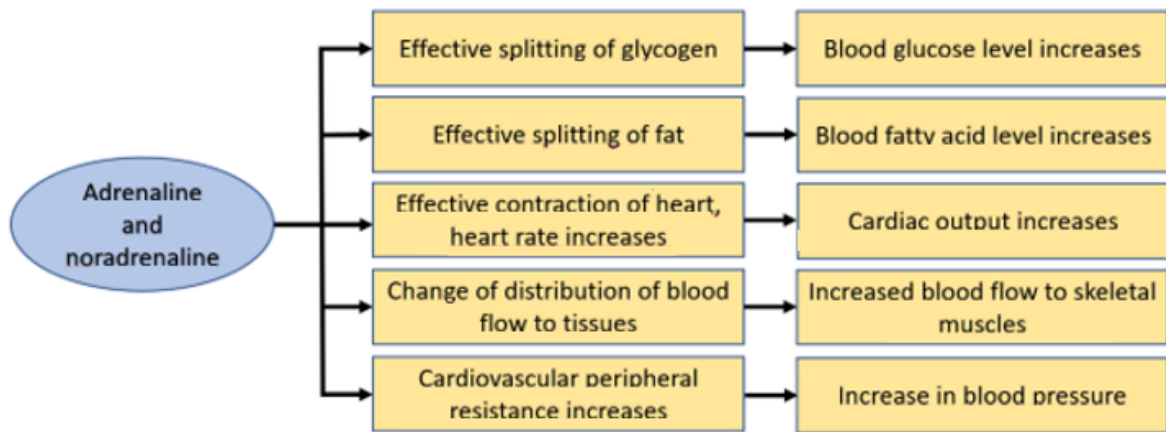
FIGURE 6. Main effects of catecholamines adrenaline and noradrenaline during the stress response. Modified from Sand et al. (2014). With the effects of catecholamines the human body is ready to rapidly adapt to stressors.

The acute catecholamine response is timely almost immediate (Kraemer & Rogol 2005; Szivak 2016). When in a normal state, adrenaline concentration in the blood is negligible. The half-life is very short as described previously, but when under training stress, adrenaline may be elevated for up to 5 minutes post-exercise (Nussey & Whitehead. 2001; Szivak 2016).

The responsible brain circuitry for these autonomic modulations and activation of the SAM axis includes projections from PVN, LC and RVLM to pre-ganglionic sympathetic neurons in the spinal cord (Ulrich-Lai & Herman. 2009). The pre-ganglionic fibers connect with wide array of neurons of post-ganglionic type located in sympathetic paravertebral nuclei or pre-spinal ganglia (Boron & Boulpaep. 2009). Some pre-ganglionic neurons make synapses directly with the adrenal medulla's chromaffin cells (McCorry 2007). Especially, the LC seems to have an important role when responding to stressors that are acute (Myers et al. 2017). However, if activated chronically, it is possible that activation of the LC can have a role in the developing of certain pathological behaviors that are stress-related (George et al. 2013, Reyes et al. 2015).

For chronic adaptations, there seems to be a training effect in the catecholamine response to stress (Szivak 2016). Even though the adrenal medulla is only approximately 10% of the total adrenal gland weight, it can hypertrophy in response to chronic exercise, which leads to

increased capacity of adrenaline secretion during maximum intensity training (Szivak 2016). It also seems that when these adaptations happen, individuals have decreased catecholamine response to submaximal work, but increased response to maximal exercise stress (Kraemer et al. 2015; Szivak 2016). This might mean that for a trained individual, submaximal workloads do not represent enough stress that release of more catecholamines would be needed.

2.2.3 The HPA axis, release of glucocorticoids

Produced in the adrenal cortex middle and inner layer, glucocorticoids derive their name from their effect to glucose metabolism. The most important glucocorticoid is the cortisol, which circulates in blood freely, and it also binds to corticosteroid-binding-globulin (CBG). Cortisol exerts its effects through free cortisol molecules. (Sand et al. 2014.) Effects of cortisol include promoting fat and protein breakdown, and glucose synthesis. It is responsible for regulating and supporting many important metabolic, cardiovascular, immunologic, and homeostatic functions. (Thau et al. 2021.)

During the stress response, when the HPA axis is activated, this activation leads to the release of cortisol (Figure 7). Cortisol excretion is governed by ACTH which is excreted from the anterior pituitary gland. ACTH excretion is controlled by the hypothalamus, which produces ACTH freeing CRH from the PVN, which is also called corticotropin-releasing factor (CRF) and corticoliberin. The secretion of CRH is potentiated by arginine vasopressin (AVP) release from the supraoptic and paraventricular nuclei. CRH signals the pituitary to secrete ACTH, and ACTH secretion signals the adrenal cortex to synthesize and excrete cortisol. (Sand et al. 2014, Szivak 2016, Russell & Lightman. 2019.) Free cortisol has a negative feedback effect, so when high cortisol concentrations are detected in the blood, the feedback loop inhibits HPA activity, effecting the hypothalamus, pituitary gland and other brain structures, such as the hippocampus which is important in inhibiting the HPA axis, effecting pituitary gland ACTH-excretion and the excretion of CRH (Dallman et al. 1994,Russell & Lightman 2019, Godoy et al. 2018, Sand et al. 2014). However, when under heightened stress or circadian patterns release time, this negative feedback can be overridden (Szivak 2016).
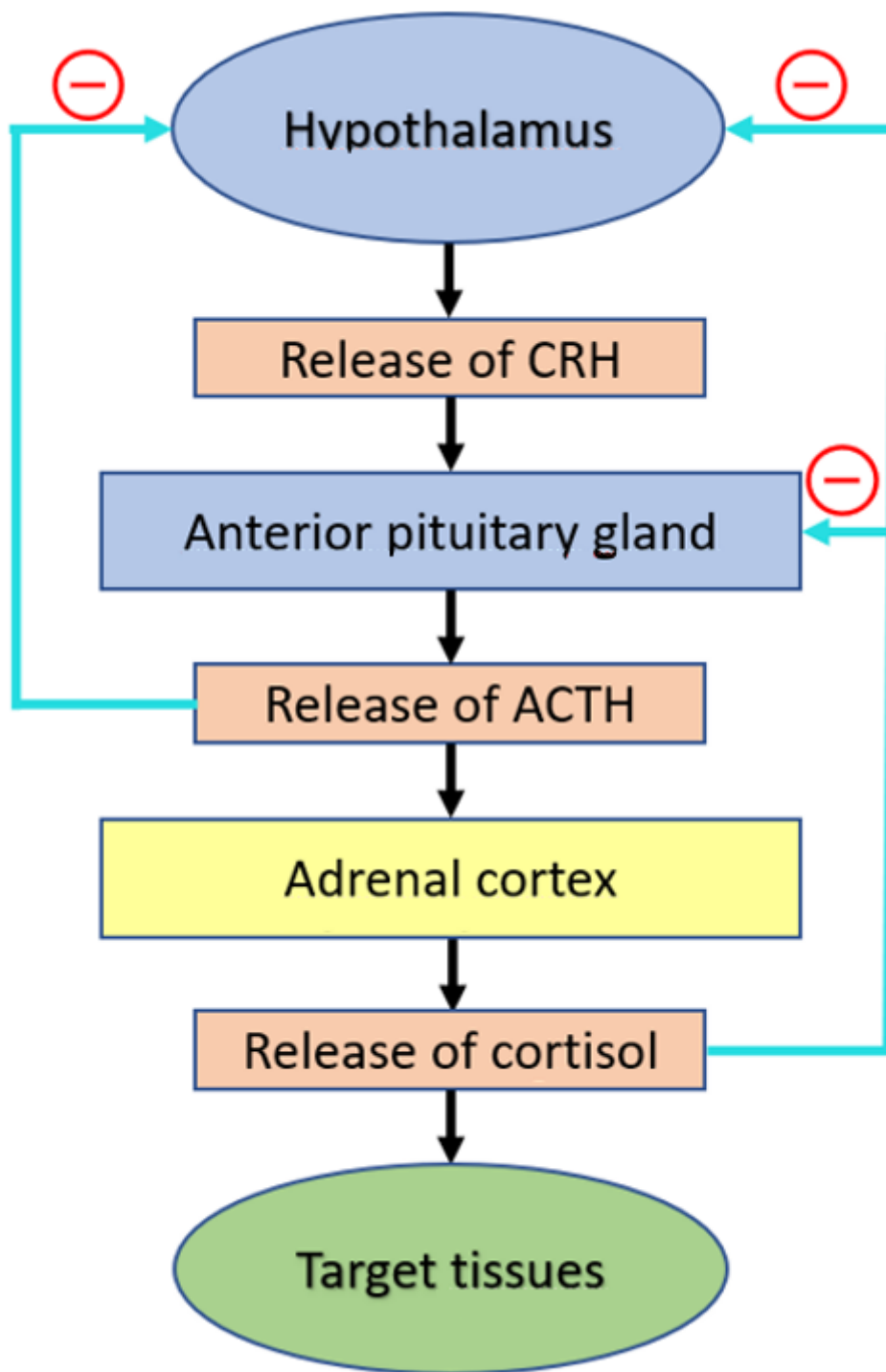
FIGURE 7. HPA-axis and the release of cortisol. Hypothalamus releases CRH which stimulates the APG to release ACTH. When ACTH is released from the APG, it is released to circuit in the blood, and when it reaches the adrenal cortex, it stimulates cortisol production. Cortisol is synthesized and released to circulation, from where it travels to its target tissues and produces

its effects. Negative feedback loop is pictured in light blue. (Sand et al. 2014.) The negative feedback system prevents over-secretion of cortisol, a state called hypercortisolism (Kraemer & Rogol 2005; Szivak 2016).

As opposed to catecholamines, when in normal conditions, cortisol does have a circadian pattern of secretion. Basal cortisol levels are at their highest moments before waking, which is followed by a stable decline during the day to the lowest levels during sleep. This rhythm is coordinated and regulated by projections that are indirect from the SCN to the PVN, which can inhibit CRH release during inactive phase of cycles. When reacting to psychological and physiological stressors, the limbic system and brainstem also regulate the HPA activation with projections to the PVN. (Russell&Lightman. 2019.) This circadian rhythm also means that when measuring cortisol, it is very important to consider the timing of the measurements to ensure reliability.
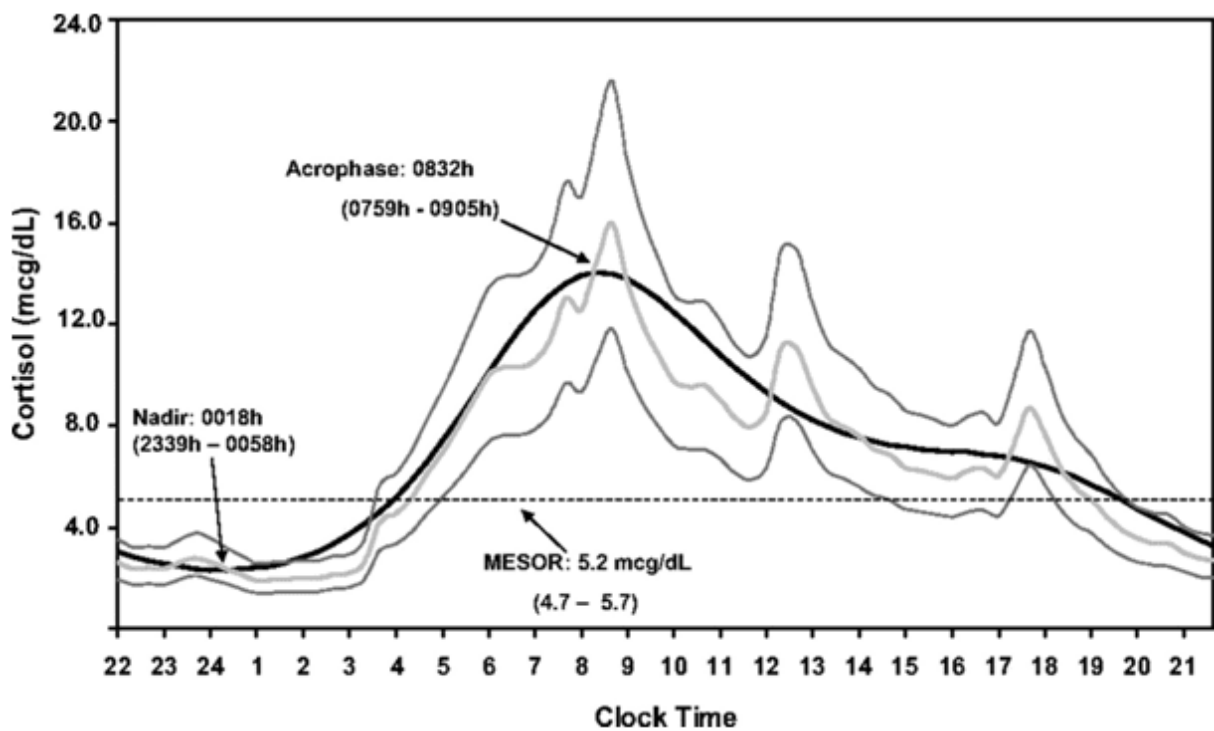
FIGURE 8. Cortisol circadian rhythm over 24 hours. Peak 15.5 µg/dl at 08:32 hours, and trough of less than 2.0 µg/dl at 00:18 hours. (Grossman, 2010.)

Cortisol is often described as a somewhat negative hormone since it has catabolic and immuno-suppressive effects. It is often linked to disrupted states such as overreaching, overtraining, and chronic stress. However, cortisol is important for proper regulation and function of the body, especially during periods when stress is high. (Nussey & Whitehead 2001; Szivak 2016). Cortisol has a long half-life of 66 minutes in normal hormonal levels (McKay & Cidlowski. 2003).

Cortisol is synthesized from cholesterol along with other major steroid hormones that are produced in the adrenal cortex. The synthesis pathway is illustrated in Figure 9.
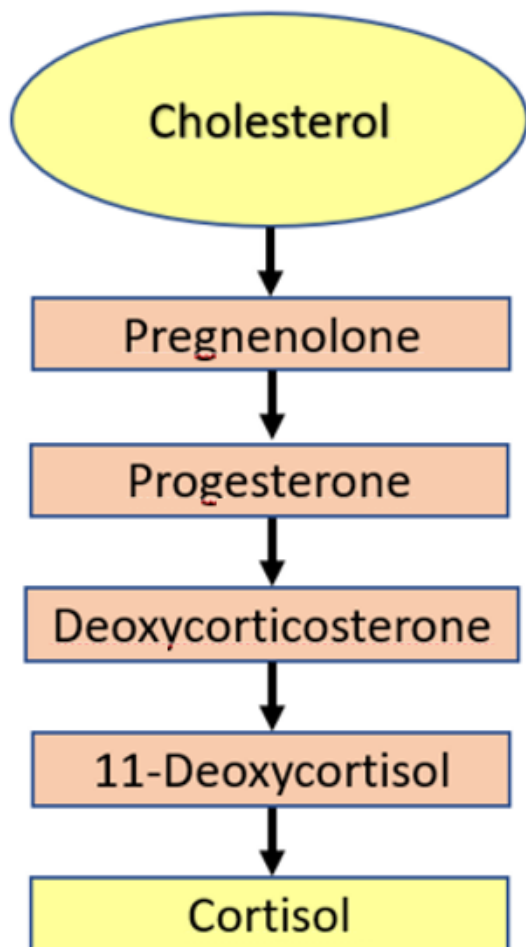
FIGURE 9. Cortisol biosynthesis, adapted from Peake (2003).

Cortisol receptors (glucocorticoid receptors) are typically located inside the cell cytoplasm, but cortisol can also bind to membrane receptors, especially when cortisol's transport protein cortisol-binding globulin acts with cell surface receptors (Szivak 2016).

Cortisol excretion is increased in all stress reactions, and its main function is the regulation and conservation of blood glucose. It affects all cells of the body and has many different effects. Major effects are: 1. Cortisol works as an important stress hormone, mainly by increasing blood glucose levels, which ensures the energy demands of different tissues during increased stress. The way cortisol increases levels of glucose in the blood, is by stimulating protein and fat breakdown, which increases blood amino acid and fatty acid concentrations. Amino acids are used to build glucose in gluconeogenesis. The usage of fatty acids as energy increases, so use of glucose is conserved. This way, cortisol raises the level of glucose in the blood and increases tissues glycogen storages. This effect is also called cortisol's "anti-insulin-effect". If this effect stays elevated chronically, it can lead to catabolic effects in muscle and bone tissues. 2. During stress, cortisol inhibits DNA-synthesis and increases protein breakdown in many tissues and thus its effects are catabolic. When under stress, cortisol regulates energy demands away from anabolism, and instead ensures cells energy production. (Sand et al. 2014.) When under increased physiological stress, for example, in long-duration exercise, cortisol stimulates the breakdown of muscle tissue to amino acids, which through gluconeogenesis in the liver can provide muscle with glucose (Szivak 2016). 3. With large concentrations, cortisol has an anti-inflammatory effect. For example, in the case of tissue damage, cortisol inhibits prostaglandin synthesis and decreases white cells function in the damaged area. Anti-inflammatory effect inhibits the development of inflammatory processes to be too large, since too large inflammatory responses could cause tissue damage. Large amounts of cortisol in the blood also inhibits function of the immune system, by decreasing the number of lymphocytes and lymphatic tissue. Therefore, release of antibodies is decreased. (Sand et al. 2014.)

The effects of cortisol are complementary to those of adrenaline during the stress response. When it reaches the adrenal medulla, it stimulates phenylethylamine N-methyl transferase (PNMT) enzyme, which works as a catalyst in the conversion of noradrenaline to adrenaline. Therefore, it also increases adrenaline secretion. Cortisol also regulates cardiac blood pressure as well as signaling of catecholamine and angiotensin 2 in the heart. (Szivak 2016.)

When doing physical activity which counts as a physical stressor, cortisol synthesis and secretion from the adrenal cortex is increased. The amount of cortisol secreted is correlated to the intensity of the exercise. (Szivak 2016.) Increases typically occur at above 60% VO_2max. It seems that exercise which includes substantial anaerobic components might cause greater increases in cortisol. Even anticipation of exercise can cause increases in cortisol (Kraemer & Rogol 2005; Szivak 2016.) For overreaching and overtraining, basal hormone levels do not seem to be good predictors, but if the ACTH response to stimulation is blunted, it might work as a predictor of overtraining syndrome, functional or nonfunctional overreaching states (Cadegiani & Kater. 2017).

2.3   Adapting to stress

"Stress inoculation" is a concept which underlies training interventions that affect the stress response positively (Flanagan et al. 2012). It is a training method where an individual is exposed to simulated stressors in a controlled setting. The goal is to prepare the human body to better respond to stressors when faced in the real world. Often used in military training and other tactical populations and high-risk activities, as it relates to preparation for combat. It seems that by exposing individuals to stressors repeatedly in a controlled setting, the stress processing of the brain and bodily responses seem to become more prepared to actual stressors (Szivak 2016.)

With chronic exercise, changes occur for example to hormonal responses. Ability of the adrenal medulla to secrete catecholamines increases when exercising at maximal intensity, while exercising at a low intensity, the amount of secretion decreases (Kraemer et al. 2015). In addition, structural changes occur, as the adrenal medulla can hypertrophy due to chronic exercise. This means that through training-induced adaptations, secretion of adrenaline increases and, therefore, the body can face greater challenges. These adaptations are more often seen in elite athletes, but also in elite-level soldiers who train for high-risk scenarios, with the goal to optimize performance under very stressful conditions, where human lives are at stake. This could lead to an improved ability to respond to stressors, and that previous exposure to stress could help when responding to future stressors, thus increasing resilience to stress. This ability of responding to stressors effectively and returning to homeostasis indicates positive

health outcomes, whereas chronic elevations in stress hormones can lead to negative maladaptation. Such as increased fat storage, blood pressure, cardiovascular disease, and negative effects on memory and cognition. This would implicate that optimizing the stress response through optimal training strategies could impact individuals' resilience, both physically and physiologically, which could lead to better long-term health and function ability in high-stress occupations, such as the military. (Szivak 2016.)

2.4 Time domain of stress

Stress response also depends on the timing and duration of exposure to the stressor, which has consequences that can be short- and/or long-term (de Kloet 2013). Stress responses can occur at a timescale that varies from milliseconds to days (Joëls & Baram. 2009). After detecting the stressor, the acute response in the brain begins within seconds (Bains et al. 2015). In general, it is thought that the initial acute effects that are carried by catecholamines and peptides starts in seconds when faced with a stressor (Joëls & Baram. 2009). After hours of the stressor exposure, delayed effects occur on structures on the limbic-cortical area (Joëls et al. 2012). This happens through effects of glucocorticoids (Joëls & Baram. 2009). These effects restore homeostasis and can retain information to assist in coping with similar situations when faced again in the future (Joëls et al. 2013). However, although these stress modulators have a major role in contributing to the stress response, it is also clear that a majority of the modulators also additionally play minor parts in short and long-time frames. For example, catecholamines can also activate certain genes which extends catecholamines effects to a time domain that is more delayed. Glucocorticoids can also swiftly change brain functioning through pathways that are non-genomic. (Joëls & Baram. 2009.)

When an overexposure to stressors that lasts from hours to days occurs, structural changes can happen in areas that are limbic-cortical, and also in the reward system (Joëls et al. 2013, Russo & Nestler. 2013). After chronic exposure, dendritic complexity can also be reduced progressively in the hippocampus and PFC (Holmes & Wellman. 2009). Neurons in NAc and BLA can, however, increase the density of dendrites (Godoy et al. 2018). At a cellular level, LTP induction in CA1 region of the hippocampus is impaired, and alpha-amino-3-hydroxy-5-

methyl-4-isoxazolepropionic acid (AMPA) and n-methyl-D-aspartate (NMDA) -mediated synaptic transmission is reduced (Joëls et al. 2012). These structural changes can be associated with behavioral consequences such as behavior considered to be anxious, probably because due to the amygdala experiencing hypertrophy (Mitra & Sapolsky. 2008). Also, learning-related deficits have been observed, which could occur due to impaired structures considered hippocampal and PFC (Joëls et al. 2012, de Kloet. 2013).

2.5 Measuring stress during arduous military training

Stress during military training and operations is very multifaceted – it includes cerebral, neuroendocrine, cardiac, and cognitive characteristics. In military operations, soldiers are exposed to stressors such as sleep deprivation, hunger, dehydration, different environmental challenges, psychological strain, and fatigue induced by exercise. (Lieberman et al. 2016). Resulting from this, if the coping capacities are challenged enough, critical biological and cognitive functions important for soldiers' health and performance during operations are degraded (Taylor et al. 2007) This means, it is necessary to integrate many different methods of measurement to be able to characterize it. Extreme military training such as the SERE course provides a structured, unique medium to examine human stress under a realistic military context. (Taylor et al. 2007.)

Stress responses have also been evaluated in other contexts. For example, stress has been assessed in college examinations and in situations where the levels of stress can be manipulated in a laboratory setting such as the Stroop test, the cold pressor task, but also during for example public speaking, and other situations considered stressful. These studies have identified that such acute stress can lead to a range of cognitive, mood, and perceptual effects. (Lieberman et al. 2016.) Effects include changes in different memory functions (Schoofs et al. 2009,Schwabe et al. 2012, Wolf 2009), elevated anxiety, depression, agitation and negativity (Van Eck et al. 1996), negative effects to decision making (Gok & Atsan, 2016), reductions in attention (Sänger et al. 2014), impaired attentional inhibition (Skosnik et al. 2000), changes in perceptual and psychomotor performance (Staal, 2004), reduced executive functioning (Starcke et al. 2016) and degradation in sleep quality (Han et al. 2012). Hormonal changes also occur, which include

increased cortisol, dehydroepiandrosterone (DHEA), reduced testosterone (Lieberman et al. 2016), insulin-like growth factor 1 (IGF-1) (Nindl et al. 1997). Heart rate and blood pressure increase (Kudielka et al. 2004, Fischer et al. 2017), alterations in skin and body temperature occur (Vinkers et al. 2010), electrodermal response and respiratory rate elevate (Cacioppo et al. 2007), and heart rate variability (HRV) decreases (Teisala et al. 2014). However, real-word stressors are different than laboratory-induced, and a scientific review of gathering the physiological responses to extreme military training induced stress has not been done. This is important, because the findings that from authentic (non-laboratory) studies indicate that they seem to be more stress-inducing than stress induced and measured in a laboratory setting. (Lieberman et al. 2016). Logically, the results are more valid when measured in settings that simulate real situations, since measurement is more specific.

To describe and understand the human stress response, behavioral, hormonal, and physiological processes should be assessed concurrently. Assessments should be comprehensive and be done in realistic environments. (Taylor et al. 2007.)

TABLE 1. Taylor et al. (2007) suggested methods of measuring stress during military SERE training. Mostly used methods when measuring extreme military stress are the neuroendocrine sampling methods and also to some degree HRV has been used. (Taylor et al. 2007.)

Technique	Key Measurement Factor	Advantages	Disadvantages
fMRI	Amygdala function, Hippocampal structure and function, and frontal activation	Specifies neuroanatomical regions of interest	May be impractical for real-time monitoring
ASER	Startle reflex; amygdala-modulated defensive reflex to aversive stimuli	Accessible, portable, affordable, minimally invasive; easily synchronized with other stress measures (HRV, GSR) with available software	Possible technology limitations
HRV	Sympathetic and parasympathetic activation	Sensitive to changes in emotional state, stress, and physical exertion; easily synchronized with other measures	Lack of real-time measurement capabilities
Neuroendocrine Sampling	HPA/Sympathomedullary activation	Strong scientific basis linking to stress (predictive power); portable detection systems and patch technology may be available options for operational use	No apparent disadvantages

HRV is sensitive to psychological and physical stress (Taelman et al. 2011). It is a electrocardiographic method that is noninvasive, used to measure activity of the autonomic

nervous system (Kim et al. 2018). HRV measures the variation of heart rate between heart beats (McCraty & Shaffer, 2015). Most often the used measure is the standard deviation (SD) of successive R-wave intervals during the cardiac cycle. Variation in the short-term can be mathematically calculated to picture different frequencies which estimate the autonomic modulation of heart rate. The high frequency (HF) component (0.15-0.5Hz) is thought to correspond to modulation of the cardiac cycle by the stimulation of the vagus nerve, which could therefore reflect the transmission of acetylcholine in inhibiting heart cells by opening ion channels directly. The low-frequency component (LF) (0.05-0.15Hz) corresponds to heart rates baroreflex control and represents mixed parasympathetic and sympathetic modulation. This response is not quick as the acetylcholine response of the HF method, because the effect of noradrenaline on heart cells depends on a second-messenger system for the opening of ion channels. (Taylor et al. 2007.) With these methods, HRV can be used as a noninvasive test of function of autonomic nervous system, which can be affected by for example stress, emotional states and physical exertion (ESOC 1996). Lower HRV indicates an increase in sympathetic tone and a corresponding reduction in parasympathetic activity. (Kim et al 2018).To measure the complex stress reactivity more fully, HRV should also be integrated with varying, other measures of stress (Taylor et al. 2007).

Neuroendocrine sampling means measuring the levels of stress hormones, which can picture the reactivity of the SAM and HPA axes. As discussed before, when faced with a stressor, emotional responses to a perceived stressor are sent to brain areas that are subcortical and the hypothalamus. Hypothalamus activates the posterior pituitary which secretes oxytocin and vasopressin, and the adrenal medulla starts secreting adrenaline and noradrenaline. Also, the anterior pituitary releases ACTH, which activates the adrenal cortex for the release of glucocorticoids. Being chronically and severely stressed can result in excessive cortisol levels. (Taylor et al. 2007.) Cortisol can evoke suppressing effects on the hippocampus (McEwen 2001), therefore, possibly degrading perceptual processes important for encoding information and aspects of memory (Sapolsky 2003). If the cortisol levels increase to too high acutely, it can result in degradation in declarative memory, but this effect reverses when returned to normal levels. Contrast to this, chronic exposure can damage the hippocampal neurons (Sapolsky 1996) and may therefore suppress normally occurring neurogenesis. (Taylor et al. 2007.)

Cortisol and other hormones that are stress-related have been used in extreme stress research such as SERE settings. When exposed to acute, uncontrollable stress, plasma cortisol and catecholamines increase robustly (Morgan et al. 2001). The amount adrenaline and noradrenaline released after for example interrogation stress, is comparable to that seen in for example novice parachutists or intubated patients undergoing endobronchial suctioning. Cortisol levels have been comparable to novice parachutists and patients undergoing open-heart surgery. (Morgan et al. 2001.) However, it would be expected that extreme conditions, such as war and long-lasting hard operations are much more stressing than these activities. Plasma neuropeptide-y (NPY) and noradrenaline response seems to be greater in special force populations than in non-special force soldiers. Special force (SF) soldiers also demonstrate more rapid return to baseline levels of NPY when recovering. Overall, the cortisol release is also lower in the SF soldiers, which could mean less HPA axis activation in reaction to the stress. This would be in consistent with the idea that by training, "toughening" and "stress hardiness" which are characterized by an efficient and rapid response to a stressor, followed by a quick return to baseline levels, are enhanced. This is useful, since it could be hypothesized that if a person does not have "stress-toughened" neuroendocrine response to threat, the person could be more susceptible to stress-related illnesses such as PTSD. (Morgan et al. 2001.)

There are also significant differences between individuals in which stress exposure causes perturbations in neuroendocrine systems sensitive to threat (Morgan et al. 2001). It is shown that this sort of training such as simulated captivity experiences increase cortisol significantly and can remain elevated during recovery period (Morgan et al. 2000a). Also, NPY levels seem to elevate significantly compared with baseline. NPY seems to be positively correlated to cortisol levels and behavioral performance when under stress, and inversely correlated to psychological symptoms of dissociation, which implies that NPY could have a stress-buffering role (Morgan et al. 2000b). It has also been studied that dehydroepiandrosterone-sulfate (DHEA-S) ratios to cortisol seem to be significantly higher in subjects who report fewer dissociation-type symptoms and exhibit better performance during SERE training, which implies that DHEA-S could have a stress-buffering role. (Morgan et al. 2004).

SYSTEMATIC REVIEW

3 OBJECTIVES AND RESEARCH QUESTIONS

The purpose of this review is to synthesize data from studies that have measured the stress effect of strenuous military training and the recovery time from these training courses. From this data, the recovery time-courses as well as the magnitude of stress cumulated during training can be assessed, giving important information regarding recovery and the capability of soldiers to undergo stressful training and operations.

Objective 1: To identify the time-course of recovery of physical performance and biomarkers after extremely strenuous military training.

Objective 2: To identify stress-related physical performance and biomarker variables that are affected after strenuous military training, and the magnitude these variables are affected.

Research Question: How long does recovery of physical performance and biomarkers take after strenuous military training?

4 TIME-COURSE OF RECOVERY OF BIOMARKERS AND PHYSICAL PERFORMANCE AFTER STRENUOUS MILITARY TRAINING: A SYSTEMATIC REVIEW

Background: Balancing between training induced stress and recovery is important in a military population. If operational capacity is compromised during high-risk operations, consequences may be serious. Recovery has been studied extensively in athletes, but not in military populations. Physiological demands and methods of training are vastly different in these populations. Often, the training load is very high in military field training, with limited capacity to operate in optimal conditions. Thus, it is important to understand recovery in the context of military training courses and populations to optimize the adaptation and training strategies used. This review provides information about the required recovery times from some of the toughest military training courses that have been measured.

Objectives: The objective of this systematic review was to evaluate the time-course of recovery of biochemical markers and physical performance after strenuous military training, and identify which biomarkers are affected.

Methods: A systematic literature search was conducted using the databases MedLine (Ovid) and Web of Science to identify studies up to July 2021. Varying, relevant search terms were used, related to military training, special forces, physical performance, and biomarkers. Records were included according to the strict inclusion and exclusion criteria.

Results: A total of 12 studies fit the inclusion criteria and were selected for this review. A variety of physiological and psychological markers were measured, and military training length varied from 4 to 62 days, with recovery measurement times varying from 24 hours to 6 weeks. Among these studies, two showed full recovery of variables, seven studies showed almost full (79-90%) recovery, and in three studies, 44-63% of markers were recovered after the recovery period. However, in some studies, more markers could be defined as recovered depending on the criterion for recovery.

Conclusions: In majority of the studies, most of the measured variables recovered during the follow-up, but commonly some variables remained unrecovered, and sometimes only modest recovery was seen. Therefore, according to the results of this review, it seems that majority of the typically measured markers recover in a relatively short time from sustained extreme and intense stress induced by strenuous physical activity, sleep and food deprivation, environmental extremes, and psychological stress, but in some cases only modest recovery seems to occur. Overall, the recovery time seems to vary between the markers, and sometimes recovery might not occur even after longer recovery times. Therefore, it is important to measure recovery after strenuous training courses to maximize operational capability.

Key words: recovery, military training, performance, biomarkers, stress

5   INTRODUCTION

Soldiers experience several physiological and psychological stressors during military operations. The physical demands are strenuous, and include for example combat, heavy load carriage in difficult terrain, carrying and handling heavy loads, manoeuvering in difficult situations such as under ambush, and evacuating (Szivak, 2016). Also, the psychological demands are extreme since human lives are at stake and consequences of actions can be fatal. As an example, extensive research identifies that primary risk factor for developing PTSD is combat exposure, and that combat exposure is a strong predictor of health and psychological complications in veterans. (Kintzle et al. 2018.)

The goal of military training is to prepare soldiers to be resistant to high loads of physical and mental stress which is prevalent in combat operations. Therefore, in preparation for combat, soldiers are exposed to strenuous training frequently. Training includes simulating the demands of military operations, which include high levels of physical activity, often accompanied by sleep and calorie restriction. As a result, fatigue can accumulate, and performance can be affected due to physiological impairments. Management of fatigue and recovery can be disturbed by high operational tempo, as optimal recovery might not be attained between and during operations. (Szivak, 2016.)

Intense and long-lasting training can lead to altered recovery status such as functional (FOR) or non-functional (NFOR) overreaching states. From FOR, recovery can take days up to weeks. NFOR is often thought to be the cause of imbalance between amount and intensity of training and recovery experienced for a too long period and leads to negative outcomes of performance. From NFOR, recovery typically takes weeks to months. (Vrijkotte et al. 2018.) When more severe, this imbalance can lead to the overtraining syndrome (OTS), when performance is typically affected for a long period of time, and recovery can take months or even longer (Meeusen et al. 2010). In the military, NFOR and OTS can be developed during training or operations (Szivak & Kraemer, 2015).

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Recovery is a multifaceted restorative process, occurring relative to time. If recovery status is disturbed by psychological or physical stressors, fatigue can be developed. (Halson, 2014.) Fatigue can be compensated with recovery, which means that the organismic balance is returned (Kellmann, 2002). There are many different methods to measure recovery status of soldiers. For example, physical performance tests, such as jumps, strength tests, aerobic and anaerobic tests have been used. Also, biochemical markers, such as testosterone and cortisol, could help identify the recovery status of the actual physiological processes. (Nedelec et al. 2012.) HRV can also be used (Taylor et al. 2007)

Recovery has been studied extensively in athletes, but research in athletes is not directly applicable to military populations, as athletes optimize their sleep, food intake and quality and use other recovery methods during their training (Vrijkotte et al. 2018). In military context, the extreme conditions must be endured until the mission is complete, without the possibility to individually optimize recovery during the operative stress.

Therefore, knowledge is needed about the recovery time-course after exposure to severe military training induced stress. For example, if recovery is not optimal between operations, performance can still be impaired when starting the next operation. Due to the nature of military operations, this could lead to serious consequences. The operational duties must be fulfilled in all situations, despite optimal recovery. However, it is still important to gain understanding about the physiological state of recovery and performance of soldiers during and after operations, so fatigue can be controlled/managed when possible.

The present systematic review aims to synthesize the data from studies measuring metabolic biomarkers and physical performance recovery time courses of soldiers during and after stress induced by strenuous military training.

6   METHODS

6.1   Data Sources and Search Strategies

A systematic literature review for relevant publications was conducted in July 2021 using the following electronic databases: Medline (Ovid) and Web of Science. Boolean search was used. The search- phrases/words used for concept 1 were: 1. (TS="Navy SEAL training"), 2. (TS="Navy SEAL") 3. (TS="Military Person*"), 4. (TS="Ranger Training"), 5. (TS="Survival training"), 6. (TS="SERE"), 7. (TS="SERE training"), 8. (TS="Special Forces"), 9. (TS="Sustained operatio*"), 10. (TS="Military operatio*), 11. (TS="Military deployment"), 12. (TS="Military operatio* stress"), 13. (TS="Military training"), 14. (TS=Soldier*), 15. (TS=SUSOPS). Search phrases/words for concept 1, 1-15 were combined with OR, which was search number #16. Search words for concept 2 were: 16. (TS=Recovery), 17. (TS="Physical performance") 18. TS= ("Neuromuscular performance"), 19. TS= ("Strength performance") 20. (TS=Biomarker*) 21. (TS=Endocrine), 22. (TS=Testosterone), 23. (TS=Cortisol), 24. (TS=IGF-1), 25. (TS="Growth hormone"), 26. (TS=Catecholamine*), 27. (TS=Hormon*), 28. TS=("Endurance performance"), 29. TS=("Resistance performance") Search words for concept 2, 16-29 were combined with OR, which was search number #30. Thereafter, in the final search #16 was combined with AND with the search #30.

In Web Of Science, search was restricted to English language documents, and document type was restricted to: Article. Web Of Science search was conducted on 7th of July 2021. #16 AND #30 yielded 1,441 results.

In Medline (Ovid), the same search with the same search words, phrases and combinations was conducted on July 9th – July 13th, 2021. This search was restricted to English language documents. As a default function in Medline, .mp was added to all keywords, e.g "Navy SEAL training".mp. This search yielded 2,240 results.

6.2 Article Screening / Study Selection

The screening of articles for potential relevance was first determined based on the title of the article, and second on abstract. Articles consisting of data from strenuous military training or operations/deployment and measuring metabolic, endocrinal, or physical performance factors before, during and after strenuous military training or operations, were included. Studies were excluded based on abstract if they were not relevant (e.g., subject obviously not relevant), other field of study, too short duration, not strenuous (e.g., basic training) included actual physical training such as prolonged deployments, the main factors were not military training but e.g., weather or nutrition or sleep, participants had a medical condition (e.g., PTSD), if stated on abstract that no recovery measurement was conducted, measured markers were not relevant, the stress induced was not relevant (e.g., underwater) etc. Studies that only included female soldiers were excluded due to differences between sexes (Vikmoen et al. 2020) and limited availability of data, which limits the drawing of conclusions.

Of the abstract-screened and included articles, full texts were obtained and read. One author (JG) analyzed the articles. Articles were included (in addition to the previous criteria) if they measured recovery of physical performance and/or metabolic or endocrinological factors after strenuous military training. Studies were excluded for the following reasons:

1. There was no recovery measure, or the recovery period was less than 12 hours.

2. The study was conducted on instructors.

3. The training lasted too long (over 63 days) or was too short (less than 48 hours).

4. Training was not conducted on military personnel.

5. All of the measured variables were not relevant for this review (e.g., body composition)

6. Training was not considered strenuous ("strenuous" was defined as training that severely challenges physiological systems and is most often done by special forces, basic training interventions or simulations were not included. The training had to be defined as strenuous/arduous/extreme, in the article or obviously be strenuous. If not, it was decided by the first author if the training was considered strenuous enough. When in doubt, second author (HK and TO) decided if the article was to be included or not.)

7. Study protocol was not relevant.

8. Included female soldiers and genders were not differentiated in analysis (note: if gender

was not stated in the full-text, assumption was that the soldiers were male).

9. Study included a pharmacological intervention.

10. Relevant data not reported in numbers in tables and/or text.

11. No BL measurement for relevant markers.

12. Only or mainly focused on psychological stress.

13. Recovery measures not compared to baseline in statistical analysis for all markers.

14. Majority of participants got sick during training.

If the first author was in doubt on including an article, a second and third author decided if the article was included or not (HK and TO).

6.3 Data extraction

Included studies were reviewed by one author (JG), who extracted information on participants, type and descriptions of training, energy intake/deficit, amount of sleep, measurements of physical performance and biomarkers, main outcomes, and main results about recovery relevant for this review.

6.4 Quality Assessment

Quality assessment of included studies was completed by one author (JG). The quantitative quality assessment tool "QualSyst" was used when assessing the methodological quality of each selected study. It includes 14 questions, which are scored from 0 (criterion not met) to 1 (criterion met partially) and 2 (criterion met fully). Items not applicable to study design were marked as "N/A" and were not included in the calculation of the overall score (Kmet et al., 2004). The outcome score is then divided by the total possible score. A study is considered of high quality if score is 75% or higher, moderate quality if score is between 55% and 75% and weak quality if score is lower than 55%. This assessment toolkit has been used in previous systematic reviews in military context, for example, in Vrijkotte et al. (2018) review about overtraining syndrome in soldiers. Slight modifications were made to better suit the military context: Item 3 was shortened to only include "Method of subject selection?", item 4 was

shortened to "Subject characteristics sufficiently described?", item 8 was shortened to: "Outcome measures well defined and robust to measurement/misclassification bias? Means of assessments reported?".

7   RESULTS

7.1   Study Selection

The literature search conducted on both databases yielded an overall number of 3,681 results. Web of Science search yielded 1,441 results, and Medline (Ovid) search yielded 2,241 results. Following abstract screening of all 3,681 studies, 3,535 were removed in accordance with the inclusion/exclusion criteria. 146 records were included for full-text review. Of these, 54 duplicates were removed. 92 reports were sought for retrieval, and of 7 articles, full text could not be retrieved. Therefore, a total of 85 reports were assessed for eligibility in the full-text screening. Following the full-text screening, a total of 12 studies were included in the review. Reasons for exclusion following the full-text screening are presented in the PRISMA flow diagram (Figure 1) and former chapters.
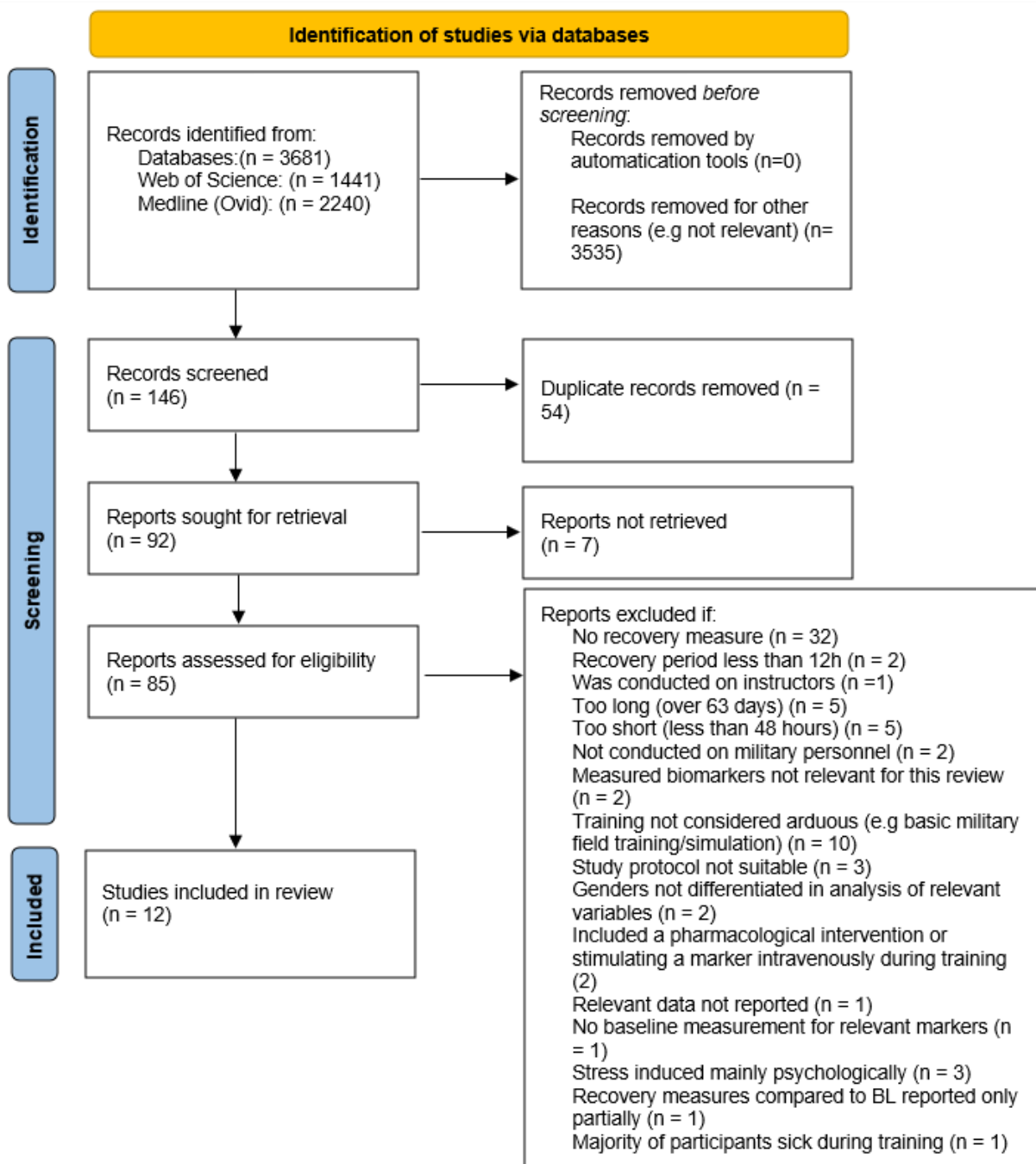
FIGURE 1. PRISMA flow diagram.

7.2 Description of studies

A detailed description of the included studies is presented in table 1 and table 2. Participant details and description of training is described in detail in table 1, and measurement times and measured outcomes, as well as the results of measurements and recovery are described in detail in table 2.

7.2.1 Participant details

Half of the studies (n=6) were conducted on soldiers in Special Forces, one study consists of applicants conducting a selection course to Special Forces, one study was performed during a corporal training course, two among military academy cadets, and one study with Finnish soldiers. The ages varied between 18-35 years, with most commonly described mean age around 22-24 years. Due to similar age and occupation, the populations could be considered as mostly homogenic. Majority of the studies were conducted in the United States military (n=4) and in the Norwegian military (n=4). One study was conducted in the Finnish military, one in the Brazilian military, one in the Austrian military, and one in the Greek military. The number of participants (n) varied between 7-43, with the mean value being 18.

7.2.2 Description of training courses

The most often described course was the U.S Army Ranger course (n=3), followed by different SERE courses (n=2). All of the courses ranged in length from 4 to 62 days, and all courses were extremely stressful due to continuous physical exertion, load carriage, very little sleep if at all, and remarkable energy deficits. Three of the courses lasted 61-62 days, one course 2 weeks, one course 6 weeks, and seven courses between 4 and 7 days, For the study by Kyröläinen et al. (2008), only the first seven days were counted as heavy training, and the rest of the course was considered as recovery time. Participant details and description of training is described with details in table 1. Note: The study by Hamarsland et al. (2018) did not describe if participants were male or female. Due to soldiers in Special Forces more commonly being

males, it was presumed in agreement with the second authors (HK and TO) that the participants were male.

7.2.3   Measured outcomes

Physical performance of participants was measured in five studies, and biomarkers in 11 studies. The measures of physical performance and biomarkers and methods of measurement varied widely between studies. Most commonly measured physical performance parameters were different types of strength tests, which were measured in five studies. Endurance performance (aerobic or anaerobic) was measured in two studies.

A variety of blood biomarkers were measured, including hormones, muscle damage and inflammataroy as well as oxidative stress markers. All of the studies measured multiple relevant biomarkers. A total of 61 different biomarkers were measured across studies. The most commonly measured biomarkers were basic stress-related outcome markers, such as testosterone (n=8) and cortisol (n=6). Measurement times and measured outcomes, as well as the results of measurements are described in detail in table 2.

Of the 11 studies that measured biomarkers, a total of 61 different markers/outcomes were measured: In 8 studies, total testosterone was measured. In five studies, cortisol and thyroxine (T4). Four studies measured creatine kinase (CK), triiodothyronine (T3), IGF-1, and thyroid-stimulating hormone (TSH). Three studies measured sex-hormone binding globulin (SHBG) and c-reactive protein (CRP). Two studies measured free testosterone (FT), insulin-like growth factor-binding protein 3 (IGFBP-3), epinephrine, norepinephrine, dopamine, DHEA-S, luteinizing hormone (LH), transferrin, ferritin, lactate (LA), estradiol (ES), human growth hormone (HGH), glucose. The following were measured only once across all studies: free T3, free T4, free IGF-1, IGFBP 1,2,4,6, myoglobin (MB), alpha 1-acid glycoprotein (AGP), lactate dehydrogenase (LDH), NPY, DHEA, brain-derived neurotrophic factor (BDNF), Cytokines interferon-gamma (IFN-y), interleukin- 1 (IL-1) IL-4, IL-6, IL-8, IL-10, tumor necrosis factor alpha (TNF-alpha), thyroxine-binding globulin (TBG), prealbumin, glycerol, nonesterified fatty acids, high-density lipoprotein (HDL), hemoglobin (Hb), hematocrit, packed cell volume

(PCV), erythropoietin (EPO), iron (Fe), haptoglobin (Hapto), progesterone, 17a-hydroxy-progesterone (17a-HP), androstenedione, prolactin (PRL), urea, follicle stimulating hormone (FSH), insulin, plasma protein concentration, plasma heat capacity profiles, albumin and globulin peak enthalpies and temperatures. Therefore, more than half of the measured biomarkers (33) were measured only once, and the rest (28) were measured twice or more often.

7.2.4   Recovery assessments

Recovery was assessed from at least 24 hours to six weeks after the end of course. In majority of studies (n=8), recovery was assessed for no longer than 2 weeks, and the majority of studies included multiple recovery measurements in different time points. One study (Szivak et al., 2018) assessed recovery for all parameters only after 24 hours as the only measurement point. For two studies, recovery was assessed at only the time point of 30 (Mourtakos et al., 2021) or 35 days (Nindl et al., 1997) after the course, which might be considered to be long as the only measurement point compared to the majority of the studies. Some studies also did not measure the post- measurements immediately after the course: Conkright et al. (2020) performed the first measurements after 2 weeks, and in the study of Hamarsland et al. (2018), physical performance tests were performed 8 hours after the course. Two studies measured recovery during the course: Santos et al. (2018) during a 4-day course at 72h, and Szivak et al. (2018) during a 2-week course at 10-day mark. All other studies did the post-measurements immediately after the course. The results will be discussed in the following chapters.

TABLE 1. Participant details and description of training

Study	Participants	Type of training	Description of training	Energy expenditure or deficit / amount of food provided	Sleep
Conkright et al., 2020	n=10, age 24.0+-5.0 yr. Active-duty male U.S Army 75th Ranger Regiment soldiers	Ranger course	62-day length, one of the military's most challenging courses. Training small unit tactics and leadership under conditions of severe stress created by sleep and caloric restriction, physical exertion, and graded evaluations. Approx. 20h of training per day, 7 days a week, 30-40kg carry.	Energy deficit Approx. 1200 kcal per day, on average	Less than 4 hours per night
Hamarsland et al., 2018	n=15, age over 18, apprentices applying for Norwegian Naval Special forces	First 6 weeks of Naval Special Forces selection course	First 3 weeks: military camp with heavy physical activity and sleep restriction in a stressful environment, week 4: "hell week", consisting of sleep and calorie restriction and extreme amounts of physical activity for 20h per day in a very stressful and difficult environment with about 35kg of carry. Weeks 5-6: recovery.	First 3 weeks food intake: ad libitum. Hell week: 10 000 kcal combat ration provided at the start, for the whole week	First 3 weeks: not stated. Hell week: 2-3h of sleep per night
Santos et al., 2018	n=43, age 18-23, Brazilian 1st Command Action Battalion male	Army Corporal Training Course, Combat Simulation exercise	4 full days of 24-hour continuous operations, evaluation of leadership potential in combat. 25kg added weight + other material to carry.	R2 ration includes 3000-3600 kcal of energy. Day 1: full R2 ration, Day 2: ½ R2 ration, Day 3: 1/3 R2 Ration,	Day 1: 2h, Day 2: 2h, Day 3: 1h, Day 4: --
Szivak et al., 2018	n=20, age 18-35, active-duty men serving in the U.S Navy and Marine Corps	Navy SERE course	Highly classified. ~2 weeks of highly realistic SERE training including multiple stressors: environmental extremes, physical demands, food & sleep deprivation, psychological stress. First 4 days didactic phase, followed by field training phases: Evasion phase: several days of practicing evasion techniques in difficult terrain. Capture phase: several high-stress training scenarios of realistic captivity experience.	Several days of food restriction	Several days of sleep deprivation

Henning et al., 2013	n=23, age 23.0+-2.8yr. U.S Army 2/75th Ranger Regiment male soldiers who	Ranger Training Course	61 days, 30-40kg load carry, over 200 miles of movement during the course, food & sleep deprivation. Same course as Conkright et al., 2018.	2200 kcal food provided per day	0-5 hours of sleep per night
Nindl et al., 1997	n=10, U.S male soldiers from Army Ranger Training Course	Army Ranger Course	Demanding 62-day training program, designed to teach and evaluate leadership and small unit tactics under physically and mentally challenging conditions. Multi-stressor environment, 20 hours of training each day in forest, forested mountains, coastal swamp, and desert	Estimated energy expenditure 4200 kcal/day. Caloric intake 3200kcal/day. A deficit of 1000kcal/day	Description indicates maximum of 4 hours per night, might be lower
Gunga et al., 1996	n=29, age 22.2+-2.8, male members of Austrian Army special forces training unit	Survival training course	5 - day survival training, 430-570m above sea level in a wooded area. Incl. 90km marching, tactical missions with 22.3kg carry.	1st day breakfast 1500kcal, after that mean energy intake was 150kcal/day. Water was limited to 1 liter/day (+1l 1st day morning and 4th day	Overall 20 hours of sleep during 5 days (no tent and no sleeping bag)
Opstad, 1994	n=10, age 22-26, male cadets of the Norwegian Military Academy	"Military training course"	5-days continuous physical exercise (infantry activities) around the clock in a forest area at 500m altitude	Energy expenditure of 40 000kj/24h (9560 kcal), energy intake 5000 kj/24h (1195 kcal)	No organized sleep, some minutes between activities, total 1-3h during the whole course.
Opstad, 1982	n=11, two groups (iso-calory: n=5, age 22.9. low-calory: n=6, age 22.8). Norwegian Military Academy	Norwegian Military Ranger training course	5-day ranger training course with continuous and heavy activities	Energy expenditure of 8000-11000kcal/day. Low-calory group intake was 1500kcal, deficit 7000-10000kcal. Iso-calory group intake was	Less than 2 h of total sleep during the course

Kyröläinen et al., 2008	n=7, Finnish male soldiers, age 24+-2 years	Prolonged military field exercise	20-day field exercise, three phases: First 7 days: Phase 1, very heavy, consisting of walking 20-25km per day in the forest carrying approx. 50kg of gear. 6 days of phase 2: Easy, walking 5-10km per day with 20-25kg of gear. Last week phase 3: heavy, approx. 15km per day with 30kg carry.	Daily energy intake average 2938+-454kcal/day, no differences between different phases. Energy deficits were 4000, 450 and 1000 kcal/day in P1	Average sleep 6h per night during the whole field exercise
Vikmoen et al., 2020	n=23 men, age 19.3+-1.8yr, Norwegian conscripts who completed a selection exercise	Armed Forces Special Command, Parachute Ranger Platoon selection	Selection exercise, extremely demanding field exercise that lasts ~5 and half days. Designed to test physical and mental resilience in extreme situations in sub-optimal conditions. Consists of large amounts of physical activity in addition to sleep and food restriction. Main activities: loaded marching and various mentally and physically challenging tasks. Carried load varied between 20-40kg during exercise.	Energy expenditure estimated 7235+-408 kcal/day. Food intake was 575 kcal/day, except for day 3 it was 3755 kcal.	1-6 hours/day
Mourtakos et al., 2021	n=14, age 22.7+-1.7 yr, male Greek Special Forces volunteers	"Hell Week" of BUD/S of the Hellenic Navy SEALs	5-day "Hell Week" of the 32 week "brutal" BUD/s schedule. During "Hell Week", candidates participate in training course characterized by extreme mental and physical fatigue, e.g walking 300km and doing physical training for more than 20 h per day in harsh conditions.	Not reported	No sleep at all during the entire week

TABLE 2. Measurements times, main outcomes, main findings, and recovery

Study	When was testing conducted	What (relevant) markers were measured	Main findings	Recovery of markers?
Conkright et al., 2020	Baseline (BL) pre-Ranger School, two-weeks post (P1), and six-weeks post (P2) Ranger School	Physical performance with modified Ranger Athlete Warrior assessment. Speed & mobility: IAT test, muscular endurance (push): metronome push-up, muscular strength/endurance (pull): overhand pull-up, core strength: heel clap, anaerobic capacity: 300yd shuttle run, aerobic fitness 20-m multistage beep test. Strength: 185-lbs bench press and 225-lbs deadlift rep max.	Significant declines across time points in all performance measures except deadlift and bench. BL to P1 declines: push-ups ↓~24%, pull-ups ↓~28%, heel claps ↓~35%, IAT ↓~9%, beep test ↓~20%. 300yd run no decline at P1, only at P2. Push-up and pull-up returned to BL by P2. Other measures related to speed/mobility, anaerobic capacity, and aerobic fitness remained under-recovered at P2 related to BL: IAT ↓~15% and 300-yard run ↓~7% slower, heel clap ↓~27% decline, beep test ↓~23% decline related to BL.	Partial. Push-up and pull-up recovered to BL after 6 weeks, other variables did not.
Hamarsland et al., 2018	(BL): day 2 of 1st week and Pre: day before hell week (HW). Post: Blood samples immediately after termination of hell week, physical performance 8 h later. Recovery: all measures after 24h, 72h, 1wk, and phys perf 2wk.	Physical performance: counter-movement jump (CMJ), isometric leg press, isometric chest press. Blood samples: Testosterone, cortisol, T/C ratio, SHBG, CK, CRP, TSH, T3, T4, T3/T4 ratio IGF-1 and IGFBP-3. FT calculated.	After HW: Physical performance at post: CMJ ↓28%, leg press ↓20%, chest press ↓10%. No clear signs of recovery after 72h. 1 wk after, chest press returned to pre-levels. Leg press recovered after 2wk, CMJ still depressed after 2wk (↓14%). Testosterone pre-post ↓70%, after 1 wk return to normal. FT ↓39% at post, ↓60% after 24h, ↓50% at 72h, normal after 1wk. SHBG pre-post ↑24%, still elevated at 72h, normalized after 1wk. Cortisol ↑154% at post, elevated after 1wk (↑43%). T/C ratio ↓87% at post, ↓63% at 24h, ↓58% at 72h, back to baseline after 1wk. IGF-1 & IGFBP3 both ↓(45/37%) at post, gradual rec and normalized after 1wk. T3 and T4 ↓(32%/12%) at post, gradual recovery to pre within 1wk. T3/T4 ratio ↓77% at post, gradual recovery toward pre within 1wk. TSH significant increase (↑58%) only after 1wk. CK elevated at post (700%), decrease to below pre- values after 1wk. CRP ↑1300% at post, ↑1500% at 24h, below pre values within 1wk.	Partial. Some hormones normalized after 1wk, some not. Recovery of chest press after 1wk, leg press after 2wk. CMJ still depressed after 2 weeks

Santos et al., 2018	BL/T0 before beginning of activities (fasted), T1 at 72 hours after baseline after 100km march, and T2 at 63 hours after the end of military activity	Blood samples: Creatine phosphokinase (CPK), MB, CRP, AGPA, LDH, Lactate	CPK ↑1035% at T1, return to baseline at T2. LDH: ↑122% at T1, still ↑37% increased at T2. Lactate ↑127% at T1, return to baseline at T2. MB: ↑728% at T1, return to baseline at T2. CRP: ↑182% at T1, return to baseline at T2. AGPA: ↑14,7% at T1, return to baseline at T2. Thus, markers increased significantly at T1 and returned close to baseline at T0, except LDH which did not.	Yes, except one marker (LDH), marker recovery occurred after 63 hours
Szivak et al., 2018	(BL)/T1, first day of SERE. Stress assessment (T2), 10 d after T1. Recovery assessment (T3), 24h after T2.	Blood samples: Epinephrine, norepinephrine, dopamine, cortisol, testosterone, NPY at all testing points. Physical performance: Vertical jump, dominant handgrip, nondominant handgrip at test points T1 and T2, no recovery measure.	Physical performance did not decrease from T1 to T2. Exposure to stress resulted in significant increases in plasma epinephrine ↑70%, plasma norepinephrine ↑191%, plasma dopamine ↑186% and serum cortisol concentration ↑525%, and a reduction in testosterone concentrations ↓63% No significant elevations in plasma NPY, however NPY decreased significantly at T3 (↓56%). Of the markers that showed increase at T2, only epinephrine recovered at T3, others still elevated from BL values after 24 hours (Norep ↑82%, Dop ↑79% Cor ↑172%, Test ↓54%).	No. Of the affected markers, only epinephrine levels recovered after 24 hours.
Henning et al., 2013	Before (BL) and immediately after (Post) Army Ranger course. Recovery measures after 2-6 weeks. Note = n=23 at BL and post, n=9 on the recovery measures.	Blood samples: Cortisol (no R.D, Recovery Data), T3, T4 (no R.D), TSH (no R.D), DHEAS (no R.D), BDNF, total and free IGF-1, IGFBP 1 (no R.D on 2-6), Cytokines (INF-y (no R.D), IL-1 (no R.D), IL-4, IL-6, IL-8, IL-10 (no R.D), TNF-alpha (no R.D), CRP (no R.D)), total testosterone, SHBG.	Total testosterone decreased ↓70% at post. Serum SHBG ↑46% at post. Cortisol nonsignificant increase, DHEAS no change at post. BDNF ↑33% at post. T3 showed a trend to decrease (↓8%) at post. TSH ↑85% at post. No change in T4 at post. Total IGF-1 decreased ↓38.7% and free IGF-1 ↓41% at post. IGFBP-1 ↑534,4%, IGFBP-2 ↑98,3% and IGFBP-3 ↑14,7% at post. IGFBP-6 ↓23.4% at post. Il-4 ↑135,3%, IL-6 ↑217,2%, and IL-8 ↑101,4%. No changes in INF-y, IL-1B, Il-10, TNF-alpha or CRP. After 2-6 weeks, all markers with recovery data recovered to BL concentrations except T3 (↑17%).	All markers with recovery data recovered to BL after 2-6 weeks, except T3 elevated.

| Nindl et al., 1997 | Pre: before the start of the course. Post: after 62 days after initial testing (at the end of Ranger course). Recovery at 35 days after completion of course. | Physical performance: Machine simulating power clean (strength) vertical jump (jump height and calculated explosive power). Serum hormones: IGF-1, T3, T4, TGB, TSH, LH, SHBG, Testosterone. Metabolic markers: Transferrin, prealbumin, ferritin (not reported), glycerol, nonesterified fatty acids (not reported), HDL (not reported), lactate. | Strength declined ↓21,2%, explosive power ↓22%, vertical jump height ↓18% at post. IGF-1 (↓50%), LH (~↓28%), T3 (↓22%), T4(↓10%) declined. SHBG (~↑100%), TBG (~↑15%) and TSH (~↑125%) increased. Testosterone declined largest: ↓86%. Ferritin, HDL and nonesterified fatty acids could not be reported due to dichotomies in text and tables. Prealbumin was significantly lower (↓21%), no differences in transferrin, glycerol, or lactate. Recovery: Physical performance recovered to pre at 5 weeks of recovery. Most hormones recovered to pre levels, but T3 and IGF-1 increased compared to pre, and TBG and SHBG only recovered to normal values, not BL. All metabolic markers recovered or were in the normal range except for lactate, which interestingly showed an increase (↑96%) in recovery. | Partial. Phys. Perf recovered. TBG and SHBG only to normal values (not considered recovered), lactate high at rec. T3 and IGF-1 increased. All else recovered. |
| Gunga et al., 1996 | T1: Day 1, before course started, T2: After 72 hours, T3: After 120h at the end of the course, T4: After course, 48 hours and T5: 72 hours of recovery. | Hb, Haematocrit, PCV, EPO, Fe, Hapto, Transferrin, Ferritin. | EPO decreased during the course but was over control (pre) values during recovery period. Fe increased during the course and remained above control (pre) concentrations after recovery. Hapto decreased during the course and remained below control concentrations at T4 and T5. Transferrin decreased during training and recovery continuously. Fer increased during the course, returned to control (pre) concentration at T5. Hb increased from T1 to T2, had decreased below control levels at T5. PCV increased from T1 to T2, was below control levels at recovery. | Partial. |

Opstad, 1994	BL/control the week prior to the course, 1st day of course (day 1-2), last day of the course (day 4-5), and 4-5 days after course (recovery) (REC).	Circadian rhythm blood measures, done 7 times during 24h. Measures: Dopamine (Dop), noradrenaline (Norad), adrenaline (Ad), cortisol (Cor) and Plasma cortisol, progesterone (PS), estradiol ES, testosterone (T), DHEA, 17a-hydroxy-progresterone (17a-Hp), DHEA-S, androstenedione (AS), T4, FT4, T3, FT3, TSH, HGH, glucose.	Circadian rhythms: Cor: almost extinguished during last 24h, normalized during REC, plasm Cor rhythm still different. PS: almost extinguished on last day, normal after REC. DHEA-S: No rhythm on last day, no significant alterations during recovery. AS: almost extinguished on last day, not re-established during REC. DHEA: almost abolished on last day, re-established during REC. 17a-Hp: Abolished on last day of course, not re-established during REC. T: last day no rhythm, not re-established at REC. E: No rhythm shown. Norad: did not show rhythm. Ad, Dop did not show rhythm. HGH: No apparent circadian variations. TSH: Alterations in rhythm, re-established at REC. T4: No circadian rhythm shown. FT4: No circadian variations at control and recovery, slight variation in levels during course. T3, FT3: No circadian variation. Glucose: no rhythm was found.	Partial.
Opstad, 1982	Pre, Every morning of 5-day combat course and 6 days after.	Prolactin (PRL), Testosterone, estradiol (ES)	ES: remained stable level during the first two days of activity, decrease from day 3, lowest value on day 4 ($\downarrow$50% from precourse values). Recovery to pre values after 6 days. Testosterone decreased after 12h of activity, decreased about $\downarrow$75% of precourse values on day 3 and remained low, however recovered 6 days after. PRL decreased after 12h, and lowered after that point, but recovered after 6 days. No effect on group.	Yes, all hormone levels recovered after 6 days.
Kyröläinen et al., 2008	Pre/BL: one day before start, days 5 (P-1mid), 8 (P-2pre), 14 (P-3pre), 16 (P-3mid) and 21 (P-3post) **(NOTE= Only first 7 days considered as the "intervention". All else recovery)**	Blood: Cortisol (COR), growth hormone (GH), glucose (GLU), LA (no data reported), creatine kinase (CK), Urea (U), total testosterone (TT), free testosterone (FT), T4, FSH, LH), insulin (INS), Plasma volume (PV) (limited data on plasma volume to assess recovery).	Blood GLU no change on day 5, $\downarrow$13,3% at the end of P-1 (day 7). Back to BL on day 8. At P1-mid (5-days), COR $\uparrow$32%, GH $\uparrow$616% and INS $\downarrow$70%. After these initial raises, COR and GH returned to BL at P-2pre, and INS at the end of P-3post. At P1-mid, TT $\downarrow$27%, FT $\downarrow$26% and LH $\downarrow$46%, no change in FSH. All these returned to BL by P-3pre. Serum T4 p1mid $\downarrow$9% non-significant, was lower and urea concentration higher after the whole exercise than BL. No changes in T4 and urea during first part of exercise. PV changed slightly during the course. CK increased at P-1mid $\uparrow$555%, returned to BL on day 16.	Yes, except T4 lower and urea concentration higher after the exercise.

Vikmoen et al., 2020	Before (BL), and post 0 (only physical perf) 24h (physical perf + blood) 1, 3, 7, and 14 days after field exercise.	Blood: Cortisol (Cor), testosterone, creatine kinase (CK), IGF-1. Physical performance: CMJ (n=17), medicine ball throw (MBT) (n=18), evacuation test for anaerobic performance (EVAC) (n=18).	Physical performance: CMJ height decreased after the exercise ($\downarrow$7,5cm), still $\downarrow$6,6cm reduced after two weeks recovery. CMJ max power followed a similar pattern. EVAC test times were about 50% slower after exercise, recovery to BL after 2 weeks. MBT: $\downarrow$0,5m, back to BL after 1 week of recovery. Blood: Testosterone $\downarrow$58% 24h after the exercise. Still $\downarrow$20% at 72h rec. Increase compared to BL after 1 ($\uparrow$87%) and 2 weeks ($\uparrow$113%) recovery. Cor: Increase during exercise ($\uparrow$26%), back to BL after 72 h of recovery. IGF-1: decrease during exercise, was $\downarrow$28% lower at post. After that, IGF-1 increased gradually, and levels were higher than BL after one week of recovery. CK was increased largely 24h after exercise ($\uparrow$353+-430%), back to pre-values after 72h recovery, decrease to below pre values after 1wk and 2wk of recovery ($\uparrow$85%).	Partial. Blood biomarkers recovered after 1 week. CMJ did not recover at 2 weeks, MBT recovered after 1wk and EVAC after 2wk.
Mourtakos et al., 2021	BL: 7 days prior "Hell Week". During: On each 5 days of "Hell Week". Recovery: 30 days after completion.	Plasma protein concentration, plasma heat capacity profiles, albumin and globulin peak enthalpies and temperatures	Main finding was that thermal stability of plasma albumin was enhanced and denaturational transition to higher temperatures shifted. Major effect of exercise was continuous upward shift of the albumin peak by 2-3 celsius, tending to plateau at 5$^{\text{th}}$ day. Some redistribution of the denaturational enthalpy was also observed during exercise: globulin peak increased relative to albumin peak, especially during first 4 days. Total recovery to the initial signature pattern after 30 days recovery.	Yes.

7.3   Quality assessment

Table 3 presents the critical appraisal of the studies. 7 of the studies were rated as "Moderate" quality according to the "QualSyst" checklist, and 5 studies were rated as "Weak" quality. Therefore, no studies were considered as high quality. Highest score was 15 points which was reached by two studies. No studies scored less than 10 points. It is noteworthy, that due to the nature of the studies, no studies received points from the item "controlled for confounding". Also, in general, the sample sizes were considered to be low. Sample sizes below 20 (of persons included in analysis) were considered as low and were rated for 1 point only. Only two studies got two points for sample size. However, in all of these "low" sample sized studies, significant outcomes were found for majority of main outcomes, so therefore sample size could also be considered as adequate. However, the low sample size still accommodates bias, which is especially relevant for certain hormonal measurements where the measurement ranges vary widely, and therefore majority of studies were not rated worth two points. Also, due to the nature of field experiments and the measurement bias of selected markers, only two studies got two points for "outcome measures well defined and robust to measurement/misclassification bias", with the rest of the studies receiving 1 point. In addition, variances were rarely reported for main outcomes, which lowered the overall score for all except 4 studies. Also, mainly due to the nature of field experiments, study designs tended to lack appropriateness to be rated worth full two points.

TABLE 3. QualSyst

	Conkright et al.	Hamarsland et al.	Santos et al.	Szivak et al.	Henning et al.	Nindl et al.	Gunga et al.	Opstad, 1994	Opstad, 1982	Kyröläinen et al.	Vikmoen et al.	Mourtakos et al.
Question/objective sufficiently described?	2	2	1	2	1	2	1	2	1	2	2	1
Study design evident/appropriate?	1	1	1	1	1	1	2	1	1	2	1	1
Method of subject selection described and appropriate?	1	1	1	1	1	2	1	1	1	2	2	1
Subject characteristics sufficiently described?	2	1	2	1	2	2	2	1	2	1	2	1
Random allocation possible/described?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0	N/A	N/A	N/A
Blinding of intervention and investigators possible/described?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Blinding of intervention and subjects possible/described?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Outcome measures well defined and robust to measurement/misclassification bias? Means of assessments reported?	2	1	1	1	2	1	1	1	1	1	1	1
Sample size appropriate?	1	1	2	1	1	1	2	1	1	1	1	1
Analytic methods described/justified and appropriate?	2	1	2	2	2	2	2	1	1	2	1	1
Some estimate of variance reported for main results?	0	0	0	0	2	0	0	2	1	0	1	0
Controlled for confounding?	0	0	0	0	0	0	0	0	0	0	0	0
Results reported in sufficient detail?	2	2	2	1	2	1	1	2	1	1	2	1
Conclusions supported by results?	1	1	2	1	1	0	1	2	2	2	2	2
Total	14/22	11/22	14/22	11/22	15/22	12/22	14/22	14/22	12/24	14/22	15/22	10/22
Rating	Mod	Weak	Mod	Weak	Mod	Weak	Mod	Mod	Weak	Mod	Mod	Weak

7.4   Effects of training on physical performance

The results are provided in detail in table 2. Of the studies that measured physical performance, significant decreases were observed after the training course, except for the study by Szivak et al. (2018), in which physical performance decrements were not observed for any measure. It is also worth noting that in Szivak et al. (2018), recovery of physical performance was not measured. Therefore, 4 out of 5 studies showed significant decreases in physical performance. In these studies, all the measured physical performance outcomes declined, with the exception of Conkright et al. (2020). In the study by Conkright et al. (2020) describing Ranger course, all other performance measures declined after the course, except deadlift repetition strength with 225-lbs, and bench press repetition strength with 185-lbs. It is also noteworthy that the test measuring anaerobic capacity (300yd shuttle run) only showed decrease at the six-weeks post- point, and not two weeks post. Also, in the Conkright et al. (2020) study, the first measurement point after the course was 2 weeks, so there was no real "post" measurement.

7.5   Recovery of physical performance

In the 4 studies, where physical performance decreased after training and recovery was measured, all measures of physical performance recovered during the study period only in Nindl et al. (1997), where recovery of all outcomes occurred after 5 weeks. The measures were strength (machine simulating power clean), vertical jump height and explosive power.

In the other studies, recovery occurred only for some outcomes. In the study of Conkright et al. (2020) describing the 62-day Ranger course, only push-ups and pull-ups returned to BL after 6 weeks of recovery, while other measures (speed/mobility, anaerobic capacity, aerobic fitness) remained under-recovered. In the study of Hamarsland et al. (2018), which included 6 weeks of Naval Special Forces selection course, no clear signs of recovery were seen at 72h after the course, chest press recovered after 1 week, leg press after 2 weeks, but CMJ remained depressed after 2 weeks. In the study of Vikmoen et al. (2020) in which the training consisted of a 5.5-day selection exercise to Special Forces, MBT which measured upper body power, recovered after 1 week, EVAC test which measured anaerobic performance recovered after 2

weeks, but CMJ remained depressed after 2 weeks. Therefore, only one study shows complete recovery of physical performance, while three studies show only partial recovery.

TABLE 4. Summary of physical performance recovery in studies

Study	Physical performance markers measured	Physical performance markers recovered	Physical performance markers not recovered	Physical performance markers not affected during training	Recovery measured for
Conkright et al.	8	2	4[a]	2	6 weeks
Hamarsland et al.	3	2	1	0	2 weeks
Nindl et al.	3	3	0	0	5 weeks
Vikmoen et al.	3	2	1	0	2 weeks

Note: "physical performance markers measured" includes only markers and studies of which data was reported also during recovery. Therefore, study by Szivak et al. (2018) is not included here due to missing recovery data on physical performance measures. Note: if a marker was increased over pre values at recovery after being decreased compared to pre during training, it was considered recovered. Or, if a marker was decreased during training, but increased compared to pre at recovery point, it was also considered recovered). [a]= 300yd run time only increased at recovery point, not at post-measurement, therefore can't be counted as recovered or not. Categorized here to not be recovered.

7.6   Effects of training on biomarkers

In general, large stress-related responses were observed in most biomarkers in all studies. The results of effects on most commonly measured biomarkers and recovery are presented in table 5. In all studies, most biomarkers were affected negatively after the training course. "Negatively affected" does not necessarily mean a negative adaptation occurred, but that a stress-induced reaction of biomarker was evident after the training, affecting homeostasis which would have to be restored. In 5 studies (Santos et al. 2018, Gunga et al. 1996, Opstad 1982, Vikmoen et al. 2020, Mourtakos et al. 2021), it was reported that all measured biomarkers were affected at the post- measurement after the course. These studies were 4-5 days in length and included less markers measured than the rest of the studies. However, it must be considered that all other studies measured more markers and lasted longer in time. The markers in the 6 studies that did not show significant change will be provided below. Table 5 also includes a detailed report on the effect of biomarkers that were measured most commonly (at least in two studies) and recovery data across studies.

In 6 studies, it was reported that most biomarkers decreased, but some did not show significant change. In the study of Hamarsland et al. (2018) which included first 6 weeks of a Naval Special Forces' selection course, all biomarkers except TSH were affected at the post measurement point. However, it must be considered that TSH did interestingly increase at the 1-week recovery point. In the study of Szivak et al. (2018), which described a 2-week Navy SERE course, all markers but NPY were reported to be negatively affected at post-measurement. However, NPY was affected at the recovery measurement point. It is worth noting, that in this study the "post"-measurement occurred during the course and the stress induced exactly before measurement point was highly psychological (interrogation), although the participants had done physically demanding SERE training for multiple days before that. In the study of Henning et al. (2013) describing a 61-day Ranger course, all others but the cytokines INF-y, IL-1B, TNF-alpha or CRP were reported to be negatively affected, and T3 only showed a trend to decrease, but not significantly. Also, there was no change in T4. As a side note, of these markers, only T3 had recovery data measured, so the rest are not relevant for the review. Also, T3 was affected at the recovery point. Cortisol showed an increase, but it did not reach statistical significance. In the study of Nindl et al. (1997), describing a 62-day

Ranger course, all others but transferrin, glycerol and lactate were reported to have differences at the post-measurement. However, data of these markers was mixed in the study tables and text, therefore they are not noticed in this review. In the study of Opstad (1994), describing a 5-day military training course, effects (or no circadian rhythm) were shown for all but glucose, T3, T4, FT3, HGH, adrenaline, noradrenaline, dopamine, and estrogen circadian rhythms. In the study of Kyröläinen et al. (2008), describing a 20-day field exercise, change was reported for all markers except FSH. T4 and Urea was not affected during the heavy training (first 7 days) but were affected after that.

Most of the biomarkers were affected largely, which was expected. A detailed description of responses of most commonly measured biomarkers is provided in table 5. For example testosterone decreased in all the studies (8) measuring it, and the decreases were of large magnitude in the studies that reported the actual percentage change or it could be calculated: Hamarsland et al. (2018) -70% (with a concomitant increase of +24% in SHBG), Henning et al. (2013) -70% (with a concomitant increase in SHBG +46%), Nindl et al. (1997) -86%, Opstad (1982) -75%, Kyröläinen et al. (2008) -27%, Szivak et al. (2018) -63% and Vikmoen et al. (2020) demonstrated a -58% decrease. In the study of Opstad (1994), testosterone circadian rhythm was extinguished on last day.

As another example, cortisol, which is often considered the "main" stress hormone and representative of the HPA axis activity, increased in all studies where it was measured (5) except in the study by Henning et al. (2013), which showed an increase but did not reach statistical significance. In Hamarsland et al. (2018), cortisol increased +154%, and T/C ratio decreased 87%. In Szivak et al. (2018), cortisol increased +525%. In Opstad (1994), cortisol circadian rhythm was "almost extinguished". Kyröläinen et al. (2008) demonstrated an increase of +32%, and Vikmoen et al. (2020) a +26% increase. According to this and the in-detail data presented in table 5, it can be concluded that all studies did elicit large effects on the stress system and multiple biomarkers.

TABLE 5. Results of the most commonly measured single biomarkers (measured in at least two studies), and recovery time course (or no recovery time course) of markers.

10 studies measured these	Hamarsland et al.	Santos et al.	Szivak et al.	Henning et al.	Nindl et al.	Gunga et al.	Opstad, 1994	Opstad, 1982	Kyröläinen et al.	Vikmoen et al.
Total testosterone	-70%	-	-63%	-70%	-86%	-	Ext	-75%	-27%	-58%
Full recovery =	1wk	-	No(24h)	2-6wk	5wk	-	No(4-5d)	6d	9d	1wkElev
Cortisol (n=5)	+154%	-	+525%	-	-	-	~Ext	-	+32%	+26%
Full recovery =	No(1wk)	-	No(24h)	-	-	-	4-5d[c]	-	3d	72h
T4 (n=5)	-12%	-	-	NE	-10%	-	NE	-	NE^	-
Full recovery =	1wk	-	-	-	5wk	-	-	-	?	-
CK (n=4)	+700%	+1035	-	-	-	-	-	-	+555%	+353%
Full recovery =	1wk	63h	-	-	-	-	-	-	11d	72h
T3 (n=4)	-32%	-	-	No^	-22%	-	NE	-	-	-
Full recovery =	1wk	-	-	?	5wk	-	-	-	-	-
IGF-1 (n=4)	-45%	-	-	-39%	-50%[a]	-	-	-	-	-28%
Full recovery =	1wk	-	-	2-6wk	5wk	-	-	-	-	1wkElev
TSH (n=4)	+58%[b]	-	-	+85%	+125%[a]	-	Alt	-	-	-
Full recovery =	No(1wk)	-	-	ND	5wk	-	4-5d	-	-	-
SHBG (n=3)	+24%	-	-	+46%	+100%[a]	-	-	-	-	-
Full recovery =	1wk	-	-	2-6wk	No					
CRP (n=3)	+1300%^	+182%	-	NE	-	-	-	-	-	-
Full recovery =	1wkLow	63h	-	-	-	-	-	-	-	-
Free testosterone	-39%^	-	-	-	-	-	-	-	-26%	-
Full recovery =	1wk	-	-	-	-	-	-	-	9d	-
IGFBP-3 (n=2)	-37%	-	-	+15%	-	-	-	-	-	-
Full recovery =	1wk	-	-	ND	-	-	-	-	-	-
Epinephrine (n=2)	-	-	+70%	-	-	-	NE	-	-	-
Full recovery =	-	-	24h	-	-	-	-	-	-	-
Norepinephrine	-	-	+191%	-	-	-	NE	-	-	-
Full recovery =	-	-	No(24h)	-	-	-	-	-	-	-
Dopamine (n=2)	-	-	+186%	-	-	-	NE	-	-	-
Full recovery =	-	-	No(24h)	-	-	-	-	-	-	-
DHEA-S (n=2)	-	-	NE	-	-	-	Ext	-	-	-
Full recovery =	-	-	-	-	-	-	4-5d	-	-	-
LH (n=2)	-	-	-	-	-28%[a]	-	-	-	-46%	-
Full recovery =	-	-	-	-	5wk	-	-	-	9d	-
Transferrin (n=2)	-	-	-	-	No	Dec	-	-	-	-
Full recovery =	-	-	-	-	-	No	-	-	-	-
Ferritin (n=2)	-	-	-	-	N/A	Inc	-	-	-	-
Full recovery =	-	-	-	-	-	3d	-	-	-	-
Lactate (n=2)	-	+127%	-	-	NE^	-	-	-	-	-
Full recovery =	-	63h	-	-	?	-	-	-	-	-
Estradiol (n=2)	-	-	-	-	-	-	NE	-50%	-	-
Full recovery =	-	-	-	-	-	-	-	6d	-	-
GH (n=2)	-	-	-	-	-	-	NE	-	+616%	-
Full recovery =	-	-	-	-	-	-	-	-	3d	-
Glucose (n=2)	-	-	-	-	-	-	NE	-	-13%	-
Full recovery =	-	-	-	-	-	-	-	-	1d	-

7.7   Recovery of biomarkers

Table 5 and table 6 present the information about biomarker recovery. A summary of the results of table 5 concerning biomarker recovery is provided here. When looking at single biomarkers (table 5), the most commonly studied biomarker, testosterone, recovered in 6 studies, and not in 2 studies. However, the studies that did not show recovery, the recovery period was short, 24h and 4-5 days. In the other studies that did show recovery, the recovery periods varied from 6 days to 6 weeks. A summary for the rest of the biomarkers which were commonly measured (in this case, measured at least 3 times, the results for the markers that were measured 2 times are provided in table 5) will be provided next. Cortisol recovered in 3 studies and did not recover in 2 studies. In these two studies which did not show recovery, a short recovery time frame does not explain this, although the other study was the one by Szivak et al. (2018) with 24 hours recovery, the other was the study by Hamarsland et al. (2018) in which recovery was measured for 1 week. However, the study by Szivak et al. (2018) shows a much greater increase in the levels of cortisol compared to the other studies in which cortisol was recovered in a shorter time frame. A greater increase in cortisol could take a longer time to recover. T3 recovered in all studies in which recovery of it could be assessed, as did CK, T4, IGF-1, and CRP. These and the rest of the results are seen in detail in table 6, which provides information about biomarker recovery (of markers that recovery data was reported) in studies, summarizing the information of how many biomarkers recovered in a study and how many did not, or were not affected during training.

TABLE 6. Summary of biomarker recovery in studies

Study	Biomarkers measured	Biomarkers recovered	Biomarkers not recovered	Biomarkers not affected during	Recovery measured for
Hamarsland et	13	11	2[a]	0	1 week
Santos et al.	6	5	1	0	63 hours
Szivak et al.	6	1	5[b]	0	24 hours
Henning et al.	10	9	1[c]	0	2-6 weeks
Nindl et al.	12	6	3[d]	3	5 weeks
Gunga et al.	8	5	3	0	72 hours
Opstad 1994	19	6	4	9[e]	4-5 days
Opstad 1982	3	3	0	0	6 days
Kyröläinen et al.	11	8	2[f]	1	2 weeks
Vikmoen et al.	4	4	0	0	1 week[g]
Mourtakos et al.	4	4	0	0	30 days

Note: "Biomarkers measured" includes only markers of which data was reported also during recovery. Note: if a marker was increased over pre values at recovery after being decreased compared to pre during training, it was considered recovered. Or, if a marker was decreased during training, but increased compared to pre at recovery point, it was also considered recovered). [a]= TSH increased only after 1 week, no effect at post, therefore can't be concluded if recovered or not. Categorized here to not be recovered. [b]= NPY was not affected at post, but was decreased at recovery point, therefore not counted as recovered. [c]= T3 was not affected at post, but elevated at recovery point, therefore not counted as recovered. [d]= Lactate was not affected at post, but elevated at recovery point, therefore not counted as recovered. [e]= or no rhythm shown. [f]= T4 and urea were not affected at post (at 7-8 days), but higher at recovery, therefore not considered recovered. [g]= Recovery was measured for two weeks, but all biomarkers recovered within one week.

In the 11 studies that measured biomarkers, all measures of biomarkers recovered during the study period in three studies. However, in the rest of the studies, except Szivak et al. (2018), majority of the biomarkers recovered, and in four studies only one or two biomarkers remained unrecovered. In all studies, more biomarkers were recovered than not recovered, except in Szivak et al. (2018), in which only one out of six biomarkers. However, in the Szivak et al.

(2018) study, the recovery time course was exceptionally short compared to the other studies – only 24 hours.

Therefore, the recovery of biomarkers could be summarized as follows: in three studies, all biomarkers recovered. In four studies, all but 1-2 biomarkers were not recovered. In three studies, all except 3-4 biomarkers were not recovered, and in one study, 5 biomarkers were not recovered.

Also, when noting the indexed letters ([a,b,c,d,e,f]), it is possible that some more markers could be considered recovered with different criterion for recovery, depending on if those markers which were not affected at post but were affected only at the recovery measurements would be considered as recovered or not counted at all. If those would be considered recovered, the summary would be: 5 studies full recovery, 3 studies with 1-2 biomarkers not recovered, and 3 studies with 3-4 biomarkers not recovered.

7.8   Summary of recovery of all markers

Summary of recovery and, therefore, the results for the main purpose of this review are provided in table 7. In short, two studies showed 100% (or full) recovery (or no effect on) of measured markers, 7 studies showed that 79-90% of measured markers were recovered (or were not affected), and in 3 studies, recovery (or no effect was seen) on 44-63% of markers. Stated differently, in two studies, no markers were unrecovered, in three studies 1 marker was unrecovered, in one study 2 markers were unrecovered, in three studies 3 markers were unrecovered, in two studies, 4 markers were unrecovered, and in one study, 5 markers were left unrecovered.

TABLE 7. Summary of physical performance and biomarker recovery.

Study	Biomarkers recovered (or not affected during training?	Physical performance markers recovered (or not affected during training)?	% Of measured markers recovered/not affected?	Recovery measured for
Conkright et al.	Not measured	4/8	50%	6 weeks
Hamarsland et al.	11/13	2/3	81%	1+2 weeks[a]
Santos et al.	5/6	Not measured	83%	63 hours
Szivak et al	1/6	3/3	44%	24h + no[b]
Henning et al.	9/10	Not measured	90%	2-6 weeks
Nindl et al.	9/12	3/3	80%	5 weeks
Gunga et al.	5/8	Not measured	63%	72 hours
Opstad 1994	15/19	Not measured	79%	4-5 days
Opstad 1982	3/3	Not measured	100%	6 days
Kyröläinen et al.	9/11	Not measured	82%	2 weeks
Vikmoen et al.	4/4	2/3	86%	1+2 weeks[c]
Mourtakos et al.	4/4	Not measured	100%	30 days

[a]= Biomarkers were measured for 1 week, and physical performance for 2 weeks. [b]= Physical performance recovery was not measured at all. However, since no physical performance markers were affected at post, the data is reported on the physical performance column. [c]=All markers were measured for two weeks, but all biomarkers recovered within one week.

8 DISCUSSION

The present review examined the current evidence for recovery of physical performance and biomarkers after strenuous military training or operations. Therefore, the main purpose was to assess, if recovery occurs, and how long would recovery take. Secondary purpose was to investigate, which markers are affected after strenuous military training. However, this depends on which markers the researchers have chosen to measure. The main area of investigation was stress-related biomarkers, and the overall stress response of the human body. "Stress related" are biomarkers that are mainly affected by the SAM and HPA responses of the human stress response, such as cortisol and testosterone, which were the most commonly measured biomarkers across studies. However, a lot of different biomarkers were measured and, therefore, a larger picture of the physiological response and recovery to/from extremely strenuous activity can be discussed.

A total of 12 studies were included. In 11 studies, biomarkers were measured along with physical performance being measured in five studies, with four including recovery data. One study only measured physical performance, not biomarkers. In the rest (4) of the studies that measured physical performance, also biomarkers were measured simultaneously.

Based on the evidence gathered, it appears that large physiological decrements occur during and after strenuous military training across the military populations. Full recovery seems to take a varying time and no clear time frames for recovery after a certain length/type of training can be clearly concluded. However, it can be stated that everything less than six days seem to not be enough, and after 1-2 weeks, most markers have probably recovered, although in one study some markers were still measured to be unrecovered even after 6 weeks. Although full, complete recovery of all measured markers only occurred in two studies, almost full recovery (79-90% markers recovered) occurred in majority of the rest of the studies (seven). In three studies, recovery occurred for only 44-63% of the studied markers. These will be discussed with more details below.

When looking at the data of the three studies, where only 44-63% of markers recovered, first, in the study by Conkright et al. (2019), where only physical performance was measured and

50% of markers recovered, the study length was among the longest in this review (62-day Ranger course). However, also recovery was measured for a longer time, 6 weeks. This would indicate that even 6 weeks was not enough for physical performance to recover after an arduous and long training course such as the Ranger training. However, as recovery was assessed, only at the 2 weeks (which was the "post" measurement) and 6 -weeks point, it is such a long recovery time that it could be possibly explained also by maladaptation, if the participants did not conduct the same type of training/activity as before the study. If it is recovery related, it would seem a severe case of NFOR or even OT, as 50% of physical performance markers remained unrecovered after 6 weeks. It would have been interesting if biomarkers were also measured in this study.

The present study included two other studies in which the training courses were the same length and the same training course (U.S Army Ranger course) was conducted. It is interesting that in the study of Nindl et al. (1997), physical performance recovered completely after 5 weeks of training. However, not all, but 9/12 of biomarkers were recovered or not affected. Therefore, the recovery of both physical performance and biomarkers was 80% in this study examining the Ranger course. It is an interesting notion that in Nindl et al. (1997) study, all physical performance measures recovered, but biomarkers did not. This would indicate that even the commonly used indicator of recovery, physical performance, might not factually indicate a complete physiological recovery status, and that physical performance could recover faster than some biomarkers. However, in the study of Vikmoen et al. (2020), which describes a much shorter (5.5- day) extremely demanding field exercise, the opposite result occurred: biomarkers recovered fully within one week, but one physical performance marker (CMJ) remained unrecovered even after two weeks. It is to be taken into account that in the study of Vikmoen et al. (2020), only four biomarkers were measured but the markers were comparable to other studies and decrements were large, for example, testosterone declined -58%. In other studies which measured biomarkers and physical performance, only physical performance was not affected in Szivak et al., (2018), and some biomarkers and some physical performance markers remained unrecovered in Hamarsland et al., (2018). Also, in the study by Nindl et al. (1997), although TBG and SHBG did not return to pre-levels, they did return to normal values within reference range. However, for this review they were not considered recovered due to difference between pre- and recovery measures. This "non-recovery" could be explained by normal differences between measurements, and it is possible that these two markers would not have

returned further toward pre values even if given more recovery time. The last remaining non-recovered biomarker was lactate, which interestingly increased only at recovery point. This could also likely be the result of measurement conditions or errors, as it would not be likely that lactate which pictures acute anaerobic energy production, would elevate only after 5 weeks of training. Therefore, all markers in Nindl et al. (1997), could also be considered recovered, which is an interestingly different result than in Conkright et al (2019).

The third study, which included the Ranger training course, Henning et al. (2014) showed that 9/10 of markers recovered after 2-6 weeks. Only T3 was not recovered and was elevated at recovery point. However, T3 was not affected at post- measurement, therefore, it is difficult to distinguish if it was affected due to the training or for other reasons. In this review, markers, which reacted this way, were not counted as recovered due to a difference to the pre-measurements. However, the results of 90% markers' recovery are also a very different result than in Conkright et al. (2019). When looking at the differences between these studies, there does not seem to be much difference in the training descriptions or demographics. All studies measured the long-lasting U.S Army Ranger course, and the amount of sleep was similar across studies. Energy deficits were not reported to be very different: The energy deficits were 1200 kcal per day (Conkright et al. 2019), 1000 kcal per day (Nindl et al. 1997), and only an amount of 2200kcal of food provided per day was reported by Henning et al. (2014). Therefore, the energy expenditure was probably higher in the study of Henning et al. (2014) than in the other studies. The energy expenditure and amount of sleep seems to not explain the difference in recovery results in Conkright et al. (2019), and clearly more data would be beneficial to examine recovery after long-lasting and extremely strenuous military training. Also, the study by Hamarsland et al. (2018) compares best to the Ranger courses, as it was six weeks in length. In this study, a total of 81% markers were recovered (11/13 biomarkers after 1 week, and 2/3 physical performance markers after 2 weeks), even though the decrements were large, as for example testosterone was lowered by -70%, therefore the recovery of it in one week would seem effective. Here, TSH was not affected at post but only at recovery, therefore it could also be counted as recovered due to not being affected at post. Therefore, cortisol would be the only biomarker remaining unrecovered. It can be concluded, that in these longer lasting training courses, in all the rest except Conkright et al. (2019), a great majority of markers did recover.

Second of the studies in which the least recovery of markers occurred was the Szivak et al. (2018) study. In this study, which lasted for approximately two weeks and included highly demanding SERE training, only one biomarker picturing the acute SAM- axis stress reaction (epinephrine) out of six measured biomarkers had recovered, and as the three physical performance markers were not affected at all, a total of 44% of markers were considered recovered or not affected. In this study, the obvious explanation for "non-recovery" is the time that recovery was measured for, which was only 24 hours. This can obviously be disclosed as too short recovery time after 2 weeks of SERE training. Unfortunately, no other training courses included in the review lasted for two weeks, so direct comparison is difficult to be made here. It is very interesting, however, that physical performance (strength) was not affected at all in this study by Szivak et al. (2018), but all biomarkers were. However, although the participants had done strenuous SERE training for several days, a particular difference was that the stress induced exactly prior to the stress measurement was mainly psychological, simulating a prisoner of war interrogation scene, and therefore the results might not represent responses to a physically extremely demanding training course as well as the other studies, and might explain some of the results on physical performance not being affected.

The third study, which showed the least recovery of biomarkers was the study by Gunga et al. (1996), in which 63% (5/8) of biomarkers measuring a somewhat different aspect than most other studies: markers that are related to blood oxygen transportation, such as EPO and hemoglobin, was measured. As the markers are different than in the rest of the studies and only two of the markers were measured in another study, comparing the markers to other studies is difficult. However, reasons for the relatively low recovery rate can still be discussed. In the study, the recovery measurement was only 3 days, which is a very probable explanation for full recovery not occurring. The training course was also relatively short, as it lasted 5 days. Majority of the included courses (n=7) lasted between 4-7 days, so comparison in terms of length of training intervention is easy.

In all the other studies, in which the training lasted for 4-7 days, recovery was measured to be more complete. For example, the two studies (Opstad, 1982 and Mourtakos et al. (2021) in that full recovery occurred, the training was conducted for five days. However, a common theme in these two studies was that only a few markers were measured, with three markers being

measured in Opstad (1982), and four markers in Mourtakos et al. (2021) It is, however, to be noted that in Mourtakos et al. (2021), the markers were different from the other studies and not even one of the measured markers was measured in other studies, as the markers measured plasma protein denaturation profiles. Therefore, these studies might not represent factual full physiological recovery status as well as most of the other studies, which measured more markers. The recovery periods were 6 days in Opstad (1982), and 30 days in Mourtakos et al. (2021). Despite the fairly short duration of training in the study of Opstad (1982), a large decrement (second largest in all studies) in testosterone (-75%) was seen and recovered from after only 6 days. Also, as a side note, the study by Opstad (1982) included two groups – one group with an energy intake of 1500 kcal per day, and one group with an intake of 6400kcal per day, with the energy expenditure in both groups being a remarkable 8000-11000kcal/day. Also, sleep was less than 2 hours for total during the 5-day course. It is an interesting finding that there were no differences between the groups in the affected markers and recovery times. Therefore, according to the study by Opstad (1982) it seems that the calorie intake/energy deficit does not seem to be the most driving factor causing stress related alterations in biomarkers. Also, according to other research, for example, the reductions in testosterone are mainly explained by the continuous physical stress, not sleep deprivation or energy deficit (Opstad 1992).

For the other four studies which lasted between 4-7 days (Santos et al. 2018, Opstad 1994, Kyröläinen et al. 2008, and Vikmoen et al. 2020), 79-86% of the studied biomarkers recovered. In these studies, recovery was measured for different time-courses: in the study of Santos et al. (2018), 63 hours, with 83% recovery, in the study of Opstad (1994), 4-5 days, with 79% recovery, in the study of Kyröläinen et al. (2008), 2 weeks, with 82% recovery, and in the study of Vikmoen et al. (2020), 1 week, showing 86% recovery of markers. It is interesting that although the training course lengths were similar, but recovery times varied with every study from 63 hours to 2 weeks, not too much difference can be seen in the percentage of markers recovered in these studies. However, it is also to be noted that different measurements and different measurement times were used, and that although the courses are the same in length, the intensity and the amount of food and sleep also varied between studies. It is also hard to make conclusions about intensity since it cannot be fully "standardized". However, according to the inclusion and exclusion criteria, the intensity should be somewhat similar across studies,

but differences in intensity are probable and hard to quantify, since in majority of studies only a description of training along with the amount of food and sleep is provided.

Limitations

Some limitations were already discussed earlier. A major limitation is, that although this review attempted to search for the most strenuous training courses possible, the courses do not necessarily compare to real-life situations. Real-life situations, when in a war-environment, can be unimaginably stressful and simply cannot be simulated in training. First, the psychological stress of potential death cannot be simulated, which could be thought of as a major stressor in addition to the other extremes. Some of the effect of this "real-life" experience has been studied, for example by the study by Trousselard et al. (2009), in which the participants, who were trained and qualified submariners, participated in underwater escape training. The participants had to escape from a land-based tank simulating a submarine that was close to the surface at a depth of 6 meters, and another time from an actual submarine in the depth of 30m on the sea floor. Compared to the simulated exercise at 6 meters, the physiological responses were vastly greater in the experiment from the sea floor, e.g., salivary cortisol was doubled. This indicates that the realism of conditions influences the physiological responses majorly, even though the mission is factually similar.

Another major limitation is the quality of the studies, as described before. As all studies are field studies, it is difficult to reach high scores on quality assessment. Also, due to the nature of majority of the markers, measurement errors and times might play a role in the values. Also, the number of participants were generally low, however, significant changes occurred for majority of the measured markers, which indicates a great effect on measured markers of the training course. It is not also very clear, what the recovery times consisted of, but in majority of cases it was probably lighter military related activity.

Conclusions

It seems that, in most of the studies, at least almost full recovery of markers used to measure recovery would occur when given the appropriate time to recover, although the time seems to

be very varying and in one study only 50% of markers were recovered even after 6 weeks. Also, it is concerning, that in only two studies full recovery occurred, but in majority of markers and majority of studies recovery occurs almost fully. However, it is very common that some markers remain unrecovered. As discussed earlier, some more markers could be considered recovered than reported here, due to differing criteria for recovery. Especially if only one or two markers are not recovered, it might not necessary be related to recovery status, but other factors also may play a role here, as majority of markers would indicate recovery. Overall, the recovery time seems to be varying, but majority of the time, relatively short. The data and results presented are noteworthy due to the extreme nature of the courses and provides promising information about the capacity to recover from extremely strenuous activity in a relatively short timeframe, as majority of the typically measured markers recovered in a relatively short time after extremely strenuous training, sleep and food deprivation, psychological stress, and environmental extremes. However, no recovery strategies were reported to be used, so recovery could possibly be made more effective. As a takeaway, it is important to measure recovery with various markers, especially after longer strenuous training courses.

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