CORTICAL AND MUSCULAR PROCESSES OF MOVEMENT PREPARATION:

AN ELECTROPHYSIOLOGICAL APPROACH IN HEALTHY AND LOW BACK PAIN POPULATIONS

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AN ELECTROPHYSIOLOGICAL APPROACH IN HEALTHY AND LOW BACK PAIN POPULATIONS

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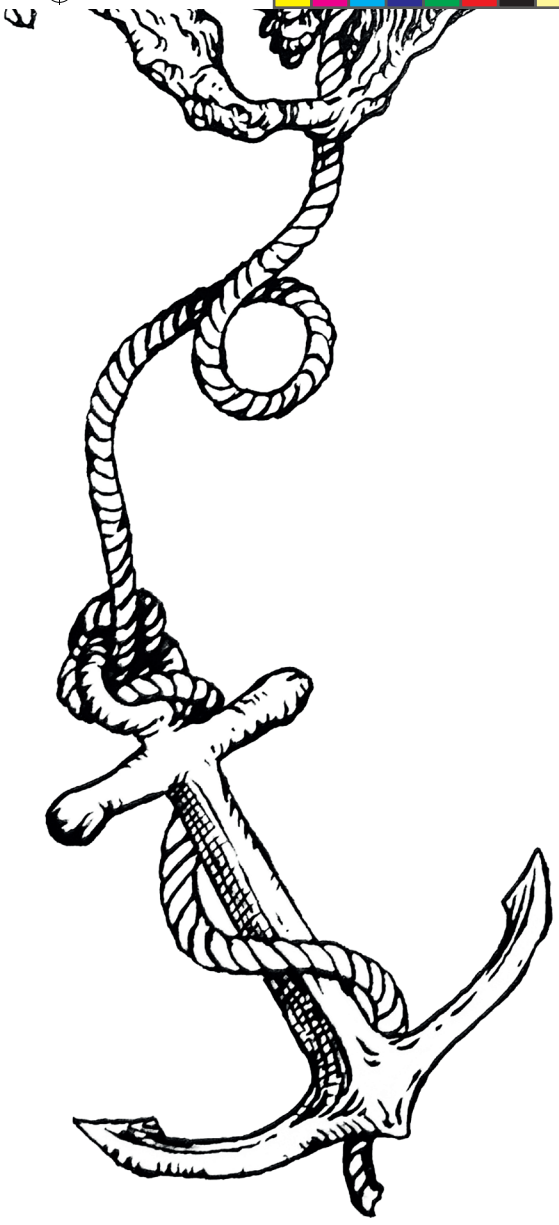
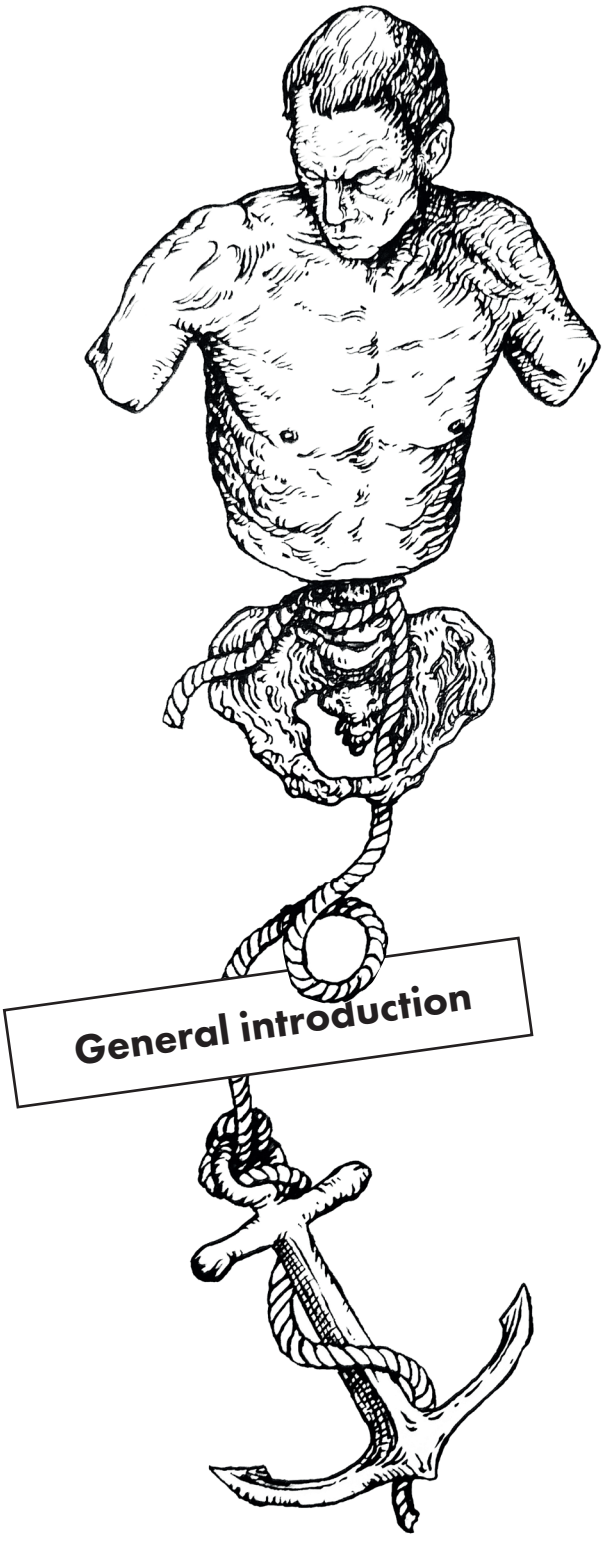


Abbreviations

AD — Anterior Deltoid muscle
ADL — Activities of daily living
AEP — Auditory Evoked Potential
ALBP — Acute low back pain
APA — Anticipatory postural adjustment
BDNF — Brain Derived Neurotrophic Factor
BP — Bereitschaftspotential
CE — Cognitive exertion
CIS — Checklist Individual Strength
CLBP — Chronic low back pain
CMRR — Common mode rejection rate
CNS — Central nervous system
CNV — Contingent Negative Variation
COMT — Catechol-O-methyltransferase
CSI — Central Sensitization Inventory
CSQ — Coping Strategy Questionnaire
CT — Computed Tomography
DOI — Diffuse Optical Imaging
EEG — Electroencephalography
EMG — Electromyography
EO — External Oblique muscle
ERP — Event Related Potential
ES — Erector Spinae muscle
FABQ — Fear-avoidance Beliefs Questionnaire
(f)MRI — (functional) Magnetic Resonance Imaging
FRN — Feedback-Related Negativity
FRR — Flexion-relaxation ratio
FVAS — Visual analogue scale for fear
HADS — Hospital Anxiety and Depression Scale
HC — Healthy control
ILT — Iliocostalis Lumborum pars Thoracis muscle
IO — Internal Oblique muscle
IPAQ — International Physical Activity Questionnaire
LBP — Low back pain
LoC — Level of conclusion
LoE — Level of evidence
LRP — Lateralized Readiness Potential
MCMI-II — Millon Clinical Multiaxial Inventory
MET — Metabolic equivalent
MF — Multifidus muscle
NE — No exertion
NOS — Newcastle-Ottawa scale
OPRM 1 — μ-Opioid Receptor
PASS — Pain Anxiety Symptoms Scale
PCL — Pain Cognition List
PCS — Pain Catastrophizing Scale
PE — Physical exertion
PEP — Perturbation Evoked Potential
PET — Positron Emission Tomography
PHODA — Photographs of Daily Activities
POMS — Profile of mood State
PRISMA — Preferred Reporting Items for Systematic reviews and Meta-Analyses
PVAQ — Pain Vigilance and Awareness Questionnaire
RA — Rectus Abdominis muscle
RAM — Rapid arm movement task
RLBP — Recurrent low back pain
RLBP- — Pain free recurrent low back pain
RLBP+ — Pain flare recurrent low back pain
RMDQ — Roland-Morris Disability Questionnaire
RoB — Risk of bias
ROM — Range of motion
RPE — Rating of perceived exertion
RT — Reaction time
sALBP — Subacute low back pain
SD — Standard deviation
SEP — Somatosensory Evoked Potential
SMC — Sensorimotor control
TrA — Transversus Abdominis muscle
TSK — Tampa Scale for Kinesiophobia
VAS — Visual analogue scale



1 Prelude

The brain can be regarded as the central drive that defines all human behavior through the guidance of our senses, thoughts, emotions and movements. All voluntary movements are initiated in the brain and are continuously adapting to the ever changing environment that surrounds and affects us humans. However, if the brain is the 'software' of human behavior, it needs the appropriate hardware, i.e. the body consisting of all peripheral structures, muscles, joints, organs, arteries,... in order to function and be.

"Mens sana in corpore sano." (Decimus Iunius Iuvenalis)

This well-known quote, which is Latin for "A healthy mind in a healthy body", illustrates the important interplay between mind and body, software and hardware, central nervous system (CNS) and peripheral factors that makes us who we are... or which can break us if things short-circuit, for instance in chronic pain. One of the most common and most disabling, but still insufficiently understood (chronic) pain syndromes is low back pain (LBP). Since a lot of mechanisms underlying or contributing to LBP are still unclear, this dissertation examined the interplay of both peripheral and central factors associated with movement preparation in relation to LBP in order to try and further elucidate this enigma.

2 Low back pain

2.1 Definition and epidemiology

Low back pain (LBP), commonly characterized as pain arising between the lower border of the rib cage and the inferior gluteal folds[133], is one of the biggest health issues of our modern day society[240]. It is highly important to stress that low back pain is not a diagnosis, but rather a symptom presentation of one or more underlying disorders, whether or not these underlying disorders are known.

About 70-85% of all people experience at least one episode of LBP during their lifetime[4, 9], which leads to very high global point prevalence rates for LBP ranging between 19-37%[82]. In 90% of the cases an acute episode of LBP is followed by an adaptive healing and recovery process and pain complaints disappear over time. However, the remaining 10% will experience ongoing symptom recurrence or persistence throughout their lifetime.[80, 241, 242] Recurrence rates of LBP episodes range between 20–44% within one year for working populations[57, 236], and can even amount up to 85% for lifetime recurrence rates[236]. As for the majority of LBP patients the complaints cannot be precisely diagnosed, about 85% of all cases are deemed non-specific LBP.[68] However, factors like higher level of baseline functional disability and presence of sciatica at the acute LBP onset[42], previous episodes of LBP, presence of other chronic disorders, poor mental health, smoking, obesity, low levels of physical activity, genetics, heavy manual labour, and bad posture are often considered as risk factors for persevering complaints.[98] The impact of these ongoing LBP complaints cannot be underestimated, as CLBP is thé leading cause for disability worldwide[240] and the number one reason for sick leave and early retirement in Europe[27]. Despite a growing amount of research, prevalence and incidence rates of LBP have increased over the years and still a lot of uncertainties regarding the chronification process of LBP remain. Reported years of disability due to LBP increased with 54% between 1990-2015 and the prevalence of activity-limiting LBP increased with 17.3%. worldwide between 2005-2015.[240] This puts a very high toll on the socio-economic system of several countries. Both direct costs, due to an increased burden on healthcare systems, and indirect costs, due to work absenteeism, sick leave and a diminished productivity are rocketing sky high.[58]

2.2 (Low back) pain neurophysiology in a nutshell

In order to properly understand LBP, chronification, and the often-used terminology in this regard, a short overview of the most important mechanisms and key terms in pain neurophysiology is required.

Acute pain is an adaptive response to sensory input which is interpreted by the CNS as being threatening or harmful and which acts as a warning signal aimed at protecting the organism for further harm or pain.[248] Two major types of input that can cause acute pain can be discerned. The first type, **nociceptive pain**, is pain that arises from actual or threatened damage to non-neural tissue which activates nociceptors.[118] The second type is caused by a lesion or disease of the peripheral somatosensory nervous system and is called **peripheral neuropathic pain.**[118]

The nervous system is a highly adaptive system with a lot of capabilities for alterations in its structure, function and connections.[55] Due to pain, neuroplastic changes might arise, which often cause sensitization of the peripheral and/or central nervous system.[195, 232]
Peripheral sensitization can only occur when actual tissue damage is present, and can often be found in acute LBP[211]. Due to the release of biochemical byproducts the responsiveness of peripheral nociceptors is increased[189], which results in **primary hyperalgesia** (= enhanced pain from a stimulus that normally evokes pain[118], but only in the vicinity of the damaged area)[137] and enhanced signaling of pain stimuli towards the CNS as well[56].
Central sensitization refers to enhanced excitability of nociceptive neurons in the central nervous system to normal or subthreshold stimulation.[118] It is most often characterized by three main mechanisms: **1) secondary hyperalgesia** (= enhanced pain from a stimulus that normally evokes pain[118], but in distant body parts which are not in the vicinity of a damaged area), **2) allodynia** (= pain due to a stimulus that does not normally provoke pain[118]) and **3) generalized, widespread and referred pain**. Possible underlying mechanisms for central sensitization are enhanced wind-up[165, 212] and long-term potentiation[124, 141, 150] of the neurons in the spinal cord and brain. Furthermore, top-down central endogenous pain inhibiting and facilitating mechanisms exist, which can down- or upregulate the pain experience. A disbalance in these central modulating mechanisms, i.e. enhanced facilitation and/or diminished inhibition, can also be responsible for hyperexcitability of the CNS.[102, 254] Cognitions, emotions, attention, stress,... originating from the brain are considered to play an important role in these central mechanisms since these factors can contribute to pain facilitation or diminished inhibition.[73, 185, 191] This highlights the importance of studying cognitive-affective factors in relation to (low back) pain.
Pain that is caused by neuroplastic alterations of the CNS, and which mostly arises due to central sensitization mechanisms, has recently received a new name and definition endorsed by the International Association for the Study of Pain, i.e. **nociplastic pain** (= pain that arises from altered nociception despite the fact that there is no clear evidence for the activation of peripheral nociceptors due to actual or threatened tissue damage nor evidence for a disease or lesion of the somatosensory system, which could cause the pain).[118]

If pain perseveres beyond the physiologically expected time-frame of its natural healing process it is called **chronic pain**. In most of the cases, especially in non-specific pain syndromes, this type of pain is no longer related to peripheral damage. Hence, it does not have a biological warning function for threat of further harm as is the case with acute pain.[97] Chronic pain is often associated with adaptations in pain processing due to several of the aforementioned neuroplastic changes and central sensitization processes. Hence, we often see widespread pain and nociplastic pain complaints in these patients.[176, 177]

2.3 LBP classifications

Due to the immense heterogeneity of possible causes for LBP complaints, the group of LBP sufferers should not be assessed as one and the same entity. Therefore, with regards to the classification of LBP disorders, distinctions on several levels have been made in previous literature.

2.3.1 Causality-based classification.

A first important distinction is typically made between specific and non-specific LBP, which refrains to the causality of the complaints. The term **specific LBP** refers to complaints with a clear and well-diagnosed underlying cause, with often structural deficiencies, like for instance vertebral fractures, spondylolysis, -isthesis, metastases, fractures, rheumatological diseases, infections, tumors, disc herniations, sprains or strains, and degenerative processes. Non-specific LBP, however, is characterized by the absence of or inability to detect any patho-anatomical explanations for the complaints at hand.[158] Importantly, **non-specific LBP** sufferers are also more likely to develop a recurrent (RLBP) or chronic state of LBP (CLBP).[18, 179] This brings us to the second important distinction that can be made when talking about LBP, i.e. a distinction based on the duration of complaints.

2.3.2 Duration-based classification.

Four major groups can be defined: acute, subacute, recurrent and chronic LBP.

Acute low back pain (ALBP) is commonly defined as a solitary pain episode suddenly occurring, without a previous history of LBP complaints in the 6 months before onset of that episode, and not exceeding a duration of 6 weeks.[133]

Subacute low back pain (sALBP) is commonly defined as a solitary pain episode suddenly occurring, without a previous history of LBP complaints in the 6 months before onset of said episode. It differs from ALBP with regards to the time frame of complaints that exceeds 6 weeks up to maximally 12 weeks.[133]

Recurrent low back pain (RLBP) is commonly defined as episodic LBP with an onset of at least 6 months ago and a minimum of 2 pain episodes[210], also called pain flares, per year. One pain episode is characterized by minimally 24 hours of pain preceded and followed by a pain free period of at least 1 month.[64] Depending on whether a RLBP sufferer is currently experiencing pain or not, a further subdivision is often made into pain free RLBP (RLBP-) and RLBP during a pain flare (RLBP+).

Chronic low back pain (CLBP) is commonly defined as continuous LBP with an onset of at least 3 months ago.[118] Based on recommendations of the United States National Institutes of Health Task Force on Research Standards for CLBP, the pain should also be present in at least half of the days since first onset.[67] In this dissertation, this group is further distinguished from the RLBP group by the extra criterion of experiencing complaints for at least 3 days per week, without prolonged pain free periods in between complaints.

In previous research this subdivision is not always adhered to. Oftentimes only CLBP and ALBP groups are described or mentioned and the sALBP and RLBP subdivisions are overlooked. Some authors do not even recognize the difference between episodic RLBP and continuous CLBP, assessing these two clearly different groups as one entity. In this connection, acute and subacute LBP are sometimes referred to as early stage LBP, and if these complaints would persist beyond their designated time frame or tend to recur over time they would enter into late stage LBP, which respectively entails RLBP and CLBP. However, based on recent studies in our and other research groups it is suggested that the chronification process of LBP might be a continuum. In this continuum, it is proposed that LBP might gradually evolve from ALBP and sALBP over RLBP to CLBP, with increasing functional[93] and muscle structural alterations[93, 116], and different pain processing mechanisms and behaviors[92] in the later stages of LBP. The key of further unraveling the chronification process might lie within the presence or absence of some of these associated factors or the extent to which they present themselves in an individual. Therefore, we believe adhering to the abovementioned classification of ALBP-sALBP-RLBP-CLBP and distinctly examining these groups when conducting LBP research can be recommended in order to diminish heterogeneity in the studied populations and outcomes.

Furthermore, this will make it possible to further explore differences between these groups that might add to the understanding of the chronification process.

2.3.3 Location-based classification.

Back pain can also be classified based on the anatomical presentation of the main complaints. **Local pain** refrains to pain at the low back or lumbosacral area. **Referred pain** is pain of an often more distant source which extends towards areas with a shared embryological origin. **Radicular pain** is pain represented in distinct dermatomal areas related to a specific nerve root that is involved in the LBP complaint.[78] Besides this, LBP complaints can also have a **unilateral, central** or **bilateral** localization in relation to the spine. LBP can sometimes be part of more **diffuse or multi-site pain** syndromes which comprise multiple anatomical pain locations. For instance, some people suffer not only from LBP, but concurrently experience pain in other spinal regions such as the thoracic, cervical or sacral areas. Moreover, in some cases chronic pain can even be distributed over more distant body locations as well (arms, legs, hands, feet, knees,...). This is called **chronic widespread** pain, and is most often related to fibromyalgia.[10, 79, 223, 247] However, it can also be the consequence of other specific systemic disorders (e.g. neurological disorders, rheumatic disorders, non-rheumatic musculoskeletal conditions, myelopathy, spinal stenosis, myopathy, myositis, mental health disorders,...)[100], or it can be a result of CNS adaptations which is the case in central sensitization.[125]

2.3.4 Pain mechanism-based classification.

It often remains an enigma why in a group of (sub)acute LBP sufferers with seemingly similar initial complaints some people tend to develop persisting or recurring complaints, whereas others fully recover. This implies that even when using a duration-based classification to describe LBP populations, within each of these groups an important heterogeneity might remain present. Especially in the non-specific LBP group various, often unknown or unclear, causes or contributing factors to the complaints might be at play within each one of the subgroups. For instance, two non-specific CLBP sufferers seldom present themselves with an identical presentation and evolution of complaints. In order to guide clinicians' clinical reasoning process concerning pain several mechanism-based classifications for (low back) pain have been developed over the years, which attempted to take this heterogeneity into account.[12, 39, 48, 66, 90, 91, 127, 147, 175, 206, 237, 249, 250] This mechanism-based reasoning applies a multi-dimensional perspective on pain, since it acknowledges the simultaneous presence of multiple mechanisms during the experience of pain. However, the mechanism(s) which is(are) dominant in the onset and/or maintenance of the pain experience of an individual patient determine(s) the classification.[90, 91, 128] The following pain mechanisms were initially proposed and form the basis of most of these mechanism-based classifications: nociceptive, peripheral neuropathic, central (now termed nociplastic), autonomic and motor, and affective mechanisms.[91, 127] Louis Gifford[90] expanded on this by combining the knowledge of stress biology and pain neurophysiology with a biopsychosocial perspective on pain in the development of the 'Mature Organism Model' **(FIGURE 1)**. More recently Smart et al.[206, 207] proposed a derived mechanism-based classification with three categories, i.e. nociceptive, peripheral neuropathic, and central (i.e. nociplastic) mechanisms, as they believe this to be a more practical terminology for clinicians.

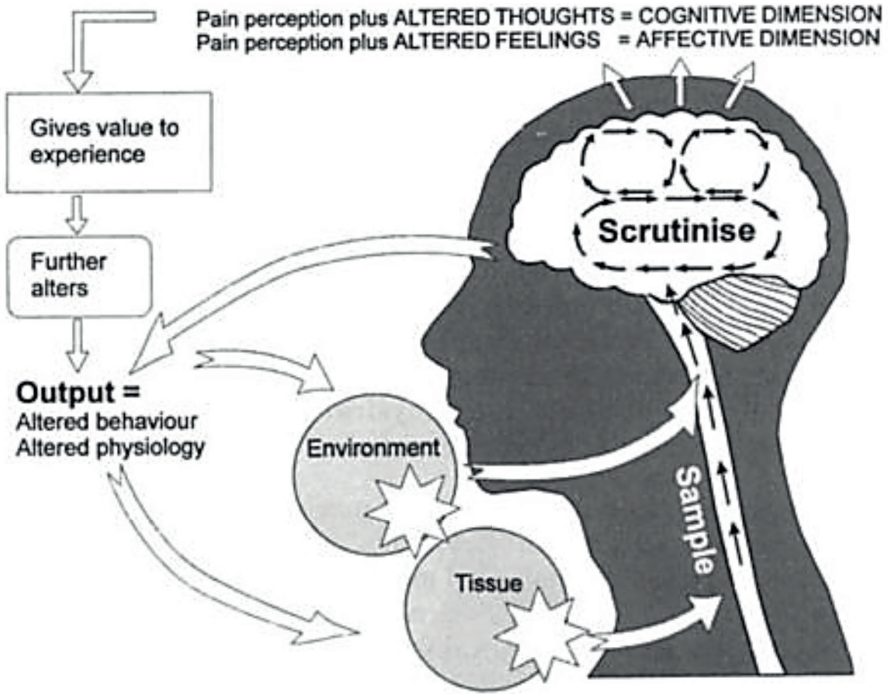


FIGURE 1. The mature organism model illustrates how stimuli or stressors from the environment or body tissues (= input) are scrutinized in the brain (= processing). Based on factors like factors like thoughts, emotions, previous experiences, knowledge, beliefs, and socio-cultural aspects these stimuli are then either interpreted as painful or not, which on its turn affects the organism's behavior and physiology (= output). This altered output can have an effect on the input again as well and could constitute an ongoing cycle. Furthermore, these responses show a high adaptability due to the plasticity of the CNS which is constantly scrutinizing itself, the information it receives, and the responses it generates. Adapted from Gifford et al.[90]

There is no clear consensus about the various aforementioned mechanism-based classifications, but in essence they mostly discern highly similar pain mechanisms. Hence, an integrative view on these different classifications from a neurophysiological perspective can be summarized as follows: **1) input** can be considered as stimuli of nociceptive, peripheral neuropathic or humoral origin, as well as mechanisms of the immune system, and environmental factors captured with the general senses; **2) processing** of the aforementioned input, and interpretation of this input as either painful or not, can be regulated by cognitive-affective influences (thoughts and emotions), nociplastic mechanisms and central sensitization processes; **3) output** refers to autonomic, neuroendocrine, immune, and motor system responses to the pain.[39, 90, 91, 206]

The primary focus of the experimental part of this dissertation will lie on the non-specific LBP groups in the recurrent and chronic stages from a biopsychosocial perspective, since the ethiopathology of these types of LBP are insufficiently understood and have the least favorable treatment outcome. Furthermore, processing and output mechanisms in relation to these LBP groups are of high interest for this dissertation as disturbances in these mechanisms are considered to play an important role in LBP chronification. The following paragraphs will provide some more background specifically concerning the motor response system (output) in relation to LBP, whereas later on in the general introduction cognitive-affective factors (processing) will be discussed as well.

2.4 Low back pain-motor interactions

It was established earlier (in '2.1 Definition and epidemiology') that LBP has an enormous impact on our society, and healthcare system. Besides this rather economical point-of-view it is essential to assess the impact of LBP on an individual level as well. One of the most important consequences of LBP is that it can affect the way patients move[114], which is also reflected in the altered motor system responses concerning the output mechanisms of the aforementioned mechanism-based reasoning models. In an initial phase, e.g. in acute pain, modifications in movement can be adaptive and aimed at reducing pain and discomfort, or protecting tissues from further harm and deterioration of the LBP complaints[94]. However, when these modifications persist in the long-term, for instance in chronic patients, they often become maladaptive. This means that due to altered tissue loading and prolonged mechanical stress on several tissues, detrimental rather than beneficial effects on the LBP complaints and movement performance can arise[38, 61, 180]. Movement alterations in LBP are highly variable and not always present in all patients. Furthermore, it is often difficult to distinguish whether specific movement alterations are causative for LBP, consequential to LBP, or both. Movement alterations found in patients might have arisen prior to the back pain and could be part of the cause of the complaints. Whereas, altered movement might be a consequence instead of a cause of the LBP complaints as well. Studies that induced experimental pain to mimic LBP in healthy people have been able to reproduce similar changes in trunk (sensori)motor control (SMC), which is an underlying mechanism for movement performance, as are described in clinical LBP populations.[109, 168, 169] This highlights that certain deficiencies in SMC, and thus more generally in movement performance as well, might be secondary to pain. However, this does not rule out that LBP might also be consequential to disturbed SMC or movement impairments.[108, 235]

Regardless of this cause-effect discussion several factors that play a role in movement performance have been shown to be altered in LBP populations. For instance, delayed onset of certain trunk muscles[112], decreased trunk muscle activity[149, 202], less relaxation capacities of trunk extensor muscles during movement[199], diminished proprioception[36, 225], changes in segmental mobility[54, 135] and lumbar range of motion[54], less trunk muscle strength[22, 120, 203, 219, 222] and endurance[2, 28, 31, 231], slower movement reaction times [5] and disturbed balance parameters[41, 153, 188] were described in various LBP populations. One of the most important systems affected in LBP is trunk SMC as this plays a crucial underlying or contributing role in several of the aforementioned movement performance outcomes.

3 Trunk (sensori)motor control

3.1 Characteristics and working mechanisms

SMC can be described as "the way in which the central nervous system produces, activates and coordinates purposeful movements in interaction with the rest of the body and the environment."[140] This includes cognitive processes that influence the production of movements by integrating sensory information about the current state of the body and the outside world.

The main working mechanisms of SMC are based upon two concepts, i.e. feedforward and feedback processes. **Feedforward** is anticipatory or preparatory activity that arises before an action or movement is initiated in order to make sure that this action is optimally tailored to the task-at-hand. Past learning experiences, previously formed motor programs, and the physical and cognitive resources available at the time will determine this feedforward activity. This is reflexive, subconscious, preprogrammed activity based on internal motor programs. It can be modulated by the amount of information or resources available for the action to come, but it is outside of conscious control.[88, 119]

In order to respond and adapt to expected or unexpected input from the environment or from within the person itself, **feedback** processes are used. Feedback can only occur during or after an action has been initiated and is a process necessary for flexible adaptation to the environment or the demands or consequences of a certain task.[88]

Interaction between both processes is highly important for optimal SMC. Feedforward processes are generated in the motor cortex and instigate a motor plan for a movement or load before it is applied to the body. The subsequent

feedback loop that reacts to the sensory input of this movement/load can modify motor commands. Due to this the motor behavior in process can be adjusted if needed, for instance when the actual motor demands are in mismatch with the demands that were expected based on the feedforward motor program.[65, 204, 209] Records of these processes (i.e. 'efference copies') are being stored in higher brain centers and are used to optimize motor programs for future reference. Thus, feedback processes are paramount for motor learning, which can also lead to adaptation of feedforward processes.[119] **(FIGURE 2)**

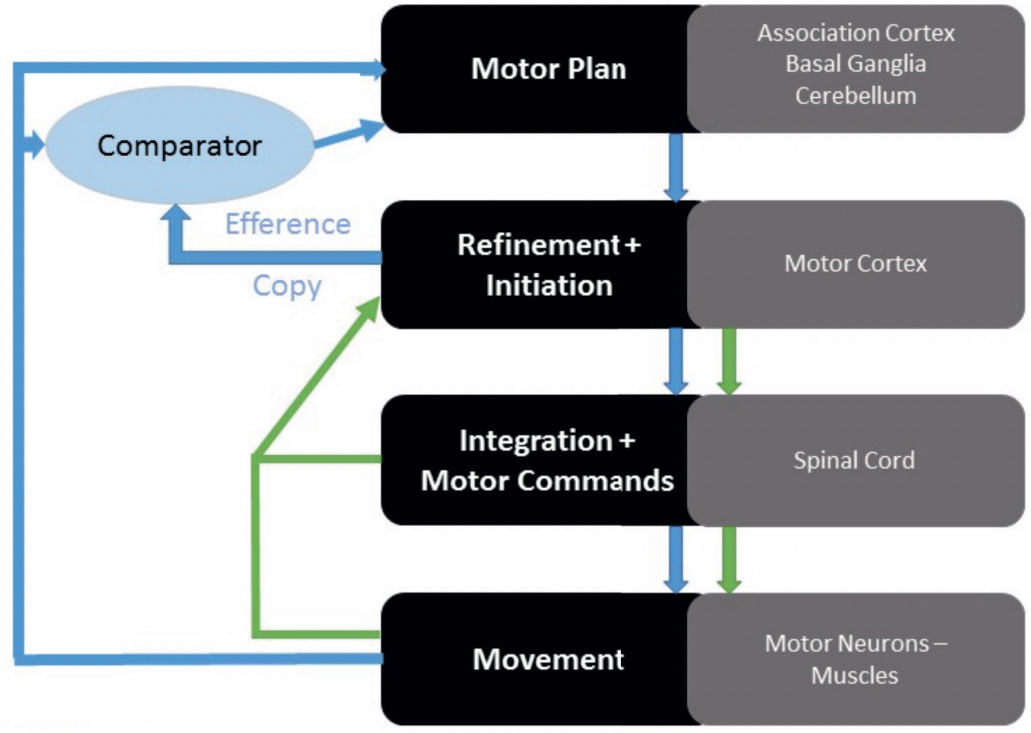


FIGURE 2. Schematic and simplified overview of feedforward and feedback processes in voluntary human movement, and the brain areas related with these processes. When conducting voluntary movement, a (variable) motor plan is formed in the higher brain areas based on information such as previous movement experiences, emotions, sensory input, the movement goal, and the context/environment the person is currently in. This motor plan is further refined and initiated in the motor cortex, which sends the motor signal down to the spinal cord. In the spinal cord sensorimotor integration takes place, i.e. integration between the aforementioned motor plan and incoming sensory information from the peripheral nervous system. This finally results in a motor command which is sent to the motor neurons in the muscles and leads to movement execution. Open-loop feedforward (blue arrows) and closed-loop feedback (green arrows) processes play an important role in these processes. Adapted and modified from Ives et al.[119].

One of the ultimate challenges of SMC is to attain and retain optimal **balance and posture control.**[108] This is acquired through the interplay of proprioception and a tailored motor output, i.e. the right timing and patterns of muscle recruitment and amount of muscle activation in order to reach or retain the required bodily positions. This is a dynamic process of constant fine-tuning of motor output in response to adaptations in sensory input[201], that can either be externally generated by changes in the environment or internally generated by changes in the individual itself[106]. This is not only the case during static behaviour. During the execution of dynamic movements these processes are also at play

in order to coordinate not only the desired movement execution, but also provide for optimal balance and posture of the entire body.[104, 111, 160] In this regard, one can easily understand that optimal SMC also contributes to strength, endurance, speed and coordination of all movement and thus has a key role in movement performance.

3.2 (Sensori)motor control and low back pain

The previous paragraphs show that SMC is an extensive and multi-faceted concept which plays an underlying or contributing, but also less visible, role in a lot of movement processes. It has already been mentioned that trunk SMC alterations often are present in LBP patients. Due to this, altered trunk SMC is regarded as one of the key factors that might underlie or contribute to ongoing and recurring LBP complaints.[11, 43, 167] Further examination of this relationship between LBP and trunk SMC might add to the understanding of the chronification process of LBP, which to this day is far from fully unraveled. Therefore, in this dissertation the focus lies mainly upon **SMC of the trunk in relation to LBP.** To date, most research has focused on either peripheral factors in trunk SMC, e.g. muscle activation and recruitment patterns, or central factors, i.e. CNS indices of movement preparation, activation, coordination or control. Very rarely both peripheral and central factors have been examined together. However, as defined earlier SMC consists of the interplay between both. Therefore, it is this dissertation's intention to examine both peripheral and central processes related to trunk SMC, and where possible to examine the interplay between these processes.

4 Peripheral factors in (sensori)motor control

4.1 Characteristics

Peripheral factors concerning SMC in this dissertation are regarded as all (sensory) input and (motor) output that is either generated by or taking place in tissues and structures innervated by peripheral nerves. In other words, everything besides the CNS is considered as peripheral. For instance, muscles, ligaments, tendons, bony structures and even the skin tissue are all structures considered to contribute to SMC.[115] The passive structures that were mentioned mostly provide sensory and proprioceptive information in the SMC process, whereas the muscles are the active effectuators in SMC. Coordinated activity of the trunk muscles can provide control of the trunk and the spine in a variety of contexts and with a synergy between external and internal forces.[108] Furthermore, muscle activity and recruitment patterns can be measured reasonably easy and are therefore optimally suited as a peripheral derivative for SMC. Therefore, muscle activation patterns were used as a main measure for peripheral trunk SMC in the current dissertation.

4.2 Trunk muscle anatomy and function (brief)

The trunk muscles are active structures guided by the CNS, and act in interplay with passive structures (e.g. joint capsules, ligaments, vertebrae and discs) in order to neutralize variable stability demands due to external and internal loads afflicted to the spine.[181] The most important functions of the trunk muscles are considered threefold: 1) absorbing or controlling external forces afflicted to the trunk, 2) maintaining segmental control and dynamic stability of the trunk during posture and movement, 3) generating movement.[26, 49, 52, 74] In the past, an **anatomical subdivision** of different muscle groups was made into 'local muscles' versus 'global muscles'.[26]

The **local muscles** (e.g. Multifidus, Transversus Abdominis muscles) were deemed mainly responsible for maintaining segmental control. This because of their close anatomical location near the vertebral segments, and their ideal orientation to control these segments by applying a compressive force on them that adds to the stability of the passive structures.[49] It was shown that without these muscles the spine would 'buckle' or collapse, even if other more superficial muscles were active.[26, 49] Furthermore, due to their mainly inter-segmental orientation and smaller

muscle mass these muscles were deemed less suited to generate large trunk movements.
The '**global muscles**' on the other hand, representing the more superficial multi-segmental muscles with larger muscle mass (e.g. Erector Spinae, Rectus Abdominis, Internal Oblique, External Oblique muscles) were thought to have their function in absorbing external forces or generating movement themselves.[26, 49]
However, **on a functional level** this subdivision was nuanced in later years, as it became clear that all trunk muscles have a role in dynamic control of the trunk, and not only the local muscles.[239] What muscles are more active for retaining dynamic control depends on the type of movement or posture, direction and amount of load of forces applied on the trunk[50]. Synchronous co-contraction of agonistic and antagonistic global muscles, resulting in a net compressive force on the spine is the underlying mechanism that also makes these global muscle groups suited for postural control and dynamic stability.[52, 142, 239] Furthermore, it is important to keep in mind that, although less suited for this type of activity, the local muscles can also contribute to movement generation. An overview of the complete anatomy of all the trunk muscles would be exceeding the purpose of this dissertation. However, the trunk muscles specifically examined in this dissertation are depicted in **FIGURES 3 and 4.**

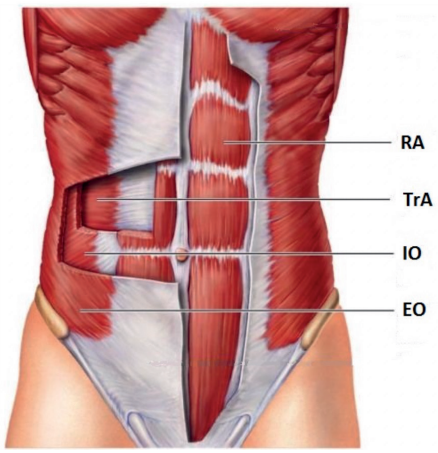


FIGURE 3. Abdominal trunk muscle anatomy. Abbreviations: EO, External Oblique muscle; IO, Internal Oblique muscle; RA, Rectus Abdominis muscle; TrA, Transversus Abdominis muscle. Adapted from Pearson Education, Inc. (2009) (https://i.pinimg.com/736x/6e/d1/e8/6ed1e8f949608d-fd905f14bc9627dfae.jpg)

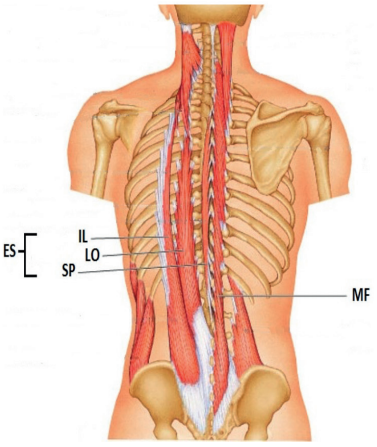


FIGURE 4. Paraspinal trunk muscle anatomy. Abbreviations: ES, Erector Spinae muscles; IL, Iliocostalis muscle; LO, Longissimus muscle; MF, Multifidus muscle; SP, Spinalis muscle. Adapted from Pearson Education, Inc. (2004) (http://www.napavalley.edu/people/briddell/Documents/BIO%20218/11_LectureOutline.pdf)

4.3 Measurement of trunk muscle activation patterns

4.3.1 Electromyography

Electromyography (EMG) is the most commonly applied measurement technique to assess muscle activity. This technique relies upon the bioelectrical byproducts that are generated when muscles contract, i.e. action potentials.[192] These action potentials are measured with electrodes that are either placed upon the skin surface above the muscle(s) of interest, or by fine-wire or needle electrodes that can be inserted into the muscle belly of less superficially located or smaller muscles. These techniques are respectively called surface **(FIGURE 5)** and fine-wire EMG **(FIGURE 6)** and both have their advantages and disadvantages.[20, 21, 45, 46, 126, 196, 243] EMG can be used to

examine timing of muscle contractions and muscle contraction patterns, as well as the amount of contraction and the endurance of contractions over time. Due to this it is exceptionally well-suited for the assessment of SMC through muscle activity.

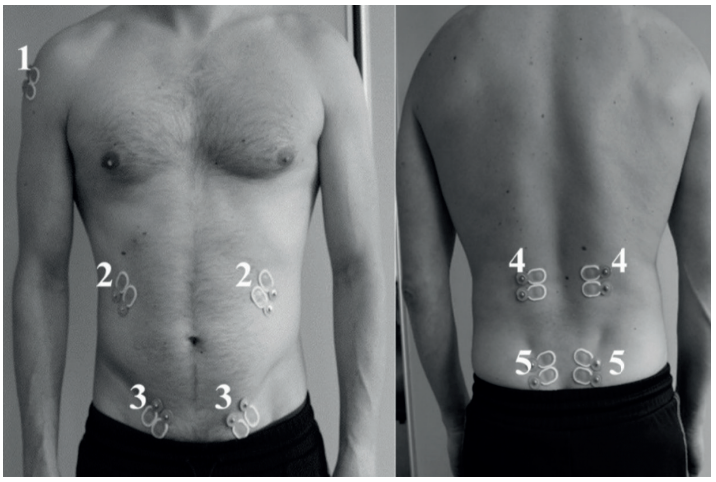


FIGURE 5. Example of electrode placement for surface EMG measurement. Legend: 1, Anterior Deltoid muscle; 2, bilateral External Oblique muscles; 3, bilateral Internal Oblique/Transversus Abdominis muscles; 4, bilateral Iliocostalis Lumborum pars Thoracis muscles; 4, bilateral Multifidus muscles.

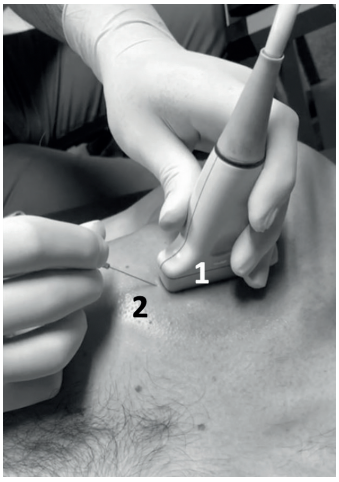


FIGURE 6. Fine-wire EMG insertion into the Pectoralis Minor muscle. Legend: 1, echographic probe; 2, needle with fine-wire EMG electrode. Image by Kelly Berckmans

4.3.2 Peripheral measurement of feedforward and feedback

It was mentioned earlier that feedforward, i.e. preparatory activity before movement, and feedback, i.e. regulatory activity during or after movement, are important mechanisms with regards to SCM. EMG can be used to assess both mechanisms on a peripheral muscle level by assessing the muscle activity during several movement tasks, of which balance tasks are the most commonly studied. The muscles of the trunk can respond in different ways to movements or perturbations that might disturb the balance and posture of an individual.

Feedback muscle activity originates after a movement was initiated, that was either externally or internally generated. It can be assessed by measurement of so-called '**compensatory postural adjustments**'.[13, 29, 162] This is reflexive muscular activity that arises to maintain or regain spinal control when getting out of balance due to a perturbation or movement. A common way to investigate this mechanism is by using external perturbations, for instance the sudden addition or removal of an external load[139, 148, 157, 187, 188, 190] or an unexpected movement of the support base on which a person is positioned[1, 34, 85, 174]. These can be described as actions originating outside the individual that cause a disruption of balance, which then need to be counteracted by an automated core muscle feedback activity. The external perturbation can either be expected or unexpected.

Alternatively, '**anticipatory postural adjustments' (APA)**, which reflect automatized preactivation of several muscles prior to a predictable balance perturbation or movement, can be studied as a measure for feedforward activity.[35, 81, 143] In this regard, internal perturbations are frequently studied. These perturbations are self-generated by the individual and might cause a predictable challenge of the equilibrium of the core. Based on the knowledge the individual has about the properties of the expected perturbation, automatic anticipatory preactivation of several muscles will occur in order to maintain a balanced and stable posture during the perturbation or movement.[77, 161, 216] These APAs are thought to be based on preprogrammed, but highly adaptive motor scripts in the supplementary and primary motor cortex of the brain.[138] Different movement tasks have been used to study APAs, but

most commonly peripheral limb movements, i.e. rapid arm[110, 253] or leg movements[172], are used to incite an internal perturbation of the trunk. The preactivation of several trunk muscles prior to the arm or leg movements that incite movement are then called APAs. Often, additional weights are attached to the peripheral limbs or maximization of the peripheral movement velocity is requested to ensure sufficient postural perturbation that will incite APAs.[129]

4.4 Anticipatory postural adjustments: theoretical background

The scope of this dissertation is to examine movement preparation processes, occurring prior to movement. Therefore, from now on in this dissertation we will only mention feedforward APA activity, without discussing feedback compensatory postural adjustment activity, as the latter occurs after movement initiation.

4.4.1 APAs in healthy people.

Since its first mention in the late 1960's[23] APAs have been extensively studied in different body areas and in relation to various movements and tasks that challenge postural control in humans. In this dissertation specifically the APAs regarding trunk motor control -and not in for instance upper or lower limb muscles- measured with EMG will be addressed.

Functions and main characteristics. The primary functions of APAs are believed to be threefold and consist of 1) centre of mass control[16, 81], 2) preservation of control and stability on a segmental level[107] and 3) initiating and guiding movement production[172]. APAs of the trunk muscles are usually studied in a time frame between -100[184] and +50ms[14] around the onset of the muscles that initiate peripheral movement, i.e. the '**prime mover(s)**'. Activity exceeding this timeframe is no longer considered as 'anticipatory'. However, within this timeframe there is considerable variability in APAs between muscles, between people and even between subsequent repetitions of one and the same perturbation.[33, 101, 112] Therefore, at least 5 to 10 repetitions of specific APA-measurements have to be assessed to attain a reliable measure.[33]

Asymmetry and directional specificity. In early research, some of the trunk muscles like the Transversus Abdominis muscle (TrA) were thought to have a symmetrical activation of left and right side muscle fibers in order to create a stabile muscle corset that controlled segmental movements and posture. Furthermore, it was believed that these trunk APAs were not dependent on the direction of the force inflicted on the body.[105, 111] However, due to further research exploring a variety of different movements and movement directions and bilateral measurements of trunk muscles it became apparent that the APA trunk muscle contractions were nonetheless asymmetrical and direction-specific. For instance, during unilateral arm movements the APA onset times of several trunk muscles, i.e. TrA, Internal Oblique (IO), Erector Spinae (ES), External Oblique (EO), display differences between left and right side.[7, 166] Concerning directional specificity, the patterns and sequences of APAs are dependent on and reactive against the external force that is applied on the body due to the internally generated postural perturbation.[14, 35] For instance, in bilateral arm movements anterior versus posterior movements generate a different and opposite perturbation force on the body, which are accompanied by different activation patterns. Respectively bigger trunk extensor versus bigger trunk flexor activity is seen.[14] Likewise, in unilateral movements laterality is dependent on the arm that performs the movement, with overall earlier muscle onsets for the side contralateral to the moving arm compared to the ipsilateral muscles.[7, 166] However, when the same arm performed movements in different directions, e.g. shoulder flexion versus extension versus abduction, no such differences were described.[105, 110, 111, 230]

Adaptive properties of APAs. As discussed earlier APAs are not just stereotypical motor programs, but they are highly adaptive to the demands of the environment and the applied forces to the body.[24] Several parameters have been examined for their influence on APAs in healthy people, i.e. movement magnitude, velocity and reaction time (RT) of the peripheral movement that incites trunk perturbation, but also externally added body mass, age, knowledge/expectations about the perturbation to come, and fatigue.

When a peripheral movement is performed and the magnitude/range of motion (ROM) of that movement is increased, without substantially altering the type of movement and the muscle groups used, APA-amplitude is not altered.[17, 200] However, if other muscle groups are used to perform a higher magnitude movement, then APA-amplitude was seen to increase with bigger movements.[15]
Increased velocity of peripheral movements is related with more feedforward activity in the trunk muscles than slower movements[113] and also with bigger amplitudes of APAs[200]. However, slower reaction times for movements are associated with earlier APAs of the trunk muscles.[205]
The addition of a short-term load that increases the body mass of a person leads to bigger amplitudes of APAs and also more co-activation between different muscle groups during subsequent movements. This in order to increase the control of the trunk, which is challenged to a higher extent.[145, 146]
With older age, APAs tend to delay due to deterioration of the CNS and diminished peripheral nerve conductance.[117]
When there is more information present about the perturbation to come before it occurs, e.g. the direction of perturbation, APAs tend to be earlier than when this information is absent.[117, 184]
The influence of fatigue on APAs will be discussed in depth in **Chapter II, part 1**.

4.4.2 APAs and LBP.

Previous research has shown alterations in trunk muscle APAs in both experimental and clinical LBP populations.

In **clinical LBP** populations, generally, delayed onset timing of several trunk muscles in relation to the peripheral prime mover muscles has been found, i.e. for the TrA, IO/TrA*, IO, EO, Rectus Abdominis (RA)[130], and Multifidus (MF) muscles[218]. These findings are most consistent regarding the TrA, which is a deep local stabilizing muscle. Concerning more superficial trunk muscles like ES and EO varying results have been described, with sometimes no differences between LBP patients and healthy controls[130, 218]. As in previous literature, and even in recent studies, often no real distinction between RLBP+, RLBP- and CLBP is made, these inconsistent findings are no surprise. Conclusions were often made on heterogenous LBP populations. That is why for this dissertation it was specifically determined to make a clear distinction between these LBP subgroups.
Another interesting effect of clinical LBP on APAs is that in some studies a decreased variability in the APAs was found, i.e. in the IO muscle both in RLBP[101] and CLBP populations[121]. This possibly reflects a diminished adaptability to demands of the environment and thus a more rigid and less flexible SMC in clinical LBP. Such a more rigid motor strategy is also apparent by a bigger preactivation, thus a larger amplitude, of several trunk muscles before predictable perturbations.[213]
Importantly, these peripheral SMC alterations often remain present even when LBP patients are not experiencing pain at the time of the assessment (e.g. RLBP patients without a pain flare during testing).[110]

In experimentally-induced LBP, similar findings have been described. The amplitude of the TrA decreased[109] and the onset was delayed after experimental pain inducement in otherwise healthy people, whereas for superficial muscles changes in APA timing and amplitude were more inconsistent[109, 168]. Furthermore, variability in muscle activation also seemed reduced with experimental pain in healthy people as was the case with clinical LBP.[168, 169]

The findings of both clinical and experimental LBP indicate that disturbed feedforward and altered SMC can already occur in the short-term in response to an acute LBP sensation, but possibly could remain present during pain-free episodes in people that have been experiencing long-lasting or recurring LBP complaints. As discussed earlier, this illustrates that, at least some, SMC alterations are secondary to the pain but might play an important role in recurrence or perseverance of pain as well. A more detailed overview of the specific alterations in APAs of the trunk muscles with LBP will be provided in the introduction of **chapter II, part 1**.

* Due to the fact that the TrA is covered by the IO muscle, EMG-activity measured with surface electrodes cannot distinguish between these two muscles and is in those cases referred to as IO/TrA

5 Central factors in (sensori)motor control

5.1 Characteristics

The importance of the CNS in (trunk) SMC can be clearly derived from the latter's definition which states it has a key role in the production, coordination and activation of movement.[140] Furthermore, in relation to frequent or long-lasting (low back) pain neuroplastic changes can occur in the CNS.[195, 232] These changes in the neural organization can lead to alterations in processing of sensory information, e.g. nociplastic pain could occur.[118] Due to the fact that SMC is based on an interplay between sensory information and motor mechanisms[140], it is highly relevant to examine central factors in relation to SMC. The CNS consists of the brain and the spinal cord. The brain can be considered as the actual epicenter of all human behavior, and the spinal cord as the numerous highways connecting the brain with the entire body and establishing an optimal communication interface between the brain, the body and its environment.

5.2 General brain anatomy (brief)

An in-depth overview of the anatomy of the brain would be redundant as the brain is one of the most complex structures in the human body and this would lead us too far beyond the focus of this dissertation. However, in order to gain insight in some of the brain processes, concepts, and terms studied and discussed in this dissertation a concise summary of the most important concepts is in its place.

The brain comprises three main structures: the cerebrum, the cerebellum and the brainstem.[178] **(FIGURE 7)** The cerebrum, also often called the big brains, is constituted out of two symmetrical hemispheres (i.e. the left and right hemisphere) which form the telencephalon, an interbrain that connects cerebrum and brainstem (i.e. diencephalon), and the deep gray nuclei. The outer layer of the hemispheres primarily consists of grey matter and is called the cerebral cortex. Underneath this cerebral cortex, the deep gray nuclei and predominantly white matter can be found. The grey matter is the neuronal basis of the brain as it is formed out of the cell bodies of the brain. White matter is the mass of myelinated axonal nerve fibers that interconnect different brain areas and connect the brain with the rest of the body through the spinal cord. Several meninges surround the brain and protect it in collaboration with the cerebrospinal fluid, which acts as a shock absorber and a buffer.

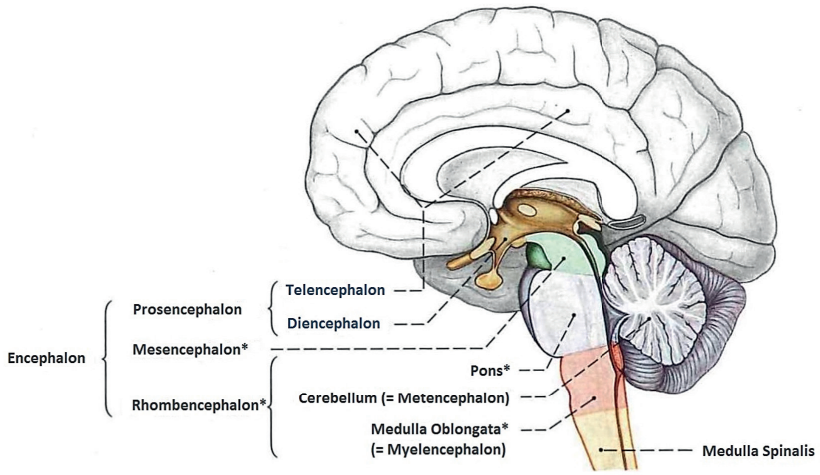


*FIGURE 7. Sagittal, cross-sectional view on the brain and its main structures. The brainstem (Truncus Cephali) comprises the structures with an *. Adapted from Hild et al.[103]*

5.3 Measurement of brain activity

The anatomy of the brain, discussed in the previous paragraphs, tells us something about brain structure and morphology. Brain morphology is most often studied by use of magnetic resonance imaging (MRI), which is a very useful technique for this purpose due to its high spatial resolution allowing for very detailed images of the brain with its different areas and structures.[8] However, specific brain areas are responsible for different and often varying functions, tasks and processes. Importantly, the main interest of the current dissertation lies in brain function and not structure, as the study of brain function can tell us something more about human behavior. It can elucidate how SMC processes might be affected by various factors or how it might be different between various groups of people or individuals, for instance people with and without LBP. Furthermore, central representations of SMC might also show similarities with the previously described peripheral measures of SMC. As of today, however, studies examining and comparing both peripheral and central factors in SMC are wanting.

Among other imaging techniques, functional magnetic resonance imaging (fMRI) has been used to examine brain function in the past (see introduction **Chapter I, part 1**). Despite its high spatial resolution, (f)MRI lacks the temporal resolution to directly measure cortical processes that often only last a couple of milliseconds. Furthermore, (f) MRI cannot be performed outside an experimental setting due to the fact that subjects need to be inserted into a large and immobile scanner device for such measurements, and because gross motor movements can induce head movements which often result in movement artifacts. Therefore, in this dissertation, electroencephalography (EEG) was the preferred technique to examine brain function in relation to SMC and LBP. Due to its higher temporal resolution[95], relatively low costs, and very high user friendly design, and its applicability in functional settings outside a laboratory, EEG was deemed the most suited technique for the studies conducted in this dissertation. This neuroimaging technique allows for sensitive registration of different functional brain processes occurring in a succession of mere milliseconds of one another in response to everyday tasks and functions, and their complex interplay.

5.3.1 Electroencephalography

5.3.1.1 General concepts and mechanisms

EEG contains a lot of similarities with the previously described EMG, as both techniques employ electrodes to capture bio-electrical byproducts that are produced by processes in the body. Of course, the main difference is that with EEG the electrodes are placed on the scalp instead of the muscles. This in order to capture voltage fluctuations over time that are related to brain processes and functioning[3, 25, 89, 123] instead of muscle activity.

5.3.1.2 Event-related potentials

Since its first mention in 1939[62, 63] the study of event-related potentials (ERPs) has exponentially grown and can now even be considered as a research domain on its own. As the name quite straightforwardly suggests, in this domain researchers examine EEG-potentials which are related to specific events. Now, before we dig deeper into this matter it is necessary to briefly explain some key concepts and terminology used in literature, which one needs to know in order to successfully interpret EEG-studies. Especially for those people who do not have prior experience or education regarding EEG this short theoretical introduction is essential, as these concepts will be quite important during the rest of this dissertation.

Raw EEG-signals are the unprocessed bio-electrical byproducts of brain activity directly measured at the scalp by use of one or more electrodes. Each electrode trace on the electrooculogram represents the voltage fluctuations measured at that superficial scalp location over time. Electrodes are conventionally named and numbered after their topographical location on the scalp and the underlying brain areas. **(FIGURE 8)**

Importantly, the raw signals that are being captured at the surface of the scalp actually represent superimposed

signals of various waveforms that can reflect different processes, functions or tasks originating in different brain areas at a time. Furthermore, similar to the 'cross-talk' which was mentioned with regards to EMG, these raw signals can be 'contaminated' by muscle activity and electromagnetic interference from apparatus in the environment. No on- or offline filtering or other data processing steps have yet been performed on this data. Thus, sensory, motor, and cognitive processes that often occur synchronously and in closely located or even overlapping topographies cannot be distinguished from one another on these signals.[152] To be able to make this distinction and really study specific brain functions, event-related potentials can be examined.

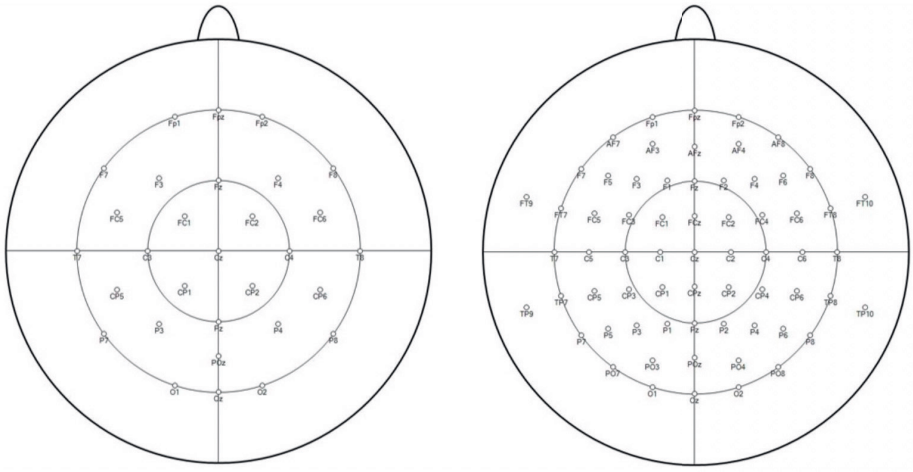


FIGURE 8. Examples of an EEG electrode cap configuration for 32 electrodes (left) and 64 electrodes (right). Uneven and even numbers respectively refrain to electrodes located on either the left or right hemisphere, while electrodes labeled with a 'z' are situated on the midline. The electrode abbreviations represent topographical areas of the underlying cortex: AF, Anterior-Frontal; C, Central; CP, Centro-Parietal; F, Frontal; FC, Fronto-Central; Fp, Fronto-Polar; FT, Fronto-Temporal; O, Occipital; P, Parietal; PO, Parieto-Occipital; T, Temporal; TP, Temporo-Parietal

Event-related potentials. An ERP still represents superimposed waveforms that might have originated in different brain areas. However, several processing steps have already been performed on this data. Due to this, ERPs can reflect consistent activity related to specific events and can provide information about brain function. In practice, this means that for ERP assessment multiple repetitions of one or more consistent events –this can be a sensory stimulus (e.g. tactile stimulus to the back), as well as a cognitive process, or motor task (e.g. arm movement)- have to be administered. Subsequently, the raw signals of all repetitions of these events are filtered and averaged in order to single out the specific activity changes in the EEG-signal that are related to the events of interest. In this way irrelevant activity for the research question, such as eye blinks, muscle activity, electromagnetic noise from the power grid, and coincidental non-event related activity can be eliminated from the signal. Hence, when designing a protocol with well-determined events and clear hypotheses about the functions needed to process those events, one can disentangle the brain activity that is related to specific functions. Assumptions about brain function can be made based upon three dimensions of the ERPs, i.e. their timing, amplitude and topographical representation.[96, 152]

Components. Despite the fact that ERPs can already give valuable information regarding brain functions, it is still a superposition of underlying waveforms. In some cases it can be useful to further examine underlying components of which some potentials are constituted as this might reflect activity originating from specific neuronal clusters. When examining components one is primarily interested in the source of the activity. Both anatomical[171] and functional[69]

approaches towards component analysis have been made in the past. These two approaches respectively examined neuronal populations that are either anatomically or functionally related. In reality a combined approach, proposed by Donchin et al.[70] is more practical and more often used. These authors defined an ERP component as "a part of the waveform with a circumscribed scalp distribution (anatomy) and a circumscribed relationship to experimental variables (function)". Whether or not a researcher decides to further look into specific components of a potential depends on the properties of the potential itself and the brain functions of interest.

Terminology. Potentials are most of the times given a specific name which usually reflects its main functional significance, for instance Somatosensory-Evoked Potential, Bereitschaftspotential, Feedback-Related Negativity, or Contingent Negative Variation. A more practical terminology is used to name the specific components of which a potential consists. A letter P or N is used to indicate whether the polarity of the component is respectively positive or negative. After this letter a number is then added which can signify two things. Either this number represents the order of the component of a specific potential or it can represent the approximate timing of the component in relation to the event. For instance, N2 can reflect the second negative peak of a specific potential. Whereas, P300 signifies the positive component that approximately arises about 300ms after an event. This terminology is illustrated in **FIGURE 9**.

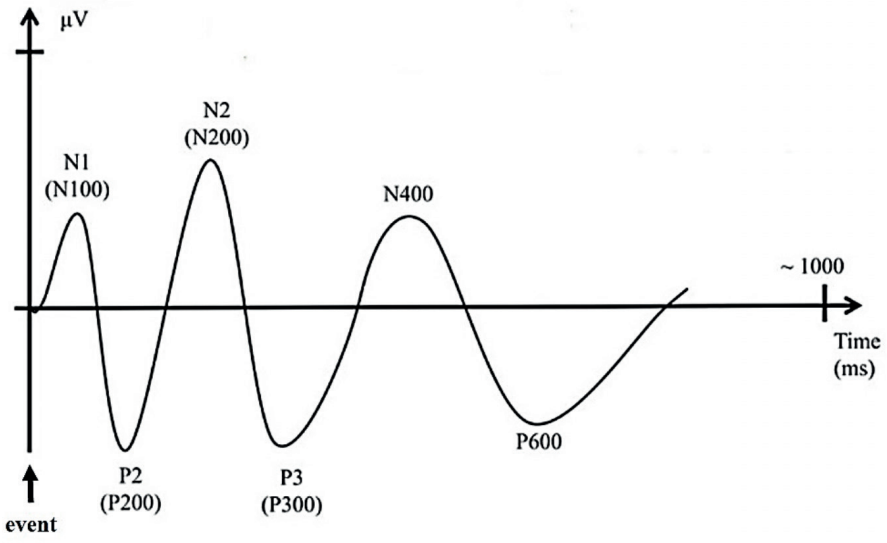


FIGURE 9. Example of a (fictive) event-related EEG-potential and its different components, i.e. N1, N2, N400, P2, P3 and P600. Adapted from Daltrozzo et al.[59]

5.3.2 Central measurement of feedforward and feedback

As mentioned before, ERPs can be used to examine various events reflecting either sensory, cognitive or motor processes. Several movement-related ERPs have been examined, e.g. the Bereitschaftspotential (BP), Lateralized Readiness Potential (LRP), Contingent Negative Variation (CNV), Movement Monitoring Potential and Perturbation-Evoked Potential (PEP). The BP, LRP and CNV can be considered as **feedforward** potentials, as these reflect anticipatory activity before movement initiation.[51, 132, 244] The Movement Monitoring Potential is associated with the movement initiation itself[251], and the PEP can be considered as a **feedback** potential that occurs after postural perturbation[186].
The general function that the feedforward potentials reflect can be easily illustrated with an example of a simple movement task, for instance a rapid unilateral arm movement. Before rapid arm movement initiation a large

slow-wave activity usually arises in the mid-central and fronto-central areas of the brain. If the movement is self-initiated, without any external cueing that indicates when the movement should be performed, this activity is called the **Bereitschaftspotential**, or in some studies the term Readiness Potential is used. Thus, the BP reflects voluntary movement preparation.[132, 182, 197, 198] When, however, a warning and go cue are used to indicate when the movement should be initiated, the slow-wave negativity that arises between these cues is called **Contingent Negative Variation**.[244] The **Lateralized Readiness Potential** is derived from either BP or CNV (depending on cueing or not). It can only be measured in paradigms that use unilateral movements of both body sides, e.g. left and right arm movements. The LRP is then calculated by subtracting contralateral and ipsilateral slow-wave activity from each other (e.g. the activity in electrode C3 minus C4 for a right arm movement, and C4 minus C3 for a left arm movement) and averaging this out. In this way only the asymmetrical activity associated with unilateral arm movement preparation is retained.[51, 75]

The main focus of this dissertation lies upon the motor processes and even more specifically motor preparation/anticipation related to SMC. Therefore, in accordance with the peripheral factors, potentials occurring after movement initiation were not further discussed here. Importantly, the CNV is the potential that will be mainly focused on in this general introduction, since it was determined as a measure for cortical movement preparation in the experimental studies of this dissertation. Due to its characteristics the CNV was deemed optimally suited to examine in synchrony with the peripheral measure for movement preparation, i.e. the APA.

5.4 Contingent Negative Variation: theoretical background

The CNV was the first cognitive ERP that was discovered by Walter et al.[244] in 1964. Since then a lot of research has been performed to unravel the brain functions it represents and factors that might modify or influence this activity. Although the CNV with its specific characteristics will be discussed in detail in the introduction of **chapter II, part 2**, it is important to already address some important theoretical aspects regarding the CNV here.

5.4.1 CNV in healthy people

Functions and main characteristics. As mentioned earlier, the CNV is a slow-wave electrical brain potential.[244] In general, it is thought to reflect response preparation and anticipatory attention for motor as well as sensory or cognitive responses.[72, 217] More specifically for this dissertation, motor preparation will be primarily examined. The CNV arises between two cues that prepare a person for a response: a first cue informing the participant about the response to come (warning cue), and a second imperative cue that requires a response (go cue).[244] Depending on the duration of the interval warning-go cue the CNV can have a shorter or longer build-up time. With longer intervals of about 2000ms and more, two phases of the CNV can be discerned, i.e. an early and a late CNV.[53] The early CNV, a first small negative deflection in the EEG-signal, is thought to mainly reflect the sensory processing of the warning signal.[131] The late CNV, a second negative deflection, starts to arise about 1-2 seconds before the go cue and reaches its peak at the go cue. It represents a combination of stimulus preceding negativity, which reflects anticipation for the sensory processing of the go cue to come[37, 60, 84, 193, 233], and feedforward preparation for the response to come[233]. The late CNV for motor responses is mainly observable in the prefrontal cortex, supplementary motor area and premotor areas of the brain[87, 136] and is thought to represent cortical movement preparation.

Adaptive properties of CNV. In healthy people, several factors have been described to have an impact on cortical movement preparation, as reflected by alterations in the CNV potential. Generally speaking larger amplitudes of the (late) CNV reflect enhanced preparation and/or attention for the task at hand. Such larger amplitudes have been reported when people received external motivation[32], when the warning cue[224] or go cue[233, 234] provided more task-relevant information, when a high response speed to the go cue[19], high force[151] or rapid force increase[234] were required for the movement task, when the interval between warning and go cue was longer (up to two seconds)[156], and when the magnitude of the perturbation in balance perturbation tasks was unpredictable[208]. In el-

derly people an altered cortical feedforward pattern has been described, with the CNV reaching its peak midway the warning-go stimulus interval instead of right before the go stimulus.[83]

5.4.2 CNV and LBP

To date, not a lot of research has been performed examining in what way LBP might impact cortical movement preparation, as measured with the CNV potential. One study described larger late CNV amplitude, as well as larger CNV peak and CNV area in a **clinical RLBP population** as compared to healthy people .[194] In that study the authors suggested that this increased CNV-activity might be due to a different postural strategy used by LBP sufferers. They often adopt a more rigid postural control strategy, which requires more conscious effort and attention, and thus requires more involvement of the prefrontal cortex. As the prefrontal cortex is one of the main generators of CNV activity this can explain the larger activity in LBP sufferers during postural control tasks compared to healthy people.

Another study that examined a **mixed chronic pain population** of patients suffering from either cervical spondylolysis or lumbar sciatica pain only described a trend of a larger CNV peak in chronic pain patients compared to healthy people, but this was not significant.[221] Of course, due to its heterogeneous sample, results of this study are difficult to compare with the study of Sadeghi et al.[194].

In an **experimental LBP population** similar but less distinct changes have been found as in clinical populations. A larger amplitude of the CNV was described in this population as well, but only on one electrode location (C4) and only with exploratory analyses.[122]

The low amount of studies discussed here clearly illustrates the need for further research in this topic.

6 The influence of fatigue and cognitive-affective factors on movement preparation

Even though the main focus of this dissertation is to examine feedforward movement preparation in relation to LBP it is important to retain a broad perspective. Especially because LBP is regarded to be of a multifactorial nature with multiple aspects that can play a role in its onset, recurrence, persistence, severity or related movement deficiencies. Therefore, other factors besides (back) pain which can influence movement preparation should be considered as well. Both in healthy and LBP populations such factors should be examined in order to be able to discern possible changes between these populations that could be related to LBP persistence/recurrence. In this dissertation, two of such factors were experimentally assessed in relation to both peripheral and central measures of movement preparation, i.e. the influence of fatigue and cognitive-affective factors.

6.1 Fatigue

Fatigue -a feeling of exhaustion arising from exertion- is a disabling symptom in which physical and psychophysiological function is limited by interactions between performance fatigability and perceived fatigability.[76, 170] Fatigue can be induced by different types of exertion, such as physical (PE) and cognitive exertion (PE).[47, 170] Through its association with decreased cognitive and/or motor task performance fatigue is often considered to be a risk factor for injuries and accidents.[32, 155, 159, 220] Since impaired motor performance, more specifically altered (trunk) SMC, was previously mentioned to be associated with LBP (see '2.4 (Low back) pain-motor interactions'), fatigue could be hypothesized as a possible influencing factor in LBP as well. However, such direct associations have not yet been described in literature. Moreover, even in healthy people the exact associations between fatigue and SMC are not yet fully elucidated. Even though different types of exertion, such as PE and CE, can induce similar perceptions of fatigue[76, 134] it is not clear whether they also similarly affect aspects of motor task performance such as (trunk) SMC, and more specifically feedforward movement preparation, in healthy people.

Concerning effects of fatigue on peripheral measures for feedforward movement preparation, previous studies point towards earlier APAs in relation to PE in healthy people.[6, 129, 163, 214-216] However, CE has not yet been studied in this regard, which makes it impossible to examine whether parallel peripheral mechanisms are at play for CE and PE.
Concerning central mechanisms, no previous studies were performed examining effects of either PE or CE on central correlates for movement preparation for SMC tasks. However, it was shown that fatiguing effects on a peripheral level are quite probably centrally mediated.[215] In order to unravel which exact processes are responsible for this central mediation, research concerning central measures for movement preparation might provide additional insights.
Hence, further research to examine fatigue mechanisms due to different types of exertion and to examine possible parallels between central and peripheral alterations in movement preparation is needed in healthy people before it could get translated to LBP populations. Therefore, the experimental studies that will be described in chapter II, were conducted on healthy populations.
A more detailed overview of previous literature and novel results regarding the influence of fatigue on APAs of the trunk muscles of healthy people will be given in **chapter II, part 1**. A similar overview regarding the influence of fatigue on CNV related to a SMC task will be given in **chapter II, part 2.**

6.2 Cognitive-affective factors

LBP complaints can disturb common day-to-day tasks, household chores, sports performance, hobbies or participation in all sorts of activities. As a person often identifies him/herself through these daily activities, diminished performance thereof or even omission of these activities can affect patients in the essence of their being and can lead to various levels of diminished quality of life, altered cognitions and emotions, and even impaired mental wellbeing[30, 240]. Vice versa, emotions and cognitions originate and are processed in the CNS, which consists of numerous networks of neurons that are connected, function in interplay, and affect each other. Therefore, it is easy to understand that such factors like cognitions and emotions can also have an impact on other processes, such as sensory and motor functions. In this connection, a biopsychosocial view on (chronic) pain has gained a prominent place in the medical field. Biopsychosocial thinking takes several factors into account besides the mere bio-physiological aspects of pain, such as cognitive-affective factors (e.g. personal factors, thoughts and emotions of the person in pain), external environmental factors, and social constructs.[86, 128] This is in sharp contrast to the former biomedical view, which stated that pain equals damage and which solely focused on biological aspects of pain.[164]
As discussed earlier in relation to the 'Mature Organism Model', cognitive-affective factors are considered to be part of central processing mechanisms of pain (see '2.3 (Low back) pain neurophysiology in a nutshell').[90] Presence of maladaptive cognitions and emotions can lead to top-down facilitation of pain stimuli, which could contribute to chronic pain[71, 99, 183, 236] and hyperexcitability of the CNS, and which can also have an impact on the motor system output[90]. Another biopsychosocial model which is often used to illustrate the possible mediating role of maladaptive cognitive-affective factors in (low back) pain chronification is the fear-avoidance model.[238] This model proposes that certain specific cognitive-affective factors such as hypervigilance, catastrophizing and kinesiophobia can modulate behavioral responses and movement in people with pain. The nature and degree of presence of these cognitive-affective factors can contribute to behavioral responses that mediate either an adaptive recovery or a maladaptive pain perseverance/recurrence loop. The current dissertation will focus on two specific cognitive-affective factors mentioned in that model, i.e. catastrophizing and fear, and their impact on movement alterations, since evidence for the distinct impact of both these factors on pain chronification is increasing. For instance, associations with increased pain and disability, and diminished physical activity have been found for these factors.[144, 173, 245, 246, 252] Insight into specific interactions between these cognitive-affective factors and distinct movement alterations in different stages of LBP could help further elucidate the chronification process in LBP. However, such insights are currently wanting.
The influence of fear and catastrophizing on peripheral movement performance, specifically in LBP populations, will be discussed more in detail in **chapter I, part II**, which summarized the available literature in

this topic. Furthermore, in **Chapter III** the results of our own experimental study that assessed **the influence of experimentally-induced fear on both peripheral and central movement preparation** will be discussed as well.

7 Interactions between peripheral and central factors in movement preparation and low back pain

An important aspect of the CNS is to provide adequate automatized dynamic postural control due to the coordination of trunk muscle activity, which can counteract postural perturbations and imbalances.[140] Therefore, changes in peripheral feedforward responses might occur as a consequence of -or might at least be related to- central alterations occurring in the CNS.[23, 40]

Only a few studies have examined the interaction between peripheral and central measures related to movement preparation. Tsao et al.[228] confirmed the previously described delayed onset of the TrA muscle in RLBP patients with fine-wire EMG. Besides this they also found central alterations due to RLBP, i.e. a shift of the cortical representation and an increase in the cortical map volume of the TrA. These peripheral and central alterations due to RLBP correlated with each other, indicating that peripheral changes in feedforward SMC associate with central reorganization in the motor cortex. Furthermore, a later study of the same research group showed that such central alterations were reversible due to specific rehabilitation consisting of selective TrA contractions. After this rehabilitation the cortical representation of the TrA activation shifted back towards areas described in healthy people. Again, this shift in cortical representation correlated with peripheral changes after treatment that highly resembled values in healthy controls, i.e. earlier APAs of the TrA.[229]

When studying the cortical representation of both the deep MF muscle and the more superficial ES, the representation of these muscles was found to 'smudge', i.e. overlap, more in RLBP patients.[227] Whereas in healthy people, distinct cortical representations could be discerned for these different muscles.[226] This might indicate a diminished capacity of selective activity between those muscles due to RLBP. Indirectly, this can be associated with peripheral strategies in RLBP that also show a loss of selectivity between deep and superficial muscles.[154]

The previously discussed studies were conducted by use of transcranial magnetic stimulation techniques on RLBP patients. As of yet, only one study examined peripheral and central interactions in a CLBP population and with EEG.[194] In this study indirect associations of delayed APAs of the EO and IO/TrA muscles with larger CNV amplitudes in CLBP sufferers were described, which is indicative of some relationship between these measures in CLBP. Furthermore, the supplementary motor area of the brain is involved in both APAs44 and CNV processes[87, 136]. Hence, an interaction between these measures of peripheral and central movement preparation could be hypothesized.

8 Aims and outline

The overall objective of this dissertation was to increase the understanding regarding underlying mechanisms to the chronification process of non-specific LBP, since this complex disorder still evokes many questions and optimal treatment modalities have not yet been found. Therefore, in this dissertation two important mechanisms that are considered to underlie or contribute to non-specific LBP, i.e. the influence of cognitive-affective factors and alterations in movement preparation, and their interactions were examined in healthy people and LBP sufferers in different stages of the chronification process. To achieve this several studies were performed, which will be discussed in three chapters.

Chapter I. Theoretical background. In a first chapter systematic reviews were performed in order to summarize the current standings regarding two subjects related to the overall objective, to point out gaps in current literature and opportunities for future research, and to gather and analyze methodological aspects which could be used in our own experimental designs.

Chapter I, part 1 explored up-to-date literature regarding functional brain alterations related to LBP as measured

with EEG. To this day most studies used fMRI to assess brain function in LBP, even though EEG has a lot of practical, but also theoretical advantages compared to fMRI. Furthermore, the brain is one of the most enigmatic structures of the human body, and still a lot of its functions and underlying mechanisms need to be explored. Discovering functional brain alterations related to LBP could lead to the development of new treatments aimed at normalizing brain processes and their functional consequences. Therefore, the use of EEG was deemed highly valuable to unravel central mechanisms related to LBP.

Chapter I, part 2 explored a broad biopsychosocial perspective in LBP, as this systematic review synthesized all relevant literature regarding the influence of two cognitive-affective factors, i.e. catastrophizing and fear, on the wide-ranging concept of movement-related outcomes. Furthermore, it aimed at comparing these parameters between different types of non-specific LBP, i.e. ALBP, RLBP and CLBP populations. This systematic review served as an important keystone for the development of the final experimental paradigm, which will be discussed in chapter III. The importance of cognitive-affective factors in the chronification process of LBP was already considered in previous literature.[71, 99, 183, 236] These cognitive-affective factors were, however, never examined in such a comprehensive manner regarding their possible mediating role in altered movement performance in different LBP entities. Knowledge on this relationship is important to further disentangle the underlying mechanisms of CLBP and to improve the biopsychosocial assessment and treatment of LBP patients in clinical practice.

Chapter II. The influence of physical and cognitive exertion on movement preparation in healthy adults. In this second chapter the influence of fatigue on movement preparation was examined through two experimental studies performed on healthy adults. Due to the fact that the exact effects of fatigue were not yet completely understood in healthy people, it was necessary to first examine this population before subjecting clinical populations to such kind of testing. The relevance of fatigue in day-to-day living and its possible relation with injuries, changes in movement performance, and association with LBP, however, cannot be underestimated. Hence, similar research on clinical populations in the future could help unravel the role of fatigue in maladaptive movement mechanisms and could be helpful for injury and pain prevention. These studies were also an excellent way of optimizing the elements of the experimental paradigm and the measurements that would also be used in the final experimental paradigm conducted in this dissertation (chapter III). Two parts will be discussed.

Chapter II, part 1 examined the influence of physical and cognitive exertion on trunk muscle onset timing (APAs) in preparation for a SMC task.

In Chapter II, part 2 both types of exertion, i.e. physical and cognitive exertion, were also induced in order to examine their influence on a central measure for movement preparation, i.e. the CNV.

In the general discussion possible synergies between these studies will be discussed.

Chapter III. A biopsychosocial perspective on the influence of fear on movement preparation in healthy people, RLBP and CLBP patients. The third and last chapter aimed at examining the influence of experimentally altered cognitive-affective states, i.e. fear and pain expectations, on both central and peripheral measures of movement preparation, and this for healthy people, RLBP and CLBP sufferers. It explored whether there were differential effects of fear and expectations for pain on movement preparation, depending on the type of LBP someone was experiencing. In this way the moderating role of cognitive-affective factors on LBP chronification through alterations in SMC could be further elucidated. Furthermore, this design made it possible to examine whether influencing factors associated with LBP would gradually develop from healthy controls over RLBP sufferers, to peak in CLBP patients. Such a continuum with gradations in cognitive-affective factors and disturbed movement performance associated with LBP chronification was hypothesized based on previous research. The findings of this study could contribute to the development of more differentiated treatment approaches based on the progression stage of LBP, but also based on the cognitive-affective vulnerability of an individual.

To summarize, the following research questions will be addressed:

- What evidence exists in current literature concerning the possible presence and nature of functional brain alterations in non-specific LBP patients compared to healthy people, as assessed by EEG? (chapter I)
- What evidence exists in current literature concerning the possible influence of catastrophizing and fear on movement-related outcomes in non-specific LBP patients? (chapter I)
- Does fatigue, induced by a single bout of either physical or cognitive exertion, affect peripheral movement preparation in healthy adult people, as assessed by examining feedforward trunk muscle activation with EMG? (chapter II)
- Does fatigue, induced by a single bout of either physical or cognitive exertion, affect central movement preparation in healthy adult people, as assessed by examining the Contingent Negative Variation with EEG? (chapter II)
- Does situational fear of back pain influence central and peripheral movement preparation in healthy people, RLBP and CLBP patients, as assessed by examining the Contingent Negative Variation with EEG and feedforward trunk muscle activation with EMG? (chapter III)

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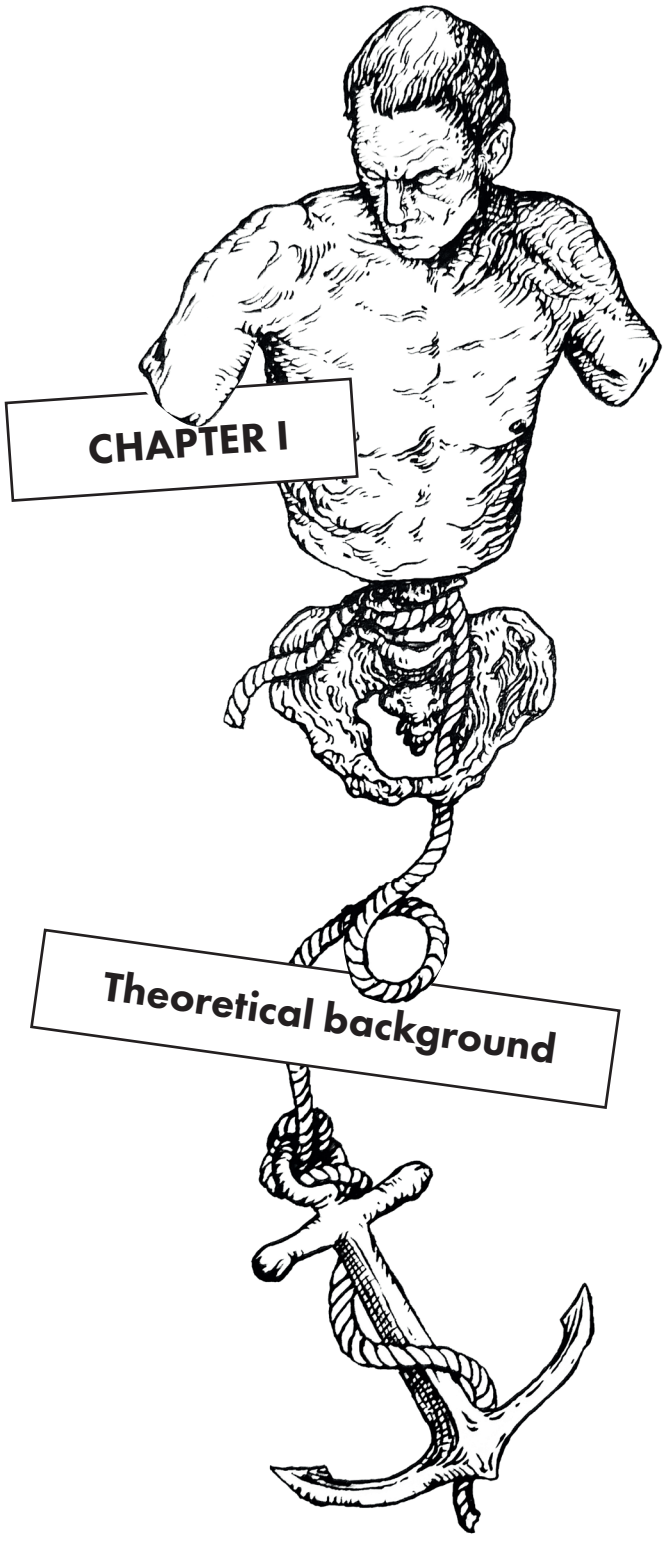

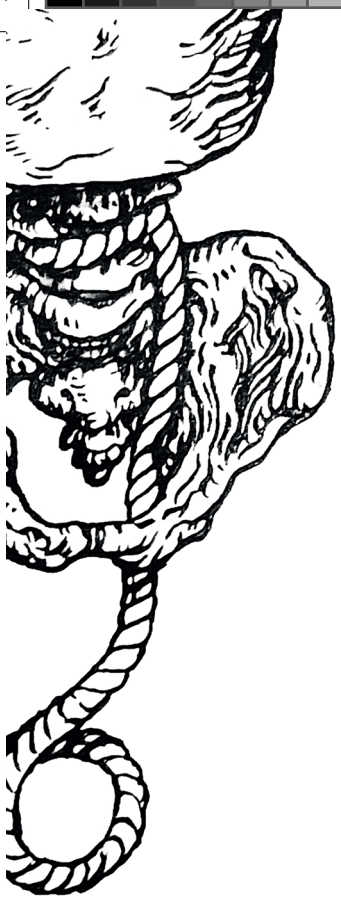

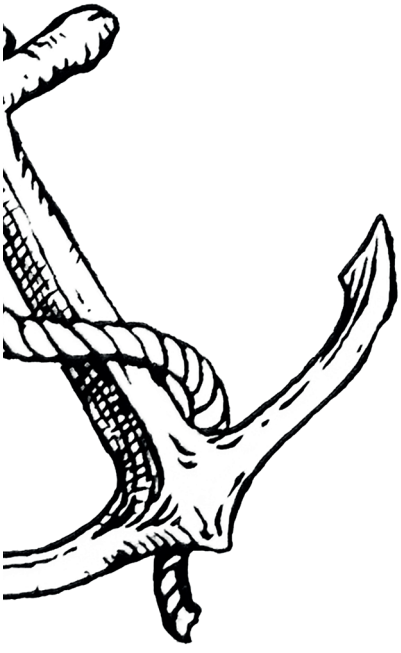

ARE FUNCTIONAL BRAIN ALTERATIONS PRESENT IN LOW BACK PAIN? A SYSTEMATIC REVIEW OF EEG STUDIES

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Abstract

This systematic review analyzed available literature on functional brain alterations in LBP measured with electroencephalography (EEG), as until now evidence thereof was unclear. Four electronic databases were systematically searched the 10th of March 2018, resulting in 12 included studies. Studies showed a risk of bias (RoB) of 37.5%-75% using the Newcastle-Ottawa Scale for case-control studies. Limited evidence reported higher amplitudes of balance-related potentials and early components of somatosensory evoked potentials (SEP) to noxious stimuli, and altered feedback-related negativity and P300 potentials during decision-making in chronic LBP (CLBP). These findings suggest postural strategies requiring a higher cortical attention-demand, increased sensory-discriminative processing of noxious input, and altered decision-making in CLBP. However, further research is warranted as these inferences were based on single studies. Moderate evidence for unaltered amplitude of late-phase SEPs to noxious stimuli and auditory evoked potentials in LBP implies that the affective-emotional processing of stimuli might be unaffected in LBP. Furthermore, moderate evidence indicated disturbed habituation of somatosensory stimuli in LBP. Most studies examined non-specific or mixed CLBP populations, hence EEG-quantified brain activity in (sub)acute or recurrent LBP still needs to be explored.

Perspective. This review presents an overview of the current understanding of the functional LBP brain measured with EEG. The limited evidence in current research suggests altered cortical function regarding balance control, somatosensory processing and decision making in LBP, and highlights opportunities for future EEG-research.

Keywords: low back pain; electroencephalography; evoked potential; central nervous system

1 Introduction

The central nervous system plays an imperative role in pain processing, and can undergo neuro-plastic changes in response to pain.[3, 38, 42, 97, 111] The neuro-matrix of pain theory proposed a neural signature of brain networks uniquely responsible for pain processing.[81] However, in the last decades this 'pain matrix' was questioned as studies showed that involved brain areas are not solely responsible for pain processing, but also for non-painful salient stimuli.[70, 88, 104, 120] The main consequence of the introduction of the 'pain matrix' is that research regarding pain processing shifted from the peripheral to the central nervous system. However, both systems need to be considered in order to understand the altered pain processing in those suffering from chronic pain, as this is generally due to a complex interplay between peripheral and central nociceptive mechanisms.

This interplay seems of particular importance in low back pain (LBP).[53] Peripheral factors like trauma or structural deficits should not be neglected for their role in LBP,[34, 73, 95] however, those peripheral factors alone are insufficient to explain the recurrence or chronification of LBP, as the pain often persists long after peripheral causes or noxious input have resolved[13, 21]. Furthermore, spontaneous LBP is not always a nociceptive process caused by peripheral injury or noxious input. For instance, sustained postural activity could drive long-lasting inflammation in the joints/ligaments/muscles involved in the stability of the lumbar spine[2] and has been found to exacerbate some types of chronic LBP (CLBP).[34] Hence, it is clear that CLBP is the result of a complex interaction between peripheral input and central changes.

Changes in the LBP brain are described in terms of structural and functional nature. Concerning the CLBP brain, moderate evidence for global and regional structural changes was found with (functional) magnetic resonance imaging (fMRI/MRI), indicating a likely decrease of gray matter volume in areas responsible for executive functions, planning, sensory-emotional processing, and memory.[66, 92] Interestingly, another study showed a causal relationship between decreased gray matter volume and back pain[6]. Ambiguous evidence for both increases and decreases in white matter are seen depending on the studied regions.[66, 92] Functional changes included altered functional connectivity in the default mode network at rest and higher activation of the medial prefrontal cortex, cingulate cortex, amygdala and insula.[66, 92] No uniform conclusions could be drawn with regards to the responses to noxious stimulation, while studies examining responses to non-noxious sensory stimulation are non-existent. Furthermore, differential responses were seen to several specific tasks.[66, 92]

Compared to (f)MRI, electroencephalography (EEG) is a cheaper and more accessible neuroimaging technique with a lower spatial[71], but higher temporal resolution[52] allowing for direct recordings in functional settings. Therefore EEG is deemed more sensitive for registering the complex interplay of different brain functional processes occurring in timespans of milliseconds. Brain functions which are extensively studied with EEG in healthy populations, are sensory processing[8, 14, 15, 19, 22, 23, 36, 84, 98, 110, 112] cognitive-emotional processing,[32, 54, 63, 69] speech,[45] motor planning and execution,[11, 16, 62, 77, 83, 85, 86, 99, 107] and executive functions[26, 39, 54, 105]. However, no clear overview exists of evidence based on EEG studies describing if and how brain function might be altered in people with LBP, despite the fact that this might help elucidate LBP chronification and direct future research in the study of the LBP brain. Therefore, this systematic review summarizes the evidence currently available regarding the presence of functional brain changes measured using EEG in LBP. Functional brain alterations can occur very quickly in response to acute pain, however it is not clear how the duration of pain influences these alterations or how quickly these responses dissipate when the pain resolves.[18] Therefore, if enough comparable literature for each of these groups can be found, the current evidence will be summarized separately for acute, recurrent and chronic LBP.

2 Methods

This systematic review is reported following the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines.[87]

2.1 Eligibility criteria

The PICO approach was applied to formulate the following research question: 'What evidence is available for changes in brain activity (Outcome; O) in patients with LBP (Population; P) compared to healthy controls (HC) (Comparison; C)?'. This systematic review was limited to studies that used EEG (Intervention; I) to examine this research question. All types of interventions or exposures, i.e. tasks or experimental paradigms performed to evoke certain EEG-responses, were considered eligible.

2.2 Information sources and search strategy

A search strategy was developed to retrieve all relevant research regarding this topic currently available in the literature. Search terms were predefined from the PICO-question. Synonyms for P, I, and O were combined using the boolean operator 'OR'. The boolean operator 'AND' was used to combine the terms of P and I or P and O with each other. The boolean operator 'NOT' was used to exclude studies that used MRI instead of EEG (I) to assess brain activity in LBP. No filters were applied. The electronic databases of Pubmed, Web of Science, Embase, and CINAHL were uniformly searched on the 10th of March 2018 with the following query: ("Low back pain" OR "Lumbar back pain" OR lumbago OR "lower back pain" OR "low back ache" OR "low backache" OR "lumbar pain" OR "lumbar spine pain" OR "lumbar vertebrae pain" OR "lower spine pain" OR "lumbar region pain" OR "lumbar region ache") AND ((EEG OR electroencephalogr*) OR (("brain changes" OR "brain adaptations" OR "brain activity" OR "brain function") NOT (MRI OR "Magnetic Resonance Imag*" OR "NMR" OR "Nuclear Magnetic Resonance")) OR (("event related potential" OR "evoked potential") AND (brain OR cortical))). In Embase the search was restricted based on preferred emtree terms and free text words, while narrower emtree terms (i.e. 'explode' function) were not used.

Furthermore, the reference lists of studies that were retrieved through electronic search and fulfilled the in- and exclusion criteria (see infra), were manually screened to identify additional relevant studies. Although review studies retrieved during the electronic search were not eligible for study inclusion in this systematic review, their reference lists were also screened to identify potentially relevant studies.

2.3 Study Selection

Predefined in- and exclusion criteria regarding design, population, and topic of the studies were used to assess the eligibility of the search results **(TABLE 1)**. No limitations were made based on type or duration of LBP, language or year of publication. However, studies which examined mixed groups of back pain consisting of patients with either lumbar/low back pain as well as patients with other spinal areas afflicted e.g. cervical, thoracic, sacral or coccygeal pain were not included. Previous studies found important differences in brain structure between lower back pain and upper back pain patients[75] or other chronic pain entities[25, 66]. Therefore, as brain function and structure are, to some extent, related to one another[7] such heterogeneous groups might distort the cohesiveness of findings with EEG and were not eligible.

After removal of duplicates, titles and abstracts of the retrieved studies were screened to examine whether the studies fulfilled the inclusion criteria. If any of the inclusion criteria were not met, the study was excluded. In case of uncertainty regarding the eligibility of the study based on title and abstract, the full text version of the study was evaluated against the inclusion criteria. The full-text versions of all studies that were considered potentially eligible and relevant were retrieved. Each full text study was read to confirm eligibility, to assess potential RoB and to extract data.

TABLE 1. *In- and exclusion criteria*

INCLUSION CRITERIA	EXCLUSION CRITERIA
Design	
• Experimental studies • Case-control design • Full text reports	• Non-experimental studies such as letters, editorials, reviews, meta-analyses, study procols, etc. • No comparison with healthy controls • Non-full text reports such as abstracts, congress proceedings, etc.
Population	
• Humans • Adults (≥18 y) • Presence or history of LBP (acute, chronic, recurrent, specific, non-specific)	• Animals • Infants, children or adolescents (<18 y) • Other populations than those with LBP • Experimentally induced LBP • Severe LBP pathologies due to cancer, spinal cord injury or myelopathy
Topic	
• Examining the influence of LBP on functional brain activity • EEG	• Examining the influence of LBP on structural brain activity • Examining resting state brain activity • Other brain imaging techniques, for instance (f) MRI, CT, DOI, PET, cranial ultrasound,...

Abbreviations: CT, computed tomography; DOI, diffuse optical imaging; EEG, electroencephalography; (f)MRI, (functional) magnetic resonance imaging; LBP, low back pain; PET, positron emission tomography; y, years

2.4 Qualification of searchers/raters

Literature was searched, screened and assessed for methodological quality by the first and second author (S.S. and S.V.O.) independently from each other. These authors compared the results from the search, screening on in- and exclusion criteria and RoB assessments. In case of disagreement, the point of difference was discussed in order to obtain consensus. When consensus could not be reached, a third opinion was provided by the last author (J.V.O). S.S. and S.V.O. obtained a MSc in Rehabilitation Science and Physiotherapy, J.V.O. obtained the degree of PhD in Rehabilitation Science and Physiotherapy and is experienced in conducting systematic reviews.

2.5 Data items and collection process

From each included study, information regarding following items was extracted into an evidence table: (1) population (type and duration of LBP, mean age, sex); (2) type of intervention or exposure that was used to examine brain activity; (3) EEG outcome measures and electrode locations; (4) statistical analysis; (5) main results (**TABLE 2** in appendix).

2.6 Risk of bias and levels of evidence of individual studies

The RoB for each included study was assessed using the Newcastle-Ottawa Scale for case-control studies (NOS)[122] (**TABLE 3** in appendix). The NOS exists of three domains: 1) 'Selection' of study groups and ascertainment of ex-

posure (four items, four stars); 2) 'Comparability' of groups (1 item, 2 stars); and 3) 'Exposure' (three items, three stars). The NOS assigns a maximum of 9 stars to each study with high scores corresponding to low RoB. In case an item was not applicable, no stars could be awarded. Therefore, the maximum amount of starts which could be achieved varied between studies. To facilitate comparability between studies, the achieved number of stars was also transferred to percentage scores. Furthermore, graphical representations of the RoB of the included studies are displayed in **FIGURE 1 and 2** in the results section. For these graphical representations star-earning responses in the NOS were categorized as "low risk of bias", other responses as "high risk of bias", and non-applicable responses as "not applicable".[76] Each study also received a total quality rating of either 'low', 'moderate' or 'high' RoB, based upon criteria developed by the Cochrane institute.[79] These criteria are depicted in **TABLE 4**.

TABLE 4. *Cochrane criteria for quality rating on study level*

RISK OF BIAS	# POINTS IN SELECTION DOMAIN	# POINTS IN COMPARABILITY DOMAIN	# POINTS IN EXPOSURE DOMAIN
Low	≥3	≥2	≥2
Moderate	2	≥1	≥2
High	0-1	0	0-1

Within the first domain 'Selection', the first item assessed whether the case definition of the LBP population was adequately described in terms of type and duration of LBP. A score of 1 star was given when adequate information regarding type of LBP, duration of complaints, as well as in- and exclusion criteria were mentioned. No stars were given when this was not the case or not sufficiently described. The second item evaluated representativeness of the cases and thus the presence of selection bias for the LBP participants. One star was assigned when the studied sample had similar characteristics as the average in the target population of the study. This could be attained when authors performed random sampling and/or participants were recruited from at least two different sources. Either all participants of the population or at least an appropriate amount, according to a priori or post-hoc power analysis, should have been included as well. When a selected group, not representative for the whole population, was described, or when the study was lacking a description or power analysis, no stars were assigned. The third item assessed whether selection bias for the control participants was present and whether controls were similar to cases, but without a LBP history. One star was assigned when controls of the same community, i.e. with the same socio-demographic background, as cases were recruited for the study. No stars were assigned, when this was not the case, not well described or when a hospital sample was used (i.e. the same community but a hospitalized population of controls). To obtain one star on the fourth item, the absence of current LBP complaints or no history of such in the control sample should be adequately described. If this was not mentioned, no stars were given.
The second domain 'Comparability' comprised of one item which assessed the presence of possible confounders in studies that compare cases and controls. One star was awarded to studies controlling for both age and medication use. A second star could be gained by controlling for at least one additional confounder (i.e. hand laterality, eye blinking or sex). When none of the above were accounted for, no stars were awarded.

Within the third domain 'Exposure' the first item assessed the intervention or exposure that was used to examine the study specific brain function(s) with EEG. One star was attained when either a validated or a well described protocol commonly used in the field was used to evoke and assess brain responses. Insufficiently described protocols gained no

stars. In case of EEG resting state studies in which no intervention or exposure was necessary to study the brain activity, 'not applicable'(NA) was scored. In the second item one star was awarded if cases and controls underwent the exact same protocol. No stars were given if the test protocol for both groups differed in one or more aspects.
The third item appointed one star if non-response rates, e.g. drop-outs or participants not responding to the intervention or exposure, were similar between cases and controls. No stars were attained if the response rates for cases and controls were significantly different or inadequately described. If no drop-outs or non-respondents were present, a study scored 'NA' on this item.

Adhering to the Dutch Evidence Based Guideline Development (EBRO) platform levels of evidence (LoE) between D and A1 were allotted to each included article, based on study design and RoB of the individual studies (**TABLE 5**).[20] All studies received a LoE B, as only case-control studies were eligible.

TABLE 5. *Level of evidence, according to the 2005 classification system of the Dutch Evidence Based Guideline Development (EBRO)*

INTERVENTION	
A1	Systematic review of at least 2 studies of evidence level A2 which were independently conducted from each other
A2	Randomized double-blinded comparative clinical research of good quality and efficient size
B	Comparative research, but not with al characteristics as mentioned for A2. This also includes patient-control research and cohort research.
C	Non-comparative research
D	Expert opinion

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2.7 Levels of conclusion

The level of conclusion (LoC) was determined after clustering studies with comparable outcomes and taking into account the consistency of the reported results and the LoE. The LoC ranges from one to four and corresponds respectively with a high (one A1 or at least two independent A2 studies), moderate (one A2 or at least two independent B studies), low (one B or C study or conflicting evidence) or no strength of conclusion at all (expert opinion) (**TABLE 6**).[80]

TABLE 6. *Level of Conclusion*

CONCLUSION BASED ON	
1	Research of evidence level A1 or at least 2 independently conducted studies of evidence level A2
2	1 research of evidence level A2 or at least 2 independently conducted studies of evidence level B
3	1 research of evidence level B or C
4	Opinion of experts or inconclusive or inconsistent results between various studies

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3 Results

3.1 Study selection

The process of study selection is depicted in a flowchart (**FIGURE 3**). The initial electronic search resulted in 483 hits. After removal of duplicates, 388 studies remained. After screening the studies on title, abstract, and full text regarding the fulfillment of the inclusion criteria, 11 studies remained. Rejection was based on not fulfilling the criteria regarding topic (N=171), population (N=108), or design (N=98). Thus, based on the electronic search, 11 studies were included in this systematic review. Hand searching resulted in 6 additional potential studies, of which one was retained after screening on in- and exclusion criteria. Hence, in total 12 studies were included in this systematic review.

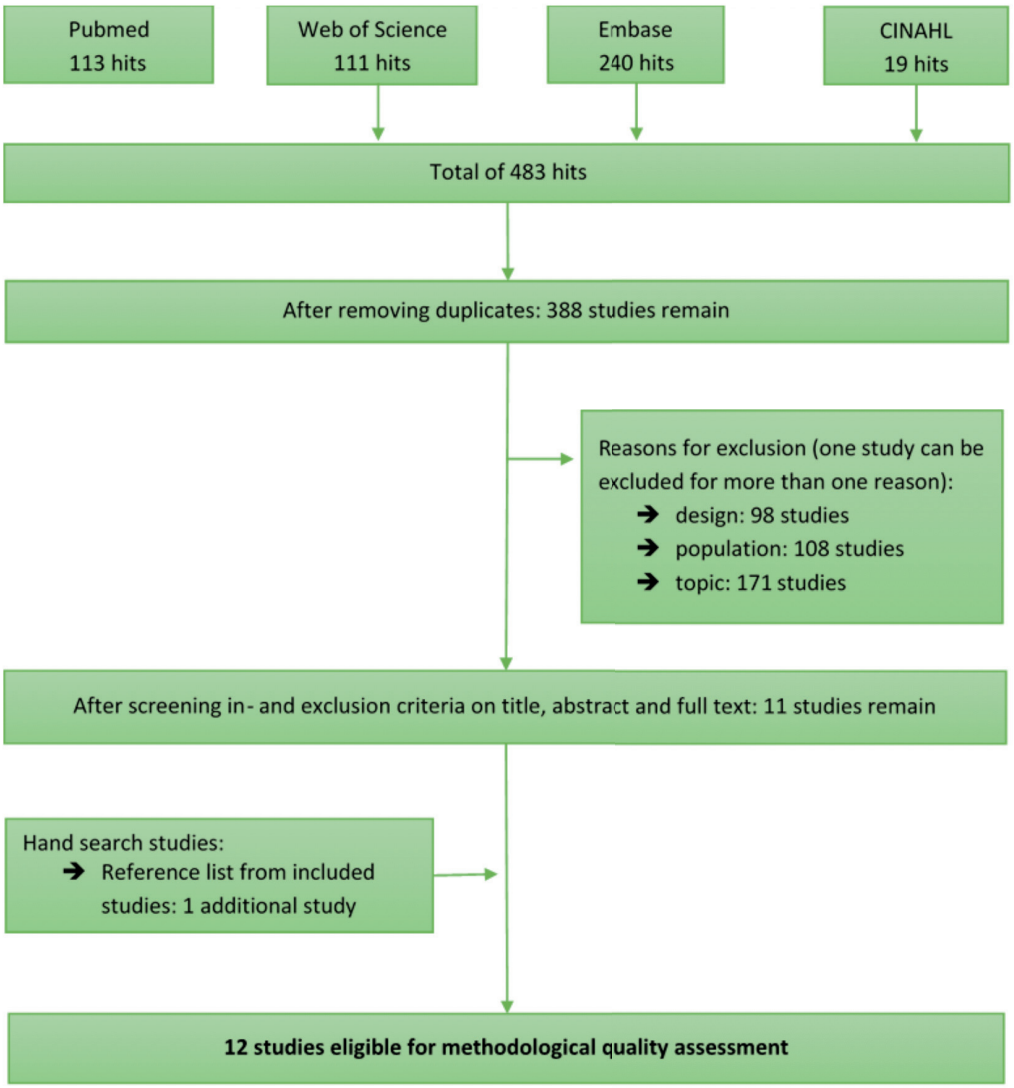

FIGURE 3. Flowchart of the study selection process.

3.2 Study characteristics

The study characteristics of each included study can be found in the evidence table (**TABLE 2** in appendix). In summary, all included studies compared non-specific CLBP patients with a healthy control population. However, in two of these studies a mixed recurrent/chronic LBP population was used.[60, 61] Regarding intervention or exposure, brain activity was investigated in response to perturbation/balance tasks in three studies,[60, 61, 103] to noxious somatosensory stimulation in six studies,[31, 43, 44, 65, 118, 119] to auditory stimulation in two studies,[27, 37] and to a decision making task in one study[109]. Based on aforementioned types of intervention/exposure the results of the individual studies were clustered into four groups in the results section (infra). Within each cluster the current evidence was summarized separately for acute, recurrent and chronic LBP. All included studies examined amplitude of the potentials of interest, five of them also evaluated potential latency.[27, 37, 44, 61, 65]

3.3 Risk of bias and level of evidence

The RoB and LoE of the different studies are displayed in a scoring table (**TABLE 3** in appendix). The observed level of agreement regarding RoB between both raters on all items was 79/98 items (80.6%). Of all studies, one scored 6/8 (75%), three attained a score of 5/8 (62.5%), 7 studies scored between 4/8-5/9 (41-60%), and one study scored 3/8 (37.5%). The mean score for all included studies was 54.17%. On study level three studies attained a 'moderate' RoB rating, whereas the remaining eight articles received a 'high' RoB.

In most studies, selection bias was not fully ruled out due to a lack of justification for chosen sample sizes through a power analysis and insufficient selection and definition of control participants. This clarifies the low overall scores on respectively items two, three and four of the 'Selection' sub-section.

Regarding the 'Comparability' subsection, 7/12 studies acquired two stars for controlling for the most important confounders. The remaining four studies scored one star as some, but not all confounders were taken into account.

Concerning measurement of the 'Exposure', i.e. the task/intervention used to evoke EEG-activity, all studies scored the maximum of one star on both item one and two. Either validated or at least well described protocols were used to measure EEG-activity which led to high scores on item one. Furthermore, the same assessment was utilized for cases and controls in all studies (item two). In only two studies there was mention of drop-outs or non-responders, leading to a NA score for the remaining nine studies for item three.

The assessment of the LoE of the included studies showed a 100% agreement between both assessors during the consensus meeting. All studies were given a level B (all case-control studies).

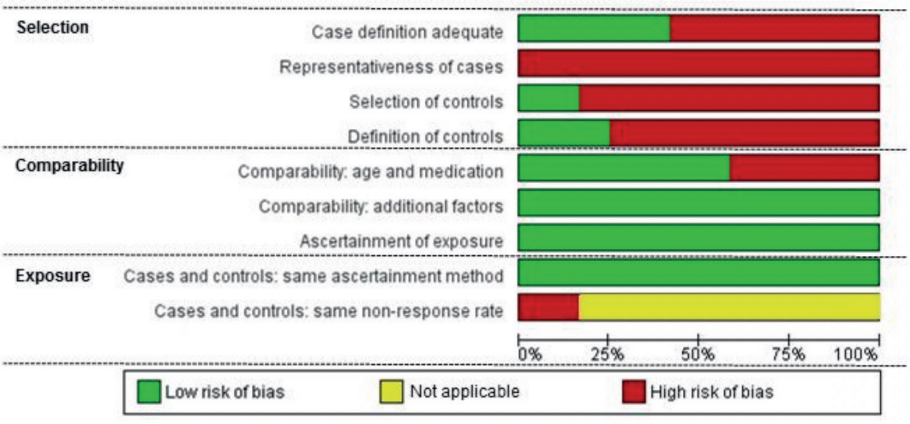

FIGURE 1. Risk of bias graph.

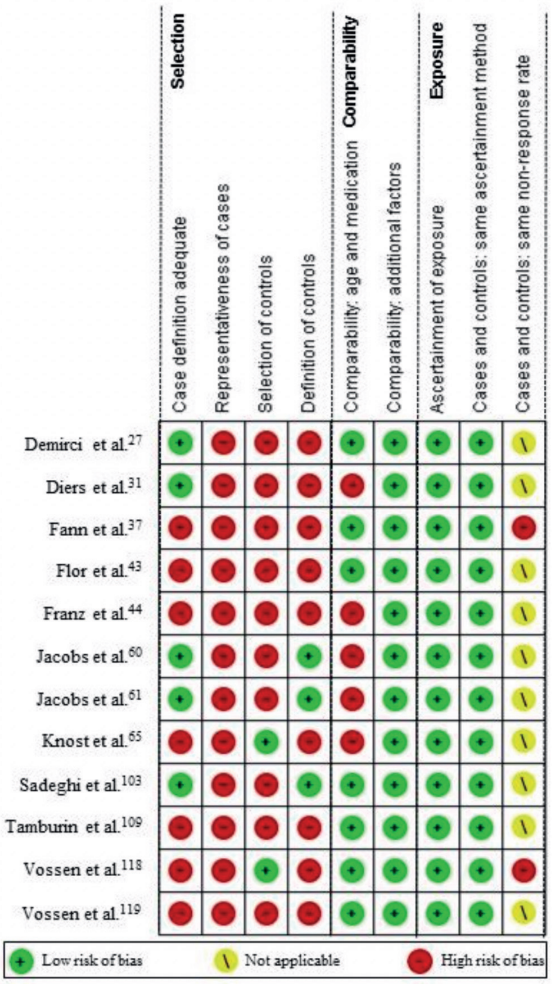

FIGURE 2. Risk of bias summary graph

3.4 Synthesis of Results

A schematic overview of the levels of conclusion per outcome is presented in **TABLE 7** in the appendix.

3.4.1 Cortical motor functions

Only studies regarding motor preparation prior to and/or motor responses following balance perturbations were retrieved. No other functional motor tasks were studied in LBP as of yet. Two of the examined balance-related potentials, the Bereitschafstpotential and contingent negative variation (CNV), play a role in anticipatory or feed-forward movement preparation prior to predictable balance perturbations. The Bereitschaftspotential arises 1-2 seconds before self-initiated movements. It is a symmetrical slow-rising negative potential mainly observed in the supplementary motor cortex (early phase) and the (contralateral) primary motor cortex (late phase), reflects voluntary movement preparation, and is often regarded as a part of the late CNV.[107] The CNV also consists of an early and late phase. However this potential arises between a warning and go cue, therefore also reflecting somatosensory processing of these cues besides movement preparation. The early CNV mainly reflects the sensory processing of the warning signal, whereas the late phase of CNV represents feedforward movement preparation

(≈Bereitschaftspotential) in combination with anticipation of the go stimulus.[16, 62] CNV activity can mainly be observed in the prefrontal cortex, supplementary motor and premotor areas.[48, 68]

Feedback processing taking place after the perturbation has already been initiated, is reflected by perturbation-evoked potentials (PEP). PEPs consist of an early first negative peak (N1) followed by a later second positive peak (P2) in the EEG-amplitude. The N1 arises mainly in the supplementary motor area 100-200ms after the perturbation onset1 and reflects somatosensory processing of the balance perturbation and postural error detection.[11, 77, 83, 86] This negative N1 peak is followed by the P2, which arises 200-400ms after perturbation onset and is thought to be responsible for monitoring the ongoing postural challenge.[85, 99]

Based on three studies, larger amplitudes for both the CNV (late CNV, p<.0005; peak CNV, p<.005; CNV area, p<.01)[103], and P2 (p<.05)[61] were present in CLBP compared to HC, but not for the Bereitschaftspotential[60] or N1[61] (LoC 3).

Additionally, one study described that in both HC and CLBP alpha event-related desynchronization, a measure for cerebro-cortical activation that coincides with excitation of the sensory-motor cortex, was present during a balance task (p<.05) (LoC 3).[60]

Potential latency in relation to balance was only studied in one study concerning PEPs. No significant differences between CLBP and HC were found for PEP latencies (N1 and P2, p>.05) (LoC 3).[61]

To summarize, based on these results and the low number of studies there is inconclusive evidence regarding cortical motor function alterations prior to and in response to balance perturbations in LBP (LoC 3).

3.4.2 Sensory processing

Noxious somatosensory processing. Early components of noxious-related somatosensory evoked potentials (SEP) are thought to reflect the sensory-discriminative aspect of pain, which is mainly processed in the SI and SII, but also in the ventral posterior nucleus of the thalamus, the posterior insula and the inferior parietal cortex.[4, 67, 123] The later components represent the emotional or affective-motivational aspects of pain, which mainly originate from the anterior cingulate cortex, the medial thalamus, the amygdala, the anterior insula, the orbitofrontal cortex, the frontal pole and the hypothalamus. [4, 67, 123]

One study described larger amplitudes for an early negative peak (N80) of SEPs to noxious stimulation in CLBP compared to HC (p=.041) (LoC 3).[31] Later SEP amplitude peaks (>100ms), specifically N150,[31, 43, 65] P300, N500,[43] N2 (±180ms) and P2 (±300ms) of the laser heat evoked potential[44], did not differ between CLBP and HC in four studies (LoC 2). Ambiguous evidence was found concerning the P260-amplitude, with one study describing smaller amplitudes in CLBP (p=.046), while two other studies found no between-group differences[31, 43, 65] (LoC 4). Furthermore, in one study high or low muscle tension in either the Erector Spinae or Flexor Communis Digitorum muscle was achieved through EMG-biofeedback showing the participants a target tension level on a monitor, which they had to maintain prior to noxious stimulation to either the back or lower arm area. This study depicted a larger N150-amplitude in response to noxious stimuli when CLBP participants were asked to apply low muscle tension compared to conditions with high muscle tension (p<.05) and compared with HC with low muscle tension (p<.05). In conditions with high muscle tension no between-group differences were found (LoC 3). Both contraction of a muscle close to the noxious stimulation site as contraction of a muscle distant to the noxious stimulation site showed similar results (LoC 3).[65]

Regarding N150-P260 peak-to-peak difference, a measure that is considered to reflect stimulus processing as well as cognition, attentional processes and response preparation and which has been shown to correlate with subjective pain experience,[14, 22, 84] no significant between group differences were described (LoC 3).[65] One study described less linear (in the 340-460ms post-stimulus interval) and inverse habituation (in the 1220-1440ms post-stimulus interval) and more dishabituation (in the 400-460ms and 800-820ms post-stimulus interval) of SEPs in response to repetitive noxious stimuli in CLBP compared to HC (LoC 3).[118]

Furthermore, one study examined somatosensory processing of noxious stimuli in CLBP in relation to genetic polymorphisms of Catechol-O-methyltransferase (COMT), Brain Derived Neurotrophic Factor (BDNF), and μ-Opioid

Receptor 1 (OPRM 1).[119] COMT is an enzyme that inactivates biologically-active catecholamines, including the neurotransmitters dopamine, noradrenaline, and adrenaline.[90] The COMT polymorphism has been associated with an increased risk of pain persistence.[30, 50, 117] CLBP patients carrying the COMT Val158**Met** allele polymorphism showed larger N2-amplitudes (96-145ms) than patients with the COMT Val158**Val** homozygote (p<.001).[119] In HC the opposite was found, namely a smaller N2-amplitude in those with COMT Val158**Met** compared to those with Val158**Val**. This led to a significant group (HC vs. CLBP) x allele (Met vs. Val) interaction (C4: β=-2.25, SE=.61, p<.001; C3: β=-1.63, SE=.5, p=.013; T4: β=-2.28, SE=.84, p=.008) (LoC 3). A similar result was found regarding the P1-amplitude of people with polymorphisms of BDNF. BDNF is a neurotrophin that supports the growth, differentiation, and survival of neurons in both the peripheral and the central nervous system. BDNF is released when nociceptors are activated and is involved in the activity-dependent pathogenesis of nociceptive pathways that may lead to chronification of pain.[106] CLBP carriers of the BDNF Val66**Met** allele showed a larger P1-amplitude compared to those with BDNF Val66**Val**, and a smaller P1-amplitude was found in HC with BDNF Val66**Met** compared to those with BDNF Val66**Val** (group x allele interaction: Fz: p=.004; Cz: p=.001; Pz: p=.004; C3: p=.001; C4: p=.013) (LoC 3).[119] The OPRM 1 gene polymorphism with guanine (G) replacing the adenine (A) allele (OPRM1 A118G), which is thought to increase the endogenous opioid system and thus associates with decreased nociceptive responsiveness[12, 41, 72,] did not significantly affect EEG-activity when compared between CLBP and HC (LoC 3).[119]

No studies regarding differences in noxious-related potential latencies were found.

To summarize, there is moderate evidence that the late components of noxious-related SEPs remain unaffected in LBP as four studies have reported such results for various SEP-components (LoC 2). Findings regarding possibly increased early-phase SEP-components, ambiguous alterations in the P260 amplitude, modulation of SEPs through muscle tension or genetic polymorphisms, unaltered N150-P260 peak-to-peak amplitude, and habituation processes of SEPs in CLBP need further confirmation due to a low number of articles and/or conflicting evidence (LoC 3).

Auditory processing. Two studies did not find differences regarding amplitude of the auditory evoked potentials (AEPs) N1, N2, P2, P300, and P50 between CLBP and HC (LoC 2).[27, 37]

Concerning latency of AEPs, one study described a delay of the P50 in CLBP (p<.05) (LoC 3) [37]. The P50-potential is related to the reticular activation system (RAS) and plays a role in regulation of arousal and sleep-wake states.[17, 36, 46, 47] Contrarily, another study described an earlier P300 latency, but only at the Cz electrode in the second half of all stimuli that were presented (p=.002) (LoC 3).[27] The P300 is thought to originate in the hippocampus, thalamus, mesencephalic reticular formation and frontal lobes[29, 51, 64, 93, 126], and thus is involved in cognitive processing of sensory information[63] and might reflect mental workload and attentional processing.[32] Regarding N1, N2 and P2 no between group latency differences were found (LoC 3).[27]

Moderate evidence for disturbed habituation of AEPs in response to repetitive stimuli in CLBP was found in two studies (LoC 2).[27, 37]

To summarize, there is moderate evidence based on two studies that AEP amplitude remains unaffected in LBP, but that habituation is disturbed (LoC 2). The inconclusive evidence regarding AEP latencies, with one study reporting a delay, another reporting earlier latencies and yet another reporting no alterations in LBP need further examination (LoC 3).

Other types of sensory processing. No EEG-studies regarding visual, olfactory, gustatory or non-noxious somatosensory (i.e. vibration, touch/pressure, temperature, proprioception) stimuli in LBP sufferers compared to HC were retrieved.

3.4.3 Executive functions

Decision making. One study examined feedback-related negativity and P300-amplitude during the Iowa Gambling task to examine the influence of decision making on brain activation. FRN is related to the early interpretation of good versus bad outcomes and more specifically when the outcome of a gamble violates the expectations of a person. The P300 has a function in the valence of feedback, performance monitoring, and behavioral adaptations

due to feedback.[26, 39, 105] No group differences between CLBP patients and HC concerning FRN and P300-amplitude were found. However, when the potentials for 'winning' bets were compared to 'losses' a disturbed feedback processing in CLBP became eminent. The FRN was larger in losses than wins with CLBP (p=.04), whereas the opposite was found for HC. Concerning P300, potentials were larger in positive feedback cases than negative feedback in HC, but in CLBP there was no difference between wins and losses (LoC 3).[109]
Executive functions are not always clearly defined. However, other tasks examining working memory, attentional processes, inhibitory control, cognitive flexibility, planning, problem solving, and higher order executive functions relying on an interplay of these aforementioned factors still need examination.
To summarize, due to the small amount of studies no conclusive statements regarding alterations in decision making, FRN or other executive functions in LBP can be made (LoC 3).

4 Discussion

The purpose of this review was to determine whether brain function alterations are present in people with LBP compared to HC, measured with EEG. Even though an agreeable amount of brain functions have been examined in LBP, follow-up studies are needed as the majority of the findings in this review are based on a small number of studies with moderate to high RoB, and thus low to moderate strength of conclusions for the majority of statements. Most importantly, this review pinpoints current lacunas in literature and highlights interesting hypotheses regarding the effects of LBP on brain function which consequently indicate directions for future research.

Limited evidence supported the presence of larger CNV amplitudes in CLBP during balance tasks[103]. Furthermore, trunk muscle onset timing in relation to the perturbation was delayed in that study, reflecting disturbed peripheral feedforward processes as well as the disturbed central feedforward which was reflected in the CNV. While inferences based on one study need further confirmation, this increased CNV might be explained by patients prioritizing attentional resources to maintain postural balance in order to protect their painful back[125] and to try and counter disturbed trunk muscle timing. For instance, CLBP patients often adopt a 'guarding mechanism', which is of higher cortical and muscular demand than the normal automated strategy seen in HC.[16, 59, 103] In contrast, BP amplitudes in CLBP were similar as in HC in another study, and no group differences in trunk muscle timing were found in this study neither.[60] As the late CNV partially reflects anticipatory attention towards the perturbation to come, while this is not the case for the BP, this might explain why only the CNV was altered in LBP. The fact that a seated balance perturbation task was used in the BP-study[60] might also explain this, as with such a task the perturbation might not have been big enough to challenge both peripheral and central movement preparation measures, as opposed to the upright balance task used in the CNV-study[103]. Regarding feedback processes in response to balance perturbations, limited evidence found that only the P2 peak was significantly larger in CLBP compared to HC, which could possibly reflect a more demanding postural challenge in CLBP.[61] Interestingly, larger P2 amplitude in CLBP was associated with a diminished center of mass displacement. This might also be related to a 'guarding mechanism', as CLBP patients tend to co-contract their muscles as a rigid postural strategy to avoid harmful movements during balance tasks, which leads to less postural displacement.[74, 94, 114] Furthermore, delayed trunk muscle onset times were described in this study as well.
Aside from balance perturbations, no studies examining other motor functions were retrieved. Increased trunk stiffness,[56, 113] poor proprioception,[28] postural dysfunction,[34, 124] limited range of motion,[35, 57, 91, 96] and altered recruitment patterns of trunk muscles[55, 115, 116, 121] in LBP have already been described on a peripheral level, but whether these changes are linked with changes in the central nervous system still needs EEG examination.

Moderate evidence showed that the middle and late phases of SEPs (>100ms) in response to noxious stimulation were similar in CLBP and in HC.[31, 43, 44, 65] These results were independent of the location, type of stimulation or stimulation intensity. However, ambiguous evidence was found for one late phase potential, i.e. P260. Either no

differences between CLBP and HC[43, 65] or smaller amplitudes in CLBP participants were found. The latter finding could be explained by a 'pain-inhibits-pain' hypothesis. Due to the tonic nature of pain in CLBP, these participants might be less responsive to phasic noxious stimuli than HC.[31, 33, 101] However, as these results were ambiguous and none of the other late potentials showed similar results, this hypothesis should be further examined. Regarding early phase peak activity (N80, <100ms) larger amplitudes were found in CLBP than in HC.[31] Although these findings reported by a single study need further confirmation, it is suggested that in CLBP the sensory processing, but not the cognitive-emotional processing of acute noxious stimuli might be increased. This is supported by positive correlations found between N80-amplitude and measures for perceptual sensitization in one study.[31] The findings of slower linear and inverse habituation, and more dishabituation in response to noxious stimuli in CLBP further support these assumptions and are suggestive of central sensitization processes in CLBP, even though more studies are needed to confirm this.[118] After all, central sensitization entails alterations in endogenous pain modulation, resulting in less ability to habituate to painful stimuli.[31, 40]

Muscle tension and genetic polymorphisms seem highly interesting for further investigation due to their possible mediating role in sensory and cognitive-emotional processing of pain in CLBP. Firstly, increased pain-related somatosensory processing in CLBP patients compared to HC, reflected by a larger N150-amplitude, was only present when a participant applied low tension to the muscles close to or distant from the noxious stimulation area, but not when a high muscle tension strategy was used. This could signify that increasing muscle tension, which is often (subconsciously) applied by CLBP sufferers, is an effective postural strategy to diminish pain, either through gate theory processes,[82] attentional processes, or both.[65] Secondly, limited evidence showed that genetic polymorphisms in COMT and BDNF factors, respectively an enzyme that affects the μ-opioid systems and dopaminergic transmission, and a neurotrophin related to pain signaling and expression, mediated pain-related EEG-activity differently in CLBP than in HC. Regarding COMT and BDNF polymorphisms in CLBP, respectively higher amplitudes were described for N2- and P1-peaks in response to noxious stimuli, whereas lower amplitudes were eminent in HC. These genetic polymorphisms may play a role in the predisposition to LBP and/or pain chronicity. However, rigid conclusions in this matter are hard to establish due to the fact that both mediating factors were examined in a single study.

There is reasonable evidence that amplitude, and limited evidence that latency of most AEP-components are not affected in CLBP as similar responses were seen as in HC.[27, 37] Only an earlier P300[27] and delayed P50[37] were found in CLBP compared to HC. Regarding the slightly delayed P50-latency[37], however, these differences were deemed not to be clinically relevant as the values in CLBP discussed in that study were similar to HC-values of previous studies.[100, 108] Moderate evidence found that habituation to auditory stimuli, reflected by significant AEP latency increases and/or amplitude decreases in response to consecutive blocks of auditory stimuli, was disturbed in CLBP.[27, 37] In the study of Fann et al.[37] this disturbed habituation was only present in a subgroup of CLBP sufferers with depressive symptoms. It is suggested, but still needs to be confirmed by further research, that this inability to adjust to repetitive stimuli is caused by a mental overload in CLBP.[27] This finding is in line with the limited evidence regarding diminished habituation to noxious stimuli in CLBP. Both findings are representative of hyperexcitability of the central nervous system in response to sensory stimuli and thus provide further indications for the presence of central sensitization in some CLBP patients.[118]

Regarding alterations in sensory processing in LBP, no studies concerning visus, olfaction, gustation or non-noxious somatosensory processing were found. Especially the study of non-noxious SEPs would be of high interest to compare between LBP and HC, as central sensitization might occur in some, but not all, of the CLBP sufferers.[102] One of the characteristics of central sensitization is a heightened sensitivity for both noxious (hyperalgesia) and non-noxious stimuli (allodynia) that normally are not painful, but due to this sensitization might be experienced as such.[42, 58, 97] Furthermore, another study showed that in healthy people expecting pain, larger SEPs to non-noxious stimuli in the pain-threatened area were present, possibly due to heightened attention for all stimuli in the area at risk.[24] Thus, processing of non-noxious somatosensory stimuli in LBP sufferers might be altered due to either central sensitization, attentional mediation, or both, and could play a role in the chronification process.

Decision-making is a complex process with involvement of many cortical areas, i.e. the prefrontal cortex, anterior cingulate cortex, fronto-stratial and limbic loops, and subcortical structures.[49] Based on limited evidence, it is suggested that in CLBP disturbed feedback mechanisms might be present compared to HC. CLBP participants seem less capable of differentiating between positive and negative feedback compared to HC, which corresponds to diminished learning effects and disturbed problem solving capacities.[109]
Other executive functions like response inhibition or set shifting are likely impaired in various chronic pain populations,[5, 9, 10, 89] however one study specifically examining CLBP found no impaired executive functioning[78]. As these have only been examined with behavioral tests in LBP, it is recommended to further explore the underlying brain processes with EEG.

Possible sources of bias were not always prevented as shown by the RoB scores. Selection bias could not always be excluded and sample size justifications were often lacking leading to overall moderate to high RoB of individual studies. No differentiations could be made based on duration of LBP as most studies investigated non-specific CLBP or mixed recurrent/chronic LBP groups. However, the comparison of brain function assessed using EEG between different durations of LBP, such as acute, recurrent and chronic LBP might give valuable information regarding the chronification process of LBP. For example, an MRI study showed that gray matter changes were related to the transition from acute to persisting LBP complaints and functional connectivity was predictive for this transition.[6] The current review points out the high potential for the use of EEG in the study of the LBP brain. In order to maximize its value in LBP research objectives of future research should be to not only confirm and validate findings described in this review, but also explore different perspectives in this regard. For instance, all studies examined EEG-amplitude, whereas latency was only discussed in three studies. Timing differences between LBP and healthy participants might however also play an important role in brain functioning and should be examined more. The study of brain-motor interactions to examine whether and to what extent peripheral and central functions are related could be of high value in further unraveling the chronification process of LBP. Novel paradigms such as studies examining movement-evoked LBP or resting state EEG, and other analysis methods such as for instance time frequency analyses could contribute to a vast expansion of the knowledge on central underlying processes of LBP.
Finally, it would be interesting for future studies to examine whether the alterations in cortical processing which are present in LBP as shown in this review can be reversed using therapy, and whether EEG is sensitive enough to detect either short- and/or long-term treatment effects. This might give valuable information regarding plasticity of the functional LBP brain, but as of yet no studies examining this have been performed.

5 Conclusion

Functional brain changes in CLBP were found using EEG. Limited evidence for larger balance-related brain activity in CLBP was found, possibly due to the use of postural strategies that are more attention demanding. Cortical representations of central sensitization and decreased habituation for both noxious and non-noxious stimuli are suggested in CLBP. Brain activity regarding pain in CLBP is suggested to only be affected for those potentials responsible for the sensory and not the cognitive-emotional aspects of pain processing. Limited evidence suggests altered decision-making processes in CLBP due to a diminished ability to differentiate between positive and negative feedback, possibly leading to maladaptive learning strategies. No differences between CLBP and HC were found regarding the N1-amplitude of the PEP, nor for most AEPs. Further research aiming not only at validating the results presented here, but also applying novel paradigms, other EEG-analysis methods, and examining other functional tasks and different types of LBP could lead to a vast expansion of the knowledge in this field and a better understanding of mechanisms underlying LBP.

6 Appendix

TABLE 2. *Evidence table with characteristics of the included case-control studies*

Author	Population	Intervention
1. Cortical motor functions		
Jacobs et al.[60]	Non-specific RLBP/CLBP (>12m); n=10; age 39.2y (±6.3); 5♀/5♂ HC; n=10; age 35.4y (±5.3); 5 ♀/5♂	Seated rapid arm task with the dominant arm at a self-selected pace (125 trials)
Jacobs et al.[61]	RLBP/CLBP (>1 y); n=13; age 37y (±6); 8♀/5♂ HC; n=13; age 35y (±5.5); 9♀ /4♂	Maintain standing balance in response to toes up (30 trials) and toes down (30 trials) rotations of the support surface
Sadeghi et al.[103]	CLBP (>3m); n=29; age 28.9y (±5.5); 0♀/29♂ HC; n=29; age 29.2y (±5.1); 0♀ /29♂	Loaded (3% body weight) right rapid shoulder flexion (60-90°) in response to an auditory go stimulus preceded by an auditory warning stimulus (30 trials)
2. Noxious somatosensory processing		
Diers et al.[31]	CLBP (>12m); n=14; age 54.9y (±9.5); 7♀/7♂ HC; n=13; age 48.4y (±9.2); 5♀ /8♂	Painful electrical stimuli (n = 800) applied intramuscular to left M. Extensor Digitorum and left M. Erector Spinae (at level L3) Painful intracutaneous stimuli (n = 800) at lower arm and back

EEG outcome		Statistical Analysis	Results
Measure	**Electrode Locations**		
1. Cortical motor functions			
BP mean amplitude (40 artefact-free trials selected out of 125 trials for EEG)	F3, Fz, F4, FCz, C3, Cz, C4, P3, P2, P4	Mann-Whitney U test Bonferroni correction	BP mean amplitudes: no significant between group differences
PEP peak amplitude: N1 P2 (number of trials retained for analysis: 27-28, ±2)	FCz, Cz, CPz	Mixed model ANOVA	N1 amplitude: no significant between group differences P2 amplitude: LBP > HC (FCz, p=.01; Cpz, p=.026) N1 and P2 latencies: no significant between group differences
CNV amplitude: Late CNV Peak CNV CNV area	Fz, Cz, Pz	One-way MANOVA	Late CNV amplitude: CLBP > HC (p<.0005) Peak CNV amplitude: CLBP > HC (p<.0005) CNV area: CLBP > HC (p<.01)
2. Noxious somatosensory processing			
Amplitude: N80 N150 P260	F3, F1, FZ, F2, F4, C3A, C1A, CZA, C2A, C5, C3, C1, CZ, C2, C4, C6, C3P, C1P, PZA, C2P, C4P	Three-way ANOVA	N80 amplitude: group effect CLBP > HC (p=.041); group x location interaction RMS CLBP > HC for the arm stimulation condition (p=.024) N150 amplitude: no global group differences CLBP < HC (p=.046) P260 amplitude: group effect CLBP < HC (p=.146)

Flor et al.[43]	CLBP (>6m); n=16; age 42.2y (±12.9); 10♀/6♂ HC; n=16; age 38.6y (±10.2); 10 ♀/6♂	Electrical intracutaneous stimuli applied at the 3rd digit of the non-dominant hand at perception threshold, pain threshold, and pain tolerance threshold (n = 10 per threshold)
Franz et al.[44]	CLBP (>3m); n=16; age 43y (±18); 8♀/8♂ HC; n=16; age 41.9y (±16.9); 8 ♀/8♂	Nociceptive laser heat stimuli were presented on the back and subsequently abdomen in 2 blocks (n = 30/block)
Knost et al.[65]	CLBP (>6m); n=13; age 44.1y (±7.7); 8♀/5♂ RLBP (3-6m); n=14; age 39.5y (±13.8); 8♀/6♂ HC; n=14; age 37.4y (±11.8); 9 ♀/5♂	Painful intracutaneous stimuli at the forearm or back while producing low or high muscle tension levels in respectively M. Erector Spinae or M. Flexor Digitorum Communis (105 trials for the back and 105 for the arm: 2/3 stimulus location matched to active muscle, 1/3 stimulus location not matched to active muscle)
Vossen et al.[118]	CLBP (>6m); n=65; age 40.9y (±15.3); 33♀/32♂ HC; n=76; age 34.8y (±13.7); 50 ♀/26♂	Electrical intracutaneous stimuli applied to the left middle finger (150 stimuli) at 5 different intensities: pain threshold, and -50%, -25%, +25% and +50% of the pain threshold
Vossen et al.[119]	CLBP (>6m); n=78; age 40.4y (±15.4); 40♀/38♂ HC; n=37; age 36.1y (±14.6); 21 ♀/16♂	Electrical intracutaneous stimuli applied to the left middle finger (150 stimuli) at 5 different intensities: pain threshold, and -50%, -25%, +25% and +50% of the pain threshold; studied for different polymorphisms: COMT Val158Met, BDNF Val66Met, OPRM1 A118G

Amplitude: N150 P260 P300 N500	Fz, Cz, Pz	Repeated measures ANOVA Post hoc comparisons with Bonferroni corrected t-test	N150, P260, P300, and N500 amplitudes: no significant between group differences
Latency and amplitude of LEP: N2 P2	Cz	Two-way ANOVA	N2 and P2 mean amplitudes and latencies: no significant between group differences
SEP peak amplitude and latency: N150 P260 SEP peak to peak amplitude: N150/P260	Fz, F3, F4, Cz, C4, C3, Pz, P3, P4	Repeated measures ANOVA Post hoc Tukey-tests with Bonferroni adjusted alpha	N150 amplitude in low tension condition: CLBP > HC ($p<.05$) P260 peak amplitude: no significant between group differences N150/P260 peak to peak amplitude: in CLBP low tension > high tension condition ($p<.01$); no significant between group differences
ERFIAs in N2 and P2 peak region 3 types of habituation: 1) linear 2) fast 3) dishabituation	Fz, Cz, Pz, C3, C4, T3, T4	Multilevel random regression analyses; performed separately on each electrode	HC show a faster linear and inverse habituation and displays less dishabituation compared with CLBP ($p<.05$)
Peak amplitude: N1 N2 P1 P2	Fz, Cz, Pz, C3, C4, T3, T4	Multilevel random regression analyses	N2 peak amplitude: CLBP COMT Val158Met > COMT Val158Val ⟷ HC COMT Val158Met < COMT Val158Val (C4: β=-2.25, SE=0.61, $p<.001$; C3: β=-1.63, SE=0.5, $p=.013$; T4: β=-2.28, SE=0.84, $p=.008$) P1 peak amplitude: CLBP BDNF Val66Met > BDNF Val66Val ⟷ HC BDNF Val66Met < BDNF Val66Val (Fz: β=1.87, SE=0.63, $p=.004$; Cz: β=1.80, SE=0.54, $p=.001$; Pz: β=1.34, SE=0.46, $p=.004$; C3: β=1.66, SE=0.49, $p=.001$; C4: β=1.40, SE=0.55, $p=.013$) OPRM1 A118G polymorphism: no significant between group differences

3. Auditory sensory processing		
Demirci et al.[27]	CLBP (>6m); n=23; age 47.6y (±12); 22♀/1♂ HC; n=23; age 43.3y (±9.1); 22 ♀/1♂	Auditory oddball task: count rare tones presented in a headphone. First trial = 1st half of tones Second trial = 2nd half of tones (30 responses/trial averaged)
Fann et al.[37]	CLBP (>3m); n=22; age 39.6y (±11.5); 13♀/9♂ HC; n=23; age 41.4y (±10.9); 14 ♀/9♂	Pairs of auditory clicks were presented with 250, 500, and 1000ms ISI within pairs and 5s between pairs (n = 64 pairs)
4. Executive functions		
Tamburin et al.[109]	CLBP (>6m); n=24; age 47.7y (±9.1); 14♀/10♂ HC; n=24; age 46.1y (±17.5); 9 ♀/15♂ EEG was measured in a subset of 12 HC and 12 CLBP (no demographic data of subset available, but no statistical difference regarding demographics between groups)	Iowa Gambling Task (100 trials)

3. Auditory sensory processing			
Latency, amplitude and habituation: N1 N2 P2 P3	Fz, Pz, Cz	One-way ANOVA	1st trial: no between group differences in latencies and amplitudes for the three recording sites 2nd trial: at Cz P3 latencies HC > CLBP (p=.002); no between group latency differences for N1, N2, P2 P3 latency and amplitude habituation: only present in HC ⟷ not in CLBP
Latency, amplitude and habituation P50	Cz, Fz	One-way ANOVA Bonferroni correction was used to compare between group effects	P50 latency at all 3 of the ISIs: CLBP > HC (p<.05) P50 amplitude: no significant between group differences P50 habituation: no significant between group differences
4. Executive functions			
Amplitude: FRN P300	Fz Pz	Mixed model repeated measures ANOVA Post hoc t-tests with Bonferroni's correction	FRN and P300 amplitude: no significant between group differences Amplitude difference (wins minus losses) FRN: HC (1.1±3.2μV) > CLBP (-1.3±1.9μV) (p=.04) Amplitude difference P300: HC (1.3±1.5) > CLBP (0.2±1.0) (p=.04)

Abbreviations: age, mean age and standard deviation; ANOVA, analysis of variance; BDNF, brain derived neurotrophic factor; BP, Bereitschaftspotential; CLBP, chronic low back pain; CNV, contingent negative variation; COMT, catechol-O-methyl transferase; EEG, electroencephalography; ERFIAs, event- related fixed-interval areas; ERP, event-related potential; FRN, feedback-related negativity; HC, healthy controls; ISI, inter-stimulus interval; LBP, low back pain; LEP, laser-evoked potential; L3, the 3rd lumbar vertebrae; m, months; MANOVA, multivariate analysis of variance; Met, methionine; n, number/amount; OPRM1, μ-opioid receptor 1; PEP, perturbation evoked potential; RLBP, recurrent low back pain; RMS, root mean square; SE, standard error; SEP, somatosensory evoked potential; Val, valine; y, years of age

TABLE 3. *Results of the methodological quality assessment including risk of bias and levels of evidence*

Study	Selection (/4)					Comparability (/2)
	1	2	3	4	Total	
Demirci et al.[27]	a*	b	c	b	*	a+b**
Diers et al.[31]	a*	b	c	b	*	b*
Fann et al.[37]	b	b	b	b	0	a*+b*
Flor et al.[43]	b	b	c	b	0	a*+ b*
Franz et al.[44]	b	b	c	b	0	b*
Jacobs et al.[60]	a*	b	c	a*	**	b*
Jacobs et al.[61]	a*	b	c	a*	**	b*
Knost et al.[65]	b	b	a*	b	*	b*
Sadeghi et al.[103]	a*	b	c	a*	**	a*+ b*
Tamburin et al.[109]	b	b	c	b	0	a* + b*
Vossen et al.[118]	b	b	a*	b	*	a* + b*
Vossen et al.[119]	b	b	c	b	0	a* + b*

Abbreviations: LoE, level of evidence of individual study; LoA, level of agreement; NA, not applicable

Selection: *1. case definition, a = well described and defined cases *, b = incomplete description or based on self-reports, with no reference to primary record, c = no description; 2. representativeness of the cases, a =consecutive or obviously representative series of cases (i.e. all eligible cases with outcome of interest over a defined period of time, all cases in a defined catchment area or all cases in a defined hospital or clinic, group of hospitals or health maintenance organization) *, b = potential for selection biases or not stated; 3. selection of controls (this item assesses whether the control series used in the study is derived from the same population as the cases and essentially would have been cases had the outcome been present), a = community controls (i.e. same community as cases and would*

Exposure (/3)				Total RoB	Total (%)	LoA (%)	LoE
1	2	3	Total				
a*	a*	NA	**	High (5/8)	62.5	62.5	B
b*	a*	NA	**	High (4/8)	50	87.5	B
a*	a*	b	**	High (4/9)	44.4	55.5	B
b*	a*	NA	**	High (4/8)	50	87.5	B
b*	a*	NA	**	High (3/8)	37.5	75	B
a*	a*	NA	**	Moderate (5/8)	62.5	87.5	B
b*	a*	NA	**	Moderate (5/8)	62.5	100	B
b*	a*	NA	**	High (4/8)	50	75	B
a*	a*	NA	**	Moderate (6/8)	75	75	B
a*	a*	NA	**	High (4/8)	50	100	B
b*	a*	b	**	High (5/9)	55.6	66.7	B
b*	a*	NA	**	High (4/8)	50	100	B

*be cases if they had the outcome) *, b = hospital controls (within the same community as the cases, i.e. not another city, but derived from a hospitalized population), c = no description; 4. definition of controls, a = no history of disease (if cases are first occurrence of outcome, then it must explicitly state that controls have no history of this outcome; if cases have new, but not necessarily first, occurrence of outcome, then controls with previous occurrences of outcome of interest should not be excluded) *, b = no mention of history of outcome;*

Comparability: *1. the participants in different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled (On this item a maximum of 2 stars is awarded if both criteria a) and b) are fulfilled. Either cases and controls must be matched in the design and/or confounders must be adjusted for in the analysis. Statements of no differences between*

*groups or that differences were not statistically significant are not sufficient for establishing comparability. Note: If the odds ratio for the exposure of interest is adjusted for the confounders listed, then the groups will be considered to be comparable on each variable used in the adjustment. There may be multiple ratings for this item for different categories of exposure (e.g. ever vs. never, current vs. previous or never), a = the study controls for the 2 most important factors: medication + age *, b = the study controls for any additional factor: handedness, eye blinking, gender *, c = the study does not control for any of the confounders mentioned in a) or b);*

Exposure: *1. ascertainment of exposure, a = existing protocol; i.e. validated measurement tool or sufficient existing references *, b = non-validated but well described or available tool *, c = no description; 2. same method of ascertainment for cases and controls, a = yes, the exact same protocol for cases and controls with the same exposure and measurements *, b = no; 3. non-response rate, a = same rate for both groups *, b = non-respondents described, c = response rate differs between groups and no designation*

TABLE 7. *Summary of evidence regarding functional brain alterations in LBP*

Function	EEG Measure	LBP alterations (compared to healthy controls)	LOC	Study
Balance task	Movement preparation:			
	• CNV	Larger amplitude	Some evidence (3)	Sadeghi et al.[103]
	• BP	No difference	Some evidence (3)	Jacobs et al.[119]
	Perturbation-evoked potentials:			
	• N1	No difference	Some evidence (3)	Jacobs et al.[61]
	• P2	Larger amplitude	Some evidence (3)	Jacobs et al.[61]
	Alpha event-related desynchronization	No difference	Some evidence (3)	Jacobs et al.[60]
Sensory processing	**Noxious somatosensory processing:**			
	• Early component: N80	Larger amplitude	Some evidence (3)	Diers et al.[31]
	• Later components: N150, P300, N500, N2, P2	No difference	Moderate evidence (2)	Diers et al.[31]; Flor et al.[43]; Franz et al.[44]; Knost et al.[65]
	• N150-P260 peak to peak difference	No difference	Some evidence (3)	Knost et al.[65]
	• P260	Smaller amplitudes (n = 1) vs. no difference (n = 2)	Inconclusive evidence (4)	Diers et al.[31]; Flor et al.[43]; Knost et al.[65]
	• Noxious somatosensory processing + low muscle tension: N150	Larger amplitude	Some evidence (3)	Knost et al.[65]

	• Habituation to noxious stimuli	Decreased	Some evidence (3)	Vossen et al.[118]
	• Sensitization to noxious stimuli	Increased	Some evidence (3)	Vossen et al .[118]
	Noxious somatosensory processing + genetic polymorphisms:			
	• COMT: N2	Larger amplitude	Some evidence (3)	Vossen et al.[119]
	• BDNF: P1	Larger amplitude	Some evidence (3)	Vossen et al.[119]
	• OPRM	No difference	Some evidence (3)	Vossen et al.[119]
	Auditory processing:			
	• Amplitude N1, N2, P2, P50, P300	No difference	Moderate evidence (2)	Demirci et al.[27]; Fann et al.[37]
	• Latency P50	Delay	Some evidence (3)	Fann et al.[37]
	• Latency P300	Earlier	Some evidence (3)	Demirci et al.[27]
	• Latency N1, N2, P2	No difference	Some evidence (3)	Demirci et al.[27]
	• Habituation to auditory stimuli	Disturbed	Moderate evidence (2)	Demirci et al.[27]; Fann et al.[37]
Decision making	Amplitude FRN, P300	No difference	Some evidence (3)	Tamburin et al.[109]
	Feedback processing FRN, P300	Disturbed	Some evidence (3)	Tamburin et al.[109]

Abbreviations: BDNF, Brain Derived Neurotrophic Factor; BP, Bereitschaftspotential; CNV, Contingent Negative Variation; COMT, Catechol-O-methyltransferase; FRN, Feedback-Related Negativity; LoC, level of conclusion; OPRM1, μ-Opioid Receptor 1

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THE INFLUENCE OF CATASTROPHIZING AND FEAR ON MOVEMENT-RELATED OUTCOMES IN LOW BACK PAIN: A SYSTEMATIC REVIEW

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Abstract

There is abundant evidence for compromised movement in low back pain (LBP). It has been proposed that not only pain severity, but also cognitive-affective factors such as fear and catastrophizing influence movement. A systematic review was performed, following the PRISMA-guidelines, to summarize and specify the influence of catastrophizing and fear on movement-related outcomes in LBP, as influence thereof was assumed in theoretical models of pain-related disability and suffering. A comprehensive search was performed in five electronic databases to identify all relevant studies. Fifty-one studies were included, the majority concerning chronic LBP. Limited evidence for muscle-dependent alterations in trunk muscle timing and activity and diminished endurance were found, whereas for trunk muscle strength results were unclear or non-significant. Task-dependent functional performance impairments in correlation with catastrophizing and fear in LBP were also described. However, these inferences need further experimental exploration as most are based upon single studies. Implementation of bio-psychosocial assessment and treatment seems valuable for LBP patients with disturbed motor control, trunk muscle endurance, mobility, and lifting performance. This systematic review specified the current evidence regarding the influence of catastrophizing and fear on altered movement-related outcomes in non-specific LBP, which was assumed in current theoretical models of pain-related disability and suffering. Catastrophizing and/or fear are related with several movement alterations and diminished performance for various functional tasks, warranting bio-psychosocial assessments and treatment in LBP.

Keywords: chronic pain; musculoskeletal pain; psychological; fear-avoidance beliefs; kinesiophobia; motor control

1 Introduction

Pain influences the way people move.[50] In non-specific low back pain (LBP) sufferers increased trunk stiffness[51, 126], poor proprioception[26], altered trunk muscle recruitment patterns[48, 129, 131, 139], postural dysfunction[30, 147], and limited range of motion[31, 52, 89, 96] have been observed. Pain can also affect cognitive-emotional aspects, i.e. depressive feelings[17, 18, 22, 71, 81, 97, 105, 111], anxiety[17, 18, 81, 111], catastrophizing[17, 64, 79], and fear-avoidance beliefs[64, 79, 146] have been reported in LBP sufferers. Furthermore, some of these cognitive-affective factors play a role in the transition from acute (ALBP) to chronic LBP (CLBP).[28, 42, 97, 132]

The link between altered movement and cognitive-affective factors in LBP has been proposed by several bio-psychosocial models, of which the 'fear-avoidance model' is one of the most widely accepted. It describes how acute pain may evolve into a chronic condition due to excessive avoidance behavior induced by maladaptive cognitive-affective processes.[135] If this avoidance behavior persists, which is often the case in CLBP, muscular and cardiovascular properties might deteriorate due to physical inactivity and disuse, which in its turn may induce functional disability.[10, 63] Fear-avoidance can arise due to the presence of catastrophizing and/or fear about pain, and can subsequently alter movement. Catastrophizing is the cognitive process of interpreting pain as extremely threatening (magnification), and involves negative thoughts about present and future pain (rumination) or feelings of helplessness.[19] Catastrophizing is considered a precursor of fear in the fear-avoidance model. Pain-related fear is an emotional reaction to the threat of pain. It instigates cognitions, behaviors, and psychophysiological changes in order to defend, escape from or prevent (further) harm that is related to the pain.[76] Due to this additional emotional dimension, the impact of pain-related fear on movement might be speculated to be higher compared to catastrophizing. However, a clear comparison in this matter is lacking.

The 'fear-avoidance model' was frequently updated and modified[11, 20, 91, 98, 133, 136] and formed the basis for an abundance of experimental research and theoretical models which aimed at identifying underlying mechanisms to LBP chronicity. Proof that both factors have a distinct impact on the chronification process is increasing. For instance, recent reviews have confirmed associations of higher levels of pain-related fear and catastrophizing with increased disability and pain, and diminished physical activity.[76, 90, 144, 145, 148] Nonetheless, identifying underlying mechanisms in the chronification process of LBP and developing optimal treatment remains challenging[8, 25, 58, 98]. Perhaps this is because the most studies primarily focused on the interaction between cognitive-affective factors and disability in LBP, whereas examination of more specific movement alterations, could yield important insights concerning underlying mechanisms. A model with a more movement-related focus is the 'contemporary theory of motor adaptation in pain'. It illustrates the role of specific movement alterations aimed at avoiding pain or the threat thereof in the chronification process of pain. Furthermore, cognitive-affective factors have a contributing role on such pain-related behavior, but exact interactions between these cognitive-affective and motor processes in LBP also remain unspecified here.[49]
Only one systematic review shortly addressed the interaction between fear/catastrophizing and several more specific underlying movement-related alterations, such as motor control, coordination and strength.[76] As the movement-related outcomes included in that review were limited and that review is outdated, an up-to-date and more comprehensive overview of this matter is warranted.

An in-depth analysis of the literature is needed to provide a profound understanding of how catastrophizing and fear (Exposure) influence specific movement-related outcomes (Outcome) in a context of LBP (Population), and whether these effects of fear and catastrophizing differ or show parallels. To answer this research question, we performed a systematic review on experimental studies (Study design) which examined this topic. A higher presence of maladaptive cognitive-affective factors in CLBP compared to recurrent LBP (RLBP) has been observed in previous studies.[37, 38] Therefore, differences based on type of LBP (acute-recurrent-chronic) will also be examined if possible.

2 Methods

This systematic review is reported following the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines.[86]

2.1 Eligibility criteria

This systematic review was limited to studies that examined whether catastrophizing and/or fear (Exposure; E) influence or were associated with movement-related outcomes (Outcome; O) in patients with non-specific LBP (Population; P). In this review 'movement-related outcomes' was chosen as a term to cover the umbrella of outcomes related to the movement system which are assessed using quantitative (e.g. electromyography, dynamometry, etc.) as well as qualitative and functional (e.g. Berg Balance test, functional reach, etc.) measures.

2.2 Information sources and search strategy

A comprehensive and extensive search strategy was developed in order to retrieve all relevant research which was currently available in the literature regarding this topic. The electronic databases of Pubmed, Web of Science, Embase, CINAHL and PsycArticles were uniformly searched the 16th of August 2018. Predefined free text search terms were deduced from the PECO-question and are presented in **TABLE 1**. Different synonyms for P, E and O were defined and combined using the boolean operator 'OR'. The boolean operator 'AND 'was used to combine the search terms of P, E and O with each other. No filters were applied.

In addition, a hand search was performed to make the search as complete as possible. Therefore, the reference lists of all the included studies retrieved by the electronic search were screened to identify additional relevant studies. Although other review studies collected with the electronic search were not included in this systematic review, their reference lists were also screened to identify potentially relevant studies. To ascertain that the search strategy was comprehensive, and no relevant studies were overlooked, internationally renowned experts regarding the topic of this review were contacted by e-mail and requested to screen the retrieved results and provide any possible additions.

TABLE 1. *Search strategy*

Population	AND	Exposure	AND	Outcome
"Low back pain"		fear		"motor performance"
"Lumbar back pain"		anxiety		"movement performance"
lumbago		anxious		"movement control"
"lower back pain"		kinesiophobia		"motor control"
"low back ache"		catastrophi*		"motor activity"
"low backache"		hypervigilance		"sensorimotor function"
"lumbar pain"		attenti*		"neuromuscular control"
		attention		"sensorimotor control"
		vigilan*		"muscle performance"
		vigilant		"muscle activity"
		interocepti*		"muscle activation"
		"sensory focus"		"muscle onset"
		distraction		"reaction time"
				recruitment
				contraction
				"motor skills"

		"motor variability" "muscle activation patterns" "postural control" "behavioral performance" "behavioural performance" strength "muscle endurance" proprioception coordination balance "muscle fatigue" ultrasonic ultrasonography "ultrasound imaging" ultrasound Electromyography EMG "muscle functional magnetic resonance imaging" "muscle functional MRI"

Abbreviations: EMG, Electromyography; MRI, Magnetic Resonance Imaging

2.3 Study Selection

Predefined in- and exclusion criteria regarding the design of the study, the studied population, the topic and language of the study were used to assess the eligibility of the search results. These criteria are presented in **TABLE 2**. No limitations were made based on year of publication, and all types of experimental study designs were initially eligible for study inclusion. Only studies which examined the influence of catastrophizing and/or fear on movement-related outcomes in LBP patients were eligible for study inclusion. Therefore, both observational studies which examined the clinical presence of catastrophizing and/or fear, as well as studies which experimentally induced or manipulated catastrophizing and/or fear were included. Studies which used experimental treatment interventions to influence catastrophizing and/or fear such as RCT's were screened to examine whether they included any relevant information on cross-sectional level (for instance associations between levels of catastrophizing/fear and movement-related outcomes reported in baseline). If this was the case this data was included. However, this systematic review did not examine the influence of experimental interventions on catastrophizing/fear and movement-related outcomes, and therefore data on treatment outcomes was not included. Solely studies which used objective quantitative measures to assess movement-related outcomes were included in this review.

The titles and abstracts of the retrieved studies were screened to examine whether the studies fulfilled the inclusion criteria. If any of the inclusion criteria were not met, the article was excluded from the literature review. In case of uncertainty regarding the eligibility of the paper based on the content of the title and abstract, the full text version of the paper was consulted and evaluated against the inclusion criteria. The full-text versions of all studies that were considered potentially eligible and relevant were retrieved. Each full text article was read to ensure eligibility, to assess potential risk of bias (RoB) and to extract data.

TABLE 2. *In- and exclusion criteria*

Inclusion criteria	Exclusion Criteria
Design	
• Experimental and observational studies. • Full text reports	• Non-experimental/observational studies such as letters, editorials, reviews, meta analyses, study protocols, etc. • Non full text reports such as abstracts, congress proceedings, etc.
Population	
• Humans • Adults (≥18 y) • Presence or history of non-specific LBP (acute, chronic, recurrent, etc.)	• Animals • Infants, children or adolescents (< 18 y) • Other populations than those with LBP • Experimentally induced LBP • Severe LBP pathologies due to cancer, traumata, etc. • Studies solely in healthy people
Topic	
Examining the influence of catastrophizing and/or fear on movement-related outcomes: • Observational studies of catastrophizing/fear • Experimental exposure to induce or manipulate catastrophizing/fear • Objective quantitative assessment of movement-related outcomes • Analytic measures of movement-related outcomes (e.g. electromyography, dynamometry, etc.) • Functional measures of movement-related outcomes (e.g. balance, lifting, bending, walking tasks, etc.)	Not examining the influence of attention and/or fear on movement-related outcomes: • No assessment of catastrophizing or fear • No assessment of influence of these factors on movement-related outcomes • Assessment of experimental treatment interventions influencing catastrophizing/fear • No assessment of movement-related outcomes • Subjective quantitative assessment of movement-related outcomes (e.g. self-report) • Qualitative assessment of movement-related outcomes (e.g. descriptive)
Language	
• Written in English, Dutch, French, German, Greek, Italian or Spanish	• Written in another language than English, Dutch, French, German, Greek, Italian or Spanish

Abbreviations: LBP, Low Back Pain; y, years

2.4 Qualification of searchers/raters

Literature was searched and screened by two researchers (S.S. and A.C.) independently from each other. The same researchers also assessed RoB of the included studies blind from each other. The two authors compared the results from the search, screening on in- and exclusion and RoB assessments. In case of disagreement, the point of difference was discussed in order to obtain consensus. When consensus could not be reached, a third and decisive opinion was provided by another author (J.V.O). S.S. obtained a MSc in Rehabilitation Sciences and Physiotherapy, A.C. obtained a MSc in Psychological Sciences, and J.V.O. obtained a PhD degree in Rehabilitation Sciences and Physiotherapy and is experienced in conducting systematic reviews.

2.5 Data items and collection process

From each included study, information regarding following items was extracted in an evidence table (**TABLE 3** in appendix): (1) population (type and duration of LBP, mean age, gender distribution); (2) type of cognitive-affective factor (catastrophizing and/or fear) which was examined and how it was assessed; (3) movement-related outcome measure; (4) statistical analysis; (5) results. The same structure was also used in the 'Synthesis of Results' section of this paper. Furthermore, it is important to make the distinction between several specific concepts when discussing fear, as these cannot all be regarded as identical psychological constructs. The most commonly assessed are 'kinesiophobia' and 'fear-avoidance beliefs' warranting a distinct paragraph for these when discussing each movement-related outcome in the 'Synthesis of Results'. Furthermore, the title 'fear-other' was developed to discuss other, less commonly studied, types of fear such as pain-related fear and general anxiety. In this way, even though these types of fear are often to some extent related to each other, distinct nuances could still be taken into account in the analysis of the literature.

2.6 Risk of bias (RoB) and levels of evidence of individual studies

The RoB for each included study was assessed using an adjusted version of the Newcastle-Ottawa Scale for case-control studies (**TABLE 4** in appendix).[142] The scale was adapted in order to assess studies with a cross-sectional design. For this reason, an additional item was added to both the 'Selection' as the 'Outcome' domain of the original checklist. The scale exists of three domains: 1) 'Selection' of study groups and ascertainment of exposure (five items, six stars); 2) 'Comparability' of groups (one item, two stars); and 3) 'Outcomes' (three items, four stars). For each study all items were scored based on the outcomes of interest for the current systematic review. A maximum of 12 stars was assigned to each study with high scores corresponding to low RoB.

Within the 1st domain, 'Selection', the 1st item assessed whether the case definition of the LBP population was adequately described in terms of type and duration of LBP. ALBP is commonly defined as a solitary pain episode suddenly occurring, without a previous history of LBP complaints in the six months before onset of that episode, and not exceeding a duration of six weeks, whereas in subacute LBP the timeframe of complaints exceeds six weeks up to maximally 12 weeks.[65] RLBP is commonly defined as episodic LBP with an onset of at least six months ago and a minimum of two pain episodes per year. One episode is characterized by minimally 24 hours of pain followed by a pain free period of at least one month.[23] CLBP is commonly defined as continuous LBP with an onset of at least three months ago.[55] The pain should also be present in at least half of the days since first onset.[27] The maximum score of one star was given when adequate information regarding type of LBP, duration of complaints, and in- and exclusion criteria was mentioned. No stars were given when this was not the case or not sufficiently described.
The 2nd item evaluated representativeness of the sample and thus the presence of selection bias. One star was assigned when the studied sample had similar characteristics as the average in the target population of the study. This could be attained when authors performed random sampling and/or subjects were recruited from at least two different sources. When a selected group, not-representative for the whole population, was described or the study was lacking a description no stars were assigned.

The 3rd item assessed whether the studied sample size was based on a valid power calculation (a priori or post hoc) and whether the studied population met the amount calculated. Both criteria had to be fulfilled in order to obtain a star.
To obtain one star on the 4th item, characteristics of respondents and non-respondents had to be indexed, response rates had to be satisfactory in accordance with the power analysis, and no statistical difference regarding sociodemographic parameters could be present between respondents and non-respondents.
In the 5th item two stars were acquired when the measurement of catastrophizing and/or fear was evaluated with a validated measurement tool or task. Only one star was given when the measurement was well described, but not yet validated. When the description of the measurement was insufficiently described no stars were assigned.

The 2nd domain 'Comparability' comprised of one item which assessed the presence of possible confounders in studies which compared two or more groups. Grouping could be based on different types of LBP or different levels of catastrophizing/fear within a certain LBP type (usually cut-off values on questionnaires were used for dichotomization). The goal of this review was not to compare healthy controls with a LBP group, thus studies with this type of design were not targeted by this item. One star was awarded to studies controlling for both age[12, 54, 59, 109, 113] and sex[70, 87], and an extra star could be gained by controlling for at least one of following additional confounders: pain intensity[32, 107, 112, 116, BMI5, 45, 124] and/or physical activity level[9, 36, 44], as these factors have been shown to be associated with alterations in movement-related outcomes. Furthermore, age[33, 40, 53, 73, 99], gender[40, 53, 73], BMI[33, 40, 72, 119], and physical activity[36, 44, 90] have also been linked to LBP incidence, prevalence and/or risk in previous literature. When none of the above were accounted for, no stars were assigned.

Within the 3rd domain the 1st item assessed the objectivity of the movement-related outcomes that were measured and awarded studies using objective outcomes with one star, whereas subjective measures were not awarded with any stars.
In the 2nd item two stars were awarded for independent and blind measurements of movement-related outcomes, whereas only one star was given when the outcome measurement was well described but not blinded. Studies with no or bad description of the outcomes scored 0 stars.
The 3rd item appointed one star when the statistical tests used for data analysis were clearly described and appropriate, and whether the measurement of the association was presented, including confidence intervals and the probability level (p value). Studies that did not reach these criteria attained 0 stars for this item.
For those studies where one or more of the items were deemed 'not applicable' (NA), these studies did not receive a score for those items and in such cases these items were also not taken into account for the denominator of the total score.

Adhering to the guidelines of the Dutch Institute for Healthcare Improvement (CBO 2007), levels of evidence (LOE) were based on study design and methodological quality of the individual studies. The studies could receive a LOE A2 (double blind randomized comparative clinical trials of good quality, sufficient size and consistency), B (randomized clinical trials of moderate quality or insufficient size or other comparative trials such as non-randomized, patient-control and cohort studies), or C (non-comparative trials).

2.7 Levels of conclusion

A level of conclusion (LOC) was determined after clustering studies with comparable outcomes. Per cluster the amount of independently conducted studies, the LOE, and the direction and consistency of the reported results were taken into account. The LOC ranges from one to four and corresponds respectively with a high (one A1 or at least two independent A2 studies), moderate (one A2 or at least two independent B studies), low (one B or C study, or conflicting results between various studies), or no strength of conclusion at all (expert opinion).[84]

3 Results

3.1 Study selection

The process of study selection is depicted in a flowchart (**FIGURE 1**). The initial electronic search resulted into 3097 hits. After removal of duplicates, 2425 studies remained. After screening the studies on title, abstract and full text regarding the fulfillment of the inclusion criteria, 47 studies met the eligibility criteria. Rejection was based on not fulfilling the criteria regarding topic (n = 1010), population (n = 882), design (n = 485), and language (n = 1, Persian). Hand searching resulted in 20 additional potential studies. After screening the full text content of these studies, three fulfilled the inclusion criteria and were retained. One additional study was received through expert suggestion. Hence, in total [51] studies were included in this systematic review.

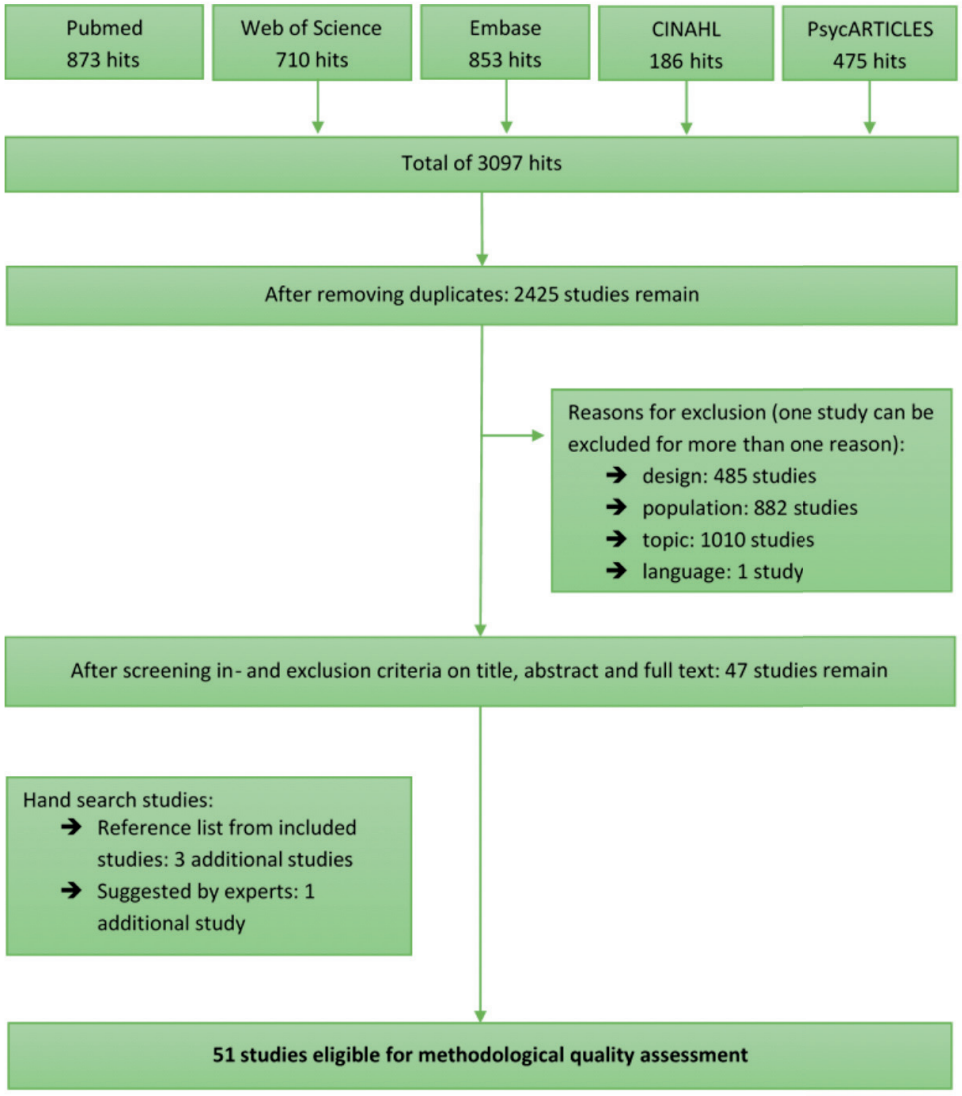

FIGURE 1. Flowchart

3.2 Study characteristics

The study characteristics of each included study can be found in the evidence table (**TABLE 3** in appendix).

From the 51 included studies, 37 studied a CLBP population[6, 7, 14, 16, 21, 24, 34, 43, 46, 56, 61, 66-69, 74, 75, 77, 83, 85, 88, 92-95, 100, 102, 104, 108, 114, 115, 125, 127, 134, 137, 140], three (sub)acute LBP populations[121-123], ten mixed LBP populations[1-4, 29, 39, 57, 82, 103, 110] and one a non-specified LBP population[60]. No studies which examined a homogenous RLBP population were found. Catastrophizing and fear were respectively studied in 18 and 47 studies. All studies used questionnaires to assess the cognitive-affective variables in concordance with movement-related outcomes. To assess the amount of catastrophizing most studies used the 'Pain Catastrophizing Scale' (PCS)[6, 21, 29, 39, 43, 60, 66, 68, 69, 74, 77, 88, 95, 100, 123], which has a total score for pain catastrophizing, as well as 'rumination', 'magnification', and 'helplessness' subscores. Three studies used the catastrophizing subscores of the 'Pain Cognition List' (PCL)[114] or 'Coping Strategy Questionnaire' (CSQ)[122, 128] which are questionnaires devised to assess a broader spectrum of cognitive constructs associated with pain. With regards to fear, various types were assessed by questionnaires with often nuanced differences. Kinesiophobia or fear of movement was most commonly assessed with the 'Tampa Scale for Kinesiophobia' (TSK)[1, 6, 16, 21, 24, 34, 39, 56, 60, 61, 66-69, 74, 77, 83, 94, 102-104, 108, 114, 115, 123, 127, 134, 137], but one study also used the 'Photographs of Daily Activities' (PHODA)[60]. The 'Fear-Avoidance Beliefs Questionnaire' (FABQ), with its total score and its two subscales for avoidance beliefs regarding either general physical activities (FABQ-pa) or rather work-related tasks/movements (FABQ-w), was often applied to assess pain-related fear and avoidance behavior.[2-4, 7, 14, 21, 29, 43, 57, 60, 61, 75, 82, 92, 93, 104, 115, 121, 122, 140] Less often used questionnaires/scales to assess pain-related fear or anxiety, were the 'Pain Anxiety Symptoms Scale' (PASS)[21, 77, 110, 125], or visual analogue scales for fear (FVAS)[24, 46]. Besides the aforementioned pain-related constructs of fear, general fear or anxiety was also assessed. The anxiety subscale of the 'Hospital Anxiety and Depression Scale' (HADS)[85] and the 'Millon Clinical Multiaxial Inventory' (MCMI)[46] were used to respectively assess clinical features and personality traits indicative for anxiety. However, both these scales assess a broader spectrum of other psychological factors as well. Additionally, one study also experimentally induced fear.[137]

Clusters were made of studies with comparable movement-related outcomes. Clusters regarding 'Trunk muscle timing' (n = 2)[57, 69], 'Trunk muscle activity' (n = 16)[29, 34, 43, 67, 77, 83, 94, 95, 100, 102, 122, 125, 127, 128, 137, 140], 'Trunk muscle strength' (n = 12)[3, 4, 21, 24, 39, 46, 56, 61, 68, 74, 85, 125], 'Trunk muscle endurance' (n = 6)[1, 7, 24, 68, 75, 94], 'Activities of daily living (ADL)' (n = 20)[2, 3, 6, 7, 14, 16, 21, 56, 61, 66, 67, 75, 93, 103, 104, 108, 114, 115, 123, 134], 'Balance' (n = 4)[16, 82, 110, 121], 'Spinal kinematics' (n = 7)[7, 24, 34, 46, 61, 67, 88], 'Proprioception and coordination' (n = 3)[56, 60, 92] were made. Furthermore, results were grouped based on LBP duration ((sub)acute, recurrent or chronic LBP).

3.3 RoB and level of evidence

The RoB scores and LOE of the different studies are displayed in TABLE 4. The observed agreement between both raters on all RoB items was 92% (483/526 stars), and 100% for the LOE. The majority of the studies had a cross-sectional design and therefore received a LOE C, 8 studies with a comparative cross-sectional design received a LOE B[43, 85, 95, 104, 110, 125, 134, 137].

The main reasons for RoB were the lack of justification of chosen sample sizes by means of a power analysis, and not reporting response rates and thus failure to compare between respondents and non-respondents, which explains the overall low scores on items three and four respectively. Regarding the measurement of exposure, i.e. the way how catastrophizing/fear was measured, 48 studies used validated tools/paradigms, which led to high scores on item five. The remaining three studies did not use validated tools, although a good description of the measurement was always provided. None of the included studies reached the maximum score for the 'Selection' domain. The 'Comparability' domain was not applicable for most studies due to the fact that only one population was studied or was deemed relevant for this systematic review.

Overall, the items of the 'Outcome' domain were fulfilled and statistical analyses were available and adequately

described. Only two studies did not use an objective movement-related outcome measure. Blinding of assessors for the outcome measures, however, was only performed in five studies.

3.4 Synthesis of Results

A schematic overview of the main results is depicted in **TABLE 5.**

TABLE 5. *Synthesis of results overview*

		Catastrophizing	
		CLBP	**other LBP**
Muscle timing	ABD	↓ (EO, cTrA/IO) ↑ (iTrA/IO) n.s. (RA)	?
	BACK	↓(ES: L3, L5, cT10, cL1) n.s. (ES: iT10, iL1)	?
Muscle activity	ABD	↑ (EO, RA)	↑ (subALBP: left EO)
	BACK	↑↑ **(ES: L2-4, L4-5, MF, left LO)** n.s. (IL, right LO)	n.s. (RLBP/CLBP: lumbar ES)
Muscle strength	ABD	?	?
	BACK	n.s.	↓ strength ↑ variability (RLBP/CLBP)
Muscle endurance	ABD	?	?
	BACK	↓	?
ADL	Lifting performance	↓ (endurance) n.s. (max weight)	↓ (ALBP: speed)

Fear					
Kinesiophobia		Fear-avoidance		Other	
CLBP	other LBP	CLBP	other LBP	CLBP	other LBP
↓ (iEO) ↑(RA) n.s. (cTrA/IO, cEO)	?	↑ (FABQ-pa: cEO) n.s. (FABQ-w: EO)	?	?	?
↓ (ES: cT10, cL1, cL3, iL5) n.s. (ES: iT10, iL1, iL3, cL5)	?	?	?	?	?
↑ (TrA/IO)	(non-specified LBP: RA)	?	n.s. (ALBP: left EO)	?	?
↓(ES: L3-5) n.s. (ES: T12, L1-5 ↓FRR	?	? ↓FRR	n.s. (subALBP: ES L3; RLBP/CLBP: ES L3)	↔ (pain-related anxiety)	?
n.s.	?	?	?	↓ (pain-related fear) n.s. (anxiety)	?
↔	?	n.s.	n.s. (ALBP) ↓ (ALBP/CLBP)	↔ (anxiety)	?
?	?	↓(FABQ-w) n.s. (FABQ-pa)	?	?	?
↔	?	?	?	n.s. (pain-related fear)	?
↓ (endurance) ↔ (max weight)	↓ (ALBP: speed) n.s. (RLBP/CLBP: max weight)	↔ (max weight)	?	?	?

		Catastrophizing	
		CLBP	other LBP
	Stair climbing	↑	?
	Walking	n.s. (speed) n.s. (distance)	?
	Hand RT	n.s.	n.s. (healthy/CLBP)
	Hand MT	?	n.s. (healthy/CLBP)
	TUG	?	?
	Sit-to-stand	n.s.	?
	One leg stance	?	?
	Static bending	?	?
	Dynamic bending	?	?
	Lower limb function	?	?
	Leg strength	?	?
	Hand grip strength	?	?

Fear					
Kinesiophobia		Fear-avoidance		Other	
CLBP	other LBP	CLBP	other LBP	CLBP	other LBP
n.s.	?	?	?	?	?
n.s. (stride length) n.s. (distance)	?	↔ (speed) ↓ (FABQ-w: distance)	↓ (elderly CLBP: speed) n.s. (RLBP/CLBP: speed)	?	?
?	n.s. (healthy/ CLBP)	?	?	?	?
?	n.s. (healthy/ CLBP)	?	?	?	?
↑	n.s. (elderly women)	?	?	?	?
n.s.	?	?	n.s. (RLBP/CLBP)	?	?
?	n.s. (elderly women)	?	?	?	?
↓ (endurance)	?	↓ (FABQ-pa) n.s. (FABQ-w)	?	?	?
n.s.	n.s. (RLBP/CLBP)	↓ (FABQ-w) n.s. (FABQ-pa)	?	?	?
n.s.	?	?	?	?	?
?	?	↓	?	?	?
n.s.	?	↓ (FABQ-pa)	?	?	?

		Catastrophizing	
		CLBP	**other LBP**
ADL	Forward reach	n.s.	?
	Cardio-pulmonary endurance	?	?
Balance		?	?
Kinematics		↓ (lumbar flexion)	?
Proprioception/ Coordination		?	n.s. (non-duration specified LBP: stiffness, damping)

Legend:

↑, *limited evidence for positive association of the movement-related outcome with the cognitive-affective factor;*

↑↑ ***, moderate evidence for positive association of the movement-related outcome with the cognitive-affective factor;***

↓, *limited evidence for negative association of the movement-related outcome with the cognitive-affective factor;*

n.s., limited evidence for non-significant associations between the movement-related outcome and cognitive-affective factor;

↔, *ambiguous or conflicting evidence;*

?, not examined yet;

c, when preceding a muscle indicates the contralateral muscle (e.g. cRA, contralateral Rectus Abdominis muscle);

i, when preceding a muscle indicates the ipsilateral muscle (e.g. iRA, ipsilateral Rectus Abdominis muscle);

Fear					
Kinesiophobia		Fear-avoidance		Other	
CLBP	other LBP	CLBP	other LBP	CLBP	other LBP
n.s.	?	n.s. (FABQ-pa)	?	?	?
?	?	↓ (FABQ-pa)	?	?	?
n.s. (CoP excursion)	?	?	n.s. (subALBP + FABQ-pa: postural stability, CoP)	?	↓ (RLBP/CLBP + pain-related fear: CoP mean velocity and area)
↔ (lumbar flexion)	?	↓ (FABQ-w: lumbar flexion n.s. (FABQ-w: lumbar extension) n.s. (FABQ-pa: lumbar, flexion, extension, side bending)	?	n.s. (anxiety: lumbar flexibility)	?
n.s. (controlled contraction TrA/MF)	↔ non-duration specified LBP: stiffness) n.s. (non-duration specified LBP: damping)	↓ (undershooting and overshooting position-reposition)	?	?	?

Abbreviations: *ABD, abdominal muscles; ADL, activities of daily living; ALBP, acute low back pain; CLBP, chronic low back pain; CoP, centre of pressure; EO, External Oblique muscle; ES, Erector Spinae muscle; FABQ-pa, physical activity related fear-avoidance beliefs; FABQ-w, work-related fear-avoidance beliefs; FRR, flexion-relaxation ratio; Healthy/CLBP, mixed population of both healthy and CLBP patients; IL, Iliocostalis muscle; IO, Internal Oblique muscle; LO, Longissimus muscle; MF, Multifidus Muscle; RA, Rectus Abdominis muscle; RLBP, recurrent low back pain; RLBP/CLBP, mixed population of both RLBP and CLBP patients; ROM, range of motion; TrA, Transversus Abdominis Muscle*

3.4.1 Trunk muscle timing

Catastrophizing. *CLBP* sufferers with high levels of catastrophizing reacted with earlier feedforward onset latencies of the bilateral External Oblique (EO) and the contralateral Transversus Abdominis/Internal Oblique (TrA/IO) muscles in relation to the moving arm during a unilateral rapid arm flexion movement ($p<.05$), according to limited evidence from a single study (LOC 3).[69] Contrarily, the ipsilateral TrA/IO showed significantly delayed onset times with higher catastrophizing in *CLBP* ($p<.05$) (LOC 3).[69] For the bilateral RA no significant associations with catastrophizing were found in this population (LOC 3).[69]

Similar limited evidence was seen regarding the back muscles, as *CLBP* sufferers with high levels of catastrophizing reacted with earlier feedforward muscle onset latencies in the Erector Spinae (ES) muscle at several levels (ipsi- and contralateral at L5 and L3 levels, contralateral at T10 level and L1 level) during a unilateral rapid arm flexion task in one study ($p<.05$), whereas in other muscles no significant correlations were found (ipsilateral L1 and T10 levels) (LOC 3).[69]

Fear-kinesiophobia. A single study found that high levels of kinesiophobia were associated with an earlier feedforward onset of the ipsilateral EO in *CLBP* during unilateral arm movements ($p<.05$) (LOC 3). However, concerning the Rectus Abdominis muscle (RA) a bilateral delayed onset was found in that study ($p<.05$) (LOC 3). No correlations between kinesiophobia and the contralateral TrA/IO and EO muscles were found in *CLBP* (LOC 3).[69]
High kinesiophobia was also associated with earlier feedforward onset of the ES at levels T10-contralateral, L1-contralateral, L3-contralateral, L5-ipsilateral in *CLBP* according to one study ($p < .05$), whereas the other sides of those muscles did not correlate with kinesiophobia (LOC 3).[69]

Fear-avoidance beliefs. In *CLBP* higher fear-avoidance beliefs regarding physical activities (FABQ-pa questionnaire scores) were associated with delayed feedforward activation of the contralateral EO during both self-initiated ($p<.001$) and cued unilateral arm flexion ($p=.019$), whereas work-related fear-avoidance beliefs (FABQ-w) were not significantly associated with EO onset latencies according to limited evidence from a single study (LOC 3).[57]

Fear-other. No other types of fear were examined.

Summary. In conclusion, trunk muscle timing changes in *CLBP* are dependent on the specific muscle studied. In general, catastrophizing is mainly associated with earlier onset times of most abdominal and paraspinal muscles studied. These associations are most prominent in the muscles at the contralateral side compared to the limb which initiates movement, whereas in ipsilateral muscles more often non-significant effects or in some exceptions delayed onset times have been described. With regards to fear, for the back muscles a similar conclusion can be made with mainly the contralateral muscles contracting earlier with kinesiophobia, whereas in the ipsilateral muscles no effects were found. For the effects of kinesiophobia on the abdominal muscles evidence is still conflicting and ambiguous. However, all these inferences were based on low evidence from a single study and thus need confirmation. No studies were found examining the influence of catastrophizing nor fear on timing of the trunk muscles in *ALBP* or *RLBP*.

3.4.2 Trunk muscle activity

Catastrophizing. With regards to the abdominal muscles, one study showed that high levels of catastrophizing were associated with higher EMG activity of the left EO during several ADL-tasks (sit-to-stand, trunk flexion, box lifting) in *ALBP* ($p=.05$) (LOC 3).[122] In *CLBP* similar limited evidence was found, i.e. higher degrees of catastrophizing were associated with higher EMG amplitudes of the RA and EO during walking ($p<.05$) (LOC 3).[95] *RLBP* was not yet studied in this regard.
Positive relationships between higher levels of catastrophizing and higher electromyography (EMG) activity of the back muscles in *CLBP* during walking[95, 128], trunk flexion-extension[43], regular standing[77], and a cold pressor stress

test[100] were demonstrated for most (ES measured at L2-4, L4-5, left Longissimus muscle, bilateral MF) (p<.05) (LOC 2), but not all, paraspinal muscles studied, as during walking no significant correlations were found for the right part of the Longissimus muscle and bilaterally for the Iliocostalis muscle[95] (LOC 3). The study of Henchoz et al.[43] described a modulation of this effect by pain expectancies. More specifically, participants with high levels of catastrophizing who expected intense pain showed higher EMG activity of lumbar muscles in full trunk flexion.[43] The study of Quartana et al.[100] described a similar modulation by attention. Higher muscle activity was only present in high catastrophizers that were instructed to suppress all feelings/thoughts about the cold pressor test, whereas attentional focus or distraction strategies did not correlate with altered muscle activity in high catastrophizers. In a mixed *RLBP/CLBP* population no significant correlations could be demonstrated between catastrophizing and muscle activity of the lumbar ES muscles during trunk flexion-extension in one study (LOC 3).[29] Regarding *(sub)acute LBP* no studies examining the relationship between catastrophizing and back muscle activity have been performed.

Fear-kinesiophobia. In a single study higher kinesiophobia was associated with higher bilateral TrA/IO activation at the end of flexion and the initiation of re-extension during a flexion-extension task in unilateral *CLBP* sufferers (p<.05) (LOC 3).[83]. In a *non-specified LBP* population higher kinesiophobia levels were associated with lower RA EMG activity according to one study (p<.05) (LOC 3), but only during unexpected perturbations as with expected perturbations no significant correlations were found.[102]
The majority of studies did not find significant associations between kinesiophobia and the amount of back muscle activity in *CLBP* during standing[77,] walking[67, 127,] lifting[137], or maximal isometric extension and side bending tasks[94]. However, two studies contradicted this by showing that with higher kinesiophobia levels lower EMG activity of the back muscles was eminent during dynamic trunk flexion-extension[34] or during expected balance perturbations[102] in *CLBP* (p<.05). Thus, evidence in this matter was conflicting (LOC 3). Furthermore, higher levels of kinesiophobia were associated with the inability to display a flexion relaxation response (FRR) (LOC 3) in *CLBP* (p<.01).[34] The FRR reflects an electrical silence of the paraspinal muscles during full trunk flexion[141].

Fear-avoidance beliefs. In *ALBP* a single study described no significant associations between the degree of fear-avoidance beliefs and activity of the left EO (LOC 3).[122] However, it must be mentioned that the right EO was not used in the correlation analysis as only EMG values showing significant between group differences (*CLBP* vs. healthy people) were included.
In both (*sub)acute LBP*[122] (LOC 3) and *mixed RLBP/CLBP*[29] (LOC 3) no significant associations between fear-avoidance beliefs and back muscle (ES level L3) activity were described by single studies. However, higher levels of fear-avoidance beliefs were associated with the inability to display an FRR in *CLBP* (p<.05) (LOC 3).[140]

Fear-other. During an isometric trunk extension, one study showed that higher pain-related fear levels were associated with lower peak EMG activity of the back extensors in *CLBP* (p<.05).[125] In contrast, Lewis et al.[77] found an inverse outcome for (pain-related) anxiety, showing an association with increased muscle activity of the back muscles in CLBP during standing (p<.05) (LOC 3).[77] Thus, regarding pain-related fear no consensus was reached in this matter (LOC 3).

Summary. Whenever catastrophizing was associated with altered muscle activity, higher muscle activity was reported in several muscles, but never diminished activity. In this connection, moderate evidence was found for increased back muscle activity in *CLBP* with catastrophizing, whereas for the abdominal muscles, or *ALBP* and *RLBP* only limited evidence was found. With regards to fear, results were rather inconsistent. Limited evidence for increased TrA/IO activity in *CLBP* was described, whereas for other muscles no or conflicting evidence was found. One consistent finding in patients with *CLBP* was that higher levels of both kinesiophobia[34] and fear-avoidance[140] beliefs were associated with the inability to display a flexion relaxation response (FRR), thus moderate evidence for a disturbed ability to relax paraspinal muscles was implied (LOC 3).

3.4.3 Trunk muscle strength

Catastrophizing. Limited evidence provided by one study showed an association between higher levels of catastrophizing and lower peak torque of the back extensors, but increased variability thereof, during trunk flexion-extension in a *mixed RLBP/CLBP* group (p<.05) (LOC 3).[39] Another study, appeared to confirm this finding in an elderly *CLBP* population. However, this association was actually mediated by the lower physical activity and higher disability levels in this specific population.[74] Furthermore, in another study no correlations between catastrophizing level and muscle strength were found.[68] Thus, in *CLBP* there is limited evidence for no association between catastrophizing and paraspinal muscle strength (LOC 3). *ALBP* populations have not yet been examined in this regard, neither has the association between catastrophizing and abdominal muscle strength.

Fear-kinesiophobia. One study found that kinesiophobia did not significantly affect flexion torque in *CLBP* (LOC 3).[56] With regards to extension, lower extension torque was correlated with higher kinesiophobia in two studies[21, 61] (p<.05), but three other studies found no correlations[24, 56, 68] in *CLBP* (LOC 3). Thus, the evidence in *CLBP* was conflicting (LOC 3). Furthermore, in the study of Goubert et al.[39] kinesiophobia was shown to be a unique predictor of peak core torque (both flexion and extension) during a trunk flexion-extension task in *CLBP* (p<.05) (LOC 3).[39] *RLBP* populations have not yet been studied in this context.

Fear-avoidance beliefs. In *ALBP* one study found no associations[3] (LOC 3), while another study in a mixed *subALBP/CLBP* population found a negative significant association[4] between higher fear-avoidance beliefs and lower back extension torque (p=.01) (LOC 3). In *CLBP* limited evidence for no associations between fear-avoidance beliefs and back extension torque is eminent (LOC 3).[21, 61]

Fear-other. Anxiety[46, 85] did not significantly affect flexion torque (LOC 3), whereas limited evidence for associations between pain-related fear[125] and lower abdominal isometric muscle strength in *CLBP* were found (p<.05) (LOC 3). Concerning extension torque ambiguous evidence was found, as one study described diminished extension strength with increased anxiety[85] (p<.01), whereas two other studies found no associations[24, 46] in *CLBP* (LOC 3).

Summary. For both catastrophizing and fear in relation to muscle strength results are unclear as there is either a lack of studies or findings are conflicting. In general, moderate evidence for no associations between catastrophizing and back muscle strength in *CLBP*, and limited evidence for diminished strength and increased variability in association with catastrophizing in *mixed RLBP/CLBP* was found. Concerning fear, moderate evidence for non-significant associations between fear-avoidance beliefs and back muscle strength, and anxiety and abdominal muscle strength, as well as limited evidence for diminished abdominal strength in *CLBP* in association with pain-related fear was found.

3.4.4 Trunk muscle endurance

Catastrophizing. In *CLBP* patients with higher levels of catastrophizing limited evidence described less back muscle endurance, expressed both as EMG amplitude as well as back extensor torque (p<.05) (LOC 3).[68] No studies were found that examined the effects of catastrophizing on muscle endurance of the abdominal muscles, nor that examined the effects of catastrophizing in *ALBP* or *RLBP* populations in this respect.

Fear-kinesiophobia. Three studies found no association between kinesiophobia and back muscle endurance in CLBP.[1, 24, 68] In these studies muscle endurance was quantified using dynamometry, EMG, center of gravity dispersion rate or Biering-Sörensen endurance time. However, when endurance of the back extensors was expressed not merely by assessing endurance time, but with EMG median frequency analysis, another study did find that with

increased kinesiophobia the endurance of the back extensor muscles was decreased in *CLBP*, but only during prone (p<.05) and not during lateral endurance tasks.[94] Thus, evidence was conflicting (LOC 3).

Fear-avoidance beliefs. One study found negative correlations between work-related fear-avoidance beliefs and abdominal muscle endurance in *CLBP* (p<.05) (LOC 3).[75] No associations were found between physical activity related fear-avoidance beliefs and back muscle endurance in *CLBP* in one study (LOC 3).[7]

Fear-other. No associations were found between pain-related fear and back muscle endurance in one study in *CLBP* (LOC 3).[7]

Summary. Not much studies have been performed concerning muscle endurance, and only *CLBP* populations were examined. Limited evidence for diminished back muscle endurance in association with catastrophizing, and diminished abdominal endurance in association with work-related fear-avoidance beliefs was found.

3.4.5 Activities of Daily Living (ADL)

Catastrophizing. Limited evidence was found for associations between higher catastrophizing levels and decreased lifting bag speed (p<.05) in *ALBP* [123], and lifting bag endurance (s) (p<.01) in *CLBP* [21] during lifting bag paradigms, but not for maximal weight lifted in *CLBP* [114] (LOC 3). According to one study, high catastrophizing levels also corresponded with a larger number of climbed stairs in a given time period for *CLBP* (p<.05) (LOC 3).[114] No associations were found between catastrophizing and forward reach, sit to stand, walking speed[114] or walking distance[6, 114] in *CLBP*, nor with reaction time or movement time during a hand function task in a *mixed healthy/CLBP* population[66] (LOC 3). Another study confirmed this finding for reaction time during rapid arm movements in a non-mixed *CLBP* population (LOC 3).[69] No studies were available in patients with *RLBP*.

Fear-kinesiophobia. Limited evidence showed that higher kinesiophobia levels were associated with decreased velocity during lifting tasks in *ALBP* [123] (p<.05) (LOC 3). In *CLBP*, evidence was conflicting regarding lifting tasks as four studies found no association between the degree of kinesiophobia and the maximal weight lifted[61, 104, 108, 115], whereas another study established that with increasing kinesiophobia levels the maximum lifted weight decreased[114] (p<.05) (LOC 3). Moreover, limited evidence for higher kinesiophobia levels that were associated with lower lifting endurance time in *CLBP* was also described (p<.01) (LOC 3). [21, 134] In a *mixed LBP* population the degree of kinesiophobia was not associated with the amount of weight lifted, according to one study (LOC 3).[103]
Two studies found no effects of kinesiophobia on walking distance in *CLBP* [6, 114] (LOC 3). No effects of kinesiophobia on stride length were found during walking in *CLBP* in one study (LOC 3).[67] High levels of kinesiophobia were associated with longer 'time-up-and-go' times in a single study in CLBP (p=.038) (LOC 3). [56] However, another study that only included elderly women with *CLBP* did not find significant associations between kinesiophobia and 'time-up-and-go' times nor one leg stance performance (LOC 3).[16]
According to two studies, in a high kinesiophobic group with *CLBP* static bending endurance time was lower than in a low kinesiophobic group[104, 108] (p<.05). However, in one of these studies this association did not maintain significance following Bonferroni correction[108] (LOC 3). Two studies depicted that higher kinesiophobia levels were not associated with altered dynamic forward bending performance in *CLBP* [104] (LOC 3), and in a mixed *LBP* population (LOC 3)[3].
No associations were found between kinesiophobia and stair climbing, forward reach, sit to stand[114], lower limb function or hand grip strength in a *CLBP* population[56] (LOC 3), or with reaction and movement time of hand movements in a *mixed healthy/CLBP* population[66] (LOC 3).

Fear-avoidance beliefs. With regards to higher degrees of fear-avoidance beliefs three studies found no associations [7, 93, 115], while in two other studies only work-related fear-avoidance beliefs negatively correlated with lifting performance (p<.05), whereas physical activity related correlations were not significant[61, 104] in *CLBP*. However, in

one of these studies, this was only the case for work-related fear-avoidance beliefs in men being correlated to diminished lifting performance, and not in women (non-significant).[104] Thus evidence was conflicting (LOC 3)
One study found a negative effect of work-related fear-avoidance beliefs on walking distance[93] in a *non-specified LBP* population (p=.014) (LOC 3). Limited evidence showed that there was no association between fear-avoidance beliefs and walking velocity in *CLBP*[7, 114] or in a *mixed LBP* population[3] (LOC 3). However, another study described that physical activity related fear-avoidance beliefs are a predictor for velocity deficit in a *mixed LBP* population (LOC 3).[2] In a specific population of *elderly people with CLBP*, higher fear-avoidance beliefs regarding physical activities were associated with decreased gait speed[14] (p<.001) (LOC 3).
The type of fear-avoidance beliefs determined its associations with static or dynamic bending performance in one study in *CLBP*. In this study, physical activity-related beliefs negatively correlated with static bending (p<.05), but not with dynamic bending performance (non-significant), whereas work-related beliefs positively correlated with dynamic bending performance (p<.05), but not with static bending performance (non-significant) (LOC 3).[104]
Fear-avoidance beliefs related to physical activity were not associated with a loaded reach task in *CLB*[7] or physical performance assessed using the sit-to-stand test in a *mixed LBP population*[3] (LOC 3). However, according to a single study physical activity related fear-avoidance beliefs were associated with reduced hand grip (p<.05) and leg strength (p<.05), and cardiopulmonary endurance (p<.01) in *CLBP* (LOC 3).[75] In addition, the presence of higher work-related fear-avoidance beliefs was also associated with reduced leg strength in *CLBP* (p<.05) (LOC 3).[75]

Fear-other. No other types of fear were examined.

Summary. The effects of catastrophizing and fear on daily activities highly depended on the type of task being performed, but in general if effects were found these illustrated diminished performance on daily activities. In this summary the moderate evidence results will be summarized, whereas for the limited evidence results we refrain to **TABLE 5** for a schematic overview. Moderate evidence for no associations between walking distance and both catastrophizing and kinesiophobia in *CLBP* were found. Furthermore, concerning kinesiophobia also moderate evidence associations with diminished lifting endurance have been described in CLBP. Effects of fear-avoidance beliefs were also very task dependent and often even depended on specific work versus physical-activity related beliefs and therefore we refrain to the detailed overview and **TABLE 5** for these results.

3.4.6 Balance

Catastrophizing. No studies evaluated the effects of catastrophizing on balance in *LBP*.

Fear-kinesiophobia. In *CLBP*, no significant associations were found between kinesiophobia and center of pressure excursion during standing, which represents the amount of body sway (LOC 3).[16]

Fear-avoidance beliefs. In *(sub)acute LBP*, no associations were found between physical activity related fear-avoidance beliefs and upright postural stability in a single study (LOC 3).[121] No associations were found between physical activity related fear-avoidance beliefs and center of pressure in a *mixed LBP* population in one study (LOC 3).[82]

Fear-other. In a *RLBP/CLBP population*, limited evidence showed that people with higher pain-related fear had lower center of pressure mean velocity and area while standing upright than low pain-related fear subjects (p<.05) (LOC 3).[110]

Summary. Catastrophizing was not yet studied in relation to balance. Limited evidence for diminished CoP velocity and area in relation to pain-related fear in *RLBP/CLBP* was found, as well as non-significant associations between kinesiophobia and CoP, or fear-avoidance beliefs and postural stability and CoP in *subALBP*.

3.4.7 Spinal kinematics

Catastrophizing. Limited evidence based on one study showed that a higher degree of catastrophizing was associated with diminished range of motion (ROM) during the straight leg raise test due to pain in the back or leg, and during forward bending of the trunk in *CLBP* (p=.001) (LOC 3).[88] With regards to the effect of catastrophizing on kinematics no other LBP populations were studied in literature as of yet.

Fear-kinesiophobia. Limited evidence showed that kinesiophobia does not affect spinal flexibility when measured with a finger-floor task in *CLBP* (LOC 3)[24]. Additionally, lumbar kinematics were not affected by kinesiophobia during gait[67] in a *CLBP* population (LOC 3). In contrast, a significant association between higher kinesiophobia levels and lower lumbar flexion angles in *CLBP* was found by Geisser et al.[34] (p<.01.) Thus, evidence in this regard is ambiguous (LOC 3).

Fear-avoidance beliefs. One study showed that work-related beliefs correlated with diminished flexion (p<.01), but not with extension (non-significant) range of motion in *CLBP* (LOC 3).[61] However, limited evidence for lack of correlations between physical-activity related beliefs and neither flexion, extension,[7, 61] or lateral bending[7] measures was also found in *CLBP* (LOC 3).

Fear-other. Limited evidence found no effects of general anxiety on lumbar flexibility either assessed with a finger-floor task[7] or dynamometry[46] in *CLBP* (LOC 3).

Summary. Limited evidence for an association between catastrophizing and diminished flexion mobility in *CLBP* was described, whereas the association thereof with kinesiophobia was ambiguous. Moderate evidence found no significant associations between physical activity related fear-avoidance beliefs and flexion, extension and side bending mobility, and also no significant associations between general anxiety and lumbar flexibility in *CLBP*. However, with regards to work-related fear-avoidance beliefs limited evidence for diminished flexion and no evidence for associations with extension were found in *CLBP*. No studies regarding specifically *RLBP or (sub)acute LBP* were retrieved.

3.4.8 Proprioception and coordination

Catastrophizing. No significant associations were found between catastrophizing and trunk stiffness (ability to resist displacement) nor damping (ability to resist velocity) in one study concerning a *non-duration specified LBP population* (LOC 3).[60] Other *LBP* populations have not yet been studied in this regard.

Fear-kinesiophobia. According to one study kinesiophobia did not correlate with trunk damping, and associations with trunk stiffness were ambiguous in a *non-duration specified LBP population* (LOC 3).[60]
With regards to the controlled contraction of the TrA and MF as assessed with pressure biofeedback, Ishak et al.[56] described no correlation with kinesiophobia in *CLBP* (LOC 3).

Fear-avoidance beliefs. One study found that in case of more fear-avoidance beliefs subjects tended to undershoot (i.e. diminished lumbar lordosis) during a seated position-reposition task, whereas in case of less fear-avoidance beliefs the opposite effect (i.e. overshooting towards excessive lumbar lordosis) was observed in *CLBP* (p=.002) (LOC 3).[92]

Fear-other. No other types of fear were examined.

Summary. With regards to proprioception and coordination as of yet only a low amount of studies was performed, with limited or conflicting evidence regarding non-significant associations between catastrophizing and kinesiophobia with trunk stiffness and damping in a non-duration specified *LBP* population, and non-significant associations

between kinesiophobia and TrA and MF control in *CLBP*. Furthermore, limited evidence for altered proprioception in association with fear-avoidance beliefs was found.

4 Discussion

This review discusses the current evidence regarding the interplay between catastrophizing and fear, and movement-related outcomes in non-specific LBP. For a detailed overview of the findings per outcome see **TABLE 5** and the 'Summary' paragraphs in the results.

Trunk muscle timing.

In previous research, without consideration of cognitive-affective factors, delayed trunk muscle timing was found in *CLBP* compared to healthy people, primarily in the contralateral muscles during unilateral movement[62, 120]. In association with catastrophizing and kinesiophobia the current review describes opposite findings, i.e. earlier onset timing of most contralateral trunk muscles in *CLBP*.[69] Hence, it is hypothesized that catastrophizing and kinesiophobia might facilitate muscle activation and counteract delayed muscle timing in *CLBP*. However, timing alterations are highly muscle dependent as in some (mainly ipsilateral) muscles no altered timing or even delays were reported[69]. Contrarily, fear-avoidance beliefs rather contributed to delayed muscle timing of the contralateral EO in *CLBP* in one study[57]. Importantly, these findings are based on single studies, which need further substantiation.

Trunk muscle activity.

With catastrophizing a tendency towards increased activity in *CLBP*[43, 77, 95, 100, 128] and *subALBP*[122], primarily in the back muscles, can be seen. However, in some muscles no altered activity was found in *CLBP*[95] or *mixed RLBP/CLBP*[29]. Concerning fear, limited associations between kinesiophobia and increased Tra/IO muscle activity in *CLBP*[83], but ambiguous findings for the ES in *CLBP*[34, 67, 77, 94, 102, 127, 137] and the RA in a *non-duration specified LBP* population[102] were found. With regards to fear-avoidance beliefs no significant associations with muscle activity in *ALBP*[122] and *mixed RLBP/CLBP*[29] were found, and concerning pain-related fear conflicting evidence regarding back muscle activity was found in *CLBP*[77, 125]. One consistent finding for both kinesiophobia[34] and fear-avoidance[140] was their association with a diminished relaxation capacity of the back muscles in *CLBP* (disturbed FRR). Increased activity with catastrophizing and diminished relaxing with fear could be explained by a continuation of "guarding mechanisms". People with CLBP tend to have increased activity in the superficial muscles[35, 78] which could be due to unconscious mechanisms that 'guard' their body for further harm[80, 95, 127] and which possibly compensate for a loss of motor control due to diminished activity in the deeper muscles[41, 47, 118, 129].

Trunk muscle strength and endurance.

There is moderate evidence for unaltered back muscle strength with catastrophizing[68, 74] in *CLBP*, but in *RLBP/CLBP* limited evidence for diminished back muscle strength and higher variability[39] was found. Concerning fear, there was moderate evidence for no associations between fear-avoidance beliefs and back muscle strength[21, 61], and between **anxiety** and abdominal muscle strength[46, 85] in *CLBP*, and limited evidence for diminished abdominal strength with higher pain-related fear[125]. Other evidence regarding fear and muscle strength was conflicting.[3, 4, 21, 24, 39, 46, 56, 61, 68, 85]

There is limited evidence for reduced back muscle endurance with catastrophizing in CLBP[68], and there are indications that work-related fear-avoidance beliefs are associated with less abdominal muscle endurance in CLBP[75], whereas other associations between fear measures and muscle endurance were non-existent[7] or ambiguous[1, 24, 68, 94].

It could be hypothesized that the inconsistently reported diminished strength and endurance of trunk muscles in *(C)LBP*[117] could be caused by deconditioning, which in biopsychosocial models is thought to be affected by avoidance behavior due to the presence of fear and catastrophizing[49, 136]. However, need further confirmation, as only small yet inconclusive indications towards such mechanisms were found.

Functional performance.

Both with higher levels of catastrophizing and various fear measures there were indications for diminished functional task performance in LBP. Concerning catastrophizing suboptimal lifting performance with reduced speed in *ALBP* [123] and decreased endurance[21] in *CLBP*, and diminished lumbar flexion mobility in *CLBP*[88] have been found. Walking distance[6, 114] and speed[114], hand reaction and movement time[66, 69], sit-to-stand, forward reach, [114] and trunk coordination[60] did not seem to be affected by catastrophizing, while stair climbing performance seemed better in high versus low catastrophizers[114] in *CLBP* or mixed *LBP* groups. Concerning kinesiophobia moderate evidence for diminished lifting endurance in *CLBP*[21, 134], and limited evidence for diminished lifting speed in *ALBP*[123], increased time-up-and-go times[56], and decreased static bending endurance[104, 108] in *CLBP* was found. Whereas, in *CLBP* no or conflicting associations between kinesiophobia and maximal weight lifted[61, 104, 108, 114, 115], stair climbing[114], walking parameters[6, 67, 114], sit-to-stand[114], dynamic bending[104], lower limb function, hand grip strength,[56] forward reaching[114], CoP excursion[16], lumbar flexion[24, 34, 67], and TrA/MF control[56] were found. In *mixed LBP* populations maximal weight lifted[103], hand reaction and movement time[66], dynamic bending performance[3], and proprioception and coordination[60] were also not associated with kinesiophobia, as well as time-up-and-go times and one leg stance performance in elderly women[16]. Associations between functional tasks and fear-avoidance beliefs are often dependent on whether these beliefs are work-related or physical activity related and are depicted in detail in **TABLE 5**. Moderate evidence for no associations between anxiety and lumbar flexibility in *CLBP*[7, 46], and low evidence for diminished balance in *mixed RLBP/CLBP* in relation to pain-related fear[110] was also described.

Several hypotheses were stipulated. First, the improved stair climbing performance was nuanced as catastrophizing only explained 1% of the variance in stair climbing.[114] Second, high versus low levels of fear-avoidance beliefs were associated with respectively undershooting and overshooting of lumbar lordosis during a position-reposition task in CLBP.[92] This might indicate that CLBP diminishes the position-reposition sense generally, but that the amount of fear determines in which direction. High fear patients primarily avoid excessive lumbar lordosis (undershooting) possibly to protect the spine, whereas low fear patients primarily overshoot lumbar lordosis as they might not avoid excessive movements. Concerning the other tasks, diminished performance might be due to less efficient movement patterns, which is reflected in the previously described muscle alterations concerning timing, activity, strength and endurance. Furthermore, it is hypothesized that people with high catastrophizing and fear in LBP might shift their priorities towards avoiding further pain and also focus more of their attention on the pain[101], which could be at the expense of optimal task performance.

General inferences.

Overall, firm conclusions were hard to establish, due to often limited or conflicting evidence. A recent systematic review explained inconsistent findings in trunk motor control research by the existence of a 'loose' versus 'tight' control phenotype in LBP, respectively reflecting a pattern of decreased versus increased excitability of trunk muscles.[130] The current review suggests that fear and catastrophizing could predispose towards 'tight control', as the findings of altered trunk muscle timing and increased activity or diminished relaxing of the superficial trunk muscles are in line with that phenotype and previously described 'guarding mechanisms' can be considered as a form of 'tight control'. However, the higher variability in muscle strength in high catastrophizers in the current review did not comply with the 'tight' control theory, which proposed the contrary. Based on the current review it seems that the amount of catastrophizing and fearful cognitions/emotions related to pain might have a bigger influence on the presence of 'tight' over 'loose' control in LBP rather than the sensory pain experience itself, since pain intensity itself does not correlate with muscle activity[67, 127], while catastrophizing and fear did in this review. As 'tight' control is a less efficient movement strategy it might also account for diminished muscle strength and endurance, and consequently the impaired functional performance that was found in this study.

Despite findings for both cognitive-affective factors being quite similar for most movement-related outcomes, associations with catastrophizing were more consistent, whereas fear often displayed more ambiguous associations. This might be due to the fact that fear entails both emotional and cognitive processes[76], whereas catastrophizing represents primarily cognitive aspects[19, 106] and thus entails less inter-individual variation.

Limitations.

Selection bias could not always be excluded and sample size justifications were often lacking. Comparison between LBP-types was seldom possible as most studies examined CLBP (78%) patients. More studies in ALBP or RLBP could give valuable insights concerning the timing of development of maladaptive cognitions/emotions and associated movement alterations, and whether such deficits remain during pain-free periods.

Fear and catastrophizing were most frequently assessed indirectly using questionnaires. Hence, studies that experimentally manipulate fear/catastrophizing in order to gain more insight into causal associations are needed. Furthermore, experimental studies are more suited to investigate effects of situational fear/catastrophizing on movement-related outcomes, whereas mainly dispositional properties of cognitive-affective factors are examined with questionnaires. Since situational and dispositional properties of cognitive-affective factors are not always associated, multidimensional assessment of cognitive-affective factors is warranted.[15]

All but one studies[115] assessed pain intensity, but in 20/51 studies the effects of cognitive-affective factors were not explicitly controlled for by pain measures. For future research in this field it is recommended to control for pain intensity as this measure can sometimes show high variability within pain groups, and possible confounding effects on the cognitive-affective factors should be examined.[13]

Implications.

It is recommended to evaluate the presence of catastrophizing and fear in LBP patients, and use a multidisciplinary bio-psychosocial approach that tackles both physical and cognitive-affective dysfunctions. Such type of therapy has added effects compared to usual care[27, 58, 67], as it can help break down therapeutic barriers which often arise due to maladaptive thoughts/emotions. Especially for patients with motor control deficits, diminished endurance capacity of trunk muscles, impaired mobility and decreased performance on lifting tasks such an approach seems valuable as these outcomes were most likely associated with catastrophizing and fear. Furthermore, since catastrophizing and fear are related to diminished functional performance this can impact the participation and societal role of LBP patients, which is reflected in increased disability with fear and catastrophizing in LBP as reported in previous reviews[76, 90, 143-145, 148], and should therefore be effectively targeted.

High-quality experimental studies that compare well-defined LBP groups (acute-recurrent-chronic), that use experimental paradigms besides self-report measures in order to have an assessment of both dispositional and situational properties of catastrophizing and fear, and that examine the causal effects of cognitive-affective factors on movement-related outcomes in LBP are still needed. Other cognitive-affective factors which were not studied here and might also influence movement-related outcomes, e.g. hypervigilance, can also be examined.

5 Conclusion

Several theoretical models have proposed an important role for cognitive-affective factors, by (in)directly altering movement-related outcomes, in the chronification process of LBP. This review provides limited evidence for muscle-dependent alterations in trunk muscle timing, activity and diminished endurance, whereas for trunk muscle strength results were unclear or non-significant in association with fear and catastrophizing. Task-dependent functional performance impairments in correlation with catastrophizing and fear in LBP were also described. High quality studies comparing ALBP, RLBP and CLBP with use of experimental paradigms besides questionnaires for the study of catastrophizing and fear on movement-related outcomes are required to examine causal relationships.

6 Appendix

TABLE 3. *Evidence Table*

Trunk muscle timing (n=2)			
Author (year)	**Population + LBP criteria**	**Catastrophizing/Fear**	
		Type	**Measure**
Jacobs et al.[57]	Mixed RLBP/CLBP; n = 13, mean age 37y (±6), 8 female/5 male	Fear- avoidance beliefs	FABQ
Lariviere et al.[69]	CLBP (> 3m); n = 59, mean age women 40y (±8), mean age men 40y (±9), 29 female/30 male	Kinesiophobia	TSK
		Catastrophizing	PCS

Trunk muscle timing (n=2)			
Movement-related outcomes		**Statistical analysis + controlled for pain intensity (PI)?**	**Results**
Type	**Measure**		
Seated rapid shoulder flexion	sEMG ES, IO, EO, and dominant AD muscles (onsets ms)	Mixed model ANOVA, Pearson correlation analysis. PI controlled: yes	• FABQ-pa ~ delayed onset contralateral EO for self-initiated (r^2 = .66, p < .001) and cued arm movements (r^2 = .40, p = .019) • FABQ-w does not ~ with muscle onset of contralateral EO for self-initiated (r^2 = .07, p = .40) and cued (r^2 < .01, p = .84) arm movements
Rapid right arm flexion movement: activation latency	EMG MF, ILL, LO, RA, EO, IO and AD muscles (onsets ms)	Pearson correlation analysis PI controlled: yes	• CLBP subjects with high TSK ~ earlier muscle latencies in ES L5 right (r = -.16), L3 left (r = -.16), L1 left (r = -.13), T10 left (r = -.12), EO right (r = -.16) (p < .05); delayed muscle latencies in RA bilateralal (r = .15, p < .05); no significant correlations with L5 left (r = -.03), L3 right (r = .01), L1 right (r = -.03), T10 right (r = -.06), EO left (r = -.06), Tra/IO left (r = -.06); • CLBP subjects with high PCS ~ earlier muscle latencies in ES L5 (left: r = -.18; right: r = -.21) and L3 bilateral (left: r = -.24; right: r =-.11), L1 left (r = -.21), T10 left (r = -.17), EO bilateral (left: r = -.23; right: r = -.20), TrA/IO left (r = -.18) (p < .05); delayed muscle latencies in TrA/IO right (r = .13) (p < .05); no significant correlations with L1 right ((r = -.04), T10 right (r = -.06), RA bilateral (left: r = .02; right: r = .03)

Trunk muscle activity (n=16)			
Author (year)	**Population + LBP criteria**	**Catastrophizing/Fear**	
		Type	**Measure**
Dubois et al.[29]	RLBP/CLBP (criteria von Korff et al.138), n = 52, 18♀ (39.3 ± 12.1y)/34♂ (40.1 ± 11.4y)	Fear-avoidance beliefs Catastrophizing	FABQ PCS
Geisser et al.[34]	CLBP (> 3m), n = 76 (40.6 ± 11.9y), 42♀/32♂	Kinesiophobia	TSK
Henchoz et al.[43]	CLBP (> 6m), n = 22 (32.1 ± 15.0y), 11♀/11♂	Catastrophizing Pain expectations	PCS Manipulation of expectations
Lamoth et al.[67]	CLBP (> 3.5m), n = 22 (38y; range 21-52), 13♀/9♂	Kinesiophobia	TSK
Lewis et al.[77]	CLBP (> 3m), n = 47 (46.2 ± 11.1y), 29♀/18♂	Kinesiophobia Catastrophizing Pain-related fear	TSK PCS PASS

Trunk muscle activity (n=16)			
Movement-related outcomes		**Statistical analysis + controlled for pain intensity (PI)?**	**Results**
Type	**Measure**		
Muscle strength	RMS EMG lumbar ES L3-4 (amplitude) during flexion-extension task	ANOVA's PI controlled: yes	Psychological factors are not associated with chronic neuromuscular adaptations and neuromuscular responses to experimental pain
Dynamic EMG Flexion-Relaxation Ratio	RMS EMG ES L3, L5 (amplitude)	Zero-order correlation analysis, path models PI controlled: yes	• ↑TSK ~ ↓EMG amplitudes during flexion (maximal EMG during flexion: r = -.55; maximal EMG during extension: r -.38), and ↓FRR (r = -.45) (p < .01), but not during sustained maximal flexion in the end range (r = .02, p>.05) • Relationship pain-related fear and EMG during flexion and extension: mediated by reduced lumbar flexion
Muscle activity	RMS EMG lumbar ES (amplitude)	ANOVA, Pearson correlation analysis PI controlled: no	• ↑PCS ~ ↑EMG L4-5 in full flexion (r = .54, p < .05), when expecting strong pain; • no significant correlations between FABQ and EMG values of the trunk extensors
Muscle activity during walking	EMG ES T12, L2, L4 (amplitude)	Spearman correlation analysis PI controlled: yes	No significant correlations between the TSK scores and ES muscle activity
Muscle activity	EMG ES L1-2, L4-5 (% of reference voluntary contraction)	Pearson Correlation analysis PI controlled: yes	Muscle activity ~ anxiety (r = .31), pain-related anxiety (r = .29) and catastrophizing(r = .29) (p < .05) βnot with kinesiophobia (r = .20, p > .05)

Trunk muscle activity (n=16)			
Author (year)	**Population + LBP criteria**	**Catastrophizing/Fear**	
		Type	**Measure**
Masse-Alarie et al.[83]	unilateral CLBP (> 3m), n = 12 (34.4 ± 13.1y), 6♀/6♂	Kinesiophobia	TSK
Pagé et al.[94]	CLBP (> 3m) - baseline: n = 53 (44.09 ± 13.26y), 23♀/30♂ - follow up 6m: n = 46 (mean age not clear),♀/♂= ?	Kinesiophobia	TSK
Pakzad et al.[95]	CLBP (> 3m) - Low catastrophizing group, n = 15 (32.5 ± 6.4y), 9♀/6♂ - High catastrophizing group, n = 15 (34.1 ± 6.8y), 9♀/6♂	Catastrophizing	PCS
Quartana et al.[100]	CLBP (> 6m), n = 68 (47.5 ± 15.5y), 40♀/28♂	Catastrophizing	PCS
Ramprasad et al.[102]	CLBP (duration not specified), n = 25 (40.68 ± 10.60y), 7♀/18♂	Kinesiophobia	TSK

Trunk muscle activity (n=16)			
Movement-related outcomes		**Statistical analysis + controlled for pain intensity (PI)?**	**Results**
Type	**Measure**		
Abdominal muscle activity	Normalized EMG of IO, EO and MF during trunk flexion-extension task	Spearman rank-order correlation analysis between muscle activity and TSK scores PI controlled: no	↑TSK scores ~ ↑TrA/IO activation at the end of a trunk flexion movement (ρ = .61; p = .03) and the onset of trunk extension movement (ρ = .60; p = .04)
Trunk muscle activation	EMG of left and right ES muscles at level L3 during maximal isometric extension and maximal isometric lateral bending (MVC)	Pearson correlation analysis PI controlled: no	TSK does not correlate with muscle activity during trunk extension (r = -.11) nor lateral bending (r = -.02) (p > .05)
Trunk muscle activation	EMG of RA, EO, IL, LO and MF muscle during gait (% of submaximal MVC)	Dichotomization into High and Low catastrophizing LBP groups based on cut-off score of PCS (High ≥21/52; Low ≤20/52); partial correlation analysis between PCS and muscle activity scores PI controlled: yes	PCS scores ~ EMG amplitude bilateral RA, bilateral EO, left LO and bilateral MF (range r = .376 to .532; p < .05) ↔ no significant correlations with right LO (r = .306, p = .11), and IL bilateral (left: r = .255, p = .19; right: r = .112, p = .57)
Muscle activity lumbar	paraspinal muscles EMG L2-L4, Trapezius Muscle regions (amplitude)	Multiple regression analyses PI controlled: no	Lumbar paraspinal muscle activity during cold pressor task: high PCS > low PCS group (p = .025), but only when participants were asked to suppress thoughts/feelings about pain/distress. ↔ not when attention was focused on or distracted away from the pain/distress.
Muscle activity	RMS EMG RA, lumbar ES L3-4 (mean peak of voluntary response)	Pearson correlation analysis, linear regression analysis PI controlled: no	• TSK ~ ES activity during unstable-expected task (r = -.593, p = .002) • TSK ~ RA activity during

Trunk muscle activity (n=16)			
Author (year)	**Population + LBP criteria**	**Catastrophizing/Fear**	
		Type	**Measure**
Svendsen et al.[122]	(Sub)acute LBP (0-6m, not adequately described), n = 12 (38.6 ± 9.8y), 3♀/9♂	Catastrophizing Fear-avoidance beliefs	CSQ FABQ
Thomas et al.[125]	CLBP (> 6m) - low fear group: n = 10 (22.2 ± 8.5y), 5♀/5♂ - high fear group: n = 10 (25.7 ± 6.2y), 6♀/4♂	Pain-related fear	PASS
van der Hulst et al.[127]	CLBP (> 3m), n = 63 (41 ± 11y), 30♀/33♂	Kinesiophobia	TSK

Trunk muscle activity (n=16)			
Movement-related outcomes		**Statistical analysis + controlled for pain intensity (PI)?**	**Results**
Type	**Measure**		
			stable-unexpected task (r = -.691, 95% CI: -.85 to -.40, p < .001)/unstable-unexpected task (r = -.470, 95% CI: -.72 to -.09, p = .018); • No significant correlations between TSK and RA activity during expected perturbations
Muscle activity	RMS EMG EO (amplitude)	Pearson correlation analysis PI controlled: no	• CSQ-catastrophizing ~ RMS L EO (r = .572, p = .05) ⟷ but not with NRMS L EO (r = .439, p = .15); • FABQ-w does not significantly correlate with L EO RMS (r = -.201, p = .53) nor NRMS (r = -.141, p = .66); • FABQ-pa does not significantly correlate with L EO RMS (r = .272, p = .39) nor NRMS (r = .505, p = .09).
Paraspinal and abdominal muscle activation (isometric)	Peak EMG RA, EO, IO, ES L2, MF L5 during maximum isometric contraction in flexion, extension, sidebend, rotation	One-way ANCOVA's after dichotomization of patients in low- vs. high-pain related fear groups based on median split PASS-scores PI controlled: yes	Specific values per muscle: table 2 and 3 Averaged across all movement directions: high PASS had peak EMG of the abdominals that was only 40% of peak EMG of low PASS group; peak EMG of trunk extensors in the high PASS group was 59% of the peak EMG of participants with low PASS
Back muscle activity during walking		SRE EMG ES (L1, L4; amplitude) Random coefficient analysis PI controlled: no	No sinificant association between SRE values in the different periods of stride and TSK

Trunk muscle activity (n=16)			
Author (year)	**Population + LBP criteria**	**Catastrophizing/Fear**	
		Type	**Measure**
van der Hulst et al.[128]	CLBP (> 3m), n = 63 (41 ± 11y), 30♀/33♂	Catastrophizing	CSQ
Vlaeyen et al.[137]	CLBP (> 3m), n = 31 (41.61 ± 10.7y), 16♀ /15♂	Kinesiophobia	TSK Tension inducing video exposure
Watson et al.[140]	CLBP (> 6m), n = 36 (43.7 ± 9.3y), 21♀ /15♂	Fear-avoidance beliefs	FABQ

Trunk muscle activity (n=16)			
Movement-related outcomes		**Statistical analysis + controlled for pain intensity (PI)?**	**Results**
Type	**Measure**		
Back muscle activity during walking	SRE EMG ES (amplitude, ratios)	Pearson correlation analysis PI controlled: yes	CSQ-catastrophizing ~ mean SRE values ($r = .26$, $p < .01$), with 1 point increase in the catastrophizing score corresponding to an increase of 1.1 µV in averaged SRE value of the ES per stride ⟷ but not with SRE ratios (r between -.01 and .04, $p > .05$)
Back muscle activity	Lifting bag test (5,5kg holding time in stretched arm; s) + RMS EMG left & right ES L3 (amplitude)	MANOVA and ANOVA analysis after dichotomization in 2 groups based on median score of TSK = 40 PI controlled: yes	• Fear: no overall effect on baseline muscular reactivity of the ES (Wilks Lambda = .95, $F(2,25) = .717$, $p = .498$); • Video exposure: muscle reactivity high-fear = low-fear group ($p > .561$)
Back muscle activity	FRR during flexion-extension task. (EMG RMS ES L1/2, L4/5)	Pearson correlation analysis and linear regression analysis pre- and post-pain management program PI controlled: no	• Pre-treatment: FABQ ~ FRR left/right ES L1-2 ($r = -.28$, $p = .05$), FRR left/right ES L4-5 ($r = -.29$, $p = .04$) • Post-treatment: FABQ ~ change in FRR left ES L1-2 ($r = -.43$, $p < .03$), change in FRR right ES L1-2 ($r = -.41$, $p < .04$), change in FRR left ES L4-5 ($r = -.41$, $p < .04$) ⟷ not with change in FRR right L4-5 ($r = -.30$, $p > .06$); FABQ accounted for 6-16% of variance for changes in FRR after treatment

Trunk muscle strength (n=12)			
Author (year)	**Population + LBP criteria**	**Catastrophizing/Fear**	
		Type	**Measure**
Al-Obaidi et al.[4]	Mixed subALBP/CLBP (> 7w), n = 63 (36.34 ± 8.5y), 29 ♀/34♂	Fear-avoidance beliefs	FABQ
Al-Obaidi et al.[3]	Mixed LBP (> 2m), n = 42, 20♀ (39.25± 5.8y)/22♂ (45.0 ± 6.2)	Fear-avoidance beliefs	FABQ
Crombez et al.[21]	CLBP (duration not specified) - study 1: exclusion - study 2: n = 38 (40.84 ± 10.02y), 25♀/13♂	Kinesiophobia Fear-avoidance beliefs Pain-related fear	TSK FABQ PASS
Demoulinet al.[24]	CLBP (> 3m), n = 50 (44.2 ± 9.5y), 25♀ /25♂	Kinesiophobia	TSK FVAS (Fear VAS)
Goubert et al.[39]	RLBP/CLBP (> 3m), n = 84 (40.32 ± 11.06y), 44 ♀/40♂	Kinesiophobia Catastrophizing	TSK PCS
Hickey et al.[46]	CLBP (> 3m), n = 96, 35♀ (33.63 ± 7.6y)/61♂ (36.89 ± 9.5)	Anxiety Fear of reinjury	MCMI-II VAS
Ishak et al.[56]	CLBP (> 6m), n = 63 (70.98 ± 7.90y),♀/♂= ?	Kinesiophobia	TSK

Trunk muscle strength (n=12)			
Movement-related outcomes		**Statistical analysis + controlled for pain intensity (PI)?**	**Results**
Type	**Measure**		
Spinal isometric strength capacity	Isometric torque back muscles (Nm)	Stepwise regression analysis PI controlled: yes	FABQ-physical activity ~ isometric muscle strength at 0-48° of spinal flexion (r = -.33 to r = -.43; p = .01)
Isometric lumbar extensor strength (ILES)	Lumbar extensor exercises (Nm)	Bivariate correlation matrix PI controlled: yes	Anticipated pain nor FABQ correlate with lumbar muscle strength
Study 2: back muscle force	Isokinetic trunk extension-flexion (Nm)	Pearson correlations, multiple regression PI controlled: yes	- Study 2: TSK and FABQ-physical activity are significant negative predictors for peak core muscle torque ($p < .05$)
Muscle strength back extensors	Extension torque (Nm)	Linear regression analyses PI controlled: no	TSK ($p = .889$) and FVAS ($p = .087$) are not significantly associated with strength
Muscle strength	Trunk extension–flexion test, torso rotation test, knee extension-flexion test (Nm)	ANOVA PI controlled: yes	TSK ($p < .005$) and PCS ($p < .05$) are unique predictors of the peak torque of the trunk-extension flexion test
Muscle strength	Isokinetic trunk dynamometer: torque trunk extensors and flexors (Nm)	Multiple regression analyses PI controlled: yes	Fear of reinjury and anxiety do not significantly affect average extension nor flexion torque ($p > .01$)
Abdominal and paraspinal strength	Mechanical push-pull dynamometer (Nm)	Pearson correlation analysis between TSK and motor outcomes; multivariate linear regression PI controlled: yes	No correlation between TSK and abdominal ($r = .126$, $p = .314$) and back muscle strength ($r = .079$, $p = .537$)

Trunk muscle strength (n=12)			
Author (year)	**Population + LBP criteria**	**Catastrophizing/Fear**	
		Type	**Measure**
Kernan & Rainville[61]	CLBP (> 3m), n = 68 (43 ± 10y), 38♀/30♂	Kinesiophobia Fear-avoidance beliefs	TSK FABQ
Lariviere et al.[68]	CLBP (> 3m), n = 32, 13♀ (35 ± 9y)/14♂ (43 ± 10y)	Kinesiophobia Catastrophizing	TSK PCS
Ledoux et al.[74]	elderly CLBP (> 6m), n = 29 (69 ± 7y), 14♀/15♂	Kinesiophobia Catastrophizing	TSK PCS
Michalski & Hinz[85]	CLBP (> 3m), n = 685 (47.3 ± 12.6y), 388 ♀/297♂	Anxiety	HADS
Thomas et al.[125]	CLBP (> 6m) - low fear group: n = 10 (22.2 ± 8.5y), 5♀/5♂ - high fear group: n = 10 (25.7 ± 6.2y), 6♀/4♂	Pain-related fear	PASS

Trunk muscle strength (n=12)			
Movement-related outcomes		**Statistical analysis + controlled for pain intensity (PI)?**	**Results**
Type	**Measure**		
Muscle strength	back extensor strength (Nm)	Pearson correlation analysis PI controlled: yes	Pre-treatment: TSK ~ back extensor strength ($r = -.323$, $p < .05$); FABQ-w ($r = -.134$, $p > .05$) and FABQ-pa ($r = -.159$, $p > .05$) were not significantly correlated with back extensor strength
Back muscle strength	Dynamometer (Nm)	AN(C)OVA, dichotomization of LBP subjects in 2 groups per gender based on median values of TSK (high vs. low) PI controlled: yes	Dynamometer: no effect of TSK level ($p = .180$) nor PCS level ($p = .157$) on muscle strength
Functional trunk capacity (strength, endurance)	Isometric force back extensors (Nm)	Linear regression analyses PI controlled: no	PCS ~ peak force scores in CLBP (extension: $r = -.67$, $p < .001$; side bridge: $r = -.63$, $p < .001$); however, regression analysis showed that physical activity (51%) and disability (39) drove this association
Muscle force	Isometric torque trunk extensors and flexors (Nm)	Pearson correlation analysis. PI controlled: no	Fear ~ isometric force of trunk extensors ($r = -.19$) and trunk flexors ($r = -.15$) ($p < .01$)
Isometric trunk muscle force	Peak pull force (lbs)	One-way ANCOVA's after dichotomization of patients in low- vs. high-pain related fear groups based on median split PASS-scores PI controlled: yes	• Flexion and bilateral side bending: peak force high PASS group < low PASS group ($p < .05$) • Extension and rotation: no group differences in force

Trunk muscle endurance (n=6)			
Author (year)	**Population + LBP criteria**	**Catastrophizing/Fear**	
		Type	**Measure**
Abboud et al.[1]	Non-specific RLBP/CLBP (duration deVet), n = 46 (43.7 ± 13.6y), 19♀/27♂	Kinesiophobia	TSK
Anderson et al.[7]	CLBP (> 3m), n = 96 (37.5 ± 10.4y), 49♀/47♂	Fear-avoidance beliefs for physical activities	FABQ-pa
Demoulin et al.[24]	CLBP (> 3m), n = 50 (44.2 ± 9.5y), 25♀/25♂	Kinesiophobia Pain-related fear	TSK FVAS
Lariviere et al.[68]	CLBP (> 3m), n = 32, 13♀ (35 ± 9y)/14♂ (43 ± 10y)	Kinesiophobia Catastrophizing	TSK PCS
Lee & Park[75]	CLBP (> 3m), n = 131♀ (21.6 ± 1.3y)	Fear-avoidance beliefs	FABQ-pa FABQ-w
Pagé et al.[94]	CLBP (> 3m) - baseline: n = 53 (44.09 ± 13.26y), 23♀/30♂ - follow up 6m: n = 46 (mean age not clear),♀/♂= ?	Kinesiophobia	TSK

Trunk muscle endurance (n=6)			
Movement-related outcomes		**Statistical analysis + controlled for pain intensity (PI)?**	**Results**
Type	**Measure**		
Motor variability	EMG: dispersion of CoG in ES during modified Biering-Sörensen	ANOVA, t-tests PI controlled: no	No significant correlation is found between TSK and dispersion
Endurance back extensors	Biering-Sörensen (s)	Spearman correlation analysis PI controlled: yes	No significant correlations between FABQ-pa and Biering-Sörensen endurance time (r_s = -.058)
Endurance back extensors	Biering-Sörensen (s)	Linear regression analyses PI controlled: no	TSK (standardized β = .015, p = .936) and FVAS (standardized β = -.199, p = .264) are not significantly associated with endurance
Muscle endurance	Dynamometer (Nm) EMG of lumbar MF, IL lumborum and LO (amplitude, median frequency)	AN(C)OVA, correlation analysis, dichotomization of LBP subjects in 2 groups per gender based on median values of VAS (high vs. low), TSK (high vs. low) and PCS (high vs. low) PI controlled: yes	• Dynamometer: no significant effect of TSK on predicted muscle endurance (p = .903); PCS high patients show significantly lower predicted back muscle endurance (p < .05) than PCS low patients • EMG: most variables confirm lower endurance in the PCS high group
Endurance abdominal muscles	Number of sit-ups in 30s	Pearson correlation analysis PI controlled: no	FABQ-w ~ Abdominal muscle endurance (r = -.193, p < .05)
Endurance back extensors	Prone endurance (s) + lateral endurance (s) + Median frequency slope lumbar ES L3	Pearson correlation analysis PI controlled: no	TSK ~ Baseline prone endurance (r = -.22, p < .05) and median frequency slope (r = .23, p < .05) ↔ not with lateral endurance (r = -.17, p > .05)

Activities of Daily Living (ADL) (n=20)			
Author (year)	**Population + LBP criteria**	**Catastrophizing/Fear**	
		Type	**Measure**
Al-Obaidi et al.[2]	Mixed subALBP/CLBP (> 7w), n = 31 (36.1 ± 8.1y), 15♀ /16♂	Fear-avoidance beliefs for physical activities	FABQ-pa
Al-Obaidi et al.[3]	Mixed LBP (> 2m), n = 42 ,20♀ (39.25 ± 5.8y)/22♂ (45.0 ± 6.2y)	Fear-avoidance beliefs	FABQ
Alschuler et al.[6]	CLBP (> 3m), n = 20 (46.1 ± 9.35y), 9♀ /11♂	Kinesiophobia Catastrophizing	TSK PCS
Anderson et al.[7]	CLBP (> 3m), n = 96 (37.5 ± 10.4y), 49♀ /47♂	Fear-avoidance beliefs for physical activities	FABQ-pa
Camacho-Soto et al.[14]	CLBP (> 3m), n = 200 (73.9 ± 5.8y), 114 ♀/86♂	Fear-avoidance beliefs	FABQ
Champagne et al.[16]	CLBP (> 6m), n = 15 (68.9 ± 6.6y), only ♀	Kinesiophobia	TSK
Crombez et al.[21]	CLBP (duration not specified) - study 1: exclusion - study 2: n = 38 (40.84 ± 10.02y), 25♀/13♂ - study 3: n = 31 (41.61 ± 10.7y), 16♀/15♂	Kinesiophobia Pain-related fear Catastrophizing	TSK PASS PCS

Activities of Daily Living (ADL) (n=20)			
Movement-related outcomes		**Statistical analysis + controlled for pain intensity (PI)?**	**Results**
Type	**Measure**		
Gait parameters	Walking velocity (cm/s)	Stepwise regression analysis PI controlled: yes	• FABQ-pa predicts 67% of the deficit in preferred walking velocity • Fast walking: anticipation of pain predicts 83% of the deficit; FABQ-pa predicts 4% of the deficit in velocity
Physical performance	Modified sit to stand (s), forward bending (s), fast walking (velocity)	Bivariate correlation matrix PI controlled: yes	Anticipated pain nor FABQ correlate with the physical performance test
Physical ability Physical activity	6 minute walk (m) ambulatory monitoring with accelerometer	Multiple regressions, Pearson correlations PI controlled: yes	TSK and PCS do not correlate with physical ability (r =-.20; r = .22) or activity (r = -.02; r = -.25)
Physical performance	15 meter walking test (m/s), PILE (max kg lifted with signs of exhaustion), Loaded reach 3 or 4 kg (cm)	Spearman correlation analysis PI controlled: yes	No significant correlations between FABQ-pa and any of the motor function outcomes: 15m walking test (r_s = .012), PILE (r_s = -.151), spondylometry (r_s = -.130), lateral mobility (r_s = -.104), loaded reach (r_s = -.050)
Gait parameters	Walking velocity (m/s)	Pearson correlation analysis PI controlled: yes	FABQ-physical activity in older adults ~ gait speed (r = -.25, p < .001)
Functional performance	Timed-up and Go task (s), one leg stance test (s)	Independent t-tests PI controlled: no	No systematic linkages between kinesiophobia and Timed-up and Go nor one leg stance in elderly women
Study 3: endurance	Lifting bag time (s)	Pearson correlations, multiple regression PI controlled: yes	Study 3: lifting bag time ~TSK (r = -.49, p < .01), PASS (r = -.33, p < .05) and PCS (r = -.43, p < .01)

Activities of Daily Living (ADL) (n=20)			
Author (year)	**Population + LBP criteria**	**Catastrophizing/Fear**	
		Type	**Measure**
Ishak et al.[56]	CLBP (> 6m), n = 63(70.98 ± 7.90y), ♀/♂= ?	Kinesiophobia	TSK
Kernan & Rainville[61]	CLBP (> 3m), n = 68 (43 ± 10y), 38♀ /30♂	Kinesiophobia Fear-avoidance beliefs	TSK FABQ
Kusters et al.[66]	CLBP (> 3m), n = 13 (56.5 ± 9.7y), 6♀/7♂	Kinesiophobia Catastrophizing	TSK PCS
Lamoth et al.[67]	CLBP (> 3.5m), n = 22 (38y, range 21-52), 13♀/9♂	Kinesiophobia	TSK
Lee & Park[75]	CLBP (> 3m), n = 131♀ (21.6 ± 1.3y)	Fear-avoidance beliefs	FABQ-pa FABQ-w

Activities of Daily Living (ADL) (n=20)			
Movement-related outcomes		**Statistical analysis + controlled for pain intensity (PI)?**	**Results**
Type	**Measure**		
Functional performances	Timed up and Go (s), 30s chair rise, hand grip strength (Nm)	Pearson correlation analysis between TSK and motor outcomes; multivariate linear regression PI controlled: yes	• No correlation between TSK and lower limb function (r= -.195, p = .125) nor hand grip strength (r = .043, p = .740) • TSK ~ TUG (r = .263, p = .038)
Movement performance	PILE	Pearson correlation analysis PI controlled: yes	Pre-treatment: TSK (r = -.213, p > .05) and FABQ-pa (r = -.068, p > .05) did not significantly correlate with lumbar PILE; FABQ-w ~ PILE (r = -0.287, p < .05)
Movement performance	Hand function task: RT (Reaction Time), MT (Movement Time) (ms)	Pearson correlation analysis PI controlled: yes	• No significant correlations between RT and PCS (r = -.022 to -.363) or TSK (r = -.032 to -.140) (p > .05) • No significant correlations between MT and PCS (r = .127 to .143) or TSK (r = -.187 to -.206) (p > .05)
Trunk coordination and back muscle activity during walking	Stride length	Spearman correlation analysis PI controlled: yes	No significant correlations between the TSK scores and lumbar kinematics
Physical capacity	Hand grip strength (Nm), leg strength (Nm), cardiopulmonary endurance (6 minute bicycle task)	Pearson correlation analysis PI controlled: no	• FABQ-w ~ Leg strength (r = -.180, p < .05) • FABQ-pa ~ hand grip strength (r = -.184, p < .05) ~ leg strength (r = -.177, p < .05) ~ cardiopulmonary endurance (r = -.263, p < .01)

Activities of Daily Living (ADL) (n=20)			
Author (year)	**Population + LBP criteria**	**Catastrophizing/Fear**	
		Type	**Measure**
Oesch et al.[93]	Non-specific CLBP (duration not specified); n = 126 (44.1y ± 10.4y), 32♀/94♂	Fear-avoidance beliefs for work	FABQ-w
Reneman et al.[103]	Mixed LBP (no specific group), n = 64 (38.0 ± 8.9y), 10♀ /54♂	Kinesiophobia	TSK
Reneman et al[104]	CLBP (> 3m) - study 1: n = 79 (37.8y ± 9.0y), 30♀ /49♂ - study 2: n = 58 (35.6 ± 8.3y), 19♀ /39♂	Kinesiophobia fear-avoidance beliefs	TSK FABQ
Schiphorst Preuper et al.[108]	CLBP (> 3m), n =92 (38.5 ± 8.7y), 32♀ /60♂	Kinesiophobia	TSK

Activities of Daily Living (ADL) (n=20)			
Movement-related outcomes		**Statistical analysis + controlled for pain intensity (PI)?**	**Results**
Type	**Measure**		
Walking speed Movement quality/ performance	6 minute walking distance (m) Lifting floor to waist task (maximum weight in kg)	Multivariate regression analysis PI controlled: yes	Unstandardized coefficient of FA-BQ-work (β = -2.50, 95% CI: -4.47 to -.52) for 6 minute walking distance is significant (p = .014), lifting task shows no significant associations
Movement performance	Functional Capacity Evaluation Lifting task (maximum weight in kg)	Pearson correlation analysis PI controlled: yes	No significant correlations between TSK and lifting (r = -.01, p = .93) nor Functional Capacity Evaluation (r = -.04, p = .75)
Movement performance	Functional Capacity Evaluation: lifting task (max kg), static forward bend 30-60° (s), dynamic bending (20 times; s)	Pearson correlation analysis PI controlled: yes	• TSK ~ static bending time (r = -.23, CI: -.43 to -.01, p < .05) ↔ but not with dynamic forward bend (r = .14, CI: -.08 to .35,), nor lifting performance in men ((r = -.12, CI: -.46 to .25) and women (r = -.17, CI: -.31 to .12) (p>.05); • FABQ-pa ~ static bend (r = -.33, CI: -.54 to -.08, p < .05) ↔ but not with dynamic forward bend (r = .07, CI: -.19 to .32), nor lifting performance in men (r = -.13, CI: -.43 to .19) and women (r = -..7, CI: -.51 to .40)(p>.05); • FABQ-w ~ dynamic bend (r = .30, p < .05) and lifting performance in men (r = -.37, CI: .05 to .52, p < .05) ↔ but not with static bend (r = -.25, CI: -.48 to .01), nor lifting performance in women (r = -.03, CI: -.48 to .43) (p>.05)
Movement performance (endurance)	Static forward bend 30-60° (s), lifting (max kg), carrying weights (max kg)	Pearson and Spearman correlation analyses PI controlled: no	• TSK ~ static forward bend in standing (rs = -.24, p < .05), however after Bonferroni correction, this correlation does

Activities of Daily Living (ADL) (n=20)			
Author (year)	**Population + LBP criteria**	**Catastrophizing/Fear**	
		Type	**Measure**
Smeets et al.[114]	CLBP (> 3m), n = 221 (41.6 ± 10y), 105♀ / 116♂	Catastrophizing	PCL- catastrophizing subscale
		Kinesiophobia	TSK
Soer et al.[115]	CLBP (> 3m), n = 53 (38.5 ± 9.8y), 21♀ /32♂	Kinesiophobia	TSK
		Fear-avoidance beliefs	FABQ

Activities of Daily Living (ADL) (n=20)			
Movement-related outcomes		**Statistical analysis + controlled for pain intensity (PI)?**	**Results**
Type	**Measure**		
			not persist • TSK does not significantly correlate with lifting in men (r = -.04) and women (r = -.09) (p> .05) • TSK does not significantly correlate with weight carrying in men (r = -.17) and women (r = -.07)(p>.05)
Physical capacity	One minute stair climbing test (number of stairs) PILE (max kg lifted 4x within 20s) Forward reach with 4.5kg load (distance in cm) Sit to stand test (average time in s) 50 feet walking speed test (time in s) 5 minute walking test (distance in m)	Multiple regression analysis PI controlled: yes	• High PCS: ↑ climbed stairs (p < .05) ↔ no significant associations with PILE, forward reach, sit to stand, walking speed nor walking distance (p> .05) • Higher levels on TSK: ↓ PILE cycles (p < .05) ↔ no significant associations with stair climbing, forward reach, sit to stand, walking speed nor walking distance (p> .05)
Movement performance (endurance)	Functional Capacity Evaluation lifting test (WWS; maximum kg lifted 5x) PILE (maximum kg lifted 4x)	Pearson correlation analysis PI controlled: no	No significant correlations (p < .05): • TSK ~ WWS (r = -.08), PILE (r = .02) • FABQ-pa ~ WWS (r = .08), PILE (r = .20) • FABQ-w ~ WWS (r = .06), PILE (r = .20)

Activities of Daily Living (ADL) (n=20)			
Author (year)	**Population + LBP criteria**	**Catastrophizing/Fear**	
		Type	**Measure**
Swinkels-Meewisse et al.[123]	acute LBP (< 4w), n = 93 (44.8 ± 11.5y), 48♀ /45♂	Catastrophizing Kinesiophobia	PCS TSK-activity avoidance TSK-harm
Vlaeyen et al.[134]	Study 2: CLBP (> 3m), n = 33 (42.2 ± 9.7y), 25♀ /8♂	Kinesiophobia	TSK
Champagne et al.[16]	CLBP (> 6m), n = 15 (68.9 ± 6.6y), only ♀	Kinesiophobia	TSK
Maribo et al.[82]	Mixed LBP (> 8w), n = 96 (44.9 ± 10.0y), 51♀ /45♂	Fear-avoidance beliefs for physical activities	FABQ-pa
Shanbehzadeh et al. [110]	RLBP/CLBP (> 6m or > 3 episodes last year); - low fear group: n = 19, mean age 29.6y (±5.6), female/male = ?, PASS < 30 - high fear group: n = 19, mean age 27.7y (±4.1), female/male = ?, PASS > 30	Pain-related fear	PASS-20

Activities of Daily Living (ADL) (n=20)			
Movement-related outcomes		**Statistical analysis + controlled for pain intensity (PI)?**	**Results**
Type	**Measure**		
Movement performance	Lifting bag time (7 kg; total lifting bouts within 300s)	Zero order correlations; hierarchical linear regression analyses PI controlled: yes	• PCS ~ lifting time (r = -.26, p < .05 • TSK ~ lifting time (r = -.27, p < .05 • pain-related fear predicts performance on lifting task (p = .021) • TSK-activity avoidance ~ lifting time (p = .005), whereas no associations with TSK-harm (p > .05)
Motoric behavior	BAT = lifting bag test (5,5kg holding time in stretched arm; s)	Pearson correlation analysis after dichotomization in 2 groups based on median score of TSK. PI controlled: yes	study 2: TSK ~ BAT (r = -.44, p < .01) Balance (n = 4)
Postural stability	CoP	Independent t-tests PI controlled: no	No systematic linkages between TSK and postural steadiness in elderly women
Postural stability	CoP	Spearman correlation analysis PI controlled: no	No clinical relevant association between FABQ-pa and CoP-measures: normalized velocity of displacement (r = .02, p = .82), normalized anterio-posterior displacement (r = -.02, p = .89)
Postural stability	CoP assessment with force plate: mean total velocity (cm/s), area (cm^2), maximal range of COP displacement anterior–posterior, and medial–lateral range	Mixed model ANOVA's, post-hoc Bonferroni, dichotomization in high vs. low fear group based on cut-off score 30 on PASS-20. PI controlled: no	• CoP mean velocities: low fear CLBP > high fear CLBP (p < .05) • CoP area: low fear CLBP > high fear CLBP; high fear CLBP sway area double tasks < single tasks

Activities of Daily Living (ADL) (n=20)			
Author (year)	**Population + LBP criteria**	**Catastrophizing/Fear**	
		Type	**Measure**
Sung et al.[121]	(sub)acute LBP (< 3m), n = 33 (32 ± 14y), 20♀/13♂	Fear-avoidance beliefs	FABQ
	Spinal kinematics (n=7)		
Anderson et al.[7]	CLBP (> 3m), n = 96 (37.5 ± 10.4y), 49♀/47♂	Fear-avoidance beliefs for physical activities	FABQ-pa
Demoulin et al.[24]	CLBP (> 3m), n = 50 (44.2 ± 9.5y), 25♀/25♂	Kinesiophobia Pain-related fear	TSK FVAS
Geisser et al.[34]	CLBP (> 3m), n = 76 (40.6 ± 11.9y), 42♀/32♂	Kinesiophobia	TSK
Hickey et al.[46]	CLBP (> 3m), n = 96, 35♀ (33.63 ± 7.6y)/61♂(36.89 ± 9.5y), 35♀/61♂	Anxiety Fear of reinjury	MCMI-II VAS
Kernan & Rainville[61]	CLBP (> 3m), n = 68 (43 ± 10y), 38♀/30♂	Kinesiophobia Fear-avoidance beliefs	TSK FABQ
Lamoth et al.[67]	CLBP (> 3.5m), n = 22 (38, range 21-52), 13♀/9♂	Kinesiophobia	TSK

Activities of Daily Living (ADL) (n=20)			
Movement-related outcomes		**Statistical analysis + controlled for pain intensity (PI)?**	**Results**
Type	**Measure**		
Postural stability	CoP	Pearson correlation analysis PI controlled: yes	No significant correlations between FABQ and postural stability measures (r ranging from -.16 to .24, (p > .05)
		Spinal kinematics (n=7)	
Trunk flexibility	Spondylometry (degrees flexion); lateral spine mob. (finger-floor distance in cm)	Spearman correlation analysis PI controlled: yes	No significant correlations between FABQ-pa and trunk flexibility in the sagittal nor frontal plane
Spine flexibility	Finger floor distance test (cm)	Linear regression analyses PI controlled: no	TSK (p = .797) and FVAS (p = .076) are not significantly associated with flexibility
Spinal flexibility	Goniometer (°)	Zero-order correlation analysis, path models PI controlled: yes	TSK ~ reduced lumbar flexion angles during flexion and extension (p < .01)
Trunk flexibility	Trunk extension & flexion Range of Motion (°)	Multiple regression analyses PI controlled: yes	Fear of reinjury and anxiety (p > .01) do not significantly affect trunk ROM
Flexibility	Trunk flexion-extension, SLR (°)	Pearson correlation analysis PI controlled: yes	Pre-treatment: FABQ-w ~ flexion (r = -.292) and average SLR (r = -.936) (p < .01), but no correlation with extension was found (r = -.191, p > .05); correlations between TSK/FABQ-pa and trunk flexion, extension or average SLR were all non-significant (see table 3 of full text for values)
Kinematics	Rotational amplitudes spine (°), rotational distributi	Spearman correlation analysis	No significant correlations between the TSK scores and rotational amplitudes, nor spine-pelvis rotational distribution

Spinal kinematics (n=7)			
Author (year)	**Population + LBP criteria**	**Catastrophizing/Fear**	
		Type	**Measure**
Moseley[88]	CLBP (> 4m), n = 121 (36 ± 6y),♀/♂= ?	Catastrophizing	PCS
Proprioception and coordination (n=3)			
O'Sullivan et al.[92]	CLBP (> 3m), n = 15 (31.3 ± 10.3y), 5♀ /10♂	Fear-avoidance beliefs	FABQ
Ishak et al.[56]	CLBP (> 6m), n = 63 (70.98 ± 7.90y), ♀/♂ = ?	Kinesiophobia	TSK
Karayannis et al.[60]	LBP (not specified), n = 19 (43, range 26-65), 13♀/6♂	Kinesiophobia	TSK
		Fear-avoidance beliefs	FABQ
		Catastrophizing	PCS
		Perceived harm-fullness of physical activity	PHODA

Spinal kinematics (n=7)			
Movement-related outcomes		**Statistical analysis + controlled for pain intensity (PI)?**	**Results**
Type	**Measure**		
	on spine-pelvis (ratio)	PI controlled: yes	
Hip flexion mobility Lumbar flexion mobility	SLR (°) Forward bending task (cm)	Multiple regression analysis PI controlled: no	Change in PCS ~ change in SLR (β= -1.0, p = .001) and forward bending (β = -1.40, p = .001)
Proprioception and coordination (n=3)			
Proprioception	Repositioning error (position-reposition test)	Pearson and Spearman correlation analysis PI controlled: no	Fear-avoidance ~ constant error during repositioning in sitting (r = -.577, p = .002), whereas no associations with absolute (r = -.577, p = .002) or variable error (rs = .076, p = .787)
TrA and MF control	Pressure Biofeedback Unit (mmHg)	Pearson correlation analysis between TSK and motor outcomes; multivariate linear regression PI controlled: yes	No correlation between TSK and TrA (r = .050, p = .694) and MF control (r = .156, p = .222)
Mechanical trunk properties	Trunk stiffness (ability to resist displacement) & damping (ability to resist velocity)	Second order linear model, dichotomizations based on median split of TSK and median split of FABQ PI controlled: yes	• Regression analysis: TSK ~ trunk stiffness (r^2 = .33, p = .03) during forward perturbation; no other significant associations were found between TSK/FABQ/PCS/PHODA and stiffness or damping during forward and backward perturbations (see full article table 4 for all values) • After dichotomization: trunk stiffness high TSK > low TSK during forward perturbation (p = .03); trunkstiffness high FABQ-w > low FABQ-w during forward perturbation (p < .01); no significant differences for backward perturbations nor FABQ-pa subgroups

Legend:

Symbols. ~, associates with; ↔, opposed to; ↑, higher or increase; ↓, lower or decrease; y, mean age in years ± SD; n, number; ρ, rho (Greek)

Muscles. AD, Anterior Deltoid Muscle; EO, External Abdominal Oblique Muscle; ES, Erector Spinae Muscle; IL, Iliocostalis Muscle; ILL, Iliocostalis Lumborum muscle; ILT, Iliocostalis Thoracis Muscle; IO, Internal Abdominal Oblique Muscle; LL, Longissimus Lumborum Muscle; LO, Longissimus Muscle; LT, Longissimus Thoracis Muscle; MF, Multifidus Muscle; RA, Rectus Abdominis Muscle; TrA, Transversus Abdominis Muscle;

Questionnaires. CSQ, Coping Strategy Questionnaire; FABQ, Fear-Avoidance and Beliefs Questionnaire (FABQ-pa, physical activity subscale; FABQ-w, work subscale); FVAS, Fear Visual Analogue Scale; HADS, Hospital Anxiety and Depression Scale; MCMI-II, Millon Clinical Multiaxial Inventory; PASS, Pain Anxiety Symptoms Scale; PCL, Pain Cognition List; PHODA, Photographs of Daily Activities scale; TSK, Tampa Scale for Kinesiophobia;

Measures. BAT, Behavioural Approach Test; CoP, Center of Pressure; FRR, Flexion Relaxation Ration; PILE, Progressive Isoinertial Lifting Exercise; SLR, Straight Leg Raising task; SRE, Smooth Rectified Electromyography; WWS, Work Well Systems functional capacity evaluation

Statistics. ANOVA, Analysis of Variance; ANCOVA, Analysis of Covariance; CI, confidence interval; GLM, General Linear Model; PI, pain intensity; r, Pearson correlation coefficient; rs, Spearman correlation coefficient; RMS, Root Mean Square

TABLE 4. *Methodological assessment 'Modified Newcastle Ottawa Scale'*

Study	**Selection (/6)**						**Comparability (/2)**
	1	**2**	**3**	**4**	**5**	**Total**	
Abboud et al.[1]	a*	c	b	c	a**	***	NA
Al-Obaidi et al.[4]	b	b*	b	c	a**	***	NA
Al-Obaidi et al.[3]	b	b*	b	c	a**	***	NA
Al-Obaidi et al.[2]	b	b*	b	c	a**	***	NA
Alschuler et al.[6]	a*	c	b	c	a**	***	NA
Anderson et al.[7]	a*	b*	a*	c	b*	****	NA
Camacho-Soto et al.[14]	a*	d	b	c	a**	***	NA
Champagne et al.[16]	b	d	b	c	a**	**	NA
Crombez et al.[21]	b	c	b	c	a**	**	NA
Demoulin et al.[24]	a*	c	b	c	a**	***	NA
Dubois et al.[29]	b	b*	b	c	a**	***	NA
Geisser et al.[34]	a*	d	b	c	a**	***	NA
Goubert et al.[39]	a*	c	b	c	a**	***	NA
Henchoz et al.[43]	b	d	b	c	b*	*	a*+b*
Hickey et al.[46]	b	c	b	c	b*	*	NA
Ishak et al.[56]	a*	b*	a*	c	a**	*****	NA
Jacobs et al.[57]	a*	c	b	c	a**	***	NA
Karayannis et al.[60]	b	b*	b	c	a**	***	NA
Kernan & Rainville[61]	a*	b*	b	c	a**	***	NA
Kusters et al.[66]	a*	b*	b	c	a**	****	NA
Lamoth et al.[67]	a*	b*	b	c	a**	****	NA
Lariviere et al.[68]	a*	d	b	c	a**	***	NA

Outcome (/4)				LoE
1	2	3	Total	
a*	c*	a*	***	C
a*	c*	a*	***	C
a*	c*	a*	***	C
a*	c*	a*	***	C
a*	c*	a*	***	C
a*	c*	a*	***	C
a*	c*	a*	***	C
a*	c*	a*	***	C
a*	c*	a*	***	C
a*	c*	a*	***	C
b	c*	a*	**	C
a*	c*	a*	***	C
a*	c*	a*	***	C
	a**	a*	**	B
a*	c*	a*	***	C
a*	c*	a*	***	C
a*	c*	a*	***	C
a*	c*	a*	***	C
a*	c*	a*	***	C
a*	c*	a*	***	C
a*	c*	a*	***	C
a*	c*	a*	***	C

Study	Selection (/6)						Comparability (/2)
	1	2	3	4	5	Total	
Lariviere et al.[69]	a*	b*	b	c	a**	****	NA
Ledoux et al.[74]	b	a*	a*	c	a**	****	NA
Lee & Park[75]	b	c	a*	c	a**	***	NA
Lewis et al.[77]	a*	c	b	c	a**	***	NA
Maribo et al.[82]	b	b *	b	c	a**	***	NA
Massé-Alarie et al.[83]	a*	d	b	c	a**	***	NA
Michalski & Hinz [85]	a*	b*	b	b	a**	****	a*
Moseley [88]	b	b*	b	c	a**	***	NA
Oesch et al.[93]	b	b*	a*	c	a**	****	NA
O'Sullivan et al.[92]	a*	c	b	c	a**	***	NA
Pagé et al.[94]	a*	b*	a*	c	a**	*****	NA
Pakzad, et al.[95]	a*	b*	b	c	a**	****	a*+b*
Quartana et al.[100]	b	b*	b	c	a**	***	NA
Ramprasad et al.[102]	b	c	b	c	a**	**	NA
Reneman et al.[103]	b	c	b	c	a**	**	NA
Reneman et al.[104]	a*	b*	b	c	a**	****	a*+b*
Schiphorst Preuper et al.[108]	b	b*	b	a*	a**	****	NA
Shanbehzadeh et al.[110]	a*	d	b	c	a**	***	a*+b*
Smeets et al.[114]	a*	b*	a*	c	a**	*****	NA
Soer et al.[115]	a*	b*	b	c	a**	****	NA
Sung et al.[121]	b	b*	b	c	a**	***	NA
Svendsen et al.[122]	b	c	b	c	a**	**	NA
Swinkels-Meewisse et al.[123]	a*	b*	b	c	a**	****	NA
Thomas et al.[125]	b	b*	b	c	a**	***	a*+b*
van der Hulst et al.[127]	a*	b*	b	c	a**	****	NA
van der Hulst et al.[128]	a*	b*	b	c	a**	****	NA
Vlaeyen et al.[134]	b	c	b	a*	a**	***	a*+b*
Vlaeyen et al.[137]	b	b*	b	c	a**	***	b*
Watson et al.[140]	b	b*	b	c	a**	***	NA

Legend:

Selection

1. *Case definition*
   - *a) Well described and defined study population(s).**
   - *b) Poor or lacking description and definition of study population(s).*
2. *Representativeness of the sample*
   - *a) Truly representative of the average in the target population, i.e. random sampling.**
   - *b) Somewhat representative of the average in the target population, i.e. non-random sampling.**
   - *c) Selected group of participants.*
   - *d) No description of the sampling strategy.*
3. *Sample size*
   - *a) Justified and satisfactory (power calculation).**
   - *b) Not justified.*

Outcome (/4)				LoE
1	2	3	Total	
a*	c*	a*	***	C
a*	c*	a*	***	C
a*	d	a*	**	C
a*	c*	a*	***	C
a*	c*	a*	**	C
a*	c*	a*	***	C
a*	c*	a*	***	B
a*	a**	a*	****	C
a*	a**	a*	****	C
a*	c*	a*	***	C
a*	c*	a*	***	C
a*	d	a*	**	B
a*	c*	a*	***	C
a*	a**	a*	****	C
a*	c*	a*	***	C
a*	a**	a*	****	B
a*	c*	a*	***	C
a*	d	a*	**	B
a*	b**	a*	****	C
a*	c*	a*	***	C
a*	c*	a*	***	C
a*	c*	a*	***	C
a*	c*	a*	***	C
a*	c*	a*	***	B
a*	c*	a*	***	C
a*	c*	a*	***	C
a*	c*	a*	***	B
a*	c*	a*	***	B
a*	c*	a*	***	C

4. Non-respondents

*a) Comparability between respondents and non-respondents characteristics is established, and the response rate is satisfactory.**

b) The response rate is unsatisfactory, or the comparability between respondents and non-respondents is unsatisfactory

c) No description of the response rate or the characteristics of the respondents and the non-respondents

5. Ascertainment of the exposure (= catastrophizing, fear, attention)

*a) Validated measurement tool.***

*b) Non-validated measurement tool, but the tool is available or described.**

c) No description of the measurement tool.

Comparability

1. The subjects in different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled.

*a) The study controls for the 2 most important factors: age + gender.**

*b) The study controls for any additional factor: pain intensity, BMI and/or physical activity.**

c) The study does not control for any of the confounders mentioned in a) or b).

Outcome

1. *Type of outcome*
   - *a) Objective.**
   - *b) Subjective.*
2. *Assessment of outcomes*
   - *a) Independent blind assessment.***
   - *b) Record linkage.***
   - *c) Adequate description, but not blinded.**
   - *d) No description.*
3. *Statistical test*
   - *c) The statistical test used to analyze the data is clearly described and appropriate, and the measurement of the association is presented, including confidence intervals and the probability level (p value).**
   - *b) The statistical test is nog appropriate, not described or incomplete*

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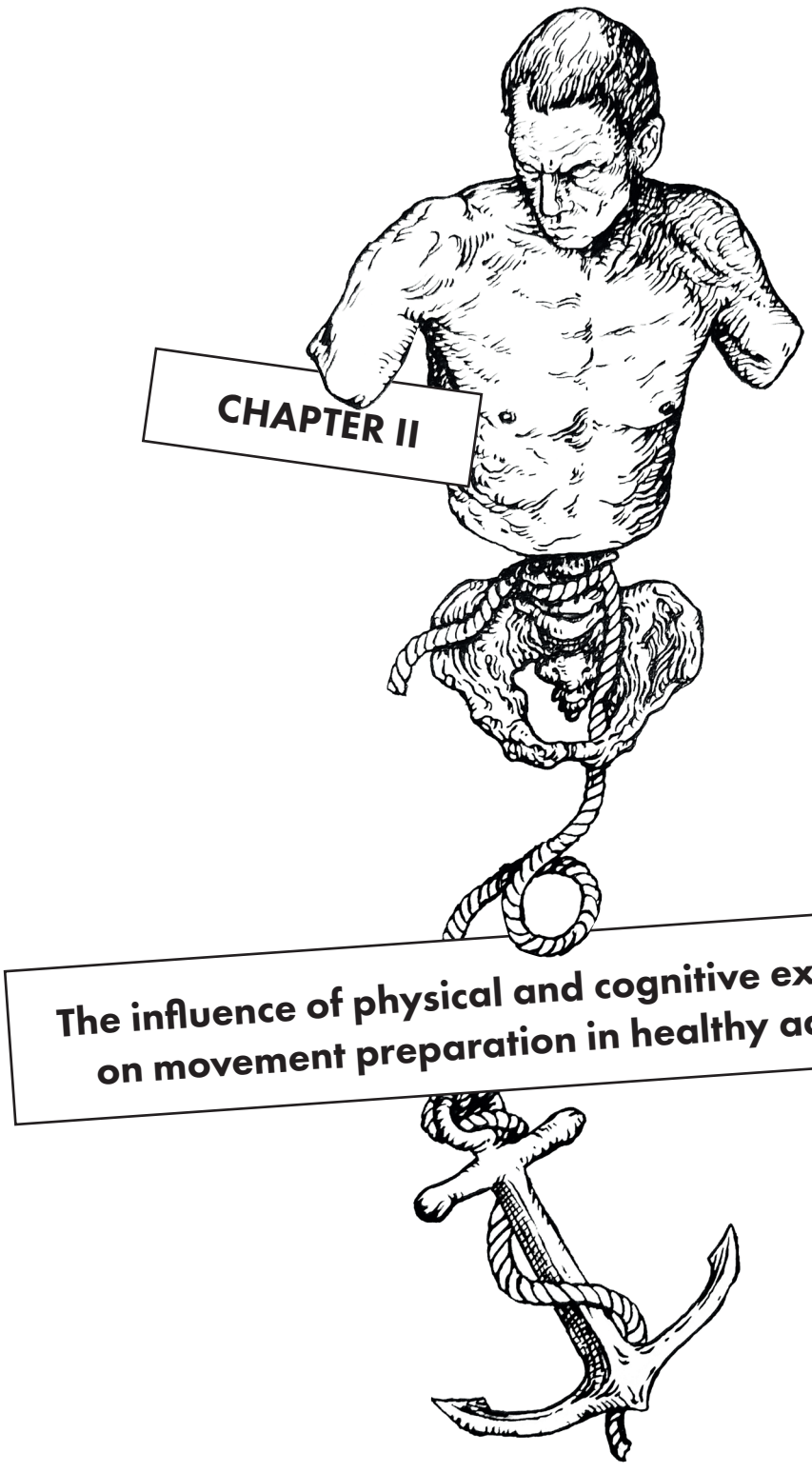
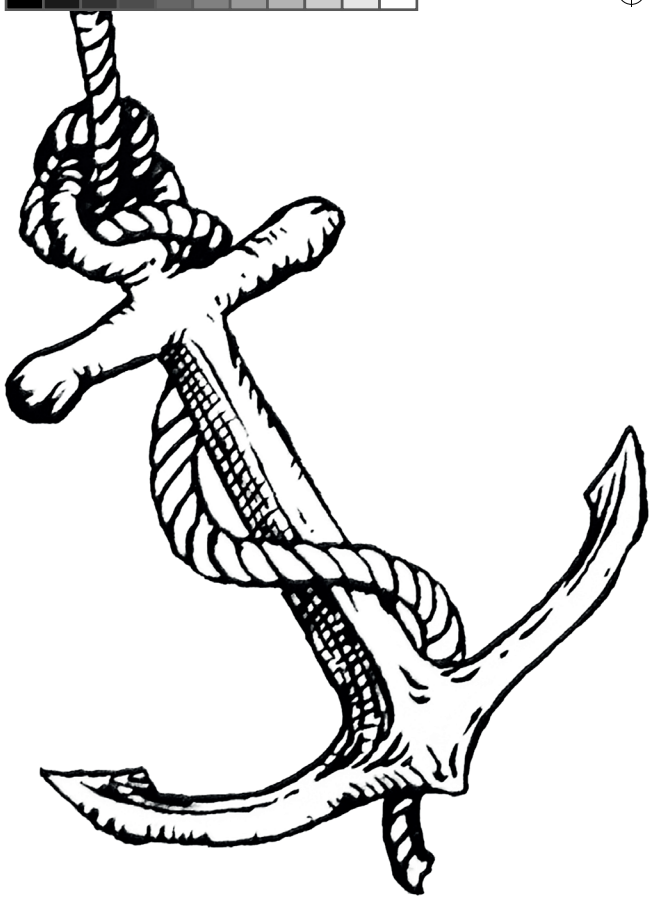


The influence of physical and cognitive exertion on movement preparation in healthy adults



PHYSICAL AND COGNITIVE EXERTION DO NOT INFLUENCE FEEDFORWARD ACTIVATION OF THE TRUNK MUSCLES: A RANDOMISED CROSSOVER TRIAL

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Abstract

Fatigue arises during everyday activities, diminishes movement performance, and increases injury risk. Physical (PE) and cognitive exertion (CE) can induce similar feelings of fatigue, but it is not clear whether these also similarly affect movement performance. Therefore, this study examined the influence of PE and CE on anticipatory postural adjustments (APAs) of trunk muscles, which are feedforward mechanisms that contribute to motor control and controlled movement. Rapid arm movement tasks (RAM) were used to induce APAs of the trunk muscles prior and following three experimental conditions in 20 healthy adults: seated rest without exertion (NE), a combined isometric modified Biering-Sörensen and static abdominal curl to induce PE, and a modified incongruent Stroop colour-word task to induce CE. Fatigue was assessed using self-reported measures, and APA onset latencies of the trunk muscles with surface electromyography. Statistical analyses revealed that neither PE or CE influence APAs of the trunk. Therefore, it is hypothesized that the influence of fatigue on movement performance might not be through altered motor control, but rather by reduced motivation. However, the possibility that fatigue might influence other mechanisms which contribute to trunk motor control, such as APA amplitude and variability, cannot be excluded and need further examination.

Keywords: sensorimotor control; electromyography; anticipatory postural adjustments; exertion

1 Introduction

Anticipatory postural adjustments (APA) are feedforward muscle reflex activities aimed at maintaining whole-body balance which are programmed in the central nervous system and occur in preparation of predictable balance disturbances.[4, 15, 18, 59] These APAs are an essential part of the motor control system, and are needed to minimize the forces applied to the body and to attain controlled movements[46]. For instance, when performing rapid arm movements feedforward activation of several trunk muscles precedes the actual onset of the arm muscles and counteracts balance perturbation.[82] When the feedforward activation of the trunk muscles is delayed it ultimately increases injury risk.[19] This is the case in for instance low back pain[46, 82] and ageing[16, 39, 44]. In addition, several other factors such as physical activity[13], posture[81], vision[47], and fatigue[4, 28, 45, 60, 78] have been shown to affect the timing of APAs and might contribute to injuries.

Fatigue - a feeling of exhaustion arising from exertion - is a disabling symptom in which physical and psychophysiological function is limited by interactions between performance fatigability and perceived fatigability.[29, 66] Importantly, fatigue can be induced through different tasks such as physical (PE) or cognitive exerting tasks (CE). Even though such different tasks induce highly similar perceptions of fatigue[29, 48], it is not yet clear whether they also have a similar effect on muscle function as the underlying mechanisms for both are different. One important aspect of muscle function which could be affected by fatigue is the timing of APAs. As in everyday tasks, work, leisure and sports fatigue can arise due to both PE and CE it is important to assess their respective impact on APAs, because of the paramount role APAs have in motor control, and consequently movement performance and injury risk.
PE is characterized by a decreased force production due to diminished neural excitation or due to failure of muscles to respond to neural excitation[8, 22, 51] caused by depletion of physiological energy resources of the body[5]. This can amount to feelings of fatigue and a decrease in physical performance.[1, 53] Fatigue induced by PE has only been associated with altered APAs in one pilot study. In healthy people APAs of abdominal and back muscles, measured during performance of a rapid arm movement task (RAM), occurred earlier after isometric PE of the trunk extensors, reflecting altered feedforward processes.[4] However, these results need to be replicated in a larger sample. Earlier trunk muscle onsets as a consequence of PE are hypothesized to be a neuromuscular compensation aimed at countering the decreasing muscle contractility which arises from fatigue.
The contribution of cognitive function to the process of movement performance and the effect of fatigue on this process should be considered as well.[1] Executive cognitive functions are recognized as a key factor in motor control.[1] Hence, when these executive cognitive functions are affected by fatigue, alterations in movement performance can occur as a result. Indeed, previous studies have found reductions in muscle activity[61], force[17, 62] and endurance performance[62] of peripheral muscles as a consequence of higher cognitive loads or CE. If and how CE affects the feedforward activation of the trunk muscles specifically has not been studied yet, but in knee muscles neuromuscular function was not affected by CE in one study[68]. However, previous research did find reduced endurance times of physical tasks after CE[55, 68], which could indicate that CE can indeed affect movement performance and motor control. Furthermore, studies which examined the cortical effects of PE and CE, showed that they both affect similar areas in the brain[6, 34, 49]. Based on these studies, it could be assumed that some of the central mechanisms underlying PE and CE entail similar processes. Therefore, a comparable hypothesis regarding CE effects on trunk motor control is formulated as with PE, i.e. earlier APAs after fatigue.

The main goal of this study is to examine the influence of PE and CE on mean onset times of APAs of the trunk muscles in healthy people, and to compare effects of both types of exertion. It was hypothesized that PE and CE would lead to 1) earlier onset times of the APAs of the trunk muscles, and that 2) both types of exertion would yield comparable results.

2 Methods

2.1 Participants

Healthy male and female participants between 18 and 45 years were recruited between September 2016 and December 2018 using advertisements. Healthy was defined as no history of/or current pain, severe pathologies or traumata. Additionally, people with colour blindness, professional athletes, women less than one year postnatal or pregnant were not eligible. Participants had to refrain from alcohol and medication without prescription for at least 24 hours, from prescribed medication at least two weeks, and from extreme physical activities 48 hours prior to testing.

2.2 Procedure

This randomised within-participant crossover trial entailed participation to two sessions with minimally five days in-between. A medical background check, a general administrative and a sociodemographic questionnaire were administered during session one. Additionally, during each session, participants completed three validated questionnaires in Dutch (see 2.6 secondary outcome measures) to assess mental/cognitive functioning, physical activity and state fatigue levels, as well as visual analogue scales (VAS) to rate sleep quality and quantity during the prior night and week. To evaluate the APAs, EMG-electrodes were placed on the trunk and the RAM was explained. APAs of the trunk muscles during RAM were evaluated in three conditions i.e. a control condition with no exertion (NE) inducement, a condition during which CE was induced, and a condition during which PE was induced. To optimize task performance and familiarize the participants with the RAM extensive instructions, practice trials and feedback were provided prior to each condition. The NE condition was performed during session one, while the CE and PE conditions were performed during session two. The test order of the CE and PE conditions was randomized in order to prevent confounding and a 30-minute rest phase was provided between these two conditions. The APAs during RAM were evaluated before (RAM1) and after (RAM2) each of these conditions. Before and after each RAM participants rated their self-perceived state fatigue on a VAS. Furthermore, ratings of perceived exertion (RPE) of the RAM and condition-specific tasks were acquired using a Borg scale. An overview of the study protocol is provided in **FIGURE 1**.

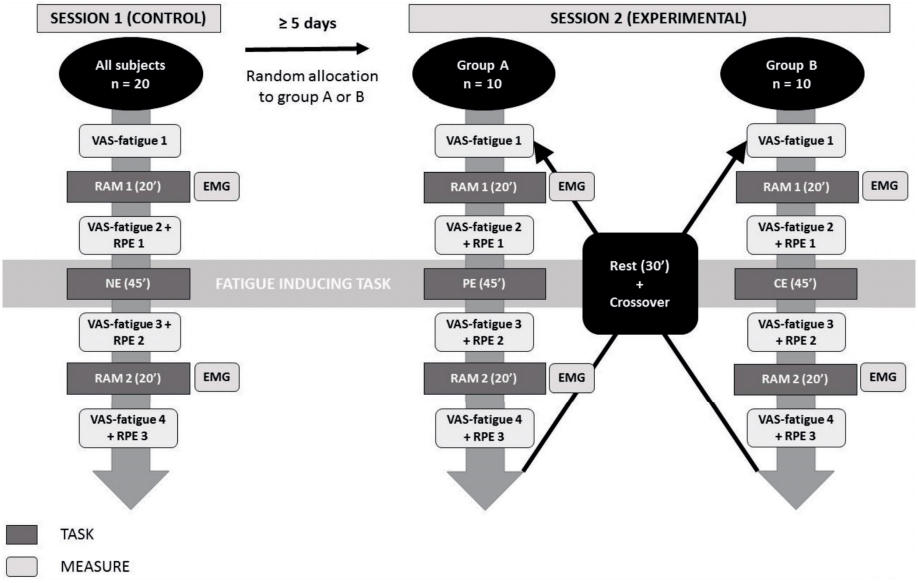

FIGURE 1. Flowchart of the study protocol. Legend: CE, cognitive exertion; n, number of; NE, no exertion condition; PE, physical exertion; RAM, rapid arm movement task; RPE, rating of perceived exertion; VAS-fatigue, visual analogue scale for fatigue.

2.3 Fatigue Inducing Conditions

2.3.1 No Exertion

To control for possible effects due to repetition of the RAM a control condition was performed during which participants spent 45 minutes sitting relaxed while watching an animated movie.

2.3.2 Physical Exertion

To induce PE of the trunk muscles both the Modified Biering-Sörensen and Static Abdominal Curl were performed. The Modified Biering-Sörensen is a validated PE task used to assess fatigue in the back extensors[21, 74] and was used to exert these muscles in the current study. Participants had to maintain a horizontal position of their upper body as long as possible, while they were positioned in a prone position with the legs strapped to a table and the upper body hanging unsupported over the edge of that table. Immediately afterwards, a Static Abdominal Curl was performed to exert the abdominal muscles[80]. Participants had to maintain an unsupported 45° angle of trunk flexion while seated with their legs strapped to a table. Standardized motivational commands were given every 30 seconds, and the tasks were discontinued when the participant could no longer retain contact with a rope that indicated the required position, or had to stop due to pain or discomfort. Endurance times were measured using a chronometer.

2.3.3 Cognitive Exertion

To induce CE a 45-minute modified incongruent Stroop task was performed identical as the protocol described by Pageaux et al.[69] During this task font dominant tasks are alternated with word dominant tasks. The duration of the Stroop was increased to 45 minutes, as in 25% of the participants 30 minutes was found to be insufficient to affect the RPE[69].

2.4 Primary Outcome Measure: anticipatory postural adjustments (APA)

Surface EMG (sEMG) was performed to assess APA onset latencies of the trunk muscles. sEMG signals were captured using a wireless 16-channel EMG system (Telemyo Desktop DTS, Noraxon Inc., USA). Skin preparations were performed to reduce electrode-signal impedance to <5kΩ (Impedance checker, Noraxon Inc., USA). Circular surface electrodes with an electrical surface contact of 1cm^2 and a maximal inter-electrode distance of 25mm (Ag/AgCl, Ambu® Blue Sensor N, 30x22 mm, Ballerup, Denmark) were positioned bilaterally over the Internal Oblique/Transversus Abdominis (IO/TrA)75, External Oblique (EO)[67], Multifidus (MF)[24, 25], the Iliocostalis Lumborum pars Thoracis (ILT)[54], and unilateral over the anterior deltoid (AD) of the dominant arm. EMG signals were analogue bandpass-filtered between 10-500Hz, pre-amplified (CMRR>100dB, overall gain 500, noise<1μV RMS) and AD-converted (16-bit) at a sampling rate of 1500Hz.

The EMG-signals were recorded during the RAM, which was first described by Hodges et al.[37] and is a frequently used, valid and reliable task for assessing APAs of the trunk muscles related to arm movements[56]. Participants stood barefoot with the feet at shoulder width and the arms hanging relaxed alongside the body[71]. A visual warning cue (white cross) appeared on a screen two meters in front of the participant, followed in a jittered interval of 1000-1500ms by a second direction-specific cue (arrow) instructing participants to move their dominant arm to the indicated direction and back to neutral as fast as possible with extended elbow[40, 41]. One of two possible direction-specific cues was presented: an upright green arrow indicating shoulder flexion to 90°[35], or a downward red arrow indicating shoulder extension to 30°. The interval between two consecutive trials was 12s with the command to relax the trunk muscles and to breathe normally[40, 41, 57, 58]. A familiarization session with feedback concerning relaxation of the abdominal muscles, performance and velocity of the arm movement was performed at the start of session one and each

session was preceded by a training phase. The experimental RAM consisted of 80 trials, i.e. 40 per movement direction presented in a randomised order. Every five minutes a short feedback with regards to maintaining maximal velocity and correct amplitude of the arm movements, and sufficiently relaxing trunk muscles after movement was implemented to ensure optimal task performance. Performance of all the RAM trials took 20 minutes.

The latencies between the EMG onset of the trunk muscles and that of the AD during the forward arm movement were analysed in Matlab version 9.1 (Mathworks Inc., US). Backward movements were performed to increase unpredictability of the movement direction and were not analysed. The EMG-data was cut into segments –3000 to +3000ms around the movement onset, that was determined by a light sensor. Information regarding participant, condition, side, trial and muscle was removed to blind the assessor. Subsequently, the raw, non-rectified and rectified 30Hz high-pass filtered signals of each segment were presented to the assessor, with the possibility to zoom in and out. After onset determination of the AD muscle the assessor visually picked[36] the onset of the trunk muscles in a time window of -1500 to +1500ms around AD onset as this technique has been shown to be reliable. Furthermore, a time frame of -150 to +400ms around AD was visually presented with dotted lines to indicate the possible time frame wherein the onset could occur (**FIGURE 2**). All 40 forward arm movement trials per RAM were analysed. Trials were excluded whenever the muscle onset could not be visually determined due to excessive baseline muscle activity, electromagnetic artefacts or interference, ECG-signals coinciding with muscle onset, EMG-signal loss or non-optimal movement execution. Furthermore, onset times occurring more than 100ms before the prime mover were also excluded, as EMG activity before that time point is unlikely to be related to the RAM. At least five trials without artefacts, but more if possible, per muscle were needed for reliable assessment[56]. Afterwards an overlay graph with all analysed trials per muscle was controlled for outliers. Trunk APAs of >100ms before AD onset were excluded, as they were unlikely to represent RAM related feedforward activation of the trunk muscles[76].

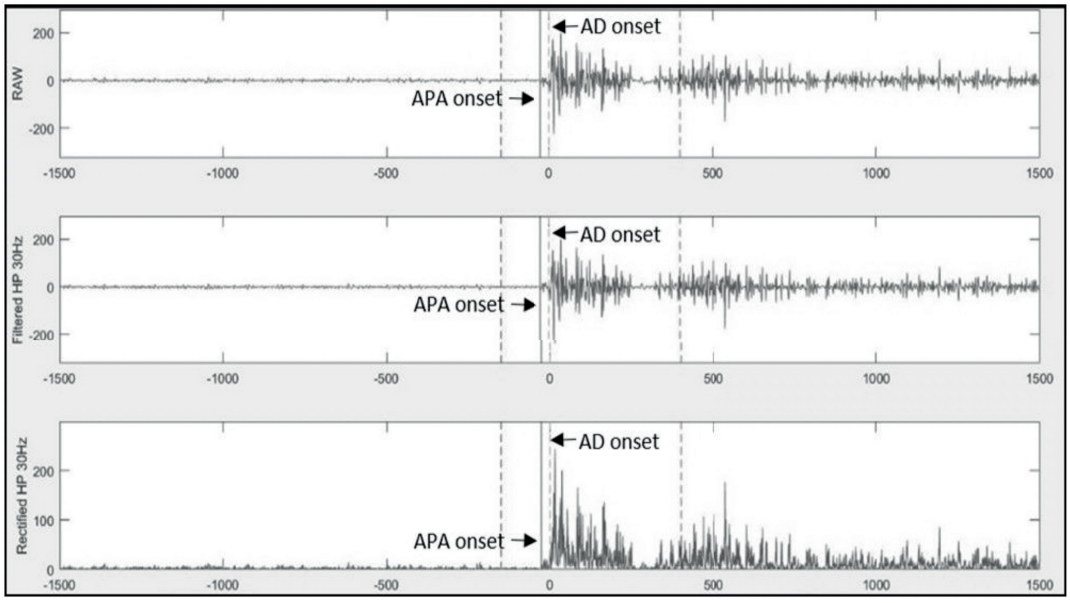

FIGURE 2. Example of visual picking an APA onset. Legend: x-axis, indicates time in ms; y-axis, indicates amplitude in microvolts; HP, High-Pass; The visual picked APA onset determination for the trunk muscle that is under analysis is represented by a full line. The time frame for visual picking is indicated by the outermost dotted lines -150 ms to +400 ms around the 0-point. The dotted line at time zero represents the onset of the Anterior Deltoid muscle.

2.5 Secondary Outcome Measures

The **Profile Of Mood State Short Form (POMS-SF)** was used to evaluate mood states.[86] It measures affective disturbances along five dimensions, namely depression, anger, fatigue, tension and vigour. Furthermore, a total score can be calculated. Higher scores reflect higher presence of the related moods. The POMS-SF has sufficient consistency, reliability, and a high validity.[27, 86]

The **International Physical Activity Questionnaire (IPAQ)** estimates physical activity levels based on the reported activities during the last seven days.[10, 79] Metabolic equivalents were calculated by multiplying the amount of minutes/week spent on work, transport, household and leisure tasks, with a factor that represents the strenuousness of the activities. The IPAQ has a fair validity and acceptable reliability.[23, 83]

The **Checklist Individual Strength (CIS)** evaluates behavioural aspects related to trait fatigue in the past two weeks.[29, 84] Four fatigue related aspects are evaluated by the following subscales; subjective fatigue (8-56 score range), concentration (5-35 score range), motivation (4-28 score range) and physical activity (3-21 score range). In addition, a total score reflecting the general amount of fatigue severity can be calculated (20-140 score range). High scores indicated more fatigue and less concentration, motivation and physical activity. For total fatigue severity, scores of <27, 27-35, and >35 respectively represent low, moderate and high fatigue rates.[84] The CIS has an excellent validity and reliability.[84, 85]

A **visual analogue scale for fatigue (VAS-fatigue)** was used to rate state fatigue[29] prior and following each RAM. A VAS is a continuous scale consisting of a 10 cm horizontal line with the left and right outer ends respectively labelled as no fatigue at all and worst imaginable fatigue ever.

The **rating of perceived exertion (RPE)** scale ranging from 6 (very, very light) to 20 (maximal exertion) was used to rate the subjective exertion of the RAM and fatigue-inducing conditions.[2, 11, 12]

2.6 Statistical Analysis

Data were analysed using IBM SPSS Statistics 25 (IBM Corp., Armonk, N.Y., USA) with the significance level set at .05. Descriptives were calculated and normality of data distribution was assessed with the Shapiro-Wilk test. As this report is part of larger study, a priori sample size calculations were based on articles describing the influence of fatigue on feedforward timing of paraspinal muscles[77] and describing the influence of fatigue on EMG amplitude and on movement-related cortical potentials[42] (results not included in the current manuscript) and resulted in a minimum of 20 participants to attain a power of .80 with significance level .05.

To assess the strenuousness of the fatigue inducing tasks, RPE-ratings were compared between conditions (NE - PE - CE) with a Friedman test and post-hoc Wilcoxon signed-rank tests with Bonferroni correction. Furthermore, VAS-fatigue ratings prior and following to the RAM performances and fatiguing tasks were compared within and between conditions (NE - PE - CE) with a linear mixed model analysis. In this model VAS-fatigue was the dependent outcome, and fixed factors condition (NE - PE - CE), task (RAM1 - fatiguing task - RAM2; with RAM1 and RAM2 respectively representing the RAM performed before and after the fatiguing task), and time to task (Pre task - Post task; i.e. whether the outcome variable was measured prior to or following the examined task), and random intercept on subject level with a variance components covariance type were implemented.

To examine whether fatigue would influence the APAs, and whether the type of fatigue inducing task would influence the effects, a linear mixed model analysis was performed with the mean onset of the APAs per muscle from each side as the dependent outcome, factors condition (NE - PE - CE) and RAM task (RAM1 - RAM2), and random inter-

cept on subject level with a variance components covariance type. These analyses were performed separately for eight muscles, i.e. IO, EO, MF and ILT of both the ipsilateral and contralateral side in relation to the dominant arm. Furthermore, Cohen's d effect sizes were calculated for each muscle in each condition comparing the difference in APA latencies from RAM1 to RAM2. Cohen's d effect sizes can range from very small (.10), small (.20), medium (.50), large (.80) up to huge (2.0).[20]

For all linear mixed models performed in this study possible confounders were assessed, i.e. age, sex, handedness, BMI, IPAQ total scores, hours of sport/week, hours of sleep/week, VAS sleep quality the night and week preceding testing, hours of sleep the night prior to testing, CIS-subscale and total scores, POMS-subscale and total scores. Confounders were retained in the model if they lowered the Akaike's Information Criterion with minimally 10 points and had a significant influence on the model, which was deemed a significant better model fit. In this regard, for the linear mixed models examining the influence of NE, PE and CE on the APA onset times of the ipsilateral MF and the ipsilateral ILT muscle respectively hours of sleep/week (week before testing) and sex were retained as a significant confounder, whereas for all other models no significant confounders were retained. Post-hoc comparisons for linear mixed model analyses were always made using Bonferroni corrections.

3 Results

3.1 Participants

Twenty-two participants were recruited. As one participant fainted during data collection and EMG-data of another participant was corrupted, the data of 20 participants (11 male, 9 female), were analysed. Participants had a mean age of 22.3 years (SD 1.23), mean height of 174.5 cm (SD 8.37), and mean weight of 66 kg (SD 10.37). Ninety percent of participants was right-hand dominant. Furthermore, mean hours of sport performance per week and mean hours of sleep per night were respectively 3.5 h (SD 2.95) and 7.6 h (SD .76). The mean endurance time for the modified Biering-Sörensen and Abdominal Endurance task were respectively 121.2s (SD 49.40) and 340.8s (SD 368.10).

3.2 Fatigue Induction

Median RPE-scores for the NE, PE and CE conditions were respectively 6.5 (range 6-12), 16.0 (range 11-18) and 12.0 (range 7-16). Thus, NE was generally considered to induce no exertion, PE was considered as a very high exertion, and CE as somewhat high. There were significant between condition differences in RPE-scores ($\chi^2(2)=32.141$, $p<.001$). The NE condition was less exerting than the PE ($Z=-1.861$, $p<.01$) and CE ($Z=-1.139$, $p<.01$) condition, whereas no significant differences were found between PE and CE ($Z=.722$, $p=.91$).

The VAS-fatigue mixed model analysis showed a significant 3-way interaction of condition x task x time to task ($F(4;322.011)=4.666$, $p=.001$). Post-hoc analyses revealed that before RAM1 and prior to the fatigue inducing conditions VAS-fatigue did not significantly differ between conditions, nor did RAM1 influence VAS-fatigue significantly. Thus, participants commenced these experiments with similar levels of fatigue. Immediately after performing the fatiguing task VAS-fatigue ratings were significantly increased in response to PE ($p=.044$), but not in response to NE ($p=.095$) or CE ($p=.156$). VAS-fatigue ratings in response to RAM2, after the fatiguing task, were significantly higher than those prior to that RAM in the NE ($p=.026$) and PE ($p=.049$) conditions.

3.3 Effects of PE and CE on APA Onset Latencies

For none of the examined muscles a significant condition x time interaction was found, i.e. IO/TrA (ipsilateral: F(2;63.776)=.324, p=.725; contralateral: F(2;36.671)=.770, p=.470), EO (ipsilateral: F(2;77.632)=2.490, p=.090; contralateral: F(2;74.428)=.110, p=.896), MF (ipsilateral: F(2;29.183)=.290, p=.750; contralateral: F(2;33.433)=1.106, p=.343) and the ILT (ipsilateral: F(2;70.350)=.643, p=.529; contralateral: F(2;92.968)=.044, p=.957).

However, a main effect of condition was found for the ipsilateral ILT muscle, with later APAs in the CE compared to the PE condition (+7.6ms, SE 2.82ms, p=.027).

Estimated mean APA onset times and effect sizes of these analyses are depicted in **TABLE 1**.

Table 1. *Estimated means of APA onset latencies*

Muscle	condition	Task	EM(ms)	SD(ms)	N	Difference RAM1-2 (ms)	P-value	ES
IO/TrAi	NE	RAM 1	1.3	17.84	14	.2	.952	.011
		RAM 2	1.5	18.24	15			
	PE	RAM 1	2.8	19.11	17	3.3	.308	.186
		RAM 2	-.5	16.89	12			
	CE	RAM 1	5.1	18.29	15	2.4	.459	.132
		RAM 2	2.7	17.84	14			
IO/TrAc	NE	RAM 1	-26.8	19.95	6	6.8	.234	.300
		RAM 2	-20.0	23.92	10			
	PE	RAM 1	-23.4	24.77	11	1.3	.797	.055
		RAM 2	-22.1	22.03	8			
	CE	RAM 1	-16.2	22.96	9	2.7	.609	.115
		RAM 2	-18.9	23.81	10			
EOi	NE	RAM 1	-7.0	26.46	16	7.2	.100	.266
		RAM 2	.2	27.61	18			
	PE	RAM 1	-5.4	28.18	19	2.0	.643	.072
		RAM 2	-3.4	26.47	16			
	CE	RAM 1	.9	26.44	16	6.4	.141	.239
		RAM 2	-5.5	27.62	18			
EOc	NE	RAM 1	-14.2	22.67	15	.4	.930	.017
		RAM 2	-13.8	24.03	18			
	PE	RAM 1	-17.9	24.03	18	1.9	.687	.082
		RAM 2	-19.8	21.70	13			
	CE	RAM 1	-14.2	23.11	16	1.0	.814	.044
		RAM 2	-13.2	23.99	18			
MFi	NE	RAM 1	-24.7	18.02	9	4.6	.298	.261
		RAM 2	-20.1	17.36	8			
	PE	RAM 1	-20.5	17.36	8	.7	.868	.044
		RAM 2	-19.8	17.31	8			
	CE	RAM 1	-24.1	15.82	6	5.8	.316	.365
		RAM 2	-18.3	15.83	6			
MFc	NE	RAM 1	-20.8	16.51	10	5.5	.112	.347

Muscle	condition	Task	EM(ms)	SD(ms)	N	Difference RAM1-2 (ms)	P-value	ES
		RAM 2	-15.3	15.21	8			
	PE	RAM 1	-18.3	17.19	11	6.2	.099	.384
		RAM 2	-12.1	13.73	6			
	CE	RAM 1	-16.5	14.53	7	.6	.865	.037
		RAM 2	-17.1	16.59	10			
ILTi	NE	RAM 1	.5	16.46	17	1.5	.704	.087
		RAM 2	-1.0	16.49	17			
	PE	RAM 1	-6.2	4.15	15	3.6	.367	.227
		RAM 2	-2.6	4.22	14			
	CE	RAM 1	4.4	4.07	16	2.4	.548	.149
		RAM 2	2.0	4.22	14			
ILTc	NE	RAM 1	-15.7	17.84	19	.4	.876	.020
		RAM 2	-15.3	18.21	20			
	PE	RAM 1	-15.1	18.21	20	.1	.990	.001
		RAM 2	-15.2	18.21	20			
	CE	RAM 1	-15.5	18.21	20	.6	.792	.033
		RAM 2	-16.1	17.84	19			

Abbreviations: c, contralateral; CE, cognitive exertion; EM, Estimated Mean; EO, External Oblique; ES, Effect Size (Cohen's d); i, ipsilateral; ILT, Iliocostalis Lumborum pars Thoracis; IO/TrA, Internal Oblique/Abdominal Transverse; N, sample number; NE, no exertion; PE, physical exertion; RAM, rapid arm movement task; SD, standard deviation; MF, Multifidus.

4 Discussion

This study found no effects of PE and CE on mean APA onset latencies of the trunk muscles during RAM in healthy people.

As the current study did not find evidence that PE influences the mean APAs of trunk muscles, it does not fully support previous findings of a pilot study[4] which on the one hand also found no effect on APAs of the IO/TrA, but on the other hand indicated earlier APAs of the EO following a fatiguing isometric trunk extensor task. However, the latter study was only performed on a sample of four participants.

Importantly, this is the first study that examined effects on the MF with surface EMG. However, as depicted in **TABLE 1**. rather low effective sample sizes for this muscle were attained, as high baseline activity of the MF and possibly cross-talk of more superficial muscles in several participants often made it impossible to detect a clear onset. Hence future studies are necessary to confirm that the MF mean APAs are not affected by PE. Especially, because the MF has a primordial role in segmental control and trunk stabilisation[26, 33, 43, 70]. As APAs of the deep, but not the superficial, parts of the MF are often delayed in low back pain patients[52], and fatigue complaints have also been described in this population[31, 72], further research regarding the fatigability of the MF and whether it affects APAs could be interesting from a clinical point of view. It would be advisable for future studies to use fine-wire EMG, which specifically allows to study the superficial and deep fibres of the MF. Furthermore, this technique could diminish drop-out based on cross-talk.

Previous studies have described earlier APAs for the Erector Spinae muscles following PE[63, 76-78], which is not in line with the non-significant findings for the ILT in the current study. However, there were important methodological

differences between these studies and the current study, making comparability difficult. For instance, other PE tasks (i.e. concentric dead-lifts[76], aerobe exertion[78], isokinetic lower limb exercises[77], or electrically induced fatigue of the AD[63]), and other types of APA-eliciting movement tasks (i.e. bilateral reach[76-78] or loaded arm movements[63]) were performed. Furthermore, none of these studies exerted both the abdominal and paravertebral muscles.
This was also the first study to examine effects of fatigue induced by CE on APAs of the trunk muscles, and analogue to the PE results no effects were found. Similarly, previous research in knee muscles also found unaltered neuromuscular function after CE.[68]
In conclusion, based on the current study no indications for altered APAs due to fatigue, either induced by PE or CE, were found. In contrast, previous research did find reduced endurance times of physical tasks after CE[55, 68], which could indicate that CE can indeed affect movement performance even though APAs are unaffected. Therefore, it is hypothesised that the influence of CE on movement performance is not through physiological adaptions in motor control, but rather by reduced motivation induced by CE[66, 69]. A similar hypothesis can be made for fatigue induced by PE as diminished movement performance was also described after PE in the past[30, 32, 65]. While in the current study effects of PE and CE on feedforward activation of the trunk muscles were studied, which is one of the mechanisms of the motor control system, and no effects were found, this does not exclude the possibility that fatigue might influence other mechanisms which contribute to trunk motor control. For instance, amplitude properties or variability of APAs could be examined in the future to examine whether these are altered after PE and CE.

Two manipulation checks were examined before addressing the main research questions. First, it was ascertained whether the fatigue-inducing condition indeed had a sufficient fatiguing effect. Based on previous literature, the tasks chosen to induce PE[21, 64] and CE[69] were valid for this purpose. Furthermore, in the current study the participants considered these tasks as heavily exerting, whereas the NE condition was considered not exerting. Self-reported state fatigue increased following both PE and CE, but the difference was only significant for PE. Even though self-reports are the only measures considered to be able to really assess fatigue[29], other measures like EMG median frequency[3, 21, 64, 73] or wavelet analysis[7] could be valuable in future research to objectify the performance fatigability of the PE used to induce fatigue. Furthermore, even though no participants in this study reported pain as a main reason for discontinuation of the PE tasks, pain was not explicitly assessed in this study. This is recommended for future research as pain and effort might confound the fatigue effects of these tasks. Additionally, analysis of Stroop scores could be useful as well to obtain more objective assessment of CE. Although these analyses were not possible in the current study, they are recommended for future studies. In this study, the duration of the fatigue-inducing tasks was standardized to 45 minutes to neutralize differences due to time between conditions. Based on previous studies, performance of the PE until exhaustion would last 3-5 minutes on average[80]. Therefore, the PE was commenced after 40 minutes of rest and was performed until exhaustion, whereas the CE had a fixed duration of 45 minutes. The fatigue experience is dependent on the cost-benefit balance of the exertion.[9] The costs for a PE until exhaustion possibly weighed more than that of the 45-minute CE task. This might explain why self-reported state fatigue after the CE task was not increased to the same extent as following the PE task.
Second, although APAs are consistent patterns that should be present in healthy adults, there is often an acquisition phase for the specific task used to evoke APAs. This might lead to differences in mean APA onsets between subsequent RAM performances.[50] However, the current study showed that repeated performance of the RAM without exertion in between (NE condition) did not alter the means of APAs of the trunk muscles, because sufficient practice trials were performed beforehand to counter these possible acquisition effects. This implies that APAs can be assessed multiple times during one session, while remaining consistent.

An important consideration of these results is the decrease in the effective sample remaining for statistical analysis after visual picking, mainly regarding the bilateral MF and the contralateral IO/TrA APAs. Due to high baseline activity in these muscles the required minimum of five trials with a clear onset detection in order to attain a reliable APA measure was often not acquired during visual picking, explaining these diminished samples. This highlights an

important challenge for future research in this matter to further look for ways to diminish baseline activity in these muscles during RAM in order to avoid losing trials for analysis. Especially, since effect sizes of APA differences due to fatigue in the current study were small, which already indicates that for future research larger samples should be included. However, this could not be anticipated as the included sample in this study amply met the required a priori sample size calculations. Furthermore, a high between-trial variability in APAs is often reported[14, 35, 38] and might explain the considerably large standard deviations seen in this data. As only healthy, young adults were examined in this study, in order to rule out ageing effects, the findings might not be generalizable to older or clinical populations, which might have less recuperation after fatigue. For future research, it would be interesting to examine fatigue in other populations to see whether the results of this study are generalizable. Older adults for example or people with (chronic) pain complaints are thought to have less recuperation capacity after fatigue than a healthy, young adult group. Furthermore, exploration of the influence of fatigue on the brain and central factors related to movement preparation might be valuable for future research as well.

5 Conclusion

This was the first study conducting an integrative analysis and comparison of fatigue induced by both PE and CE on the APAs of multiple trunk muscles which have an important role in trunk motor control. As no fatigue effects were found it is hypothesized that the influence of fatigue on impaired movement performance might not be through physiological adaptions in motor control, but rather by reduced motivation. However, even though the PE and CE tasks used here were deemed valid for inducing fatigue, effect sizes of these results were small and thus need further confirmation. Furthermore, future research is recommended to examine amplitude properties and variability of APAs, as well as studying other populations such as older adults or (chronic) pain sufferers in relation to PE and CE.

6 References

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PHYSICAL OR COGNITIVE EXERTION DOES NOT INFLUENCE CORTICAL MOVEMENT PREPARATION FOR RAPID ARM MOVEMENTS

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Abstract

Fatigue has negative effects on movement performance through its associations with diminished cognitive and/or motor task performance. The influence of fatigue on movement preparation has mostly been examined on a peripheral muscle level. The contribution of central factors to movement preparation, such as the contingent negative variation (CNV), and the influence of fatigue on such factors is less examined, even though executive cognitive functions are regarded as key elements in motor control. Therefore, this study measured CNV-amplitude with EEG in 22 healthy humans during a rapid arm movement task (RAM) prior and following three experimental conditions: 1) a no exertion/control condition, 2) a physical exertion, and 3) a cognitive exertion. CNV amplitude was not affected by a single bout of physical or cognitive exertion, nor by the control condition without exertion. Furthermore, no time-on-task effects of the RAM on the CNV were found. Cortical movement preparation was not affected by exertion, which is in contrast to previous findings regarding time-on-task effects of exertion on CNV. Based on the current findings the RAM is deemed suitable to measure cortical movement preparation of gross motor movements, without being affected by learning effects, and physical or cognitive exertion.

Keywords: electroencephalography; contingent negative variation; exertion; central nerve system

1 Introduction

Fatigue is a disabling symptom which causes limitations in physical and cognitive function due to interactions between performance fatigability and perceived fatigability.[25, 53] Different types of exertion can induce fatigue[14, 53], such as physical exertion of the muscles (PE) causing a diminished responsiveness of muscles to neural excitation and consequently a decreased force production[7, 18], and cognitive exertion (CE) which can induce "a psychobiological state with feelings of subjective tiredness and diminished energy[9] that arises when the effort costs for a task begin to outweigh the possible benefits of further continuation of that task"[72]. Consequently, a diminished value is appointed to the effortful task at hand, which leads to decreased motivation and reduced task performance.[72] Limited cognitive function is characterized by disturbed attention, action monitoring and cognitive control processes.[9, 73] The contribution of cognitive function to motor performance and the effect of fatigue on this process should be considered since executive cognitive functions are recognized as key factors in locomotor control.[1] Hence, when these executive cognitive functions are affected by fatigue, alterations in motor performance can occur as a result. In this connection, fatigue is hypothesized to affect movement preparation as it is associated with decreased cognitive and/or motor task performance, e.g. slower reaction times and diminished task accuracy.[8, 43, 45, 65]

Movement preparation is an important part of the motor control system, which plays a paramount role for attaining and retaining optimal balance and postural control.[31] In this regard, movement preparation patterns of the trunk muscles prior to peripheral movements, for instance rapid arm movements (RAM)[4, 61-63] have been examined extensively. During such tasks postural control is challenged by internal perturbation forces, and optimal preparatory activation of the trunk muscles is needed to anticipate and neutralize these forces. However, the contribution of central factors to motor control and the influence of exertion on these factors is less examined. Hence, in this study such a RAM task will be performed to assess a central indicator of movement preparation, i.e. the contingent negative variation (CNV). This is a negative-going slow-wave brain potential which is measured by electroencephalography (EEG).[78] The CNV consists of an early and late phase[16], and arises between one cue warning the participant for a movement to come, and another imperative go cue that signals the initiation of this movement[78]. The early CNV, a first small negative deflection in the EEG-signal, is thought to mainly reflect sensory orienting to the warning cue.[38] The late CNV, a second negative deflection, starts to arise about one to two seconds before the go cue and reaches its peak at the go cue. It represents a combination of anticipation for the sensory processing of the go cue[13, 20, 28, 57, 70], and response preparation for the movement to come[70]. As it is this response preparation or cortical movement preparation that is of main interest for this study, the focus from now on will lie solely on the late CNV.
Regarding PE, acute aerobic exertion was shown not to affect late CNV[24, 64, 69]. The influence of isometric trunk muscle exertion on late CNV was not yet studied. However, the 'Bereitschaftspotential' (BP), which also reflects cortical movement preparation[70], has been shown to increase following isometric hand grip tasks[26, 36, 58]. This increased BP probably reflects enhanced use of attentional resources in order to maintain optimal movement performance despite muscle fatigue, which might diminish performance[6, 26, 36, 58]. Furthermore, other studies also found larger movement-related EEG-potentials in relation to increased perception of effort during physical exertion.[22, 23] Hence, one could hypothesize an increase in the late CNV potential as well.
Regarding CE, previous studies have shown that amplitudes of both the late CNV[8] and the lateralized readiness potential[37], which reflects later stages of motor programming and activation of response execution[49, 52], decrease with time-on-task during CE. However, the effects of a single bout of CE on subsequent movement preparation for RAM has not been examined yet.

As the effects of exertion on cortical movement preparation need further clarification, this study will examine and compare the influence of both PE and CE on movement preparation in healthy adult humans. Therefore, the late phase of the CNV potential will be assessed during preparation of RAM and is hypothesized to increase with PE and to decrease with CE.

2 Methods

2.1 Participants

Twenty-two healthy participants between 18 and 45 years old were recruited for this randomized within-subject crossover trial. Participants were recruited between September 2016 and December 2018 using posters, flyers, social media and mouth-to-mouth advertisement in the Dutch-speaking part of Belgium. People with a history of pain or current pain, traumata or severe pathologies, cardiorespiratory, neurological, vestibular, endocrinologic, psychological/psychiatric, cognitive or sleeping disorders, or color blindness, major surgery, clinically relevant malalignments and deformities, or malignancies were excluded from study participation. Professional athletes, pregnant women or women < one year postnatal were also not eligible. Participants were asked to refrain from alcohol, drugs, and analgesics without prescription 24 hours prior to the experiments and to refrain from prescribed medication two weeks prior to the experiments. In addition, participants were asked not to perform extreme physical or mentally exerting activities 48 hours prior to testing.

2.2 Procedure

The study protocol was approved by the local ethics committee and all subjects provided signed informed consent before the experiments were initiated.

All participants performed two test sessions with minimally five days in between. Three conditions were examined: a no exertion condition (NE) during the first session, and a CE and PE condition (performed in randomized order) during the second session. During the first session, a general questionnaire regarding medical background, administrative and socio-demographic information was administered. Additionally, before each session, participants completed three standardized questionnaires, i.e. the Profile Of Mood States Short Form (POMS-SF), the International Physical Activity Questionnaire (IPAQ) and the Checklist Individual Strength (CIS). Furthermore, possible confounders such as sleep quality and quantity of the week and night preceding each session were also questioned with visual analogue scales (VAS). Subsequently, to evaluate the CNV, an EEG electrode cap was placed on the participants' head. During the first session the RAM procedure was explained and practiced during a familiarization session. Participants were given feedback regarding abdominal muscle relaxation, optimal arm movement performance and velocity. All three conditions were similarly structured: a short instruction phase with 40 practice trials of the RAM, then a first RAM task (RAM1/Pre-exertion) with concurrently EEG measurement, followed by the condition-specific intervention (NE, PE or CE), and concluded with a second RAM task (RAM2/Post-exertion) with concurrent EEG measurement. During the second session a 30-minute rest phase was included between PE and CE conditions. Prior to and following each RAM participants indicated their self-perceived general fatigue on a visual analogue scale (VAS-fatigue). Additionally, ratings of perceived exertion (RPE) of the condition-specific tasks and RAMs were assessed using a Borg scale. An overview of the study protocol is depicted in **FIGURE 1**.

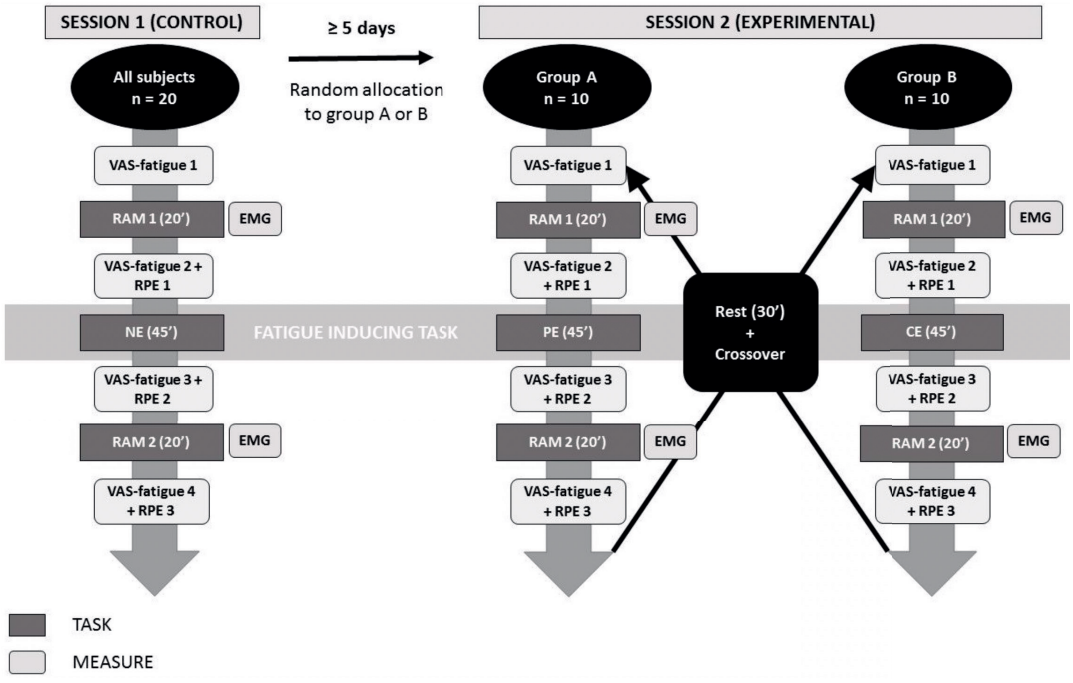

FIGURE 1. Flowchart of the study protocol. Legend: CE, cognitive exertion; n, number of; NE, no exertion condition; PE, physical exertion; RAM, rapid arm movement task; RPE, rating of perceived exertion; VAS-fatigue, visual analogue scale for fatigue.

2.3 Exerting conditions

2.3.1 No Exertion (NE)

To assess possible effects of the mere repetition of the RAM task without exertion in between, a control condition consisting out of 45 minutes relaxed sitting and watching an animated movie was used during the first session.

2.3.2 Physical Exertion (PE)

A combination of a Modified Biering-Sörensen and a Static Abdominal Curl was used during the second session to induce PE of the trunk muscles. Not the arm, but the trunk muscles were exerted, since the latter have a paramount role in postural control and movement preparation in relation to balance perturbations evoked by RAM, as opposed to the prime arm movers of the RAM itself (e.g. Deltoid muscle) which are play less of a role in postural control. During the Modified Biering-Sörensen task participants had to maintain a horizontal prone position of the unsupported upper body as long as possible, while their legs were strapped to a table. This is a validated physical exertion task which has been widely used to assess the endurance capacity of the back extensor muscles[17, 60].

A Static Abdominal Curl was performed immediately afterwards, to exert the abdominal muscles.[60, 71] The unsupported upper body had to be maintained in 45° of trunk flexion, while participants were seated with their legs strapped to a table.

During both tasks participants received standardized motivational cues every 30 seconds. The tasks were discontinued and the endurance times noted when the starting position could no longer be retained, or when participants had to take support or stopped due to pain or discomfort. (**FIGURE 2**)

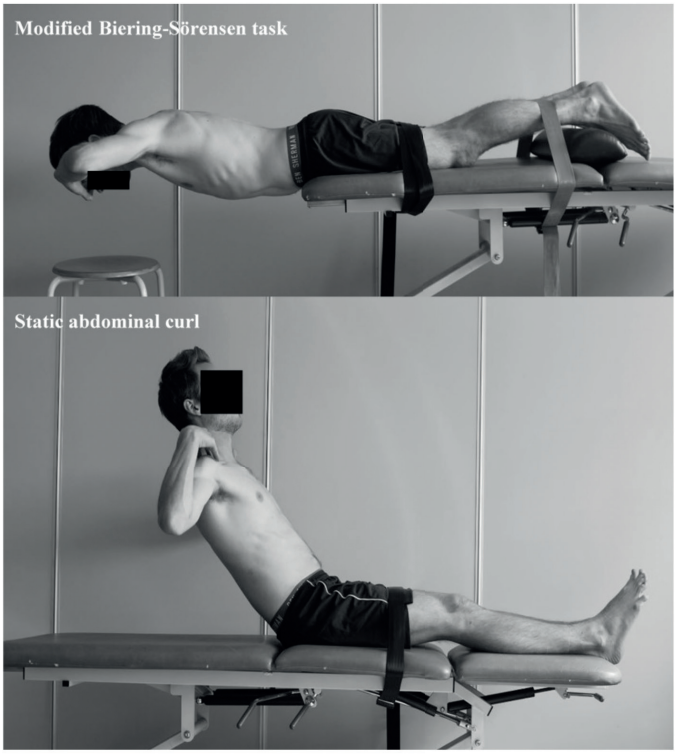

FIGURE 2. Physical exerting tasks.

2.3.3 Cognitive Exertion (CE)

A modified incongruent Stroop task analogue to the one described by Pageaux et al.[54] was used to incite CE during the second session. However, the task duration was extended to 45 minutes in the current study instead of the 30 minutes described by Pageaux et al.[54], as in the latter study for 25% of participants 30 minutes was insufficient to influence RPE ratings[54]. Participants were positioned in a camera monitored, but isolated room in front of a display. Instructions were provided by the examiner, as well as presented on the display. Participants placed their index and middle fingers of both hands on four key letters with a specific colour (red, green, blue and black). When a word appeared on the screen with the font colour green, blue or black, participants had to push the key letter corresponding to the font of the word, hence this was a font dominant task. However, a word in the color red formed an exception. In this case, the task was word dominant and participants had to push the key letter corresponding to the written word instead of the color (i.e. red) of the word. For example, if the word "black" appeared in a red font, participants had to push the black key letter, as the written word and not the font color was dominant in this case. However, if the word "red" appeared in a black font, they had to push the black key letter, as in this case the font color was dominant. Before the task started, participants were given a short training period until they fully understood the task.

2.4 Primary outcome measure: contingent negative variation (CNV)

EEG was measured using a Biosemi ActiveTwo recording system (BioSemi B.V., The Netherlands) with a sampling rate of 2,048 Hz and 64 active electrodes, placed according to the international 10-20 setting (extended). Bipolar electrodes were placed above and below the left eye and next to the outer left and right canthi to measure eye movements and blinks. A common mode sense active electrode and driven right leg passive electrode were used as online reference (CMS-DRL), and electrode offsets at all electrodes were kept between -50 and 50 μV.

In order to assess CNV as a measure for cortical movement preparation, RAM tasks were performed. This RAM task was first described by Hodges et al.[32] and is an often-used, valid and reliable task to induce and assess feedforward preparatory activity of the trunk muscles[46]. Similar tasks have already been used to assess cortical movement preparation as well[44, 68]. Participants were positioned in an upright stance with the feet at shoulder width and relaxed arms alongside their body[56]. A first visual stimulus in the form of a white fixation cross (warning cue) appeared on a display two meters in front of the participant at eye-height[35]. The appearance of a second direction-specific cue (go cue) in a random interval of 1000-1500ms after the warning cue instructed participants to move their dominant arm[34, 35] as quickly as possible back and forth with an extended elbow. The go cue either existed out of an upwards- or downwards-pointing arrow respectively instructing shoulder anterior flexion up to 90°[30] or shoulder extension up to 30°. These two arrows were equally often presented in a randomized order. Each movement was followed by a 12s rest period, during which participants were asked to relax the trunk muscles and to continue regular breathing[34, 35, 47, 48]. The experimental RAM consisted of 40 trials for each movement direction, thus 80 in total, which were presented in a randomized order. Every five minutes a short feedback was implemented to ensure optimal movement performance.

The EEG-channels were referenced to an average of all electrodes. EEG-signals were filtered with a notch filter (50Hz), and second order zero phase shift Butterworth high- (0.01 Hz) and low-pass (30Hz) filters. Subsequently, the continuous data was segmented into stimulus-locked epochs ranging from 200ms before to 1600ms after the fixation cross. Ocular correction according to the Gratton and Coles technique was performed by use of a vertical (VEOG) and horizontal (HEOG) electrooculographic artifact channel, which were calculated based on the external electrodes applied around the eyes of the participants. After that, a semi-automatic artifact rejection (criteria: lowest activity of 0.5µV allowed, maximal allowed voltage step of 50µV/ms and difference of values of 150µV) was performed in order to remove all remaining ocular movements or other artifacts occurring within the epoch timeframe. Baseline corrections were performed based on a 200ms interval preceding the fixation cross, and a second segmentation was carried out to acquire stimulus-locked epochs ranging from -1000ms to +100ms around the onset of the go cue. These epochs were averaged within each subject for each condition. Finally, grand averages per condition were calculated, as well as a collapsed localizer, which is an average of the waveforms of all participants and all conditions[41]. For the grand averages, at least 30 artifact-free trials were required per condition per subject in order for them to be included in the average. At least 6-12 trials are already considered sufficient to attain a clear CNV potential[66], but in order to minimize background noise and influence of artifacts most research in this regard applies at least 30 artifact-free trials for CNV calculation[27, 44].

Visual inspection of the topography of the collapsed localizer confirmed the central topography of the late CNV described in most CNV literature (**FIGURE 3**).[5, 33, 40, 68] Therefore, a cluster of the EEG-channels representing clear late CNV activity, i.e. C1, Cz, C2, FC1, FCz, FC2 was made.[42] Based on previous literature the timeframe for late CNV analysis was defined as the last 100ms preceding the go cue, as this timeframe is thought to be the most sensitive for preparatory activity prior to rapid arm movements[27, 44, 68]. Thus, mean area amplitudes of the aforementioned electrode cluster were exported for the last 100ms prior to the go cue for subsequent statistical analysis, as these have been reported to be an unbiased measure of EEG-amplitude[40].

As a secondary analysis, time-on-task effects were also examined. For this purpose, the continuous data of each RAM task was divided into two equal blocks, an early block representing the first half of the RAM (Block 1) and a late block representing the second half of the RAM (Block 2). For each block mean area amplitudes of the late CNV were calculated and averaged per condition over all participants. In this way the effects of time-on-task could be assessed by comparing CNV amplitude of the late blocks with that of the early blocks.

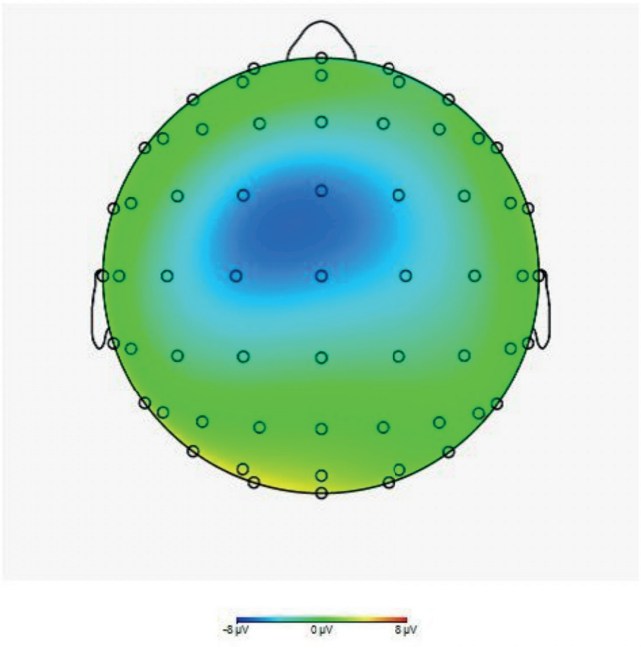

FIGURE 3. Topography of the collapsed localizer for the late CNV

2.5 Secondary outcome measures

The **Profile Of Mood State Short Form (POMS-SF)** assessed the participants' mood states by requiring them to rate 32 words in accordance with their self-perceived mood at that moment.[77] Subscores for affective disturbances regarding depression, anger, fatigue, tension and vigour, and a total score were obtained, with higher scores corresponding to higher mood disturbance. The POMS-SF has been shown to be highly valid, and sufficiently consistent and reliable.[21]

The **International Physical Activity Questionnaire (IPAQ)** indexes the physical activities participants performed during the previous 7 days to estimate their level of physical activity.[10, 67] The minutes per week spent on work, household, transport, leisure activities, sitting and walking was multiplied by a factor corresponding to the strenuousness of these activities in order to calculate metabolic equivalents (METs). This questionnaire has a decent validity and adequate reliability.[19, 74]

The **Checklist Individual Strength (CIS)** consists of 20 questions about fatigue and behavioral aspects related to fatigue for the previous two weeks.[75] Subscales regarding subjective fatigue (score range 8-56), concentration (score range 5-35), motivation (score range 4-28) and physical activity (score range 3-21), as well as a total score for general fatigue severity (score range 20-140) were calculated. Higher scores correspond with more fatigue and less concentration, motivation and physical activity. Regarding total fatigue severity low, moderate and high fatigue respectively correspond with scores of <27, 27-35, and >35 75. Excellent validity and reliability were described for the CIS.[75, 76]

Ratings on a **visual analogue scale for fatigue (VAS-fatigue)** were administered before and after each RAM. Participants were required to indicate their self-perceived fatigue on a 10 cm continuous horizontal scale ranging from 'no fatigue' to 'highest imaginable fatigue'.

The **ratings of perceived exertion (RPE)** scale assessed the self-perceived exertion caused by the RAMs and condition-specific interventions. Participants had to indicate a score between 6 (no exertion) and 20 (maximal exertion).[2, 11, 12]

2.6 Statistical analysis

Data were analyzed using IBM SPSS Statistics 25 (IBM Corp., Armonk, N.Y., USA) with the significance level set at 0.05. Baseline descriptives were calculated and the normality of data distribution was assessed with the Shapiro-Wilk test.
A priori sample size calculations based on an articles describing the influence of isometric hand grip muscle exertion on CNV area under the curve resulted in a minimum of 19 participants needed to attain a power of 0.80 with significance level .05.[58]

RPE-ratings were compared between conditions with a Friedman test and post-hoc Wilcoxon signed-rank tests with Bonferroni correction.

To answer different research questions several linear mixed model analyses were conducted, for which following factors were defined: condition (NE – PE – CE), task (RAM 1 – exerting task – RAM 2) with RAM1 and RAM2 respectively representing the RAM performed before and after the exerting task, time to task i.e. whether the outcome variable was measured prior to or following the examined task (Pre task – Post task), and block (Block 1 – Block 2) with each block representing half of the trials performed during one RAM task, respectively the first and last half of trials. The influence as possible confounders of sex, age, IPAQ MET scores, hours of sleep/week, hours of sport/week, VAS sleep quality the night/week before testing, hours of sleep the night before testing, VAS-fatigue ratings, RPE ratings, CIS and POMS subscale and total scores, was examined by evaluating how they affected the model fit. If adding a factor diminished the Akaike's Information Criterion with at least 10 points and/or if it had a significant main effect on the model, it was deemed as a confounder and kept in the analysis to improve the model fit.
Concerning VAS-fatigue, a linear mixed model analysis with VAS-fatigue as the dependent outcome, condition (NE-PE-CE), task (RAM1-exerting task-RAM2) and time to task (Pre-Post task) as the fixed factors, and a random intercept on subject level with a variance components covariance type was carried out.
To examine whether exertion would influence CNV amplitude, a linear mixed model analysis was performed with CNV mean amplitude of the last 100ms before the go cue as the dependent outcome, factors condition (PE-CE) and RAM task (RAM1-RAM2), the CIS-fatigue subscore as a covariate, and a random intercept on subject level with a variance components covariance type. In order to assess whether the repetition of the RAM itself would influence the CNV when NE was induced between two RAMs, an identical analysis was performed, with the exception that only NE as factor condition was used. Furthermore, Cohen's d_{av} effect sizes were calculated for each condition comparing the difference in the estimated means of CNV amplitude from RAM1 to RAM2. Cohen's dav effect sizes can range from very small (0.10), small (0.20), medium (0.50), large (0.80) up to huge (2.0).[15] Hedges' g correction , using the sample size of the RAM1 measurement as a standardizer (Glass' delta), was applied to these effect size calculations, as this is recommended for studies with small sample sizes.[39]
To examine time-on-task effects within one RAM performance a mixed model with the CNV mean amplitude of the last 100ms before the go cue as dependent outcome, fixed factors condition (PE-CE), RAM task (RAM1-RAM2) and block (Block 1–Block 2), VAS sleep quality the night before testing as a covariate, and a random intercept on subject level with a variance components covariance type was performed.
Post-hoc comparisons for linear mixed model analyses were performed using Bonferroni corrections.

3 Results

3.1 Confounding influences

The data of 21 participants were analyzed, as one participant fainted during testing and was excluded from data analysis. Baseline characteristics of drop-outs are not described, but were not significantly different from the other participants. The only factor that significantly affected the model fit was the CIS-fatigue subscore, which was thus retained as a covariate. Baseline characteristics and between session comparisons of other descriptives are displayed in TABLE 1 and TABLE 2.

TABLE 1. *Baseline characteristics (N = 21)*

		Mean	SD	N
Age (y)		21.76	1.221	
Gender	Male			11
	Female			10
Handedness	Right			19
	Left			2
Height (cm)		174.43	8.155	
Weight (kg)		65.90	10.119	
BMI (kg/m²)		21.54	1.984	
Education (y)		15.50	1.378	
Sport (hrs/w)		3.45	2.876	
Sleep (hrs/n)		7.69	.798	

Abbreviations: hrs/n, hours per night; hrs/w, hours per week; SD, standard deviation.

TABLE 2. *Questionnaire scores*

	Session 1		Session 2		Session diff.
	Mean	**SD**	**Mean**	**SD**	**P-value**
Mean Sleep Quality (VAS)	6.8	1.30	5.9	1.63	**.020**†
Sleep Quality day before session (VAS)	6.8	1.55	6.4	1.49	.357†
Hours of sleep/week	7.6	.88	7.3	.77	.146†
Hours of sleep day before session	7.1	.75	6.9	1.43	.608*
POMS-depression	.7	1.01	.6	1.47	.601†
POMS-anger	.8	1.41	1.5	2.75	.056†
POMS-tension	2.1	2.09	1.5	2.70	.094†
POMS-fatigue	2.1	2.33	2.9	3.46	.228†
POMS-vigour	12.3	2.83	10.8	4.56	.134*
POMS-total	18.0	5.64	17.3	8.18	.613†
CIS-fatigue	20.2	6.67	23.6	9.29	**.011***
CIS-concentration	13.2	5.68	14.8	7.15	.867†
CIS-motivation	10.3	3.69	12.1	4.47	**.021***
CIS-activity	8.1	2.63	8.2	2.98	.876*
CIS-total	35.6	12.36	42.2	17.75	**.004***
IPAQ-total work	1461.6	3374.68	1250.51	2634.03	.779†
IPAQ-total transport	645.1	433.73	815.0	806.20	.841†
IPAQ-total domestic & garden	105.8	139.62	248.8	709.20	.955†
IPAQ-total leisure	725.7	613.64	774.0	989.14	.619†
IPAQ-total walk	718.1	997.35	1068.6	1312.01	.095†
IPAQ-total moderate	951.5	1288.61	827.4	849.62	.494†
IPAQ-total vigorous	1268.6	3049.52	988.6	1435.50	.919†
IPAQ-total physical activity	2938.2	3748.35	3273.5	3246.52	.455†
IPAQ-total sitting/week	2567.1	996.96	2594.3	946.96	.911*
IPAQ-total sitting/day	366.7	142.42	370.6	135.28	.911*

Legend: CIS, Checklist Individual Strength; IPAQ, International Physical Activity Questionnaire; POMS, Profile Of Mood States; SD, Standard Deviation; VAS, visual analogue scale.

** paired student's t-test*

† Wilcoxon matched-pairs signed-ranks test

Bold figures display significance at the p <.05 level.

3.2 Effects of repetition of the RAM on CNV

The mere repetition of a RAM task (NE condition), which was performed as a control condition, did not alter mean amplitude of the late CNV in the 100ms interval prior to the go cue (p = .329). Furthermore, comparing late CNV mean amplitude during the RAM before exertion (RAM 1) between different conditions (NE-PE-CE) also did not show significant differences between repeated RAMs (p = .649). Estimated means of the CNV are depicted in **TABLE 3.**

TABLE 3. *Estimated means of CNV amplitude*

Outcome	Condition	Task	EM(μVms)	SD(μVms)	N	95% CI	Difference RAM1-2 (μVms)	P-value	ES
CNV	NE	RAM 1	-5.2	4.90	20	-7.4,-3.0	1.3	.329	.262
		RAM 2	-3.9	4.66	20	-6.0,-1.8			
	PE	RAM 1	-5.3	4.10	16	-7.4,-3.3	.3	.732	.076
		RAM 2	-5.0	4.31	21	-6.9,-3.1			
	CE	RAM 1	-6.1	4.19	18	-8.1,-4.1	1.5	.115	.342
		RAM 2	-4.6	4.28	20	-6.5,-2.6			

Abbreviations: CE, cognitive exertion; CI, confidence interval; CNV, Contingent Negative Variation amplitude; EM, Estimated Mean;ES, Effect Size (Hedges' g_{av}); N, sample number; NE, no exertion; PE, physical exertion; RAM, rapid arm movement task; SD, standard deviation

3.3 Fatigue induction

Median RPE scores regarding the NE, PE and CE interventions were respectively 6.5 (range: 6-12), 16.0 (range: 11-18) and 12.0 (range: 7-16). Thus, the NE did not induce fatigue as expected, while the PE related exertion was considered 'very high', and the CE as 'somewhat high'. This was reflected in a significant between-condition difference in RPE scores for the three condition-specific interventions ($\chi^2(2) = 32.141$, $p < .001$). The NE was experienced ass less exerting than both the CE (Z = -1.139, p < .01) and PE (Z = -1.861, p < .01) interventions. Between PE and CE, however, no significant differences in RPE scores were eminent (Z = .722, p = .91). (TABLE 4)

TABLE 4. *Median RPE*

		Condition					
		NE		PE		CE	
		Median	Range	Median	Range	Median	Range
Time	RAM 1	10.0	12.40	9.5	6.00	10.0	9.00
	Exerting task	6.5	6.00	16.0	7.00	12.0	9.00
	RAM 2	10.0	14.70	10.5	8.00	10.0	10.00

Legend: CE, cognitive exertion; NE, no exertion; PE, physical exertion; RAM, rapid arm movement task; RPE, rating of perceived exertion.

The VAS-fatigue mixed model revealed a significant three-way interaction effect of condition x task x time to task (F(4;322.011) = 4.666, p = .001). Post-hoc analyses showed that before RAM1 and right before the condition-specific interventions were performed, VAS-fatigue was not significantly different between conditions. Furthermore, VAS-fatigue was not significantly affected by performance of RAM1 (Pre-exertion). Thus, participants had similar fatigue levels before initiation of the testing and before the exerting interventions. Only the PE task performance led to a significant increase in VAS-fatigue ratings immediately following the intervention (p=.044), whereas NE or CE did not significantly affect the VAS-fatigue. VAS-fatigue ratings were also significantly increased after performance of RAM2 (Post-exertion) during NE (p = .026) and PE (p = .049), but not in the CE condition. **(TABLE 5)**

TABLE 5. *Mean VAS-fatigue scores*

				Condition					
				NE		PE		CE	
				Mean	SD	Mean	SD	Mean	SD
Task	RAM 1	Time	Pre	2.55	1.367	2.67	1.758	3.12	2.042
			Post	3.25	1.471	3.27	2.018	3.47	2.287
	Exerting task	Time	Pre	3.25	1.471	3.27	2.018	3.47	2.287
			Post	2.55	1.505	4.11	2.102	4.06	2.082
		Time	Pre	2.55	1.505	4.11	2.102	4.06	2.082
	RAM 2		Post	3.49	1.908	3.29	1.795	3.43	2.192

Abbreviations: CE, cognitive exertion; NE, no exertion; PE, physical exertion; RAM, rapid arm movement task; SD, standard deviation; VAS-fatigue, visual analogue scale for fatigue.

3.4 Effects of PE and CE on CNV

Neither significant interactions (p = .389) nor main effects were found with mixed model analysis regarding the influence of PE or CE on the late CNV in the 100ms interval prior to the go cue during RAM performance. Thus, the PE and CE inducing conditions did not significantly affect late CNV, nor did the late CNV following PE and CE differ between conditions. Estimated means of late CNV are displayed in TABLE 3 and overlay graphs representing the CNV before and after exertion for channel FCz are depicted in **FIGURE 4**.

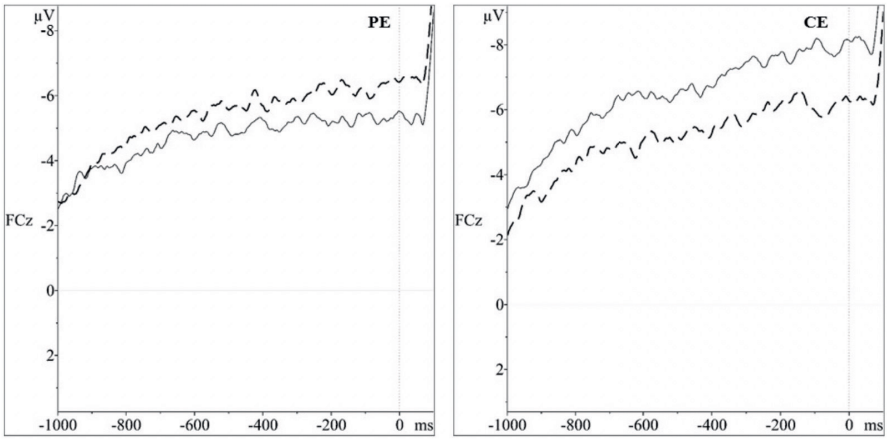

FIGURE 4. Grand average response-locked CNV potential for the physical (left plot) and cognitive exertion (right plot) conditions at the FCz electrode. The solid line represents the pre-exertion amplitude, and the dotted line represents the post-exertion amplitude. Abbreviations: CE, cognitive exertion; PE, physical exertion

3.5 Effects of time-on-task of the RAM on CNV

The time-on-task of the RAM did not affect mean amplitude of the late CNV. In a linear mixed model analysis no significant interactions or main effects were found for any of the fixed factors, i.e. condition (PE-CE, p = .456), RAM task (RAM1-RAM2, p = .310), block (Block 1-Block 2, p = .606). Furthermore, effect sizes for differences between blocks were all very low (< .08).

4 Discussion

This study found no effects of a single bout of PE nor CE on the mean amplitude of the late CNV during RAM performance in healthy people. Furthermore, the mere repetition of a RAM did not affect CNV either.

Trunk muscles play an important role in maintaining balance and posture during trunk motor control tasks. Therefore, exertion of these muscles was thought to impede with maintaining optimal performance of RAMs, which could be reflected by alterations in underlying cortical processes. However, this study found no evidence in line with this hypothesis, as CNV amplitude remained unchanged during such a task. Previous findings concerning the BP potential, however, showed increased BP amplitude after PE.[6, 26, 36, 58] The proposed mechanism behind this increased BP amplitude is that in order to maintain optimal task performance with fatigued muscles, people need to address more attentional resources to prepare for subsequent movements.[6, 26, 36, 58] Several methodological differences between the current study and the BP studies might explain why different observations were made for the CNV. Barthel et al.[6] found decreased BP amplitude after an aerobic exerting task, which rather induces central fatiguing effects than the possibly more peripheral effects of the isometric trunk muscle exertion applied in the current study. In the other BP-studies the PE task and the task for BP assessment were one and the same and exertion effects were studied by examining the effects of 'time-on-task' on the BP potential.[26, 36, 58] In the current study, however, the CNV was measured with a task that primarily addresses arm muscles as prime movers, and which has an indirect effect on the exerted trunk muscles through their function of posture preservation. Thus, even though trunk muscles play a key role in optimal RAM performance as prime posture controlling muscles, it is hypothesized that PE effects might be more task specific with cortical movement preparation for a task only being altered when the prime movers for that task are exerted. In line with a systematic review which indicated that non-localized muscle fatigue, i.e. fatigue effects on rested muscles, is highly variable, but

has the most chance of occurring with high intensity, isometric, cyclical and bilateral exertions of large muscle masses[29] it can also be hypothesized that the PE of the trunk muscles should be of higher intensity and repeated in order to effectively influence movement preparation for RAM. Furthermore, participants were mainly instructed to focus on optimal task performance of the arm movements (i.e. as fast as possible) and not on optimal posture preservation during these movements. Therefore, they might not have invested additional attentional resources towards subsequent movement preparation after PE, but possibly they rather performed these movements with less optimal posture, as PE is known to diminish postural control[55]. Future research could apply kinematic or center of pressure measurements synchronously with EEG to examine this hypothesis.
In studies examining the effects of acute aerobic exercise, similar results as in the current study were found, i.e. no effects on response preparation, reflected by no alterations in CNV amplitude after either cycling[24, 64] or running[69]. In those studies the exerting intervention was also not task-specific for the task used to assess the CNV. Dichotomization of the participants into groups with high vs. low fitness levels in two studies yielded contradictory results with one study finding no effects on CNV[64], whereas the other study stated that CNV area did increase in the frontal area after aerobic exercise, but only in the high fitness group[69]. In the current study, physical fitness was not experimentally examined, but physical activity levels based on the IPAQ-questionnaire did not significantly influence CNV amplitude.

The late CNV amplitude was not altered in response to CE in this study. This is in contrast to a previous study, which found that CNV amplitude diminished with time-on-task during cognitive exerting tasks.[8] In the latter study, the reduced CNV amplitude was thought to be mediated through decreased motivation and attention towards task continuation that occurred due to monotonous cognitive tasks.[8, 50] The fact that in the current study different tasks were performed to respectively induce CE and measure CNV, and that the latter was not cognitively exerting itself, might explain these different findings. The diminished motivation and attention due to the Stroop task might not have transferred to the rather physical RAM, and thus therefore did not affect cortical preparation for trunk muscle activity.
Manipulation checks showed that both the physical and cognitive tasks successfully induced fatigue, as both received significantly higher RPE-ratings than the NE. Furthermore, self-report measures of perceived fatigue increased after performance of the CE and PE tasks but not after NE, but this was only significant for the PE. In previous studies almost the same PE[17, 51] and CE[54] tasks as used in the current study were shown to be valid for inducing fatigue. Other measures like EMG median frequency analysis during PE[3, 17, 51, 59], or Stroop effect analysis during CE, which were not assessed in the current study, could be of additional value as they provide more objective indications of the induced exertion. Nonetheless, even such measures do not guarantee full objectivity. For instance, highly motivated people often retain task performance on the Stroop task despite fatigue. For such people, only self-reports are able to indicate the experienced exertion.

The fact that the level of self-perceived fatigue was not equal for the PE and CE task has to be taken under consideration. We avoided differences between conditions with regards to the time intervals between two RAMs. Therefore the duration of the NE and the CE tasks was fixed at 45 minutes. As the PE was performed until individual exhaustion a fixed time could not be used. Hence, the PE task was initiated after 40 minutes of rest, as previous research described average endurance times for this task between 3-5 minutes on average[71], and thus the total interval would amount to approximately 45 minutes. As it is the cost-benefit balance of the exertion that determines the fatigue experience[9], and the costs of the 45-minute CE task possibly weighed less than a PE until exhaustion, this might explain why the self-perceived fatigue after CE did not increase to a similar extent as after PE and did not reach significance. Another important consideration is that for both the exerting conditions in the RAM before exertion (RAM1) the a priori determined sample size was just missed due to loss of data because of technical issues or too many artifacts which could have diminished the power of pre-post exertion analyses.

Additional analyses were performed for two purposes. First, it had to be assessed whether the mere repetition of the RAM itself, without exertion, had an influence on cortical movement preparation. The analysis of the NE condition

and the comparison of RAM1 between conditions revealed no such effects, and indicated that the CNV remained stable between subsequent repetition blocks. This was achieved by implementing practice trials before the experimental phase, which already optimized the learning process or other improvements in movement preparation due to repetition of the RAM. Second, in the scope of the current study a time-on-task design would have been unfit to separate CE and PE effects during the RAM. Nevertheless, a secondary analysis on the data of the current study was performed to assess time-on-task effects over the course of each RAM task, as time-on-task effects have been frequently used as an outcome measure of fatigue in previous literature. No time-on-task effects were found when comparing CNV amplitudes of early with later trials of the RAM in this study. It has to be considered that only two blocks (early vs. late trials) were studied for this analysis, but, as the division of the EEG-data into two blocks for this analysis already substantially lowered the power, division of data into more and smaller blocks was deemed unreliable. In previous studies time-on-task effects on the BP amplitude were described to be dependent on the task intensity, i.e. heavily exerting isometric tasks (>70% of maximal voluntary contraction) led to a decrease in BP amplitude[26, 36, 58], whereas less exerting intensities (50% of maximal voluntary contraction) did not affect BP[26]. Even though the PE task used in the current study was highly exerting, the RAM task itself was of low intensity. Thus, the results of unaltered CNV amplitude with time-on-task of the low-intensity RAM in the current study were in line with the previous BP literature.

As this study found no influences of repetition nor time-on-task of the RAM itself on CNV amplitude, it could be deemed a suitable task to measure cortical movement preparation of gross motor movements in a consistent way, without being affected by learning effects, CE or PE. The current study findings indicate the RAM task can be applied in different settings, both experimental and clinical, without high risk of confounding effects of prolonged task performance on cortical movement preparation. However, this statement only applies to RAM performances lasting up to 20 minutes in healthy, young adults. Furthermore, physical or mental exertions performed before a test protocol should not influence the subsequent RAM assessment. Furthermore, since effect sizes of CNV amplitude differences due to fatigue in the current study were trivial to small, no strong conclusions can yet be made and future research with larger samples should be performed.

For future research it would be recommended to examine the CNV after repeated PE of the trunk muscles with high intensity (100% contraction) to further explore non-localized and non-task specific fatigue effects on movement preparation. Furthermore, RAM performance following exerting tasks that highly resemble the RAM task itself, but still are able to distinct between both types of exertion would be interesting as well. For instance, concentric or isometric arm movements for the PE task and a Go-No-go computer task for the CE. While, these type of tasks would target other muscles and cognitive processes than the Biering-Sörensen and the modified incongruent Stroop color-word task, they would allow to examine whether the specificity of the exerting task plays a role in the amplitude of the CNV after exertion.

5 Conclusion

This study was the first to show that neither a single bout of PE nor CE affected the late CNV amplitude during preparation of rapid arm movements, even though fatigue effects were expected based on previous literature. Cortical preparation for gross motor movement was not influenced by exertion when the properties of the exerting task and the task used to assess CNV were different. Thus, exerting effects might be task-specific in this regard. Future research could examine this further by developing specific PE and CE tasks tailored to the properties of the RAM task. Additionally, as no time-on-task or learning effects of the CNV during RAM performance were found, it is considered an appropriate task to measure cortical movement preparation of gross motor movements in a consistent way.

6 References

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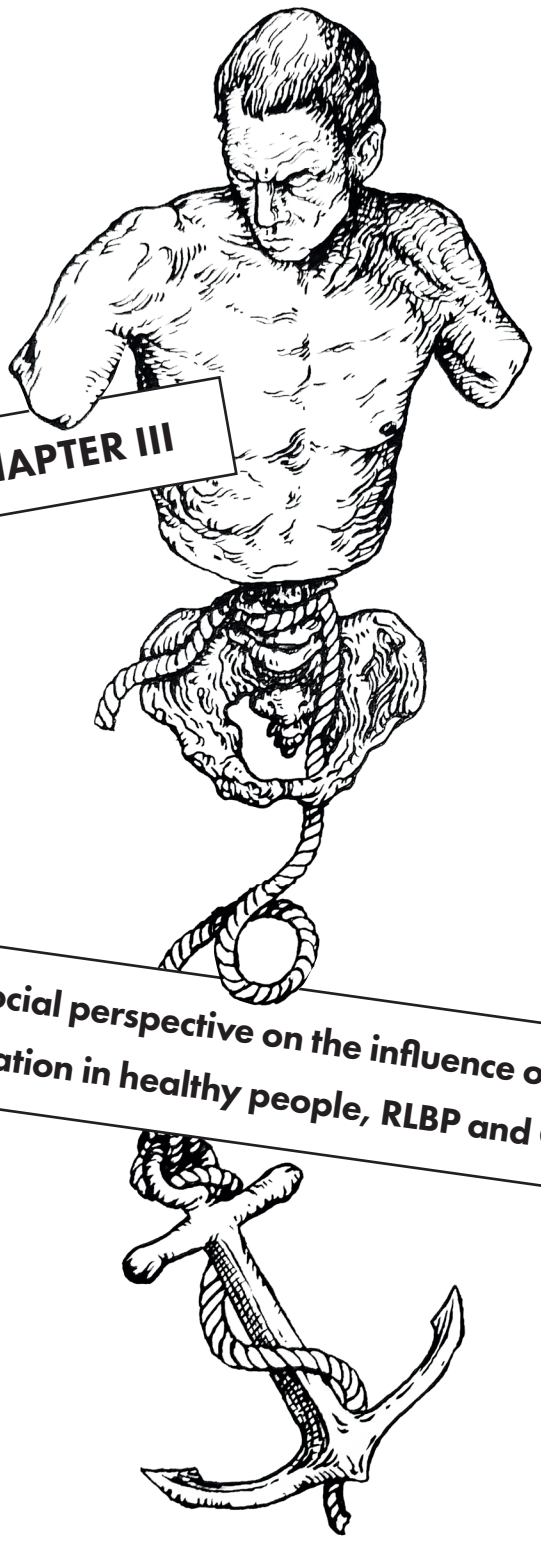
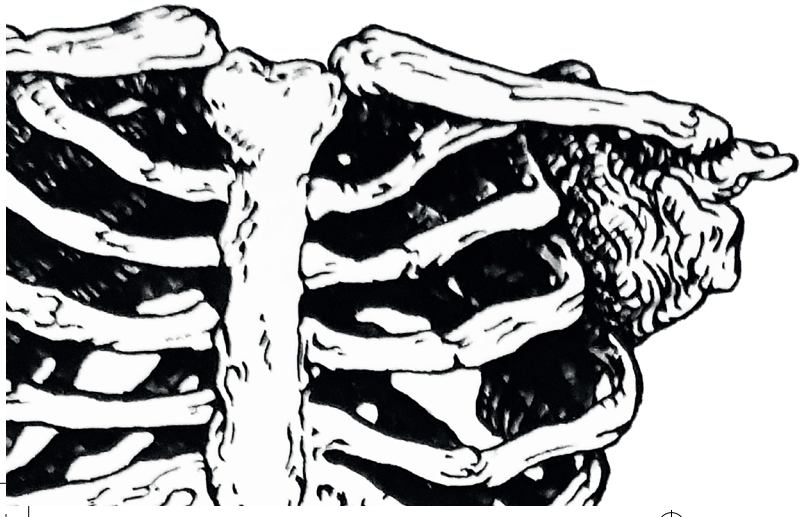


CHAPTER III

A biopsychosocial perspective on the influence of fear on movement preparation in healthy people, RLBP and CLBP patients



DOES EXPERIMENTALLY-INDUCED PAIN-RELATED FEAR INFLUENCE CENTRAL AND PERIPHERAL MOVEMENT PREPARATION IN HEALTHY PEOPLE AND LOW BACK PAIN PATIENTS?

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Abstract

Non-specific chronic low back pain (CLBP) is a multifactorial disorder. Pain-related fear and altered movement preparation are considered to be key factors in the chronification process. Interactions between both have been hypothesized, but studies examining the influence of situational fear on movement preparation in low back pain (LBP) are wanting, as well as studies differentiating between recurrent LBP (RLBP) and CLBP. Therefore, this study examined whether experimentally-induced pain-related fear influences movement preparation. In healthy controls (n=32), RLBP (n=31) and CLBP (n=30) patients central and peripheral measures of movement preparation were assessed by concurrently measuring trunk muscle anticipatory postural adjustments (APA) with EMG and Contingent Negative Variation (CNV) with EEG during performance of rapid arm movements (RAM). Two conditions were compared, one without (no fear) and one with (fear) possibility of painful stimulation to the back during RAM. Visual analogue scales were used to assess pain-related expectations/fear in both conditions. The experimentally-induced fear of pain during movement performance led to an increase in CNV-amplitude, which was similar in all three groups. Concerning APAs no effects of fear were found, but group differences with generally delayed APAs in CLBP compared to controls and RLBP patients were evident. These results suggest that with fear an attentional redirection towards more conscious central movement preparation strategies occurs. Furthermore, differences in movement preparation in RLBP and CLBP patients exist, which could explain why RLBP patients have more recovery capabilities than CLBP.

Key words: sensorimotor control; anticipatory postural adjustments; central nerve system; contingent negative variation; fear; musculoskeletal pain

1 Introduction

The chronification process of non-specific low back pain (LBP) remains elusive. Due to its multifactoriality examining multiple mechanisms could yield additional insights.

One mechanism often hypothesized to contribute to LBP recurrence/persistence is altered trunk muscle activity, which can affect postural control. Anticipatory postural adjustments (APAs) arise in anticipation of predictable voluntary movements[34, 49], e.g. the rapid arm movements (RAM) examined in this manuscript, and contribute to retaining balance and posture[44]. Delayed trunk muscle onsets have been observed in experimentally-induced[60] and clinica[l60, 114] LBP, and often remain present in LBP patients in remission[114], suggesting their mechanistic role in the recurrence/chronification of LBP. However, to confirm this prospective studies examining the possible predictive value of altered APAs in LBP recurrence/chronification are needed.

Besides altered trunk motor control, pain-related fear is also considered to influence LBP chronification.[46, 127] Interactions between both components have been evidenced in healthy people, as anticipation and fear for experimentally-induced LBP result in delayed trunk muscle onsets[82]. Contrastingly, in chronic LBP (CLBP) fear leads to earlier back muscle onsets[63], while results on the abdominals seem dependent on the type of fear and muscles studied[53, 63]. In the aforementioned clinical LBP studies dispositional properties of fear (=person-inherent traits) were examined, whereas the study in healthy people assessed situational fear (=context-specific states).[13, 41, 106, 107] Hence, we speculate that both fear constructs incite different postural strategies, explaining the contrasting APA findings. LBP could also play a role in this, but research exploring the effects of situational fear on APAs in LBP is needed.

Peripheral movement preparation is suggested to be pre-programmed centrally[76], and altered APAs of the trunk muscles have been shown to correlate with functional reorganization in the motor cortex[117]. In this regard, measures for cortical movement preparation have been studied. Specifically, the late phase of the Contingent Negative Variation (CNV) EEG-potential has been examined, which reflects feedforward movement preparation[120] and anticipation of imperative stimuli indicating movement initiation[12, 22, 33, 100, 120]. Both experimentally-induced[54] and clinical[101] LBP have shown to increase CNV-amplitude. This larger CNV is suggested to be related to altered postural strategies in LBP, which likely require more attention/effort.[101] One study in RLBP/CLBP patients did indeed observe delayed trunk muscle APAs alongside larger CNV-amplitudes, but these measures did not correlate.[101]

In healthy people larger CNV-amplitudes have been depicted in anticipation of painful stimulation[2, 3], and larger stimulus-preceding negativity was seen when fearful pictures were presented[93]. When fear is associated with pain anticipation in CLBP, it is thought to be more disabling than pain itself[21]. However, the impact of pain- or movement-related fear on CNV-amplitude has not been examined. As the contribution of psychological factors has been suggested to enhance progressively from RLBP to CLBP[66], the impact of pain-related anticipation and fear on peripheral and central movement preparation might depend on pain chronicity.

We hypothesize that experimentally-induced pain-related fear leads to delayed trunk muscle APAs and larger CNV-amplitudes during movement preparation of RAM, that these alterations are associated with each other and are increasingly present from healthy people, to RLBP and ultimately CLBP.

2 Methods

2.1 Participants

Three groups, i.e. healthy controls (HC), non-specific RLBP, and non-specific CLBP sufferers were studied. All groups consisted of male and female participants between 18 and 45 years of age. Participants were recruited between February 2017 and April 2018 using posters, flyers, social media, general practitioner referrals and word-of-

mouth advertisement in the Dutch-speaking part of Belgium. Healthy participants were defined as people without a recent history of pain (<2y) or current pain in the lumbar area and the adjoining structures. With regards to the LBP groups, only non-specific complaints, i.e. characterized by the absence of any patho-anatomical explanations for the complaints at hand, were included[72]. Furthermore, the LBP complaints had to interfere with performance of activities in the daily life and patients had to have sought medical help concerning their complaints in the past. RLBP sufferers were defined as people experiencing episodic LBP with a first onset of at least six months ago and a minimum of two pain episodes per year. One pain episode is characterized by minimally 24 hours of pain, followed by a pain free period of at least one month[25]. In the current study, these RLBP patients were tested during a pain free stage. CLBP sufferers had to experience continuous LBP for at least three days per week[27], with an initial onset of at least three months ago[48], and without prolonged pain free periods in-between complaints.
General exclusion criteria for all three groups were: severe pathologies or traumata, cardiorespiratory, neurological, vestibular, endocrinologic, psychological/psychiatric, cognitive or sleeping disorders, or color blindness, major surgery to the spine or upper limbs, clinically relevant malalignments and deformities, nor malignancies. Additionally, professional athletes, pregnant women or women less than one year postnatal were not eligible. Participants were asked to refrain from alcohol, drugs, and analgesics without prescription 24 hours prior to the experiments and to refrain from prescribed medication two weeks prior to the experiments. In addition, participants were asked not to perform extreme physical activities 48 hours prior to testing.

2.2 Procedure

The study protocol was approved by the ethics committee from the University Hospital Ghent/Ghent University and all participants provided signed informed consent before the experiments were initiated.

A general questionnaire regarding medical background, administrative and socio-demographic information was administered. Additionally, all participants completed five standardized questionnaires, i.e. the Central Sensitization Inventory (CSI), the Hospital Anxiety and Depression Scale (HADS), the International Physical Activity Questionnaire (IPAQ), the Pain Catastrophizing Scale (PCS), the Pain Vigilance and Awareness Questionnaire (PVAQ), and the Tampa Scale for Kinesiophobia (TSK). LBP patients were also required to fil out the Roland-Morris Disability Questionnaire (RMDQ) and a self-developed pain-specific questionnaire registering information on the nature of their LBP complaints. All questionnaires were in Dutch. In addition, LBP patients underwent a clinical examination to ensure their LBP was non-specific.

After these initial assessments, the experiments were conducted, existing out of electroencephalography (EEG) and surface electromyography (sEMG) measurements of feedforward movement preparation during a RAM task. These measures were performed during two different conditions: a fear, and a no fear condition, respectively with and without experimental threat of LBP inducement. In the fear condition, the threat to experience experimentally-induced LBP during RAM performance was created by conditioning the participants with visual and electrocutaneous stimuli. Trials of the fear and no fear conditions were presented in a random and mixed order. Experimental set-up preparations included skin preparations, attaching surface EMG (sEMG) electrodes on the trunk and dominant arm muscles, placing an electrode cap with EEG-electrodes over the scalp, placing electrodes at the back for painful electrocutaneous stimulus administration, placing a vibrotactor at the back for tactile stimulation, attaching an accelerometer on the radius of the dominant arm to measure arm acceleration, and attaching a light sensor to the hip for assessment of arm movement onset.

The testing started with a demo phase to familiarize the participants with the RAM, followed by a staircase paradigm to determine the intensity of the painful electrocutaneous stimulus that would be administered to the lower back area, and which served as a means to evoke the 'fear of pain'. Subsequently, a short training phase was per-

formed consisting of all the elements of the testing. In this phase the fear and no fear conditions were conditioned by coupling visual stimuli (i.e. colored dots) to the possibility of either receiving the painful stimulus during execution of the RAM or not.

The actual experimental phase consisted of a 50-minute RAM performance with a 90-second seated resting phase midway the session. Participants' expectations and fear about the painful stimuli were rated on a visual analogue scale (VAS) both before the training phase, and before, midway and at the end of the experimental phase. Furthermore, LBP intensity was rated on a VAS before, midway, and at the end of the experimental phase. A Borg rating of perceived exertion (RPE) was administered at the end of the experimental phase. Finally, maximal voluntary isometric contractions (MVIC), as described by Stevens et al.[109], were performed for all trunk muscles measured.

2.3 Rapid arm movement task (RAM)

This task was first described by Hodges et al.[45] and is an often-used, valid and reliable task for specifically assessing APA's of the trunk muscles related to arm movements[73].
Participants were standing barefoot and upright with the feet positioned at shoulder width and the arms hanging relaxed alongside the body[90]. A first visual stimulus, i.e. a colored dot, appeared on a monitor two meters in front of the participant at eye-height[52] and remained visible for a duration of 3500ms. This stimulus represented a warning cue preparing the participant for a movement to come. The color of the dot indicated whether a threat for a painful stimulus was present or not. It was randomized that for half of the participants a pink colored dot corresponded with the threat for/possibility to receive painful stimulation to the L4 region during arm movement, while a blue colored dot corresponded to no threat for/possibility to receive painful stimulation. For the other half of the participants the meaning of the colors was the opposite. In a jittered interval of 2300-2800ms after appearance of the warning cue, a vibrotactile stimulus was administered to the low back area, which allowed for sensory evoked potential analysis. A second, direction-specific visual stimulus appeared 3500ms after the warning cue and instructed participants to move their dominant arm[51, 52] to the indicated direction and back to the neutral position as fast as possible with the elbow extended (go cue) or not to move at all (no-go cue). One of three possible cues was presented: 1) an upright green arrow indicating shoulder flexion up to 90°[40, 2]) a downward red arrow indicating shoulder backwards flexion up to 30°, [3]) the word 'STOP' indicating that no movement was required. The interval after each movement trial consisted of 12s with the visual command to relax the trunk muscles and to breathe normally in order to minimize pre-activation in the trunk muscles prior to the next trial[51, 52, 74, 7]5. After a 'STOP' trial an inter-trial interval of 500ms was utilized. One third of the movement trials after a threat cue were accompanied by a painful electrocutaneous stimulus during movement, whereas the no threat cues were accompanied by an innocuous vibrotactile stimulus.

During the demo phase, feedback was given concerning the execution and velocity of the RAM performance, as well as the relaxation of the abdominal muscles and breathing patterns during the task. The subsequent training phase consisted of 20 shoulder extension and 20 shoulder flexion trials. The experimental RAM consisted of 240 trials, i.e. 120 go cues entailing 60 anterior and 60 posterior arm movement trials and 120 no-go trials, presented in a randomized order. Half of all trials (both in the training and experimental phase) followed a no threat warning cue and the other half a threat warning cue. A 90s seated rest was implemented after 120 trials, during which feedback concerning relaxation of the abdominal muscles and optimal task performance could be repeated if necessary. Participants were asked to refrain from eye blinking during the presentation of the warning and go cue and to keep their head as still as possible in order to minimize EEG- and EMG-movement artifacts or baseline fluctuations.

2.4 Instrumentation

2.4.1 Light sensor

A light sensor was placed at the thigh of the dominant arm side at a height where participants could cover it with the 5th digit while standing upright and with the arms hanging relaxed alongside their body. This sensor registered movement onsets of the RAM trials, which were used to cut the continuous EMG-data into a separate segment per trial for the EMG-analysis.

2.4.2 Surface Electromyography

sEMG was used to assess the onset latencies of the trunk muscles during APA. EMG signals were captured using a wireless 16-channel EMG system (Telemyo Desktop Direct Transmission System, Noraxon Inc., Scottsdale, U.S.A.). Before attaching surface electrodes on the muscles, participants received skin preparations, i.e. removal of body hair, skin scrub and disinfection with alcohol to reduce electrode-signal impedance (<5kOhm) and optimize signal conduction. Seven pairs of pregelled Ag/AgCl surface electrodes with an electrical surface contact of 1cm^2 and a maximal inter-electrode distance of 25mm (Ambu® Blue Sensor N, Ballerup, Denmark) were applied. Six pairs were positioned bilaterally over the Internal Oblique/Transversus Abdominis muscle (IO/TrA) midway between the Anterior Superior Iliac Spine and Pubic Symphysis, above the inguinal ligament[110]; the External Oblique muscle (EO) below the lowest rib, on an imaginary vertical line between the ribs and the Pubic Symphysis [86]; the Iliocostalis Lumborum pars Thoracis muscle (ILT) at the L1 level, midway between the lateral palpable border of the Erector Spinae muscle and a vertical line through the Posterior Superior Iliac Spines[24]. A lowercase 'i' and 'c' are used to distinguish respectively between the ipsilateral and contralateral parts of the aforementioned muscles (e.g. IO/TrAi for the ipsilateral side, and IO/TrAc for the contralateral side). One pair was placed on the anterior deltoid (AD) muscle of the dominant arm. EMG signals were captured with Myoresearch software (MR3.12.54, Noraxon Inc., Scottsdale, U.S.A.), analogue bandpass-filtered between 10-500Hz (combination of a low-pass filter of 500Hz in the data acquisition system and of a 1st order 10Hz ±10% cutoff high-pass filter inherent to the electrode sensor amplifiers), pre-amplified (CMRR > 100dB, overall gain 500, noise < 1 µV RMS), AD-converted (16-bit) at a sampling rate of 1500Hz and stored on a hard drive. All systems were synchronized and analogue triggers (from a light sensor) were imported in the EMG software by use of a 16-channel Analogue Input System (AIS 222BNC, Noraxon Inc., Scottsdale, U.S.A.).

2.4.3 Accelerometer

A 3D accelerometer (518 24G DTS 3D accelerometer, Noraxon Inc., Scottsdale, U.S.A.) was attached 50cm distally of the lateral border of the acromion on the dorsal side of the radius and parallel with the radius in order to calculate the acceleration and velocity of the arm movements.

2.4.4 Electroencephalography

In order to evaluate CNV, brain activity was recorded continuously at a sampling rate of 2000Hz with a 32-electrode portable EEG-system (EEGO Sports, eemagine Medical Imaging Solutions GmbH, Germany), placed according to the international 10/20 setting. The ground electrode was located in the active-shield cap fronto-centrally between the FPz and the Fz electrode. A measurement impedance of less than 10 kΩ for all electrodes was obtained by inserting conductive paste (Signa Gel, Parker Laboratories Inc., New Jersey, U.S.A.) in the electrodes of the EEG cap.

2.4.5 Constant Current Stimulator

Two lubricated surface electrodes with a diameter of 1cm were placed on the L4 spinous process and connected to a Constant Current Stimulator (CCS; DS5, Digitimer Ltd, Hertfordshire, U.K.). The latter was used to administer painful electrocutaneous stimuli (bipolar; 50Hz; 200ms; instantaneous rise and fall time) to the low back region. Right before the training phase, the stimulus intensity was individually determined through a staircase paradigm in which the participants could stepwise increase the intensity until they reached a 'maximal stimulus intensity that they could still tolerate'. Participants were first presented with an electrocutaneous stimulus of low intensity (0.5 mA) to prevent the initial surprise from influencing the evaluation of the stimulus. After this, the participants were presented with the same stimulus and were motivated to choose an intensity that they evaluated as unpleasant as possible, but which they were still willing to receive during the experiment. After every stimulation, the participant was asked whether the researcher was allowed to increase the intensity or not. If the participant agreed, the amplitude was elevated in steps of 0.5 mA until the participant indicated to have reached the maximum intensity (procedure in line with[16, 87]). Once a higher amplitude was chosen, the participants could not go back to a lower amplitude. Since movement can suppress the perception of sensory information (i.e. sensory suppression)[59, 123], the participants also received their individually chosen maximum intensity while performing a rapid arm movement and were asked again whether they agreed to increase the intensity or not. If they agreed, the intensity was increased in steps of 0.5 mA until they reached their maximum intensity during movement execution. After the training phase it was again inquired by the researchers whether the stimulus intensity could be increased or not. During the experimental phase this predetermined stimulus intensity was kept constant. In 1/12th of all trials the participants received a painful stimulus.

2.4.6 Vibrotactor

A vibrotactor (resonant-type tactor, C-2 TACTOR, Engineering Acoustics, Inc., Florida, U.S.A.), was attached to the lower back on the L3 spinous process. In 1/3rd of the movement trials during the no fear condition a stimulus was applied. This to ensure that participants in the no fear condition received the same amount of stimuli as those in the fear condition, even though they were not unpleasant in this case. Furthermore, in order to evoke somatosensory evoked potentials a tactile stimulus was also applied to the lower back during each presentation of a 'warning cue'. The results of the somatosensory evoked potential analysis have been discussed elsewhere.[15] The power (0.008W), frequency (300Hz) and duration (200ms) of this vibration were controlled by a self-developed software program.

2.5 Primary outcome measures

The **APA onset latency** between the EMG onset of each trunk muscle in reference to the AD onset was analyzed in Matlab version 9.1 (Mathworks Inc., Natick, U.S.A.). Only forward arm movement data was analyzed, since these are considered to induce a greater challenge to the postural control than backwards arm movements.[39] In line with previous research, the backwards movements served as a sham to ensure unpredictability of the movement direction. First, the continuous EMG-data was cut into segments from –3000 to +3000ms around the arm movement onset, as measured with a light sensor, to reflect one file per trial. Information regarding participant, condition, side, trial number and muscle was blinded for the principal investigator who performed the analysis. The blinded assessor visually picked[43] the onset of the AD and the trunk muscles based on the visualization of the raw, non-rectified and rectified 30Hz high-pass filtered signals of each segment (FIGURE 1). Afterwards an overlay graph with all analyzed trials per muscle was controlled for outliers. At least five trials without artefacts per muscle were needed for reliable assessment[73]. Trials were excluded whenever the onset of a specific muscle could not be visually determined due to excessive baseline muscle activity, artefacts, ECG-signals coinciding with muscle onset, interference, EMG-signal loss, or non-optimal movement execution. Furthermore, onset times occurring earlier than 100ms before the prime mover were also excluded, as EMG activity before that time point is unlikely to represent feedforward activation of the trunk muscles related to the RAM[111].

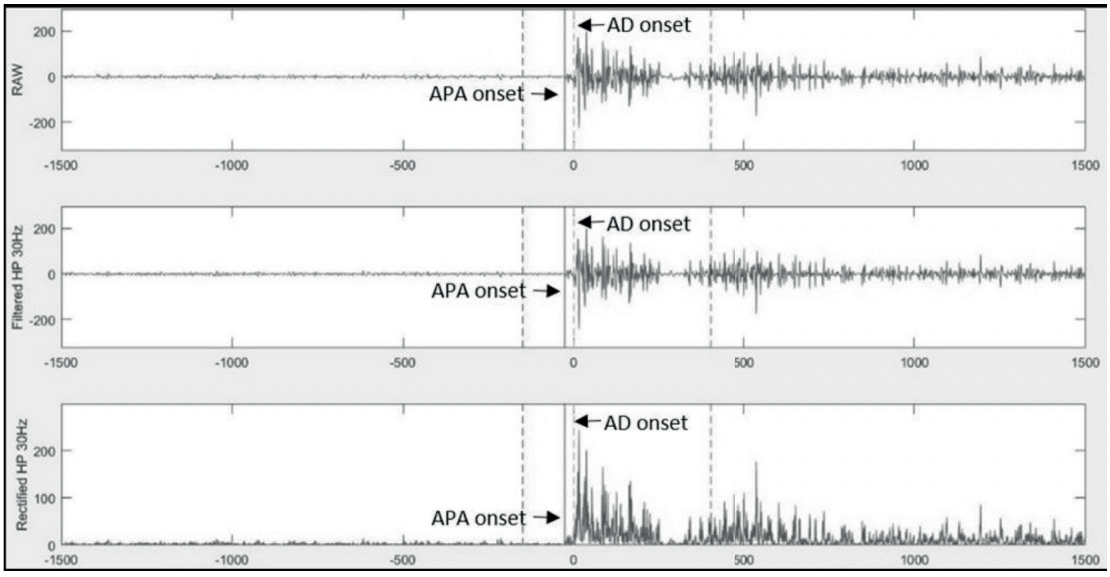

FIGURE 1. Example of visual picking an APA onset.
Legend: x-axis, indicates time in ms; y-axis, indicates amplitude in microvolts; HP, High-Pass; The visual picked APA onset determination for the trunk muscle that is under analysis is represented by a full line. The time frame for visual picking is indicated by the outermost dotted lines -150ms to +400ms around the 0-point. The dotted line at time zero represents the onset of the Anterior Deltoid muscle.

The **Contingent Negative Variation** amplitude was analyzed with Brainvision Analyzer version 2.1 (Brain Products GmbH, Gilching, Germany). The raw EEG-signals were re-referenced to an average of all electrodes. A 50Hz notch filter, and second order zero phase shift Butterworth high- (0.01Hz) and low-pass filter (5Hz) were applied. Independent component analysis was used to detect and filter out eye blinks and vertical or horizontal eye movement artifacts[58]. For this the slope algorithm was used in combination with the global field power. Subsequently, the continuous data were segmented into stimulus-locked epochs ranging from 200ms before to 3500ms after the warning cue trigger. Baseline correction of the signal was performed on a 200ms interval preceding the warning cue. This was followed by a semi-automatic artifact rejection (criteria: lowest activity of 0.5µV, maximal voltage step of 50µV/ms, range of values from -75 to +75µV) in order to remove all remaining ocular movements or other artifacts occurring within the epoch timeframe. An additional baseline correction was performed after artifact rejection. Then, segments were separated into two groups based on condition. As such, segments were separated into either no fear or fear segments, which were averaged within each participant for both conditions. Finally, grand averages per condition were calculated, as well as a collapsed localizer (FIGURE 2), which is an average of the waveforms of all participants and all conditions[68]. For these grand averages, at least 30 artifact-free trials were required per condition per participant in order for them to be included in the average as less trials are thought to be more subjectable to background noise and artifacts.

Visual inspection of the topography of the collapsed localizer confirmed the central topography of the CNV described in most CNV literature[1, 50, 67, 116]. Therefore, a cluster of the EEG-channels representing clear CNV activity, i.e. Cz, FC1 and FC2 was made.[69] Based on previous literature the timeframe for late CNV analysis was defined as the last 100ms prior to the go cue as this timeframe is thought to be the most sensitive for preparatory activity prior to rapid arm movements[32, 71, 116]. Thus, mean area amplitudes of the aforementioned electrode cluster were exported for the last 100ms prior to the movement initiation for subsequent statistical analysis, as mean area amplitudes have been reported to be an unbiased measure of EEG-amplitude[67].

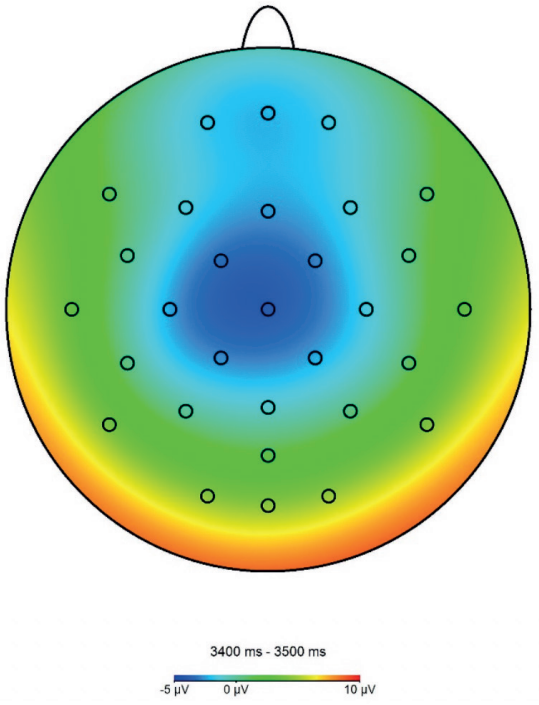

FIGURE 2. Topography of the collapsed localizer for the late CNV.

2.6 Secondary outcome measures

Movement acceleration. The peak accelerometry of the upward phase of the forward arm movements of the dominant arm was analyzed in Matlab version 9.1 (Mathworks Inc., Natick, U.S.A.).

The **Central Sensitization Inventory (CSI)** assesses self-reported signs of central sensitization, i.e. hypersensitivity for various sensory input (electrical, chemical, temperature).[77] Twenty-five items regarding health-related symptoms were rated on a Likert-scale (0="never" to 4="always"). A total score representing the degree of self-reported symptomatology (maximum score=100) was calculated. Scores exceeding a cut-off value of 40 are indicative for the presence of central sensitization (81% sensitivity and 75% specificity)[84]. The CSI, and its Dutch version as used here, have been shown to be reliable and valid.[61, 77, 84, 85]

The **Hospital Anxiety and Depression Scale (HADS)** assesses general psychological distress.[130] Fourteen items addressing emotions experienced during the last week are rated on a 4-point Likert scale, with higher scores corresponding to higher severity. A total score (range: 0-42) as well as subscores for anxiety (HADS-A, range: 0-21) and depression (HADS-D, range: 0-21) were calculated[5]. Cut-off scores for no, mild, moderate or severe anxiety/depression are respectively 0-7, 8-10, 11-14 and 14-21 on the specific subscales.[5, 118] The HADS is reliable and valid for both general[6, 42, 57, 104, 130] and chronic pain[70, 81, 94, 129] populations.

The **International Physical Activity Questionnaire (IPAQ)** estimates physical activity levels based on the reported activities during the last seven days.[18] Metabolic equivalents were calculated by multiplying the amount of minutes/week spent on work, transport, household and leisure tasks, with a factor that represents the strenuousness of the activities. The IPAQ has a fair validity and acceptable reliability[18, 124].

The **Pain Catastrophizing Scale (PCS)** evaluates catastrophic thinking about pain in 13 items that are rated on

a 5-point Likert scale. A total score (range: 0-52) as well as subscores for rumination (4 items, range: 0-16), magnification (3 items, range: 0-12) and helplessness (6 items, range: 0-24) were calculated. High scores correspond with higher catastrophic thinking about pain [115]. A fair reliability[103] and good construct and criterion validity were described for the PCS[88, 103].

The **Pain Vigilance and Awareness Questionnaire (PVAQ)** consists of 16 items assessing an individual's awareness of and attention towards pain (range: 0-80), with higher scores corresponding to a higher degree of pain vigilance and awareness.[83] The PVAQ has a good internal consistency, test-retest reliability and validity in chronic pain populations.[83, 96, 97]

The **Tampa Scale for Kinesiophobia (TSK)** consists of 17 statements concerning fear of movement or (re)injury[80], that are rated on a 4-point Likert scale (range 17-68), with higher scores corresponding to a higher degree of fear of movement[23, 95]. The TSK has excellent test-retest reliability and moderate construct validity.[95, 98]

The **Roland-Morris Disability Questionnaire (RMDQ)** evaluates the degree of LBP related disability[99, 108]. Participants had to indicate whether they perceived limitations in 24 daily activities due to their LBP complaints ('yes' or 'no'). Summation of the positive answers leads to a total score ranging from 0-24, with higher scores corresponding to higher perceived disability [108]. The RMDQ shows good reliability and validity.[11, 26, 36, 55, 105, 112] A minimal decrease of 30% on the RMDQ score was determined as the minimal clinical important difference[56].

A self-developed **pain-specific questionnaire** was filled out by the LBP participants, specifically assessing their current and past low back pain characteristics (intensity, location, duration, and treatments).

Visual Analogue Scales (VAS) were used to rate the LBP intensity, painfulness and unpleasantness of the electrocutaneous stimuli, and the extent of pain expectancy and fear of pain participants experienced during the presentation of the warning cues during the experimental phase. A VAS is a continuous scale consisting of a 10cm horizontal line with the left and right outer ends respectively labelled as no LBP/not painful/not unpleasant/no pain expectancy/no fear of pain at all and maximally imaginable LBP/ pain/unpleasantness/pain expectancy/ fear of pain.

The **Rating of Perceived Exertion (RPE**) scale ranging from 6 (very, very light) to 20 (maximal exertion) was used to rate the subjective exertion of the RAM.[7]

2.7 Statistical analysis

Data were analyzed using IBM SPSS Statistics 25 (IBM Corp., Armonk, N.Y., USA) with the significance level set at .05. A priori sample size calculations were based on previously reported differences between healthy people and CLBP sufferers regarding onset latencies of the trunk muscles during RAM with delayed onset of the IO/TrA (d=.38) and EO (d=.39) muscles[79], and the associations of self-reported fear with the performance of lumbar movements (d=.75)[121]. These calculations indicated that at least 26 participants per group were needed to obtain a power of minimum 0.80 with a significance level of 0.05, but the current study aimed at including at least 30 participants per group in order to compensate for possible drop-outs.

Normality of data distribution was assessed with the Shapiro-Wilk test, and baseline characteristics and questionnaire scores were calculated per group. Between-group differences for these variables were assessed with one-way ANOVA for the normally distributed data, and the Kruskal-Wallis test for the non-normal data. Comparisons of included participants per group with participants that could not be analyzed (i.e. drop-outs or technical loss of data) were calculated with the Mann-Whitney U test and Fisher's exact test, respectively for normally and non-normally divided data.

Several linear mixed model analyses were performed for which following factors were defined: group (HC - RLBP - CLBP), condition (fear - no fear), time (Pre-RAM - Post-RAM). Age, sex, handedness, height, weight, years of education, LBP intensity, RPE after the RAM, IPAQ metabolic equivalent values, PCS total and subscores, PVAQ total score, RMDQ total score, TSK total score, CSI total score, HADS total and subscores, and arm movement reaction time and accelerometry data were assessed as possible confounders. Additionally, for the CNV and APA mixed models expectations and fear for pain during movement were also assessed as confounders. Confounders were retained in the model if they had a significant influence on the model and lowered the Akaike's Information Criterion with minimally 10 points, which was deemed a significant better model fit. Age was retained as a covariate for the expectations and fear for pain mixed models. Concerning the APAs mixed models, covariates were added to the following specific models: IPAQ total transport and PCS helplessness score for theIO/TrAc model; LBP intensity pre-test for the EOi model; sex and LBP intensity post-test for the ILTc model. For the CNV-analyses no covariates were retained.

To examine whether, as intended, the threat warning cue induced more expectations for pain during the subsequent RAM compared to the no threat warning cue, a first linear mixed model analysis was performed. This model included three factors, group, condition and time, covariate age, and used a random intercept on subject level with a variance components covariance type. As the dependent outcome this model examined the influence of these factors on the expectations of pain. A similar model was built to examine the influence of these factors on fear for pain associated with the threat and no threat warning cues.
A third linear mixed model analysis with the late CNV cluster Cz-FC1-FC2 as dependent outcome, two factors, group and condition, and random intercept on subject level with a variance components covariance type was conducted to assess between-group and -condition effects on cortical movement preparation.
To examine whether fear for pain would influence the APAs, and whether this was dependent on the presence and type of LBP, a fourth linear mixed model analysis was performed with the mean onset of the APAs per muscle from each side (IO/TrAi - IO/TrAc - Eoi - Eoc - ILTi - ILTc) as the dependent outcome, two factors, condition (fear-no fear) and group (HC – RLBP - CLBP), and random intercept on subject level with a variance components covariance type.
To assess whether CNV-amplitude and APA onset times of the distinct muscles were related and influenced each other, a final linear mixed model analysis was performed with the mean onset of the APAs per muscle from each side (IO/TrAi - IO/TrAc - Eoi - Eoc - ILTi - ILTc) as the dependent outcome, three factors, the late CNV cluster Cz-FC1-FC2, condition (fear-no fear), and group (HC – RLBP - CLBP), and random intercept on subject level with a variance components covariance type.

Post-hoc comparisons for linear mixed model analyses were always made using Bonferroni corrections. Furthermore, Cohen's dav effect sizes were calculated for the mean differences between fear and no fear outcomes concerning APA onset latencies of each muscle and concerning CNV-amplitude, as well as Cohen's ds effect sizes for the between groups comparison of the APA onset latencies. Cohen's d effect sizes can range from very small (0.10), small (0.20), medium (0.50), large (0.80) up to huge (2.0).[17] Hedges' g correction was applied to these effect size calculations, as this is recommended for studies with small sample sizes. For the different formulas in this regard we refer to Lakens et al.[62].

3 Results

3.1 Demographics and baseline characteristics

Three groups of age- and gender-matched participants were included: 31 people experiencing non-specific RLBP complaints, 30 non-specific CLBP patients and 32 healthy controls (HC).

In total 93 participants were recruited for this study. However, the EEG-data of 15 participants could not be analyzed due to technical issues (n=10) and drop-out of participants due to physical discomfort (n=4) or unwillingness to complete the experiment (n=1). Concerning EMG-analysis, data of seven participants was not analyzed due to technical issues (n=3) and drop-out of participants due to physical discomfort (n=3) or unwillingness to complete the experiment (n=1). Baseline characteristics of included participants are described in **TABLE 1**. Baseline characteristics of the non-analyzed participants are not depicted, but were not significantly different from the other participants. The HC group displayed significantly lower PCS-helplessness (p=.040) than the CLBP group, and significantly lower scores on RMDQ (HC-RLBP: p<0.001; HC-CLBP: p<.001), CSI (HC-RLBP: p=.012; HC-CLBP: p<.001), and LBP intensity pre-test (HC-RLBP: p<.001; HC-CLBP: p<.001), mid-test (HC-RLBP: p=.001; HC-CLBP: p<.001) and post-test (HC-RLBP: p=.001; HC-CLBP: p<.001) than both patient groups. Besides this, no other between group differences were found.

TABLE 1. *Baseline characteristics and questionnaire scores*

		Group								
		HC			RLBP			CLBP			Group diff.
		Mean	SD	N	Mean	SD	N	Mean	SD	N	P-value
Sample size				32			31			30	
EEG-data excluded from analysis				5			7			3	
EMG-data excluded from analysis				3			3			1	
Age (y)		31.8	6.60		29.7	7.26		30.6	7.16		.398†
Gender	Male			15			14			13	
	Female			17			17			17	
Handedness	Left			2			3			4	
	Right			30			28			26	
Length (cm)		172.2	9.31		174.1	9.31		172.0	10.72		.654*
Weight (kg)		66.4	10.71		71.4	11.80		67.9	11.49		.211*
Study (y)		17.2	2.93		16.9	2.57		17.0	2.54		.401†

	Group								
	HC			RLBP			CLBP			Group diff.
	Mean	SD	N	Mean	SD	N	Mean	SD	N	P-value
IPAQ Work	1894.5	3884.90		4213.4	5805.99		3454.5	6144.20		.160†
IPAQ Transport	1165.7	1412.12		1082.	972.29		961.5	1135.25		.625†
IPAQ DomesticGarden	603.2	750.10		915.2	1469.48		1174.0	2072.42		.601†
IPAQ Leisure	594.0	559.70		784.3	845.40		507.4	582.91		.348†
IPAQ Walk	1399.3	1823.10		1893.1	2414.91		1760.0	2987.12		.522†
IPAQ Moderate	2224.5	2590.22		3190.5	2632.22		2474.7	2836.82		.099†
IPAQ Vigorous	633.5	1064.24		1944.8	2589.29		1862.7	3156.49		.190†
IPAQ PhysicalActivity	4257.4	4161.91		6875.0	6795.28		6097.3	7078.63		.275†
IPAQ SittingTotal	2415.3	1127.67		2227.0	1248.86		2437.0	1219.06		.757*
IPAQ Average Sitting	345.0	161.10		318.1	178.41		348.1	174.15		.757*
IPAQ Category 1			4			0			3	
2			8			9			8	
3			19			20			18	
PCS Total	10.4	9.26		11.9	7.99		13.8	8.10		.183†
PCS Rumination	4.9	3.99		5.3	3.60		5.7	3.22		.703†
PCS Magnification	1.9	1.87		2.1	1.87		2.5	1.83		.285†
PCS Helplessness	3.5	4.30		4.5	3.82		5.6	4.30		.046†, b
PVAQ	28.6	10.30		30.7	12.51		33.0	12.23		.317†
RMDQ	.3	.83		4.5	4.17		5.7	3.48		**<.001**†, a, b
TSK	30.2	10.25		32.0	10.96		31.7	10.51		.511†
CSI	22.4	8.75		31.1	13.01		35.5	14.20		**<.001**†, a, b
LBP before testing? No			29			22			4	
Yes			2			9			26	

	Group									
	HC			RLBP			CLBP			Group diff.
	Mean	SD	N	Mean	SD	N	Mean	SD	N	P-value
LBP flares per year				13	12					
LBP days per week				3.7	2.1		5.9	1.3		
Average LBP intensity all episodes (VAS)				5.18	1.92		4.30	1.41		
Average LBP intensity last episode (VAS)				4.94	2.10					
Maximal LBP intensity last episode (VAS)				5.77	2.28					
Minimal LBP intensity last episode (VAS)				1.17	1.39					
Duration last LBP episode (days)				4.57	3.50					
HADS Total	21.28	4.927		19.52	5.755		19.83	4.691		.109†
HADS Anxiety	12.50	3.331		11.16	3.532		11.27	3.039		.052†
HADS Depression	8.78	2.044		8.35	2.615		8.57	2.192		.832†
LBP intensity pre-test (VAS)	.08	.271		1.26	1.708		2.59	2.014		**<.001**†, a, b
LBP intensity mid-test (VAS)	.42	.855		2.25	2.228		4.26	2.630		**<.001**†, a, b
LBP intensity post-test(VAS)	.65	1.064		2.89	2.638		4.81	2.726		**<.001**†, a, b
Digitimer intensity ES (mA)	40.7	22.26		43.9	23.40		39.8	26.90		.829*
Subjective unpleasantness ES pre-test (VAS)	6.2	2.17		6.0	2.37		6.1	1.84		.936*
Subjective unpleasantness ES mid-test (VAS)	5.4	2.18		6.0	2.04		5.9	1.98		.464*
Subjective unpleasantness ES post-test (VAS)	5.3	2.33		5.4	2.15		5.6	2.52		.866*

	Group									
	HC			RLBP			CLBP			Group diff.
	Mean	SD	N	Mean	SD	N	Mean	SD	N	P-value
Subjective painfulness ES pre-test (VAS)	4.6	2.44		4.4	2.52		4.8	1.82		.831*
Subjective painfulness ES post-test (VAS)	4.6	2.24		4.5	2.65		5.0	2.24		.719*
Expectations for no threat stimulus (VAS)	.4	.9		.2	.7		.3	.9		.805‡
Expectations for threat stimulus (VAS)	5.4	1.9		5.2	2.7		4.4	2.6		.805‡
Fear for no threat stimulus (VAS)	.3	1.0		.3	1.2		.3	.7		.406‡
Fear for threat stimulus (VAS)	3.6	2.8		4.4	2.8		3.7	3.3		.406‡

Legend: CLBP, chronic low back pain; CSI, Central Sensitization Inventory; drop-out, refers to participants lost for analysis due to either drop-out or technical issues during the data-analysis; HADS, Hospital Anxiety and Depression Scale; HC, healthy controls; ES, electrocutaneous stimulus; IPAQ, International Physical Activities Questionnaire; N, amount; PCS, Pain Catastrophizing Scale; PVAQ, Pain Vigilance and Awareness Questionnaire; RLBP, recurrent low back pain; RMDQ, Roland Morris Disability Questionnaire; SD, standard deviation of the mean; TSK, Tampa Scale for Kinesiophobia; VAS, visual analogue scale; y, years

** one way ANOVA*

† Kruskal-Wallis test

‡ Linear mixed model

***Bold** figures display a significant between-group difference at the p <.05 level*

[a] Bonferroni post-hoc analysis displayed a between-group difference for HC and RLBP

[b] Bonferroni post-hoc analysis displayed a between-group difference for HC and CLBP

3.2 Experimentally-induced expectations/fear for pain

Electrocutaneous stimulus intensity. Both the objective intensity (constant current intensity: p=.829), and subjective unpleasantness (VAS pre-test: p=.936; VAS mid-test: p=.464; VAS post-test: p=.866) and painfulness ratings (VAS pre-test: p=.831; VAS post-test: p=.719) of the electrocutaneous stimulus intensities did not differ between the three groups.

Expectations. No interaction effects were found for group, condition and time. However, there was a significant main effect of condition on the expectations of participants towards the possibility of experiencing a painful stimulus during movement (F(1;253.009)=733.00, p<.001). The threat warning cue which was conditioned to warn participants for a possible painful stimulus indeed led to higher expectation VAS-ratings than the no threat cue that signified no stimulus could be given (+4.649, SE .172, p<.001).

Fear. VAS-ratings regarding fear were moderated by a group x condition interaction (F(2;235.165)=3.271, p=.040). Post-hoc analyses revealed that within each group the conditioned threat warning cue was significantly rated higher on a VAS-fear scale than the no threat warning cue (HC: +3.29, SE .348, p<.001; RLBP: +4.52, SE .345; p<.001; CLBP: +3.84, SE .348, p<.001). Furthermore, between group comparison showed that the RLBP group reported significantly more fear in association with the threat warning cue compared to the HC (+1.11, SE .441, p=.039). Such differences were not present when comparing HC vs. CLBP, or RLBP vs. CLBP.
Means and standard deviations of objective and subjective stimulus intensity, as well as expectations and fear ratings are depicted in **TABLE 1.**

3.3 Effects of fear on central movement preparation (CNV)

No interaction effects between condition and group were found concerning the late CNV-amplitude. Only a main effect of condition (F(1;75)=65.681, p<.001) was found, whereas no significant group differences were eminent. Post-hoc Bonferroni analyses revealed that there was a significantly larger negativity of the late CNV in the fear condition compared to the no fear condition (-1.591 µV, SE .196, p<.001). Estimated means for amplitude of the late CNV and effect sizes of these analyses are depicted in **TABLE 2**, and an overlay graph for fear and no fear CNV amplitude for the HC, RLBP and CLBP patients are respectively displayed in **FIGURES 3, 4 and 5.**

TABLE 2. Estimated means of late CNV amplitude

Group	Condition	EM (µVms)	SD (µVms)	N	95% CI	Difference Fear-no fear (µVms)	P-value	ES
HC	No fear	-2.81	2.70	27	-3.8,-1.8	1.44	**<.001**	0.52
	Fear	-4.25	2.70	27	-5.3,-3.2			
RLBP	No fear	-3.18	2.70	24	-4.3,-2.1	1.75	**<.001**	0.63
	Fear	-4.93	2.70	24	-6.0,-3.8			
CLBP	No fear	-2.58	2.70	27	-3.6,-1.5	1.58	**<.001**	0.57
	Fear	-4.16	2.70	27	-5.2,-3.1			

Abbreviations: CI, confidence interval; CLBP, chronic low back pain; CNV, Contingent Negative Variation; EM, estimated mean; ES, effect size (Hedges' g_{av}); HC, healthy controls; N, sample number; RLBP, recurrent low back pain; SD, standard deviation;

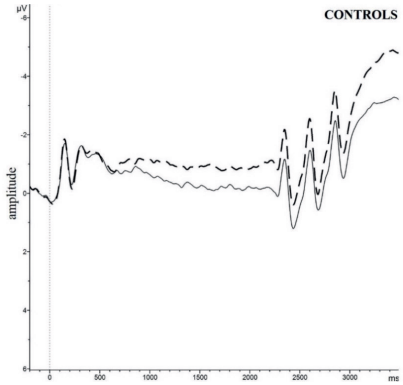

FIGURE 3. Grand average stimulus-locked CNV potential for the healthy control group at the Cz electrode. The solid line represents the no fear amplitude, and the dotted line represents the fear amplitude.

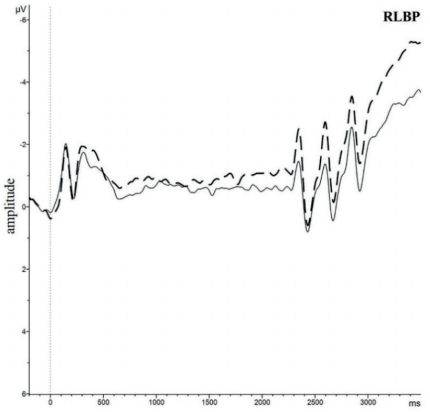

FIGURE 4. Grand average stimulus-locked CNV potential for the RLBP group at the Cz electrode. The solid line represents the no fear amplitude, and the dotted line represents the fear amplitude.

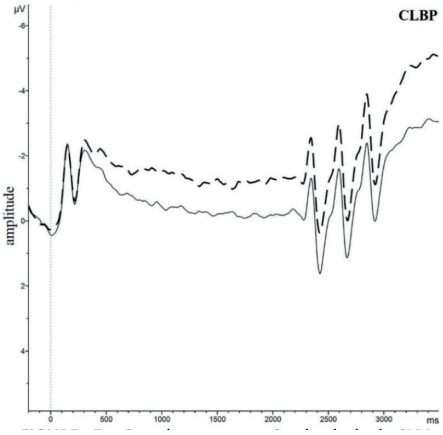

FIGURE 5. Grand average stimulus-locked CNV potential for the CLBP group at the Cz electrode. The solid line represents the no fear amplitude, and the dotted line represents the fear amplitude.

3.4 Effects of fear on peripheral movement preparation (APA)

For none of the examined muscles a significant group x condition interaction was found, i.e. IO/TrAi (F(2;41.511)=1.368, p=.266), IO/TrAc (F(2;14.372)=4.328, p=.688), EOi (F(2;32.935)=.045, p=.956), EOc (F(2;23.379)=2.295, p=.123), ILTi (F(2;35.797)=1.335, p=.276), ILTc (F(2;69.486)=1.028, p=.363).

However, a significant main effect of group on APA latencies was found for the IO/TrAc (F(2;14.022)=7.376, p=.006), EOi (F(2;42.343)=3.398, p=.043), ILTi (F(2;42.255)=3.428, p=.042) and ILTc (F(2;68.317)=7.903, p=.001), but not for the IO/TrAi (p=.614) and EOc (p=.172) muscles. Post-hoc analyses of these group effects showed that the APAs in the CLBP group were significantly delayed in comparison with the APAs of the HC group for the IO/TrAc (+38.4ms, SE 10.06ms, p=.005), and the ILTc (+18.3ms, SE 5.76ms, p=.007), but not for the ILTi (+1.1ms, SE 7.10ms, p=1.000) and the EOi (+23.3ms, SE 10.82, p=.112) muscles. Furthermore, delayed APAs were also found in the CLBP compared with the RLBP group for the EOi (+24.7ms, SE 9.82ms, p=.047) and the ILTc (+18.6ms, SE 4.98ms, p=.001), but not for the IO/TrAc (+21.9ms, SE 10.07ms, p=.142) and ILTi (+16.6ms, SE 7.10ms, p=.072) muscles. Differences between the HC and RLBP group were not significant for any of the muscles.

Estimated mean APA onset times and effect sizes of differences between fear and no fear conditions are depicted

in **TABLE 3**, group differences of APAs are depicted in **TABLE 4.**

TABLE 3. *Estimated means of APA onset latencies (ms)*

Muscle	Group	Condition	EM (ms)	SD (ms)	N	95% CI	Difference Fear-no fear (ms)	P-value	ES
IO/TrAi	HC	No fear	21.2	31.03	20	7.2,35.1	2.4	.313	.078
		Fear	18.8	28.85	17	4.7,32.8			
	RLBP	No fear	12.0	28.96	12	-4.8,28.7	.8	.772	.026
		Fear	11.1	31.02	14	-5.5,27.8			
	CLBP	No fear	9.6	29.52	17	-4.8,23.9	3.2	.211	.104
		Fear	12.8	29.52	17	-1.6,27.1			
IO/TrAc	HC	No fear	-39.6	15.33	4	-55.8,-23.4	3.8	.339	.164
		Fear	-43.4	18.09	6	-59.1,-27.7			
	RLBP	No fear	-24.8	17.22	5	-41.2,-8.4	.4	.902	.020
		Fear	-25.2	17.22	5	-41.6,-8.8			
	CLBP	No fear	-3.3	16.20	6	-17.3,10.6	.5	.876	.027
		Fear	-2.8	17.19	7	-16.6,11.0			
EOi	HC	No fear	-22.3	25.79	15	-35.7,-8.9	.6	.790	.023
		Fear	-23.0	25.80	15	-36.4,-9.5			
	RLBP	No fear	-24.3	19.73	9	-37.5,-11.1	.5	.875	.021
		Fear	-23.8	22.91	13	-36.6,-11.0			
	CLBP	No fear	.8	27.45	15	-13.4,15.1	.5	.848	.016
		Fear	.4	26.68	14	-14.0,14.7			
EOc	HC	No fear	-27.6	21.66	11	-40.9,-14.3	6.8	.055	.292
		Fear	-20.8	21.66	11	-34.0,-7.5			
	RLBP	No fear	-32.0	20.76	9	-46.1,-18.0	2.3	.552	.097
		Fear	-29.8	21.60	10	-43.7,-15.9			
	CLBP	No fear	-10.5	22.40	10	-25.0,3.9	4.0	.298	.171
		Fear	-14.6	20.58	8	-29.3,0.2			
ILTi	HC	No fear	-1.6	18.60	13	-12.0,8.7	1.4	.529	.067
		Fear	-3.0	19.76	15	-13.3,7.3			
	RLBP	No fear	-19.3	19.76	15	-29.6,-9.1	3.0	.155	.146
		Fear	-16.3	19.19	14	-26.6,-6.0			
	CLBP	No fear	-.7	18.61	13	-11.1,9.7	1.1	.643	.055
		Fear	-1.8	18.61	13	-12.2,8.6			
ILTc	HC	No fear	-30.6	19.44	27	-38.1,-23.2	2.2	.188	.110
		Fear	-28.4	19.13	26	-35.9,-21.0			
	RLBP	No fear	-30.0	16.96	22	-37.2,-22.8	.1	.942	.007
		Fear	-29.8	16.96	22	-37.0,-22.6			
	CLBP	No fear	-10.7	18.88	25	-18.2,-3.2	1.1	.495	.059
		Fear	-11.9	18.88	25	-19.4,-4.3			

TABLE 4. *Between-group differences of APA onset latencies (ms)*

Muscle	Group	EM (ms)	SD (ms)	N	95% CI	Group difference (ms)		P-value	ES
IO/TrAi	HC	20	28.30	17	6.2,33.8	HC-RLBP:	8.4	1.000	0.288
	RLBP	11.6	28.42	12	-4.9,28.0	HC-CLBP:	8.8	1.000	0.299
	CLBP	11.2	29.05	17	-3.0,25.3	RLBP-CLBP:	0.4	1.000	0.012
IO/TrAc	HC	-41.5	14.57	4	-57.1,-25.9	HC-RLBP:	-16.5	0.389	0.925
	RLBP	-25	16.79	5	-41.1,-8.8	HC-CLBP:	-38.4	0.005	2.288
	CLBP	-3.1	15.52	6	-16.6,10.5	RLBP-CLBP:	-21.9	0.142	1.244
EOi	HC	-22.6	25.37	15	-35.9,-9.4	HC-RLBP:	1.5	1.000	0.061
	RLBP	-24.1	18.82	9	-36.7,-11.4	HC-CLBP:	-23.2	0.112	0.877
	CLBP	0.6	26.20	14	-13.5,14.7	RLBP-CLBP:	-24.7	**0.047**	1.007
EOc	HC	-24.2	20.92	11	37.1,-11.3	HC-RLBP:	6.7	1.000	0.315
	RLBP	-30.9	19.83	9	-44.4,-17.4	HC-CLBP:	-11.6	0.673	0.545
	CLBP	-12.6	19.59	8	-26.7,1.6	RLBP-CLBP:	-18.3	0.195	0.883
ILTi	HC	-2.3	18.09	13	-12.4,7.8	HC-RLBP:	15.5	0.103	0.816
	RLBP	-17.8	18.74	14	-27.9,-7.7	HC-CLBP:	-1.1	1.000	0.058
	CLBP	-1.2	18.13	13	-11.4,8.9	RLBP-CLBP:	-16.6	0.072	0.872
ILTc	HC	-29.5	18.64	26	-36.8,-22.2	HC-RLBP:	0.4	1.000	0.020
	RLBP	-29.9	16.43	22	-36.9,-22.9	HC-CLBP:	-18.2	**0.007**	0.971
	CLBP	-11.3	18.41	25	-18.6,-3.9	RLBP-CLBP:	-18.6	**0.001**	1.045

Abbreviations: APA, anticipatory postural adjustment; c, contralateral muscle; CI, confidence interval; CLBP, chronic low back pain; EM, estimated mean; EO, External Oblique muscle; ES, effect size (Hedges' gs); HC, healthy controls; i, ipsilateral muscle; ILT, Iliocostalis Lumborum pars Thoracis muscle; IO/TrA, Internal Oblique/Transversus Abdominis muscle; N, sample number; RLBP, recurrent low back pain; SD, standard deviation;.

3.5 Interactions between central and peripheral movement preparation

Interaction effects were not examined. A significant main effect was found for late CNV-amplitude on APA onset times of the ILTc muscle ($F(1;113.191)=7.522$, $p=.007$), signifying that larger late CNV-amplitudes associate with later APAs of the ILTc muscle. For the other muscles, no such effects were found of CNV-amplitude on APA onset times (IO/TrAi: $F(1;54.212)=.201$, $p=.655$; IO/TrAc: $F(1;20.313)=.020$, $p=.888$; EOi: $(F1;54.193)=1.752$, $p=.191$; EOc: $F(1;47.618)=.864$, $p=.357$; ILTi: $(F(1;65.494)=1.112$, $p=.296)$.

4 Discussion

This is the first study to experimentally examine the influence of pain-related fear on both central and peripheral movement preparation processes in healthy people, RLBP and CLBP patients.

This study showed that pain-related fear during movement led to larger CNV-amplitude before movement initiation, regardless of LBP presence/degree. These results confirmed previous findings of larger negativity when expecting fearful pictures[93] or painful stimuli[2, 3]. Larger CNV-amplitude reflects enhanced preparation/anticipation for upcoming tasks.[29, 113] Additionally, it is known that "attention is biased/redirected towards stimuli conveying threat"[20, 102], which leads to enhanced somatosensory attending towards the threatened region[30, 122, 125]. Such enhanced somatosensory attending was also found during the anticipation phase for movements accompanying pain on the hands[16]. Importantly, in the fear condition of the current experiment movement is preceded by a conditioned stimulus conveying threat of LBP[91], which also enhanced somatosensory attending, since larger somatosensory evoked potentials for vibrotactile stimuli at the back were evident in that condition (these results are discussed in-depth elsewhere; article under revision[15]). Hence, these combined findings of somatosensory evoked potentials and CNV suggest that the aforementioned attentional redirection exceeds somatosensory attending and might be extended towards enhanced preparation for movements under threat as well. Thus, more effortful/conscious movement strategies, possibly to avoid harm/damage[64] or minimize the expected pain by optimizing movement, might occur when performing threat-related movements. The hypothesis that clinical LBP would influence these effects of fear on cortical movement preparation could not be supported, since no between-group differences were found.

Concerning peripheral movement preparation, no effects of experimentally-induced pain-related fear on APAs were found. Thus, the hypothesized delays in APAs with pain-related fear, based on studies which did find later onsets in anticipation of painful movements[82], could not be supported. This might be explained by the use of intramuscular EMG-electrodes in previous research[82], whereas we used sEMG, and these techniques sometimes yield different results. sEMG was preferred here, because invasive EMG-techniques already could induce fear[78], which was to be avoided. To our knowledge, this study was the first comparing APAs between distinct groups of RLBP and CLBP, whereas previous research often examined mixed RLBP/CLBP, or one group of either. However, RLBP is sometimes considered as a progression from acute LBP towards CLBP[28], showing less pronounced muscle structural[38, 47] and functional[38] alterations than CLBP. Furthermore, pain mechanisms are less altered with RLBP versus CLBP.[37] Hence, we examined whether a functional continuum with increasing degree of chronicity would also differentially affect APAs in these groups, i.e. earliest APAs in the HC, later/delayed in RLBP, and latest in CLBP. Indeed, APAs were generally delayed in CLBP compared to RLBP and HC, but these delays were muscle-dependent with significant RLBP-CLBP differences for the EOi and ILTc, and significant HC-CLBP differences for the IO/TrAc and ILTc muscles, whereas for most other muscles non-significant trends in the same direction were described. However, the hypothesized continuum in APAs could not fully be substantiated, since no significant differences between HC-RLBP were found. A trend of altered APAs in the RLBP group was found for the ILTi (earlier) and IO/TrAc (delayed) muscles, whereas for the other muscles based on effect sizes and confidence intervals no clinically relevant

differences could be discerned. Hence, we hypothesize that the motor control mechanism in RLBP patients might reflect recovery from pain flares since these patients show no distinct differences with HC, whereas delayed APAs as seen in CLBP might indicate a failure of such recovery mechanisms. Previous literature reported delayed trunk muscle onsets in mixed RLBP/CLBP groups compared to HC[60]. Interestingly, in the current study trunk muscle onset timing appears to be different in CLBP compared to RLBP, which is a novel insight and highlights the importance of separately examining both groups when studying APAs. However, additional research comparing different types of LBP is needed to further substantiate these hypotheses.

Concerning central-peripheral interactions, one study previously described increased CNV-amplitude and delayed APAs in RLBP/CLBP compared to healthy people and found no correlations between both measures[101]. Hence, it was inferred that alterations in CNV and APAs are distinct mechanisms in movement preparation. The findings of the current study largely confirm this as also no systematic effects between both outcomes were found, except for earlier ILTc APAs with smaller CNV-amplitude. However, since non-invasive EEG is not suited to measure subcortical brain activity, and structures like the basal ganglia[10, 31], cerebellum[4, 9] and thalamus[89] are considered to have a role in movement preparation as well, future studies could apply functional MRI (in combination with EMG and EEG[65]) or PET to expand the comprehension of central-peripheral connections in movement preparation.

Successful manipulation of fear of pain was a prerequisite for the validity of the fear condition, which was fulfilled since expectations and fear for pain were considerably higher than in the no fear condition. Interestingly, pain-related fear in the fear condition was significantly higher in the RLBP group than in the HC group, whereas for CLBP only a non-significant trend of higher fear compared to the HC was found. This suggests that, possibly due to the phasic nature of their complaints, RLBP sufferers are more susceptible to heightened fearful emotions concerning their LBP, as opposed to CLBP patients who are used to continuously experience pain and hence are less susceptible to phasic increases of fear.

Several considerations have to be taken into account. The electrocutaneous stimulus, since it is an unfamiliar sensation, holds less connotations of 'possible harm/damage' to the body[119] or associations with previous negative experiences and emotions, as is often the case with clinical LBP[35]. Hence the experimentally-induced fear might not fully transfer to clinical fear experienced by LBP patients. However, this type of stimulus is one of the easiest and safest ways for inducing phasic pain.
The late CNV, besides movement preparation, also reflects anticipation for sensory processing of the go cue[12, 22, 33, 100, 120]. Hence, a larger CNV-amplitude with fear could be attributed to both processes and not solely to movement preparation.
For some muscles the sample sizes for APA-analysis were diminished due to trial rejection during visual picking. Possibly, the multiple factors requiring attention during testing, i.e. RAM performance, visual/vibrotactile/electrocutaneous stimulation, in combination with the long duration of standing without blinking and head movements, impeded with relaxing the muscles between trials. Therefore, despite a demo and training phase with biofeedback, repeated instructions to relax the trunk muscles in-between trials, and filtering and rectification of the data, high baseline activity in several muscles remained present, which was the main cause for trial rejection. Nonetheless, the manual visual picking procedure was used for APA-analysis since this method entails a higher repeatability and accuracy compared to automatized methods.[43] Since effect sizes for mean differences between the fear and no fear conditions generally were small in the current study, in future research, more trials or bigger inter-trial intervals could be used to increase the amount of detectable onsets for statistical analysis.

An important implication of this study is that situational fear seems to play a role in central, but not in peripheral, movement preparation processes. This could mean that enhanced activity on a central level due to fear might already benefit peripheral movement preparation, which therefore might be maintained at its original level. How-

ever, a more likely explanation is that CNV and APA, which were used to examine movement preparation in the current study, are unrelated[101]. Additionally, the hypothesized role of situational fear as a possible underlying mechanism in differences between RLBP and CLBP patients concerning altered movement preparation could not be supported by central nor peripheral measures. Of course, long-term effects of fear of pain as proposed by a lot of biopsychosocial models[8, 19, 46, 92, 126, 128], as well as other motor control mechanisms such as feedback for instance[14], could still be at play and need further examination with regards to LBP chronification. For future research it would be interesting to also include acute LBP and to compare RLBP sufferers with versus those without an ongoing pain flare, and to conduct longitudinal studies. In this way more information regarding the influence of ongoing pain and fear on these processes and the continuum in LBP could be further elucidated. Furthermore, it is recommended to distinguish between RLBP and CLBP patients, as the results of our study indicate that, at least on a peripheral level, these groups are characterized by different functional alterations. Hence, when studying mixed groups, results with regards to APAs could be wrongly interpreted. Concerning treatment it can also be speculated to distinctly approach RLBP and CLBP, since between-group APA differences were found. Hence, in RLBP compared to CLBP perhaps a less substantial proportion of the treatment sessions should be targeted at normalizing onset timing. However, since there is still a lack of interventional studies comparing treatment effects between RLBP-CLBP these clinical hypotheses are highly speculative.

5 Conclusion

Larger CNV-amplitude, regardless of LBP presence or degree, was found with pain-related fear, suggesting an attentional redirection towards more effortful movement strategies when under threat of pain. APAs were not affected by pain-related fear, but group differences were eminent, indicating that different peripheral movement preparation mechanisms are at play for RLBP and CLBP patients. Since APAs and CNV do not systematically relate to each other, these are considered as two distinct mechanisms in movement preparation.

6 References

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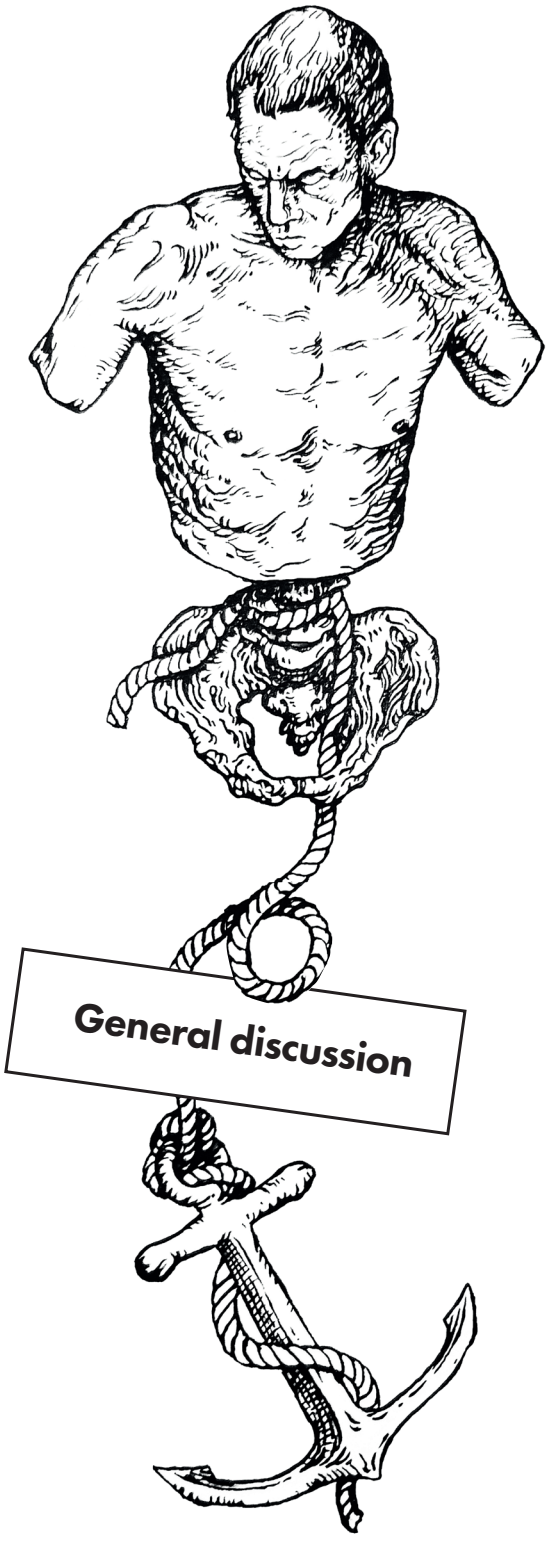

Non-specific CLBP is recognized as a complex disorder for which, despite years of research, still no univocal underlying mechanism has been discovered. Instead, CLBP is rather considered as a multifactorial disorder with multiple contributing mechanisms. The main objective of this dissertation was to further elucidate two important mechanisms that are considered to underlie or contribute to non-specific LBP, i.e. the influence of cognitive-affective factors and alterations in SMC. Furthermore, possible interactions between both were examined.

To achieve this in **Chapter I** the existing literature regarding two topics was reviewed and reported. On the one hand functional brain alterations in LBP populations compared to healthy people were examined (Part 1). On the other hand the current knowledge concerning the influence of cognitive-affective factors -more precisely catastrophizing and fear- on movement-related outcomes in LBP was analyzed as well (Part 2). **Chapter II** focused on effects of fatigue caused by either physical or cognitive exertion on peripheral movement preparation (Part 1) and central movement preparation (Part 2) in healthy adult people without LBP. Finally, in Chapter III a biopsychosocial perspective on the influence of expectations and fear for pain during movement on both central and peripheral measures for movement preparation was examined and compared between healthy adults, RLBP and CLBP sufferers.

The general discussion of this dissertation is structured as follows. The results of the aforementioned chapters will be discussed in-depth, followed by clinical and academic implications, methodological considerations, and future research perspectives. Finally, the main conclusions of this work will be formulated.

The following main research questions were investigated in this dissertation:

1. What evidence exists in current literature concerning the possible presence and nature of functional brain alterations in non-specific LBP patients compared to healthy people, as assessed by EEG?
2. What evidence exists in current literature concerning the possible influence of catastrophizing and fear on movement-related outcomes in non-specific LBP patients?
3. Does fatigue, induced by a single bout of either physical or cognitive exertion, affect peripheral movement preparation in healthy adult people, as assessed by examining feedforward trunk muscle activation with EMG?
4. Does fatigue, induced by a single bout of either physical or cognitive exertion, affect central movement preparation in healthy adult people, as assessed by examining the Contingent Negative Variation with EEG?
5. Does situational fear of back pain influence central and peripheral movement preparation in healthy people, RLBP and CLBP patients, as assessed by examining the Contingent Negative Variation with EEG and feedforward trunk muscle activation with EMG?

1 Summary and discussions of main findings

The summary of findings are presented per chapter.

1.1 Chapter I – Theoretical background

1.1.1 Chapter I, part 1 - What evidence exists in current literature concerning the possible presence and nature of functional brain alterations in non-specific LBP patients compared to healthy people, as assessed by EEG?

The assessment of central or cortical measures for movement preparation in relation to LBP was an important part of the main research objective of this dissertation. EEG, which allows for a broad range of functional and dynamic applications and which can be measured in synchrony with peripheral measures such as EMG, was chosen as the preferential measurement method for cortical movement preparation in the studies of this dissertation. Based on the assumption that brain function and structure are –at least to some extent– related[13], and based on the ample amount of (f)MRI studies already illustrating both structural and functional brain alterations in LBP[92, 122,] it was hypothesized that EEG could be used to detect such, and many more, brain function alterations in LBP as well. However, no overview in this matter existed, warranting the performance of this systematic review.

Twelve studies examining the LBP brain with EEG were found, concerning three categories of brain functions, i.e. cortical motor functions, sensory processing, and executive brain functions. However, it has to be pointed out that the inferences for each of these categories were based upon limited evidence needing further confirmation, and thus should be interpreted accordingly. Furthermore, these inferences only apply to CLBP populations, since other populations were not yet examined in this matter.

With regards to **cortical motor functions**, until now only brain potentials representing cortical feedforward and feedback processing in relation to balance tasks were studied. These findings are of high relevance for this dissertation since motor control, but more specifically feedforward movement preparation, is one of the main outcomes of interest. Concerning feedforward movement preparation, a larger CNV-amplitude in concordance with delayed APAs of several trunk muscles (reflecting peripheral movement preparation) was found in CLBP patients in comparison with healthy people.[137] It was hypothesized that this larger CNV might represent a prioritization of attention towards maintaining optimal balance and postural control[176], and might also represent efforts of counteracting the disturbed peripheral movement preparation in these patients in order to protect their back. Such a protective postural strategy, which often arises in CLBP patients and possibly requires more conscious effort and consequently a higher cortical demand, is the 'guarding mechanism'.[20, 79, 137] For the BP potential no similar effects in CLBP were described, since healthy people and CLBP patients did not differ regarding this potential.[80] The anomaly in findings between CNV and BP in this matter could be due to methodological differences, which are described in the discussion of **Chapter I, part 1**. On the other hand, the findings concerning cortical feedback mechanisms, i.e. a larger P2 potential in concordance with a diminished center of mass displacement in CLBP patients compared to healthy people after balance perturbation[82], did support the aforementioned 'guarding mechanism' hypothesis. Indeed, a more demanding and a possibly more rigid postural strategy could explain the diminished center of mass displacement.[107, 128, 157]

With regards to **sensory processing**, at the time of conducting this systematic review only noxious somatosensory processing and auditory processing were studied in LBP with EEG, whereas other sensory processing of for instance visual, olfactory, gustatory or non-noxious somatosensory stimuli (i.e. vibration, touch/pressure, temperature, proprioception) was not yet examined. In response to noxious somatosensory stimuli a larger early-phase SEP[38], which represents sensory processing of these stimuli[9, 94, 173], but unaltered late-phase SEPs[38, 52, 54, 89,] which represent the cognitive-emotional processing of these stimuli[9, 94, 173], were found in CLBP compared to healthy people. These findings led to the hypothesis that sensory, but not cognitive-emotional processing, of noxious stimuli might be increased in

CLBP. In addition, a mental overload and central sensitization processes in CLBP sufferers were suggested based on the results of diminished habituation and increased sensitization to noxious somatosensory[34] as well as to non-noxious auditory stimuli1[66] in CLBP patients. After all, central sensitization is characterized by alterations in endogenous pain modulation which often result in diminished habituation capacities to noxious stimuli[38, 49] and hyperexcitability towards painful (hyperalgesia) and normally non-painful stimuli, such as sound, light touch, etc. (allodynia)[51, 76, 131]. These findings could also reflect the presence of nociplastic pain due to neuroplastic alterations in the nervous system, which often arises in non-specific CLBP sufferers[19]. Interestingly, in one study enhanced processing of noxious stimuli was no longer present when CLBP patients applied a higher muscle tension strategy.[89] This could explain why a 'guarding mechanism', which consists of co-contraction of several muscles and can be regarded as a high muscle tension strategy, is an often used postural compensation mechanism in (C)LBP sufferers. Such a strategy might be effective in reducing pain through gate theory processes[111], attentional processes, or both[89]. Furthermore, it illustrates the important role motor output mechanisms can play in pain experience. A possible role of several genetic polymorphisms in the predisposition of people towards (C)LBP was also suggested based on their mediating effects on the processing of noxious stimulation, and is discussed in depth in the discussion of **Chapter I, part 1.** After the completion of this review an interesting novel study was conducted, which expands on the knowledge concerning non-noxious somatosensory processing of vibrotactile stimulation to the lower back region in CLBP and RLBP sufferers in comparison to healthy people[25]. This study found no between-group differences concerning early SEPs in response to the vibrotactile stimulation (P23, N30, P40, N96), which according to that study could indicate that RLBP and CLBP sufferers might have no different sensory suppression mechanisms nor are they more hypervigilant for bodily sensations than healthy people. Furthermore, these findings are also not suggestive for central sensitization processes in these LBP groups (no allodynia). On the other hand, a larger P171 potential in CLBP, indicative for a higher arousal that could lead to enhanced somatosensory responsiveness, compared to RLBP sufferers and healthy people (which did not differ from each other) was found in that study. Hence, findings of enhanced somatosensory processing in CLBP patients might be induced through a general increased arousal state in these patients, but this hypothesis needs further confirmation. With regards to **executive functions**, disturbed feedback mechanisms in a decision-making task have been found, which correspond to diminished learning and problem solving capabilities in CLBP patients compared to healthy people.[149] It has not yet been studied whether these findings would also apply to diminished motor learning and problem solving during motor tasks.

1.1.2 Chapter I, part 2 - What evidence exists in current literature concerning the possible influence of catastrophizing and fear on movement-related outcomes in non-specific LBP patients?

The biopsychosocial nature of this dissertation should be no surprise, since CLBP is widely recognized as a multifactorial and multidimensional disorder. Interactions between cognitive-affective factors such as catastrophizing and fear (among other factors like hypervigilance, depression, etc.), and movement alterations have been proposed by several biopsychosocial models to play a role in the chronification process.[18, 28, 72, 123, 132, 165] The last decades an abundance of research has been conducted to experimentally establish whether these theories can be endorsed or not, and how these insights can benefit the treatment of CLBP. However, despite all this research it remains difficult to discern clear underlying mechanisms in non-specific LBP. It was hypothesized that an in-depth analysis of all existing literature concerning interactions between catastrophizing and/or fear with objective quantitative, analytic and functional measures of movement alterations could provide a more profound understanding of mechanisms underlying or contributing to recurrence and chronification of LBP. Recent reviews have confirmed associations of higher levels of pain-related fear and catastrophizing with increased disability and pain, and diminished physical activity[101, 121, 171, 172, 177,] but an up-to-date overview concerning more specific alterations in movement-related outcomes than disability was lacking. Therefore, the current systematic review was conducted.

A schematic overview of all the findings of this systematic review is presented in **TABLE 5** of **Chapter I, part 2** and can help digest the summary and discussion of the results in the following paragraphs. Findings will be discussed per category of movement-related outcome that was studied, i.e. 'Muscle timing', 'Muscle activity', 'Muscle strength', 'Muscle endurance', and a paragraph concerning 'Functional task performance' which combines the categories 'Activities of daily living (ADL)', 'Balance', 'Spinal kinematics' and 'Proprioception and coordination'. For each category associations with both catastrophizing and/or fear based on current literature will be assessed. These paragraphs will be followed by a final paragraph discussing general hypotheses based on findings of multiple outcomes.

Muscle timing. The studies retrieved concerning muscle timing in this systematic review all handled about feedforward APA trunk muscle activation. Despite the fact that associations between catastrophizing/fear and muscle timing appear to be highly muscle-dependent, some general tendencies could be derived from the results of our systematic review. Limited evidence for associations of both **catastrophizing** and **kinesiophobia** with generally earlier muscle onsets in CLBP patients were found. This was mainly the case in the contralateral trunk muscles when unilateral peripheral limb movements were used to perturb balance, whereas for ipsilateral muscles more often no effects or sometimes even delays were found.[97] This asymmetry in trunk muscle activation with generally earlier muscle contractions of the contralateral muscles compared to the ipsilateral trunk muscles is in line with the asymmetrical activation of trunk muscle APAs which were mentioned in the general introduction of this dissertation.[6, 115] However, the indications of earlier APAs in association with a higher presence of catastrophizing and/or fear were surprising and not in line with our hypothesis. Since previous research has shown that in general trunk muscle onsets are delayed in CLBP compared to healthy people[90, 147], and since it was considered that cognitive-affective factors might play a contributing role in this process, we expected delayed muscle onsets with higher presence of catastrophizing and kinesiophobia. In contrast, with higher **fear-avoidance beliefs** we did find such hypothesized delayed APAs in the contralateral EO muscle in CLBP.[81] Hence, based on these findings one could speculate that catastrophizing and fear as opposed to fear-avoidance beliefs are factors that do not contribute to disturbed muscle timing in CLBP, but might rather be adaptive mechanisms which counteract such delays by facilitating earlier muscle activation. The presence of avoidance beliefs then, might be the decisive determinant for a maladaptive course in the chronification of LBP. However, since all these inferences are based on findings of single studies, these hypotheses have to be regarded as highly speculative at the moment.
The aforementioned findings are of high relevance for the main objectives of this dissertation, since they provide interesting insights concerning peripheral feedforward movement preparation, which is a main outcome for this dissertation. It is clear, based on this systematic review, that further experimental research in this topic is needed, and this need provides an important motive for our study described in **Chapter III**.

Muscle activity. A general propensity towards increased muscle activity in relation to higher presence of **catastrophizing** was found primarily in the back muscles of (sub)ALBP[148] and CLBP[66, 102, 128, 133, 158] patients. But again, as with muscle timing, these associations were quite muscle-dependent as in some studies for several muscles no alterations in muscle activity were found in both CLBP[128] and mixed RLBP/CLBP[40] patients. Concerning the influence of **fear** on muscle activity no general inferences could be made, since for kinesiophobia, fear-avoidance beliefs, and pain-related fear evidence was ambiguous or conflicting. However, there was moderate evidence for disturbed relaxation capacities of the back muscles in CLBP with higher kinesiophobia[57] and fear-avoidance beliefs[170] in CLBP. Hence, these findings suggest that both catastrophizing and fear could be associated with a higher presence of 'guarding mechanisms', i.e. stiffening of the superficial muscles of the spine to protect the body against further pain/harm[106, 128, 157] and to compensate for diminished activity of the deeper muscles, which relates to diminished motor control[65, 69, 144, 159].

Muscle strength. Catastrophizing is likely not to influence back muscle strength in CLBP[96, 98], whereas limited evidence for diminished back muscle strength and increased variability was found when the LBP population was less

strictly defined and consisted of a mix of RLBP and CLBP sufferers[61]. These different findings highlight the importance of studying well-defined an distinct groups of LBP sufferers. Concerning fear and muscle strength, the majority of findings were conflicting.[3, 4, 29, 35, 61, 67, 77, 88, 96, 112] However, both for **fear-avoidance beliefs**[29, 88] and **anxiety**[67, 112] moderate evidence for no associations respectively with back and abdominal muscle strength was found, whereas for **pain-related fear** limited evidence for diminished abdominal muscle strength was found in CLBP[152].

Muscle endurance. Limited evidence for associations of both **catastrophizing**[96] and work-related **fear-avoidance beliefs**[100] with diminished muscle endurance, respectively of the back and abdominal muscles, was found in CLBP. Evidence concerning other fear measures was conflicting.[1, 8, 35, 96, 125]

Deconditioning, which is often proposed by biopsychosocial models to be a consequence of avoidance behavior[17, 91], was hypothesized as a mechanism that could explain diminished strength and endurance in relation to catastrophizing and fear in CLBP. However, since the findings of our systematic review in this regard are generally speaking rather inconsistent and limited, we cannot fully confirm nor disregard this theory.

Functional task performance. It is self-evident that possible influences of catastrophizing and fear on functional task performance are highly dependent on the specific properties and characteristics of the distinct tasks that are being examined. We refrain to **Chapter I, part II** for a detailed overview of all results concerning specific tasks in relation to the various cognitive-affective factors and the distinct LBP populations that were until now studied in this regard, since recapitulation of these results here would lead us too far. For those tasks for which conclusions of a directional relationship with catastrophizing and/or fear could be made based on the retrieved literature, a general propensity towards diminished task performance in relation to higher levels of catastrophizing and/or fear was found. It is speculated that these findings of diminished functional performance might be consequential to the previously described alterations concerning trunk muscle timing, activity, strength and endurance which could reflect less efficient movement strategies. Furthermore, an attentional shift is hypothesized to occur in LBP sufferers with high levels of catastrophizing and/or fear, i.e. attention might be prioritized towards the pain experience and avoidance of further pain/harm[134], instead of towards optimal task performance. Only for one task an opposite relationship, i.e. improved stair climbing performance in relation to higher catastrophizing levels in CLBP, was found. However, this surprising relationship was hardly of any clinical relevance since catastrophizing explained only 1% of stair climbing performance in that study.[142] An interesting speculation concerning the relationship between fear-avoidance beliefs and proprioception, more precisely position-reposition sense of the lumbar area, could be made. The results of this review suggest that the position-reposition sense is generally disturbed in CLBP, but that the direction of this effect might be dependent on the amount of fear-avoidance beliefs.[124] In this connection high fear-avoiders might show a more cautious or protective strategy with undershooting of the repositioning in lumbar lordosis, whereas low fear avoiders tend to overshoot the lumbar lordosis as they might not avoid excessive movements.

General hypotheses. The current paragraph consists of additional, more integrative inferences overarching multiple movement-related outcome categories. The often limited or conflicting evidence made it challenging to discern clear-cut mechanisms concerning interactions between catastrophizing/fear and movement alterations in LBP. However, the existence of two phenotypes of 'loose' versus 'tight' control in LBP, as proposed by van Dieen et al.[160], might –to some extent– explain the large heterogeneity of findings in this population. 'Loose' control corresponds to patients with a primary pattern of diminished excitability of the trunk muscles, whereas enhanced excitability is considered to be characteristic for the 'tight' phenotype.[160] Interestingly, the findings of our systematic review relate the most to the 'tight' control phenotype, since with a higher presence of catastrophizing/fear the trunk muscle excitability in general tended to be higher in the superficial muscles (i.e. altered timing and increased activity). Furthermore, the often mentioned 'guarding mechanisms' also correspond to this phenotype. The indications of diminished muscle strength, endurance and functional performance could be consequential to the use of this possibly more energy-consuming and less efficient movement strategy. However, it is important not to overestimate the role of these phenotypes in the current results, since their main relevance might lie in the fact that studies with predomi-

nantly 'tight control' phenotypes compared to predominantly 'loose control' possibly might yield different results and could cause conflicting evidence. Furthermore, mixed phenotypes within one study could lead to null results, whereas subgrouping based on the two phenotypes might yield different results. The role of fear and catastrophizing in this regard still needs to be substantiated.

Even though for the majority of the studied movement-related outcomes the direction of effect of catastrophizing and fear was similar, findings were generally less conflicting for catastrophizing compared to fear. We suggest that this might be due to the inherent difference between both constructs. Fear represents both cognitive and emotional processes[101] and thus might entail a bigger sensitivity towards inter-individual differences, whereas catastrophizing mainly reflects cognitive processes[27, 135], which might have more consistent effects.

In conclusion, this systematic review highlights the relevance of considering both catastrophizing and fear in the study of (C)LBP, since their effects on movement cannot be disregarded, even though further clarification of the exact interactions needs to be provided. There is also an important impact of these cognitive-affective factors on the quality of life and participation of LBP sufferers, since catastrophizing and fear have been shown in other reviews to be related to higher levels of disability as well.[101, 121, 171, 172, 177]

1.2 Chapter II – The influence of physical and cognitive exertion on movement preparation in healthy adults

Due to both physical and cognitive exertion, fatigue can arise during the performance of everyday tasks, work, leisure and sports, and it is often hypothesized to play a role in altered movement[5, 42, 86, 110, 145] which could increase injury risk[24]. Furthermore, the experimental RAM paradigm devised for assessing movement preparation in **Chapter III** was known to consist of a lengthy testing (approximately 50 minutes) with both physical and cognitive demands which were hypothesized to be exerting and could induce fatigue as a byproduct of the testing. However, it was not yet clear whether and in what way fatigue might affect movement preparation and whether differential effects of fatigue could be expected for different types of fatigue-inducing exertions, more specifically physical versus cognitive exertion. Therefore, it was of primordial importance to assess the influence of fatigue on both peripheral and central measures of movement preparation in healthy adults first. In this way, possible effects of fatigue could be controlled for when performing the clinical study of **Chapter III**.

1.2.1 Chapter II, part 1 - Does fatigue, induced by a single bout of either physical or cognitive exertion, affect peripheral movement preparation in healthy adult people, as assessed by examining feedforward trunk muscle activation with EMG?

Since until now only one pilot study with a very small sample size examined trunk muscle APAs after physical exertion and described earlier onset timing of the TrA/IO muscle[5], and since no studies had yet examined effects of cognitive exertion on APAs, an experimental study to further examine the influence of a single bout of physical and cognitive exertion on feedforward trunk muscle activation was highly needed.

Based on the results of our experimental study in healthy adults, APAs of the trunk muscles were not affected by physical nor cognitive exertion, indicating that these measures in our study were rather stable and fatigue-resilient. Hence, the preliminary findings of the pilot study of Allison et al.[5] could not be supported. However, this does not necessarily mean that **physical** and **cognitive exertion** do not affect movement preparation altogether. For instance, previous research did find diminished movement performance of physical tasks after physical[46, 56, 116] and cognitive exertion[108, 126]. Even though APAs in the current study are unaffected by physical and cognitive exertion it might be that the influence of those types of exertion on movement alterations is not through physiological adaptations in motor control, but perhaps by reduced motivation, which was previously described as a mechanism through which cognitive exertion influenced movement performance[118, 127]. Furthermore, instead of onset timing of APAs,

other mechanisms related to motor control, such as amplitude properties or variability of APAs might be affected by fatigue, but this was not examined yet.

1.2.2 Chapter II, part 2 - Does fatigue, induced by a single bout of either physical or cognitive exertion, affect central movement preparation in healthy adult people, as assessed by examining the Contingent Negative Variation with EEG?

The contribution of central factors to movement preparation, such as the CNV, and the influence of fatigue on these factors has not yet been broadly examined, despite the fact that executive cognitive functions are considered as essential processes in locomotor control[2]. Due to its associations with diminished cognitive and/or motor task performance, which is reflected in decreased task accuracy and delayed reaction times[16, 105, 108, 150], fatigue was hypothesized to affect movement preparation.

Concerning **physical exertion**, previous research found no effects of acute aerobic exertion on CNV-amplitude[39, 146, 153], whereas the related BP-potential was larger when performing isometric exerting tasks[55, 84, 139], and larger movement-related potentials were also described in association with increased perception of effort for physical exerting tasks[32, 33]. Therefore, CNV-amplitude in preparation of rapid arm movements was hypothesized to enlarge as well in response to an acute bout of isometric physical exertion of the trunk muscles. However, this hypothesis was not confirmed by the findings of our experimental study, since no effects of physical exertion on CNV-amplitude were found. Hence, in our study there is no evidence for increased distribution of attentional resources towards preparation of arm movements after a single bout of physical exertion of the trunk muscles in order to optimize movement performance, as was the case for the aforementioned BP-studies[11, 55, 84, 139]. It is suggested that these differences between BP and CNV are primarily based upon methodological differences. Since in most BP-studies 'time-on-task' effects of a physical exertion in a prime mover were examined and properties of the fatiguing task and the task used to measure BP where the same[55, 84, 139], whereas in our study the properties and location of the physical exertion (i.e. exertion of trunk muscles) differed from the properties of the motor control task used to assess CNV (i.e. the RAM) it is suggested that physical exerting effects are rather 'task-specific'. Hence, despite the primordial role of the trunk muscles in maintaining postural control during RAM performance, the fact that these muscles are no prime movers for the performed task might explain the lack of effects of physical exertion of these muscles on movement preparation for the RAM. Furthermore, high intensity, isometric, cyclical and bilateral exertions of large muscle masses[63] have been shown to have the biggest chance of inducing fatigue effects that also extend towards more distant body parts not involved in the exertion itself. Therefore, the hypothesis was stipulated that repeated exertions of the trunk muscles instead of a single repetition as performed in our study could affect movement preparation for arm movements to a bigger extent, which might be reflected in altered CNV-amplitude. Another possible explanation is that no additional attentional resources were directed towards movement preparation after physical exertion, since participants mainly focused on optimal arm performance (as was instructed), but perhaps neglected retaining optimal postural control. Thus, instead of increased attention, attention might merely have been redistributed towards the main movement at the expense of other motor functions. However, this hypothesis is quite speculative and could be examined by applying postural control measures concurrently with CNV-measurement.

Concerning **cognitive exertion** an opposite hypothesis was formulated as for physical exertion, i.e. smaller CNV-amplitude after exertion, since previous studies have shown reduced amplitudes of CNV[16] and LRP[87] with time-on-task for cognitive tasks. Such reduced CNV-amplitude would then be considered to reflect diminished motivation and attention due to the monotony of a repetitive or ongoing cognitive task.[16, 113] However, again, the main hypothesis was not confirmed by the findings of our study, since no effects of cognitive exertion on CNV-amplitude in preparation of rapid arm movements in healthy adults were found. Possibly, the task-switch from the cognitive exerting task (i.e. modified incongruent Stroop) to the RAM task, which both have different properties, might have been enough to break the monotony and –to some extent– reset the motivational state of the subjects. Hence, fa-

tiguing effects due to cognitive exertion might have been neutralized in this way. Furthermore, the RAM task used in this paradigm was considered not to be fatiguing on itself, since additional time-on-task analyses displayed no difference in CNV amplitude between early trials and later trials in a RAM task.

An integrated view on peripheral and central movement preparation after exertion. The two experimental studies discussed in Chapter II hold similar conclusions, since no evidence for effects of physical and cognitive exertion on both central and peripheral measures of movement preparation for RAM in healthy adults were found. Importantly, based on these findings we suggest that the RAM is possibly a paradigm with considerable repeatability and consistency when used to assess APAs of the trunk muscles and CNV-amplitude. This paradigm was therefore deemed suitable by our research group to be applied in different experimental and clinical settings which might consist of physical and/or cognitive exerting tasks, without high risk of these tasks themselves already influencing and confounding the outcomes of the RAM. However, it is not known whether these inferences are transferrable to RAM paradigms with durations extending far beyond 20 minutes (as assessed here), and to paradigms which entail both high physical and cognitive demands at the same time, since possible cumulative effects of both types of exertion were not yet studied. Furthermore, it cannot be stated with full certainty that such results would be the same for different clinical populations, as for now this was only investigated in healthy people. For instance, in CLBP populations disturbed sleep[7], clinical insomnia[151] and increased fatigue levels[138, 143] have been described in previous research, as well as less recuperation capacity following specifically physical exertion[45]. Hence, such patients might be more susceptible to physical and/or cognitive exertion. Nonetheless, when taking such variables into account and carefully designing the experimental paradigm of a study consisting of RAM measurements, the possible confounding effects of fatigue on APAs and CNV can be minimized, and such a paradigm can be considered useful for clinical populations as well.

1.3 Chapter III – A biopsychosocial perspective on the influence of fear on movement preparation in healthy people, RLBP and CLBP patients

Does situational fear of back pain influence central and peripheral movement preparation in healthy people, RLBP and CLBP patients, as assessed by examining respectively Contingent Negative Variation with EEG and feedforward trunk muscle activation with EMG?

Despite the multifactoriality of LBP chronification, studies which combine two of the most important hypothesized mechanisms in this process, i.e. alterations in movement preparation and the presence of fear/expectations for pain, are wanting. Furthermore, regarding this matter other limitations exist in current literature (see **Chapter I, part 2**), such as a lack of situational assessments of fear and a lack of comparison between different LBP entities. The apparent need for studies addressing these issues led to the performance of the experimental study described in **Chapter III**. This study examined the influence of experimentally-induced pain-related fear on APAs of the trunk muscles and CNV during the preparation phase for rapid arm movements, since this could provide valuable insights regarding short-term interactions between situational, movement-related fear and alterations in movement preparation. Furthermore, it was examined whether progressive alterations from healthy people, over RLBP to CLBP would be present, since a hypothesized continuum in LBP complaints could be expected based on muscle structural[60, 75] and functional[60] differences, and different alterations in pain processing mechanisms[59] between distinct LBP groups. Possible CNV-APA associations were also investigated in order to examine whether these central and peripheral measures in movement preparation are related or not.

The results of **Chapter III** showed that with situational fear larger CNV-amplitude arose which indicates enhanced **central movement preparation** and attention for the task at hand[39, 146]. Enhanced somatosensory attending in bodily regions under threat of pain or during fearful situations was already previously established[25, 26, 43, 162, 163], but

the current findings provide arguments for an expansion of this attentional redirection with fear towards enhanced movement preparation for movements under threat as well. A previous study, which merely examined differences in CNV-amplitude between controls and RLBP patients without considering the influence of fear, described larger CNV in the RLBP group[137], which could not be supported by the current findings as no group differences in CNV-amplitude were found here. Methodological differences between those studies might explain this discrepancy, but in any case further research is needed to establish whether or not group differences are generally present. Hence, based on our results it can be speculated that a situational state of fear is likely to induce general attentional redirection towards both somatosensory and motor systems, but the role of the presence and amount of LBP in this process is unclear for now. It is hypothesized that such an attentional redirection could relate to altered movement strategies with more conscious effort to optimize movements in order to avoid further harm/pain[99]. However, this was not reflected in altered **peripheral movement preparation** in the current study. No differences in APAs were found in relation to fear, even though APAs were hypothesized to delay with situational fear in concordance with earlier research which described such delays in healthy people expecting pain[117]. Hence, it is speculated that the central alterations described in this chapter might already optimize movement preparation in a way that on a peripheral level no differences arise. Another hypothesis is that both measures, CNV-amplitude and APA onset timing, despite each reflecting movement preparation processes, are probably unrelated, distinct mechanisms. The latter inference can be supported by findings of no correlations between these measures in a previous study[137], and also by the lack of systemic associations between both measures in the current study. Only for one muscle, the ILTc, later APAs in association with larger CNV-amplitudes have been found in **chapter III**, whereas for all other muscles no significant associations could be found. Furthermore, the lack of effects of situational fear on APA onset timing in the current study is also not in line with the general tendency of altered APAs with dispositional fear which was described in **Chapter I, part 2**. It is logical that the influences of both types of fear constructs are different, since situational fear reflects a 'state' of acute responsiveness to an imminent threat or context-specific experience, whereas dispositional fear is more related to inherent 'traits' of an individual and his/her previous experiences regardless of the current context.[21] Therefore, it can be speculated that peripheral movement preparation is not really responsive to acute emotional changes, but possibly requires more time to be affected.

Interestingly, though, group differences in peripheral movement preparation did appear in the current study. These differences were highly muscle-dependent and are described in full detail in **Chapter III**. For most of the studied trunk muscles a similar tendency could be discerned, with in general trunk muscle onsets that were delayed in the CLBP group compared to healthy controls and RLBP sufferers. No significant differences between healthy controls and RLBP patients were found in this regard. These results were somewhat surprising as a continuum of increasingly delayed muscle onsets was expected from the controls over the RLBP patients to the CLBP patients. Mainly the lack of differences in APAs of RLBP compared to the controls was peculiar and did not confirm previous reports of delayed trunk muscle onsets in (pain free) RLBP sufferers by Hodges et al.[70, 71] during performance of a similar arm task. In the studies of Hodges fine-wire EMG was applied as opposed to sEMG in our study, which might explain these different findings to some extent. The procedure and the pain (although minimal) associated with the insertion of the needles for the fine-wire sensors, might have already induced alterations in the SMC of the RLBP patients. A study with combination of sEMG and fine-wire EMG could be useful to further explore this discrepancy. On the other hand, the results of delayed onsets in CLBP were expected and in line with previous research[90]. These surprising findings in combination with the inherent differences between RLBP (often pain free periods) and CLBP (continuous pain) patients led to an interesting hypothesis. It can be speculated that the APAs in the RLBP group, which in our study were similar to those of healthy people, are part of an adaptive motor control mechanism in these patients, which –to some extent– protects them from further harm/pain and can amount to recovery, which is reflected in the frequent pain free periods. Patients who do not have such an adaptive SMC system might be more prone to develop chronic ongoing complaints, without substantial recovery and pain free periods.

Another, non-primary, but nonetheless interesting finding of this study was that the stimulus used to induce pain (electrocutaneous stimulus) evoked more fear in the RLBP group compared to the controls, whereas for the CLBP

group no such differences with the controls were eminent. We hypothesize that this could indicate that RLBP patients, due to the recurring nature of their complaints, might be more susceptible for phasic pain and possibly associate more feelings of harm/damage with such painful stimuli and consequently experience more movement-related fear, whereas healthy people have less preconceptions concerning back pain and therefore might have a less pronounced emotional reaction towards possible painful stimulation to the back[58]. The CLBP patients then, might be less susceptible for alterations in their emotional state in association with phasic pain stimulation due to the continuous nature of their LBP complaints which might have rendered them to get used to experiencing pain to some extent.

2 Implications

Overarching concepts, parallels, and links between the three chapters will be discussed here. Specifically, new insights concerning 'guarding mechanisms' in LBP, and recommendations for assessment and treatment of LBP patients will be discussed in the following paragraphs.

The previously described '**guarding mechanism**' (see **chapter I, part 2**) is considered to be an inconsistent and highly variable mechanism, which might not be present in all LBP sufferers (i.e. also people with a 'loose' phenotype exist) and which can present itself in varying degrees. The current dissertation has several interesting results that shed a new light on this mechanism. Interestingly, a novel hypothesis of the current dissertation was that a higher level of catastrophizing and/or fear might predispose LBP patients towards a protective 'guarding mechanism' (i.e. increased muscle activity or diminished relaxation capabilities, and altered muscle timing) as opposed to a rather 'loose' motor control mechanism. Furthermore, it was hypothesized that the 'guarding mechanism' is a postural strategy which possibly requires more conscious effort. Evidence supporting this, with larger CNV-amplitude in relation to delayed APA timing and larger P2-amplitude in relation to diminished center of mass displacement in LBP sufferers, was discussed in **Chapter I, part 1**. On the short-term, presence of such 'guarding mechanisms' could be pain-relieving and rather beneficial for the treatment of patients with LBP. If patients feel safer to perform movements with use of such an unconscious movement strategy, aimed at preventing further harm/damage[106, 128, 157,] this might help rebuild their movement confidence in the initial stages of therapy. This could be especially important for those patients with high levels of catastrophizing/fear, since they have been shown to have a heightened propensity towards processes related to 'guarding' in **Chapter I, part 2**. Therefore, in such patients an early detection of catastrophizing and fear related to their pain, and subsequently a graded exposure to movements they perceive as threatening/harmful can benefit treatment outcomes on both a physical and psychological leve[175]. However, if 'guarding mechanisms' persist on the long-term they could become maladaptive and might even contribute to the recurrence/persistence of complaints, due to the higher physical strain these mechanisms place on the body[164]. Hence, we propose that normalization of muscle activation and motor strategies during movement should receive sufficient attention in the treatment very shortly after the initial stages, in order to acquire a functional movement pattern with highly dynamic segmental control as opposed to the initial, more rigid movement patterns.

The findings of this dissertation hold some other important implications for the **assessment and treatment of non-specific LBP**. However, it has to be stressed that treatment effects as such were not explicitly examined in this dissertation. Hence, the following inferences are mainly indirect observations or hypotheses that need further substantiation through treatment-based studies. The combined insights of several chapters point towards a hands-off biopsychosocial approach in a multi-disciplinary setting, which has been recommended as treatment for CLBP by previous research. From the perspective of this dissertation, two major suggestions for this approach can be made. Firstly, the importance of evaluating and treating physical dysfunctions not in a solitary manner, but in combination with appropriate assessment and consideration of dispositional fear and catastrophizing in CLBP, since such cognitive-affective factors have the potential to form therapeutic barriers which might impede treatment. It was

already mentioned in **Chapter I, part 2** that this combined approach has added value over usual care[37, 85, 95]. A prerequisite for such an approach is of course that there is further development of easy-to use questionnaires/tools to assess cognitive-affective factors in clinical practice. Or, at least that physical therapists, but also other clinicians like general practitioners, are sufficiently trained and educated to import an initial cognitive-affective evaluation in the assessment of LBP patients. Gathering forces or increasing structural cooperation with specialists in this domain, such as psychologists for instance, could be recommended even more. In this way the complaints can be tackled from different perspectives. Even though at the moment such an intense cooperative rehabilitation model is already incorporated in specialized rehabilitation centers or some –but not many– multi-disciplinary group practices, there is a lack of structural enforcement of such initiatives. Therefore, despite a more and more biopsychosocial inspired education of several clinicians which are confronted with CLBP patients, such as general practitioners, physical therapists and occupational therapists, this approach is not fully implemented in the Belgian healthcare system (nor in a lot of other countries).

Secondly, a mental overload in CLBP[34], and central sensitization[38, 49] processes have been proposed in **Chapter I, part 1** to explain for the inability to adjust to repetitive stimuli, albeit of noxious[166] or auditory nature[34, 48]. Even though previous research has shown that central sensitization does not necessarily occur in all CLBP patients[136], it is nonetheless recommended to avoid exuberant somatosensory stimulation (i.e. manual techniques, frictions, etc.) in clinical practice, and a hands-off approach seems favorable based on the current dissertation. This is fully in line with recent international guidelines which state that movement and exercise, i.e. hands-off treatment, are the most appropriate non-invasive and non-medicinal treatment methods concerning CLBP.[31] As it is not yet clear what kind of specific movement is most beneficial, only a general recommendation was made. It is also important to take into account that based on **Chapter I, part 1** limited evidence for disturbed learning due to diminished feedback processes in the brain were suggested[149]. Presently there is no evidence expanding these findings specifically to motor learning, but it is hypothesized that this process might be affected in CLBP. Thus, when conducting a mainly movement- or exercise-based therapy we suggest to provide optimal external feedback and tailored guidance (primarily in the beginning) to counter for this deficiency in internal feedback processes. Therefore, especially in the early phases of exercise therapy, visual, tactile and auditory feedback are recommended to be given by the therapist, doctors or other healthcare workers, as it could be expected that the motor learning process in LBP patients might occur slower than in people without LBP. Furthermore, it is of primordial importance in these patients to make sure that movements are being performed correctly and that patients have acquired the appropriate movement plans before several exercises are being performed at home or unsupervised.[78] Of course, since reliance on external feedback is not desirable on the long-term[140], clinicians should also provide the patients with the context to internalize these feedback processes so that they can become active participants in their rehabilitation process who are able to guide and regulate their movements and incorporate learned adaptations and movement strategies into their daily lives. Importantly, the use of manual techniques is not disregarded altogether as these still have their proper merit in the rehabilitation process of some patients, but these should comprise a minimal proportion of the whole treatment session.[31] As proposed earlier, excessive repetitive somatosensory stimulation of the painful area should be avoided when performing such techniques. These recommendations are mainly based on findings concerning CLBP sufferers, however, we believe that an early adoption of the biopsychosocial assessment and treatment of LBP might also benefit ALBP and RLBP sufferers and could possibly help in avoiding chronification of the complaints. However, this statement is highly speculative and needs further research, as the evidence concerning ALBP and RLBP was minimal, and treatment effects were not evaluated in this dissertation.

Importantly, several functional distinctions between RLBP and CLBP patients were discussed in **Chapter III,** which suggests that the treatments of these distinct populations should probably comprise different accents as well. Due to the lack of sufficient research comparing RLBP and CLBP patients, especially concerning treatment effects on both groups, we cannot make well-founded propositions for distinct treatments for RLBP compared to CLBP patients. However, based on the findings of this dissertation we can formulate some general speculations in this regard. For instance, in **Chapter III** RLBP patients showed a different pattern of APA onset times (similar onset compared

to healthy people) in most of the trunk muscles compared to CLBP patients (delayed onset compared to healthy people). It was hypothesized that the earlier APAs in RLBP reflect an adaptive motor control mechanism with more recuperation capacities, whereas in CLBP a maladaptive mechanism might be at play with delayed APAs. Muscle timing is only one aspect of SMC, and previous research did find alterations in other aspects related to trunk SMC in RLBP which were considered to contribute to recurrence of complaints, such as enhanced co-contraction patterns of the trunk muscles[30]. Hence, in our opinion trunk motor control exercises should not be disregarded altogether in the RLBP population, but perhaps a less substantial proportion of the treatment sessions in RLBP than CLBP patients should consist of exercises aimed at normalizing SMC as the former group possibly has more recuperation capacities or a less maladaptive SMC system to begin with.

3 Methodological considerations

Detailed considerations were already mentioned per chapter. In this section a general summary and extended view on the most important limitations and strengths across chapters, which is essential for a nuanced interpretation of the general discussion of this dissertation, will be provided.

3.1 Limitations

The majority of the inferences made in the **systematic reviews** of this dissertation **(Chapter I)** have to be treated with some nuance as most are based on single cross-sectional studies and therefore in a lot of the cases low levels of evidence and conclusion were attained. Furthermore, the average RoB scores for the individual studies included in the systematic reviews were quite moderate to high, mainly due to the fact that selection bias was not always ruled-out. Therefore, several of these findings require further investigation in order to make firmer statements possible. Heterogeneity was present in several of the studied outcomes in both reviews, such as different measurement methods that were applied for functional brain assessment or movement-related outcomes, use of a variety of questionnaires for cognitive-affective assessment, as well as differences in the characterization of the LBP populations that were studied. This heterogeneity impeded the possibility of pooling data. Therefore, meta-analyses could not be conducted, which is one step higher on the methodological chain compared to systematic reviews. The intention of these reviews was to compare ALBP, RLBP and CLBP populations in order to gain further insights about a possible spectrum or continuum of alterations associated with LBP. However, in reality, mostly CLBP populations were studied. The minimal amount of studies regarding ALBP or RLBP or of studies examining all three groups within one study made between-group comparison nearly impossible for the majority of the studied outcomes. Oftentimes, mixed groups of for example RLBP and CLBP patients were examined as one entity. However, since in **Chapter III** different findings regarding APAs and sensitivity to phasic fear between RLBP and CLBP patients have been described, it is plausible that these groups entail very distinct processes and mechanisms in relation to movement. Therefore, one should be cautious when interpreting results from mixed groups.

The fact that the **experimental studies** performed for this dissertation **(Chapter II and III)** all had a cross-sectional design limits direct statements about causal relationships between the examined variables, as longitudinal (prospective or retrospective) research is more suited to examine causality.
An interesting phenomenon was that, although no important risk factors or contra-indications are described for the used measurement techniques (EEG and EMG), apparently the experimental set-up of our studies predisposed to orthostatic hypotension in a small minority of the participants. Due to this phenomenon, some of the participants had to seize further continuation of testing and were considered as drop-outs. Possibly, the impressive experimental set-up with a lot of wires and devices attached to the body, and the requirement of having to perform rapid arm movements while standing upright for a considerable duration, in combination with an inherent predisposition towards orthostatic hypotension in these subjects might have caused these complaints.

It was a deliberate choice to apply surface instead of fine-wire EMG in **Chapter II, part 1 and Chapter III**. Use of fine-wire EMG could have contributed to feelings of harm or fear due to its invasive and slightly painful application, which was to be avoided.[12, 141] However, it needs to be mentioned that fine-wire EMG has the advantage to specifically measure the deep TrA and MF muscles without cross-talk of more superficial muscles, which was not possible in our studies since we used surface EMG.[22, 23, 83, 167] Concerning the analysis of the EMG data, visual picking was complicated due to the often high baseline muscle activity. This high activity was possibly caused by the long duration of the testing in a standing position and the high amount of factors participants had to pay attention to besides relaxation of the trunk muscles, i.e. the visual cues, optimization of the arm movement, refraining from blinking and keeping the head still. Due to this, in a considerable amount of trials no clear onset could be determined. Other important considerations regarding the visual picking procedure are that it remains somewhat a subjective process, despite the fact that strict guidelines concerning onset determination were adhered to, and that there was a considerable between trial variability present in the analyzed data. However, when compared to automated, software-based onset detection methods, the manual visual picking procedure remains the preferred analysis method for this type of data.[68]
Concerning the EEG-analysis in **Chapter II, part 2 and Chapter III,** slow-wave drifts and low-frequent artifacts (e.g. due to perspiration on the scalp) were delicate to remove from the raw signals without filtering-out the CNV potential itself, as this is also a low-frequent, slow-wave activity[169]. Likewise, interference of the vibrotactile stimulus, which was administered in the warning-go cue interval in the final study (for SEP analysis which is not a part of this work) could not be fully filtered out, despite the use of low-pass filters. Hence, the superposition of both signals remains visible in the CNV overlay graphs to some extent (see **FIGURES 3-5, Chapter III)**. Fortunately, this interference is of no real importance for the CNV-analysis in this dissertation since it occurs well before the interval in which the late CNV-amplitude was analyzed here (the last 100ms before the go cue).

Specifically concerning the fatigue studies in **Chapter II**, no accelerometer data was acquired and thus the velocity of the RAM performance could not be controlled for, even though previous research has shown that velocity of the arm movement could play a role in the APA onset timing[71]. However, participants were instructed to always perform the movement "as fast as possible", and this movement was extensively trained before and visually assessed during the experimental sessions in order to ascertain optimal movement performance and velocity.

With regards to **Chapter III** it needs to be considered that the electrocutaneous stimulus used to evoke anticipation/threat of pain has different characteristics than clinical LBP, since it holds less connotations of possible harm/damage to the body[155,] nor does it associate with previous negative experiences and/or emotions. Whereas, in clinical LBP a larger cognitive-emotional load is associated with painful sensations in the lower back area.[58] A final consideration for this chapter is that due to the long upright standing test position LBP complaints of most of the participants increased towards the end of testing. However, it was assessed whether LBP severity had an influence on the outcome measures of interest and whether it had to be controlled for in the statistical analyses, but this was not the case.

3.2 Strengths

Important methodological assets of the **systematical reviews** described in **Chapter I** were the fact that all studies were screened and assessed for methodological quality by two blinded researchers who reached high inter-rater agreement levels, and that all steps in conducting these reviews were performed according to the internationally accepted PRISMA guidelines[114]. Furthermore, almost all studies included in these systematic reviews utilized validated or well described testing protocols. Based on these systematic reviews important lacunas in current literature were exposed, and several methodological approaches were examined, which guided the conception and design of the experimental studies in this dissertation.

The design of the **experimental studie**s performed **in Chapter II and III** entails several methodological strengths worth pointing out. The experimental conditions that were being compared (i.e. PE vs. CE; fear vs. no fear) were always administered in a randomized manner, which ruled out possible order effects or carry-over effects from one condition to another. The possible influence of confounding variables on the outcomes of interest was minimized in two ways. Firstly, the groups under comparison were age- and gender-matched in **Chapter III** or even fully matched due to a crossover design in **Chapter II**. Secondly, several questionnaires, self-report ratings and baseline sociodemographic characteristics of participants were used to control for a variety of possible confounders such as physical activity level, amount of disability, presence of cognitive affective factors (anxiety, depression, kinesiophobia, hypervigilance,...), pain severity, sleep quality and quantity, BMI,... Furthermore, drop-out participants of the studies were always compared with the participants that remained included throughout the entire testing. No significant socio-demographic differences were noted for these drop-outs. Thus, as there was no subgroup of participants with specific characteristics more inclined to dropping-out of our test protocols, the loss of these participants is considered to have had no significant effect on the final outcomes of our testing (i.e. no attrition bias). Another strength was that the number of participants of the investigated groups conformed to predetermined sample sizes of a priori power analyses.

With respect to the measurement of peripheral movement preparation (i.e. APAs) the incorporation of a backwards arm movement besides the forward arm movement, which was the only one being analyzed, ensured unpredictability of the direction of arm movement. Unpredictability of movement direction ensured that participants would not initiate the arm movements before they viewed the go signal. Concerning the EMG-analysis of the APAs, the Matlab-based visual picking procedure used here was specifically developed, optimized and tailored to the specific characteristics of each study. The data was first fully blinded by a researcher with regards to participant number and group, type of condition, muscle, muscle side and trial number. Subsequently, another researcher, who was highly trained in the visual picking procedure beforehand, determined the onset of each blinded trial. The visual picking software included possibilities for zooming in and out, and comparing raw data versus 30Hz filtered and rectified data on one screen. Afterwards, an overlay graph was created on which all trials of one specific condition for one muscle per participant were presented and possible mistakenly placed onsets could still be removed.

The use of EEG for the analysis of cortical movement preparation (i.e. CNV) was deemed superior to the use of fMRI for the specific research questions and study designs of this dissertation. The general differences and advantages of EEG compared to fMRI were previously discussed in the introduction of **Chapter I, part 1**, with EEG having a higher temporal resolution[64] and being optimally suited to measure complex and subtle brain processes in short consecutive time-spans. The main merit of EEG in our studies, was its high-practicality in a functional setting. EEG could be used during movement while standing upright and synchronously with the EMG-measurements used for the APAs, whereas fMRI can only be performed on participants lying down, not during movement and without concurrent EMG-measurement.

Linear mixed model analysis, was an often used statistical method in our experimental studies instead of the more common used and generally known repeated measures ANOVA. Recently it is being more and more stressed that repeated measures ANOVA is only valid for datasets with a quite straightforward and simple design, with almost no missing data and normally divided residuals. Linear mixed models have more flexibility in this regard and can be used in more complex designs, such as the designs of our studies.[62, 93]

Throughout this dissertation both central and peripheral measures for movement preparation were examined and compared, which is one of the main assets of this work as assessment of possible parallels and interplay between these factors was highly needed. Especially the final study (Chapter III) made such an integrative analysis possible as both APAs and CNV were measured and analyzed concurrently. Furthermore, this final study was tailored to fill-in several important gaps, lacunas and limitations of previous research that were discovered through the first two chapters. A first important asset of this study was the combination of the use of questionnaires on the one hand and on the other hand experimental manipulation to assess cognitive-affective factors, as in this way respectively dispositional and situational aspects of cognitive affective factors could be taken into account. A second important

asset was that control subjects were compared with RLBP and CLBP sufferers in one and the same study. Such comparative, between-group studies were formerly lacking in experimental research in this field.

4 Future perspectives

The finalization of a research project should not be considered as an ending, but rather as a starting point from which new ideas and further progression of scientific knowledge can arise. As such, the findings of this dissertation form a fertile basis for the conception of some interesting ideas for the direction of future research in the broad domains of (clinical) LBP, psychology and exercise physiology.

4.1 Chapter I, part 1

Research has only scratched the surface when it comes down to the use of EEG to examine brain function in LBP populations compared to healthy people, as until now mainly balance tasks, noxious and auditory processing, and decision making processes have been studied. This dissertation already made considerable efforts to expand this knowledge by further examining cortical movement preparation for rapid arm movements in healthy and LBP populations **(Chapter II and III).** However, still a lot of other brain functions remain unexplored in this regard. Importantly, the main emphasis in EEG-research should be placed on brain functions that are thought to be related with or affected by LBP. For instance, besides altered recruitment patterns of trunk muscles[70, 159, 161, 168], alterations in several other motor functions, such as increased trunk stiffness[73, 156], poor proprioception[36], postural dysfunction[41, 174], and limited range of motion[44, 74, 120, 129] have previously been described on a peripheral level in LBP. Whether these changes are associated with alterations in brain function still requires EEG examination. Likewise, a high interest lies in the cortical processing of non-noxious somatosensory stimuli, such as vibration, touch/pressure, temperature, and proprioception in LBP sufferers compared to healthy people. Due to LBP, peripheral sensitization and in some cases even central sensitization[136] might occur. As the latter is characterized by hyperalgesia and allodynia[76, 131] the brain processing of (normally) non-noxious stimuli might be altered in this population, which could consequently be reflected in changes in the SEPs of these stimuli as well. One recent study already examined non-noxious somatosensory processing in CLBP and RLBP as compared to healthy people by studying vibrotactile stimulation to the back[25], but more similar studies are needed in order to form definite, and high-level conclusions in this regard. Besides studying other brain functions, novel paradigms and different EEG-analysis methods could also be explored in LBP populations. To name a few examples, studies examining movement-evoked LBP, specific motor learning processes, or resting state EEG, as well as time frequency analysis methods could also contribute to the expansion of knowledge on central underlying processes of LBP.

Furthermore, as several differences in brain function were found in LBP sufferers compared to healthy people, the question immediately arises whether such alterations are reversible through therapy. One previous study which examined brain function in LBP with transcranial magnetic stimulation already showed that with specific and targeted rehabilitation some functional representations of motor control function in the brain that were altered due to LBP can be reversed back to a representation in the brain resembling that of healthy controls. Moreover, this study showed that such changes were related to functional improvement as well.[154] Hence, due to the considerable degree of plasticity of the human brain it is hypothesized that several functional brain changes in LBP measured with EEG could also be reversed by the appropriate therapy. One of the main challenges for future researchers in this respect would lie in determining what kind of therapy would be best suited for this purpose. Most importantly, however, clinical outcomes should not be disregarded when performing such research. The main goal of treatment should remain clinical and functional improvement for the patient, and brain adaptations might be a reflection or control thereof, but should not be a goal on itself.

Until now only decision-making processes were examined with EEG in LBP, whereas other executive functions were left unexplored. Based on behavioral test results, one study found no altered executive functioning in CLBP patients

compared to healthy people[109], whereas in various other chronic pain populations executive functions such as set shifting and response inhibition were impaired[10, 14, 15, 119]. It is recommended to examine such other executive functions with EEG in LBP as based on these behavioral test results functional brain differences can be hypothesized.

4.2 Chapter I, part 2

The studies included in this systematic review, examining the influence of catastrophizing and fear on movement performance in LBP, mainly assessed dispositional features of catastrophizing and fear by means of questionnaires. However, multi-dimensional assessment of not only dispositional features, but additionally also more context-specific/situational features of cognitive-affective factors would yield a more comprehensive perspective of these factors and their influence on movement performance in LBP[21]. In **Chapter III** of this dissertation such a multi-dimensional approach was already implemented by experimentally inducing expectations and fear for pain during movement besides administering a battery of questionnaires assessing similar cognitive-affective factors in LBP patients and healthy people. More studies like this are required, as other cognitive-affective factors, such as attentional aspects, depression, etc. still warrant further research in this matter.

4.3 Chapter II

In this chapter we found no influence of fatigue on either peripheral (Part 1) or central (Part 2) measures for feed-forward movement preparation. As this was only investigated for healthy adult participants a next step would be to perform similar experiments in other populations to assess whether these results are generalizable. For instance, studying these effects on different age groups holds merit as previous research has shown that older participants often show diminished recovery after -specifically physically induced- fatigue than younger participants[47, 53, 103]. Such diminished recovery might in that case induce alterations in APAs of the trunk muscles or CNV prior to arm movements. Similarly, in CLBP sufferers compared to healthy people less recuperation capacity following PE has also been found[45], and disturbed sleep[7], clinical insomnia[151] and increased fatigue levels[138, 143] have also been described in CLBP populations. Furthermore, based on findings of **Chapter I, part 1** a mental overload in CLBP was suggested, which could also indicate a diminished reserve capacity for task performance (physical or cognitive) in those patients. From this perspective it is highly relevant to assess whether fatigue or impaired recovery thereof could be considered as a moderating factor contributing to back pain chronicity through alterations in movement preparation.

Previous research described that physical exertion is more likely to induce localized and non-localized fatigue when large muscle masses are applied, and several repetitions of high intensity, isometric contractions are performed[63]. The intensity of the static contraction and the muscle mass applied in the protocols of **Chapter II** were considerably high and significantly increased self-reported fatigue. However, in future research these protocols could be further optimized by increasing the amount of repetitions of the PE and applying a resistance to which participants have to perform maximal trunk muscle contractions, in order to enhance the fatigue inducement.

As APAs of the deep, but not the superficial, parts of the MF are often delayed in LBP patients [104], and fatigue complaints have also been described in this population[50, 130], further research regarding the fatigability of the MF and whether it affects APAs could be interesting from a clinical point of view. For this specific muscle, it would be advisable for future studies to use fine-wire EMG, which specifically allows to study the superficial and deep fibres of the MF and could give a more specified perspective on the activation patterns in this muscle.

4.4 Chapter III

The in **Chapter III** discussed findings of dissimilar peripheral movement preparation patterns for RLBP versus CLBP patients complement previously described differences of muscle structural[60, 75] and functional[60] nature, as well as differences in pain processing[59] between both groups. Despite these patient groups exhibiting several important

functional differences they are still too often examined as one entity. A lot of research does not differentiate between both, and often even examines mixed RLBP/CLBP groups. Based on the novel findings of this chapter we advocate for a more distinct assessment and comparison of these groups, as we believe their inherent functional differences should be further explored and might be of value for a deeper understanding of the chronification and recurrence processes in LBP. In this connection, we hypothesized earlier that the muscle activation pattern in the RLBP patients (i.e. earlier contraction compared to healthy people) might reflect an adaptive mechanism which might benefit recuperation in these patients. It would be interesting to further examine this hypothesis. For instance, by conducting a longitudinal study one could examine whether within RLBP patients those patients with more delayed APAs, and thus a muscle pattern more corresponding to that of the CLBP patients, are at higher risk of developing chronic complaints in the future. In addition, it would be highly relevant to assess and compare the aforementioned factors between RLBP sufferers currently experiencing a pain flare and RLBP sufferers in a pain free stage of their condition, since in our study primarily pain free RLBP patients were assessed.

4.5 General

Some general recommendations have arisen through the comprehensive analysis of all chapters of this dissertation. To date, there is only a small foundation for causal inferences with regards to factors that might have a possible influence on back pain and chronicity thereof as mostly cross-sectional studies have been conducted. The current dissertation was also primarily founded on cross-sectional studies. Therefore, to be able to make statements concerning causality, studies with longitudinal designs are needed in this field. Another important proposal for future study designs is to include multiple LBP entities in one and the same study, such as ALBP, RLBP and CLBP. Direct comparison between these entities could provide interesting insights into the gradation of LBP, which is often proposed to be some sort of 'continuum'. Furthermore, the current dissertation mainly focused on APA onset timing and CNV-amplitude as main outcome measures. However, investigation of other properties of both peripheral and central measures for movement preparation, such as amplitude analysis of the APAs, and latency or frequency analysis of the CNV, could be examined in relation to both fatigue and LBP as well.

5 Main conclusions

In this dissertation cognitive-affective factors, alterations in movement preparation, and their interactions were examined in healthy people and LBP sufferers in order to further elucidate these mechanisms related to LBP chronification. First, literature was searched to examine existing theories, methodological approaches and lacunas in current literature concerning the functional LBP brain, and concerning interactions between cognitive-affective factors and movement alterations in LBP. Furthermore, the main experimental paradigm of this dissertation, i.e. RAM testing with concurrent EMG- and EEG-analysis to quantify peripheral and central movement preparation, was optimized based on the literature retrieved. Subsequently, this paradigm was tested and fine-tuned on a healthy adult population, while also examining possible fatigue effects on the main outcome measures (APA and CNV). Finally, this paradigm was incorporated in a clinical study examining the effects of experimentally-induced fear on movement preparation, and comparing these effects between healthy people, and RLBP and CLBP patients.

We found limited evidence for several alterations in the CLBP brain with regards to cortical motor functions, sensory processing and executive functions. These findings suggest an attentional prioritization in CLBP sufferers towards maintaining postural control prior to and following balance disturbances, possibly in order to protect the spine for further harm. Furthermore, enhanced sensory, but not cognitive-emotional processing, and indications for a mental overload and sensory hyperexcitability, are suggestive of central sensitization processes in at least a part of the CLBP sufferers. Disturbed feedback processes in CLBP sufferers were considered to reflect diminished problem solving and learning capacities in these patients. Peripheral movement-related alterations in LBP patients were often related to catastrophizing and/or dispositional measures of fear. Indications for associations of catastrophizing/

fear with alterations in trunk muscle timing, increased activity or diminished relaxation capabilities of the trunk muscles, and diminished trunk muscle endurance, but ambiguous relationships with trunk muscle strength were described in various LBP populations (primarily in CLBP). Moreover, a general decrease in performance of a wide range of functional tasks in association with higher levels of catastrophizing and dispositional fear was also suggested and might be due to the aforementioned muscle alterations. Yet, literature on these topics often remained limited or ambiguous, and could be expanded to other brain functions, to other cognitive-affective factors (such as attention), and in association with other movement-outcomes.

Regarding the influence of fatigue, no effects of either physical or cognitive exertion on both peripheral and central measures of movement preparation prior to arm movements were found. Specifically, the findings indicated that there are no physiological adaptations in trunk muscle timing and that there is no redistribution of attentional resources towards movement preparation after performing a single bout of physical or cognitive exertion in healthy subjects. Hence, we suggest that the RAM paradigm used to assess movement preparation in this dissertation possibly has considerable resilience against physical and cognitive exertion, and might likely be a repeatable and consistent method to measure both peripheral and central movement preparation in different experimental and clinical settings, which might entail high physical or cognitive demands. However, these conclusions cannot be generalized from healthy young adults to other (clinical) populations which possibly hold less recuperation capabilities, and need further examination in this regard.

Experimentally-induced, pain-related fear was associated with enhanced central (i.e. larger CNV-amplitude), but not peripheral (APA onset timing) movement preparation, regardless of the presence or amount of LBP. Hence, it is concluded that both measures, i.e. CNV-amplitude and APA onset timing, are likely distinct mechanisms in relation to movement preparation. This was also reflected in the lack of systematic associations between both measures. Group differences between healthy people, RLBP and CLBP sufferers, however, were found for peripheral movement preparation. The surprisingly earlier APAs in the RLBP group compared to the CLBP group that were found were hypothesized to reflect a more adaptive peripheral movement preparation process in RLBP sufferers as opposed to a rather maladaptive process in CLBP. It was speculated that this different movement preparation mechanism could explain why RLBP patients have frequent pain free periods and show more recuperation capacities than CLBP patients, but this needs to be confirmed by other research.

Based on an integrative analysis of all the studies in this dissertation we found additional evidence supportive of 'guarding mechanisms' in -at least a portion of- LBP sufferers. Furthermore, recommendations towards a hands-off, biopsychosocial, multi-disciplinary approach in the treatment of non-specific (C)LBP sufferers were made. Finally, this dissertation has to be seen as a fertile basis for further research. We recommend to further apply and explore the use of EEG in the study of the LBP brain, and to examine other cognitive-affective factors (such as attention) in relation to movement in LBP populations. If possible, it would be of high interest to conduct longitudinal research in these matters to unravel causal relationships, and it would be advisable to distinctly assess different LBP entities within one study to explore possible progressions from one group to another as this could contribute to the further elucidation of the chronification process in LBP.

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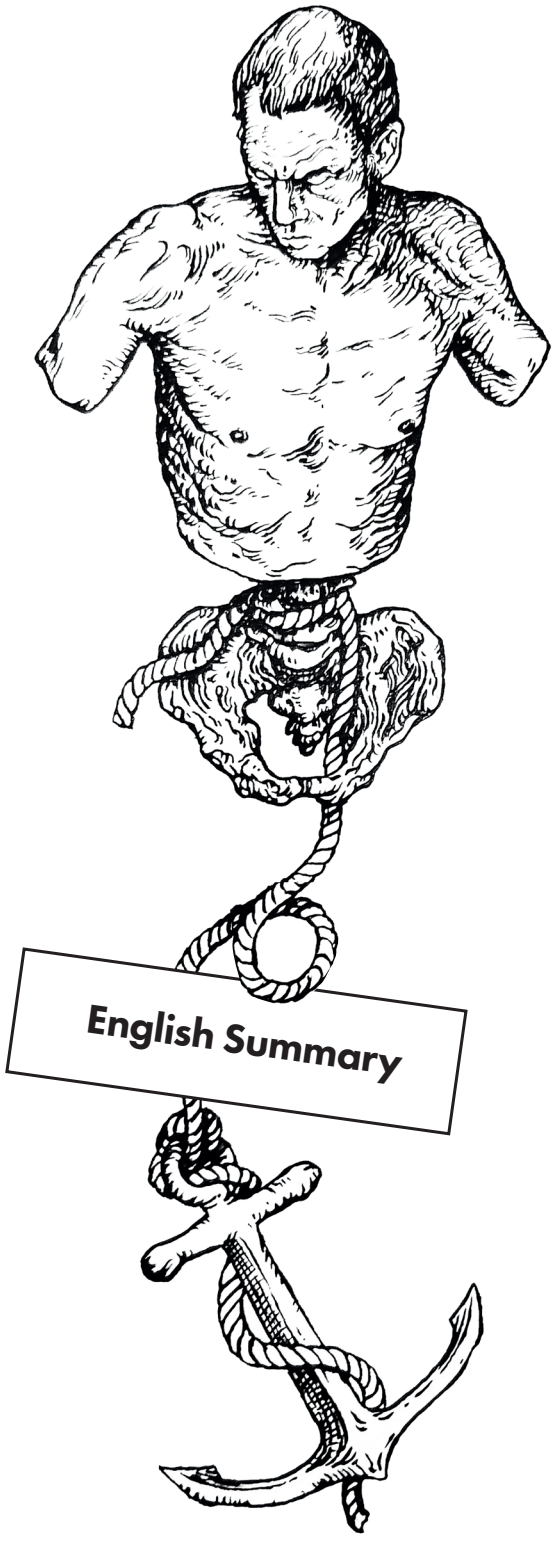


English Summary

(Chronic) non-specific low back pain (LBP) remains one of the most important health disorders of our Western society. Despite an abundance of research over the last decades, prevalence rates, disability levels, and societal and healthcare costs associated with LBP keep increasing. The fact that non-specific LBP is a multifactorial pain syndrome, but often is not addressed as such, might be one explanation for the difficulties regarding effective assessment and treatment. Therefore, the current dissertation aimed at further unraveling the nature of non-specific LBP from a multifactorial perspective. The overall aim of this dissertation was to increase the knowledge regarding several factors that were hypothesized to have an influence on both peripheral and central measures for movement preparation prior to (sensori)motor control tasks, since alterations in movement preparation previously have been related to LBP recurrence/chronification. Additionally, possible synergies between peripheral and central mechanisms in movement preparation were examined as well. The factors examined were fatigue and experimentally manipulated cognitive-affective states (fear) in different stages of clinical non-specific LBP chronification.
In this dissertation a gradual, progressive, biopsychosocial and multi-factorial research line was developed to further examine the aforementioned factors in LBP. This amounted to five studies, which were discussed in three chapters.

Chapter I. Theoretical background.
In the first chapter two systematic reviews were conducted in order to summarize the current standings regarding the overall objective of this dissertation, to point out gaps in current literature and opportunities for future research, and to gather and analyze methodological aspects which could be applied in the experimental designs of chapters II and III.
The first review (part 1) explored up-to-date literature regarding functional electroencephalography (EEG) alterations related to LBP, and found limited to moderate evidence for several functional brain alterations in chronic low back pain (CLBP) sufferers compared to healthy people. The functional EEG-alterations that were found in this systematic review reflect more attention-demanding postural strategies, presence of central sensitization processes, and altered decision making and maladaptive learning processes in CLBP sufferers when compared with healthy people. The most important finding of this study is, however, that there are still very few EEG-studies conducted in this domain. Hence, more research to further substantiate these findings, as well as research concerning other functional tasks and more diverse groups of LBP sufferers could lead to a vast expansion of the knowledge in this matter.
The second review (part 2) explored a broad biopsychosocial perspective in LBP by synthesizing all relevant literature regarding the influence of two important cognitive-affective factors, i.e. catastrophizing and fear, on the wide-ranging concept of movement-related outcomes. Furthermore, it aimed at comparing these parameters between different types of non-specific LBP, i.e. acute (ALBP), recurrent (RLBP) and CLBP populations. This review provides limited evidence for muscle-dependent alterations in trunk muscle timing, activity and diminished endurance, whereas for trunk muscle strength results were unclear or non-significant in association with fear and catastrophizing. Task-dependent functional performance impairments in relation with higher levels of catastrophizing and fear in LBP were also described. Implementation of bio-psychosocial assessment and treatment seems valuable for LBP patients with disturbed motor control, trunk muscle endurance, mobility, and lifting performance. However, these inferences need further experimental exploration as most are based upon single studies. High quality studies comparing ALBP, RLBP and CLBP with use of experimental paradigms besides questionnaires for the study of catastrophizing and fear on movement-related outcomes are required to examine causal relationships.

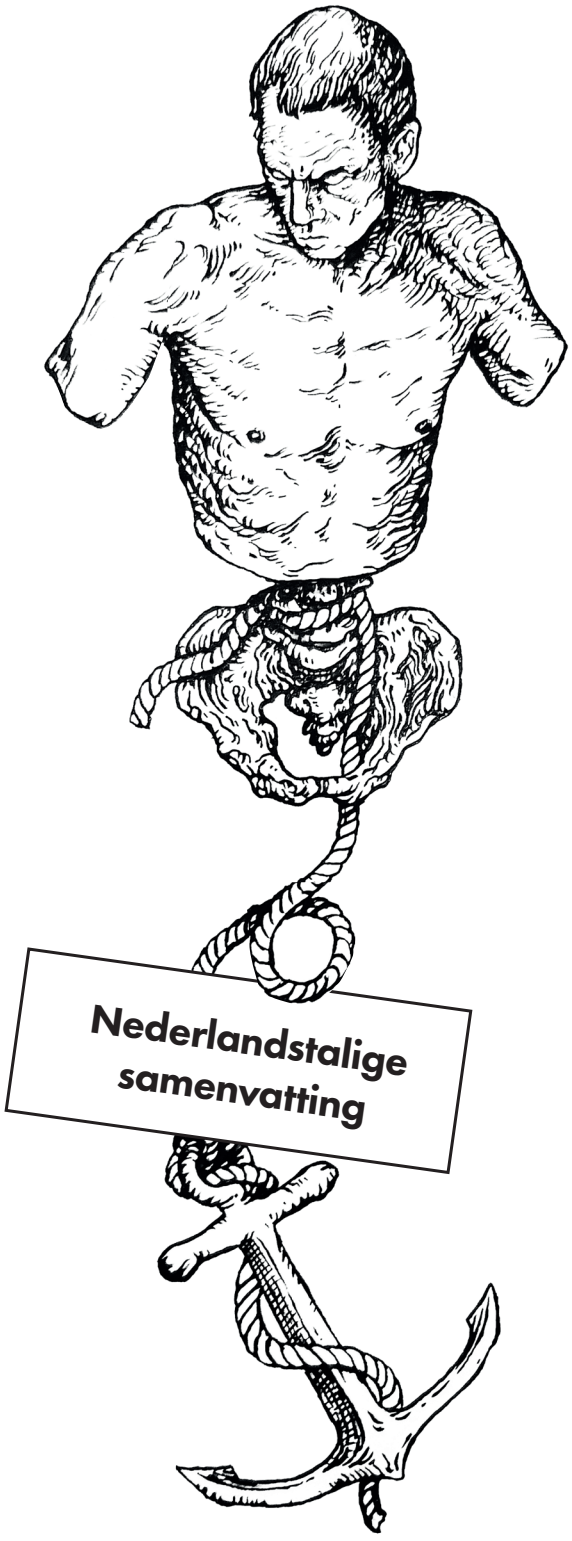
Chapter II. The influence of physical and cognitive exertion on movement preparation in healthy adults.
In the second chapter the influence of fatigue on movement preparation was examined through two experimental studies performed on healthy adults. Fatigue has a high relevance with regards to day-to-day living, because of its possible relation with injuries, changes in movement performance, and LBP. However, it was not yet clear whether

and how fatigue might affect movement preparation and whether differential effects of fatigue could be expected for different types of fatigue-inducing exertions, more specifically physical versus cognitive exertion. Therefore, movement preparation for a rapid arm movement task following physical and cognitive exertion was assessed both on a peripheral muscle level (trunk muscle onset timing, part 1) and on a central brain level (cortical movement preparation, part 2) in healthy adults. In this way, possible effects of fatigue could be controlled for when performing the clinical study of chapter III. The two experimental studies discussed in this chapter hold similar conclusions, since no evidence for effects of physical and cognitive exertion on both central and peripheral measures of movement preparation for rapid arm movements in healthy adults were found. Therefore, it is hypothesized that the influence of fatigue on movement performance, which was described in previous research, might not be through altered motor control, but rather by reduced motivation. However, the possibility that fatigue might influence other mechanisms, which contribute to trunk motor control and were not assessed here, cannot be excluded and needs further examination. Based on the current findings, the rapid arm movement task used in this chapter is deemed suitable to measure peripheral and central movement preparation of gross motor movements, without being affected by learning effects, and physical or cognitive exertion. However, these results cannot yet be generalized to other populations, such as LBP sufferers. Hence, similar research in such patients is recommended.

Chapter III. A biopsychosocial perspective on the influence of fear on movement preparation in healthy people, RLBP and CLBP patients.

The third and final chapter aimed at examining the influence of experimentally altered cognitive-affective states, i.e. pain-related fear and expectations, on both central (cortical movement preparation) and peripheral measures (trunk muscle timing) of movement preparation, and this for healthy people, as well as RLBP and CLBP sufferers. In this way the in previous literature proposed moderating role of cognitive-affective factors on LBP chronification through alterations in (sensori)motor control could be further elucidated. Furthermore, a hypothesized continuum of gradations in presence of maladaptive cognitive-affective factors and disturbed movement performance associated with different stages of LBP chronification (healthy-RLBP-CLBP) could be explored. This study found larger Contingent Negative Variation amplitude (cortical movement preparation) in preparation of rapid arm movements, regardless of LBP presence or degree, with pain-related fear, suggesting an attentional redirection towards more effortful movement strategies when under threat of pain. Trunk muscle onset timing in relation to rapid arm movements was not affected by pain-related fear, but group differences were eminent, indicating that different peripheral movement preparation mechanisms are at play for RLBP and CLBP patients. We hypothesized that the similar trunk muscle onset timing that was found in RLBP compared to healthy people might reflect an adaptive motor control mechanism which contributes to recovery from pain flares. In contrast, the delayed timing which was seen in CLBP might indicate a failure of such adaptive systems and therefore might impede recovery and might contribute to the persistence of the LBP complaints. This novel insight also highlights the importance of separately examining both LBP groups when studying trunk muscle onset timing, which in previous research was not always done accordingly. Furthermore, trunk muscle onset times and cortical movement preparation did not systematically relate to each other in this study. Hence, both are considered as two distinct mechanisms in movement preparation.

The insights of this dissertation contribute to the multi-faceted knowledge of mechanisms and processes related to LBP and its chronification process. However, further, mainly longitudinal research in line of the current work is still needed to further unravel this complex disorder.



Nederlandstalige samenvatting

(Chronische) aspecifieke lage rugpijn (LRP) blijft tot op heden één van de frequentste en belangrijkste gezondheidsproblemen in onze Westerse samenleving. Ondanks een overvloed aan wetenschappelijk onderzoek tijdens de laatste decennia blijven prevalentie- en werkonbekwaamheidscijfers, evenals kosten voor de gemeenschap en de sociale zekerheid door LRP toenemen. Een mogelijke verklaring voor de moeilijkheden qua onderzoek en behandeling van aspecifieke LRP kan gezocht worden in het feit dat LRP beschouwd wordt als een multifactorieel pijnsyndroom, maar vaak onvoldoende effectief vanuit zo'n perspectief benaderd wordt. Daarom was het de intentie van dit proefschrift om de aard van aspecifieke LRP verder te ontrafelen door wél zo'n multifactorieel perspectief te hanteren. Het was de algemene doelstelling van dit werk om bij te dragen tot de kennis over diverse factoren die een vermoedelijke invloed hebben op zowel perifere als centrale maten voor bewegingsvoorbereiding van (sensori)motorische controle taken, aangezien verstoorde bewegingsvoorbereiding in het verleden reeds gelinkt werd aan recurrentie/chronificatie van LRP. Bovendien werden mogelijke synergieën tussen deze perifere en centrale mechanismen van bewegingsvoorbereiding eveneens onderzocht. De specifieke factoren die onderzocht werden in dit kader waren enerzijds de invloed van vermoeidheid, anderzijds de invloed van experimenteel geïnduceerde cognitief-affectieve factoren (zoals angst), en mogelijke verschillen hierin tussen diverse types aspecifieke LRP patiënten.

In dit proefschrift werd een graduele, progressieve, biopsychosociale en multifactoriële onderzoekslijn uitgetekend om de eerder vernoemde factoren verder te onderzoeken in LRP. Dit resulteerde in vijf studies, die besproken werden in drie hoofdstukken.

Hoofdstuk I. Theoretische achtergrond.

Voor het eerste hoofdstuk werden twee systematische reviews uitgevoerd om de huidige kennis omtrent het hoofddoel van dit proefschrift samen te vatten, en eveneens lacunes in de huidige literatuur en opportuniteiten voor toekomstig onderzoek te identificeren. Verder dienden deze reviews ook om methodologische aspecten te vergaren en te analyseren die geïmplementeerd zouden kunnen worden in de experimentele designs van de studies in hoofdstukken II en III.

Aan de hand van de eerste review (deel 1) werd een up-to-date overzicht gemaakt van de literatuur omtrent veranderingen in functionele elektro-encefalografie metingen gerelateerd aan LRP. Er werd lage tot matige evidentie gevonden voor diverse veranderingen in hersenfunctie van chronische lage rugpijn (CLRP) patiënten ten opzichte van gezonde personen. Deze veranderingen in het CLRP-brein suggereren de aanwezigheid van houdingsstrategieën die meer aandacht vragen, indicaties voor centrale sensitisatie processen, en veranderde besluitvormingsprocessen en maladaptieve leerpatronen in CLRP patiënten ten opzicht van gezonde personen. De belangrijkste bevinding van deze studie is echter dat er voorlopig nog steeds een zeer beperkt aantal EEG-studies in dit onderzoeksdomein gevoerd zijn. Meer onderzoek, dat enerzijds de huidige bevindingen verder kan substantiëren en anderzijds andere functionele taken en/of verschillende types van LRP patiënten onderzoekt, is nodig om de kennis in deze materie verder te doen toenemen.

Met de tweede review (deel 2) werd een breed biopsychosociaal perspectief betreffende LRP uitgediept door alle relevante literatuur omtrent de invloed van twee belangrijke cognitief-affectieve factoren, nl. catastroferen en angst, op het veelomvattende concept van beweging gerelateerde uitkomstmaten samen te vatten. Bovendien was een bijkomend doel van deze studie om deze parameters te vergelijken tussen verschillende types aspecifieke LRP, nl. acute (ALRP), recurrente (RLRP), en CLRP patiënten. Er werd beperkte evidentie gevonden voor spierafhankelijke veranderingen wat betreft de timing en mate van activatie van de rompspieren, evenals verminderde rompspieruithouding in relatie tot hogere niveaus van catastroferen en/of angst. Qua rompspierkracht waren de resultaten minder eenduidig of niet significant gerelateerd aan catastroferen en angst. Daarnaast werden eveneens taakafhankelijke verminderingen in de functionele performantie van een breed scala aan functionele taken gevonden in relatie tot hogere aanwezigheid van catastroferen en/of angst bij LRP patiënten. Implementatie van biopsychosociale

onderzoeksmethoden en behandelingen in de klinische praktijk lijkt waardevol voor LRP patiënten die verstoorde motorische controle, rompspieruithouding, mobiliteit en verminderde performantie van hef- en tiltaken vertonen. Deze bevindingen vereisen echter nog verdere experimentele uitdieping, aangezien deze meestal gebaseerd zijn op unieke studies. Studies van hoge kwaliteit die ALRP, RLRP en CLRP patiënten onderling vergelijken en daarvoor experimentele paradigma's hanteren om de invloed van catastroferen en angst op beweging gerelateerde uitkomstmaten te onderzoeken, zijn nog nodig om eventuele causale relaties tussen deze factoren te onderzoeken.

Hoofdstuk II. De invloed van fysieke en cognitieve inspanning op bewegingsvoorbereiding bij gezonde volwassenen.

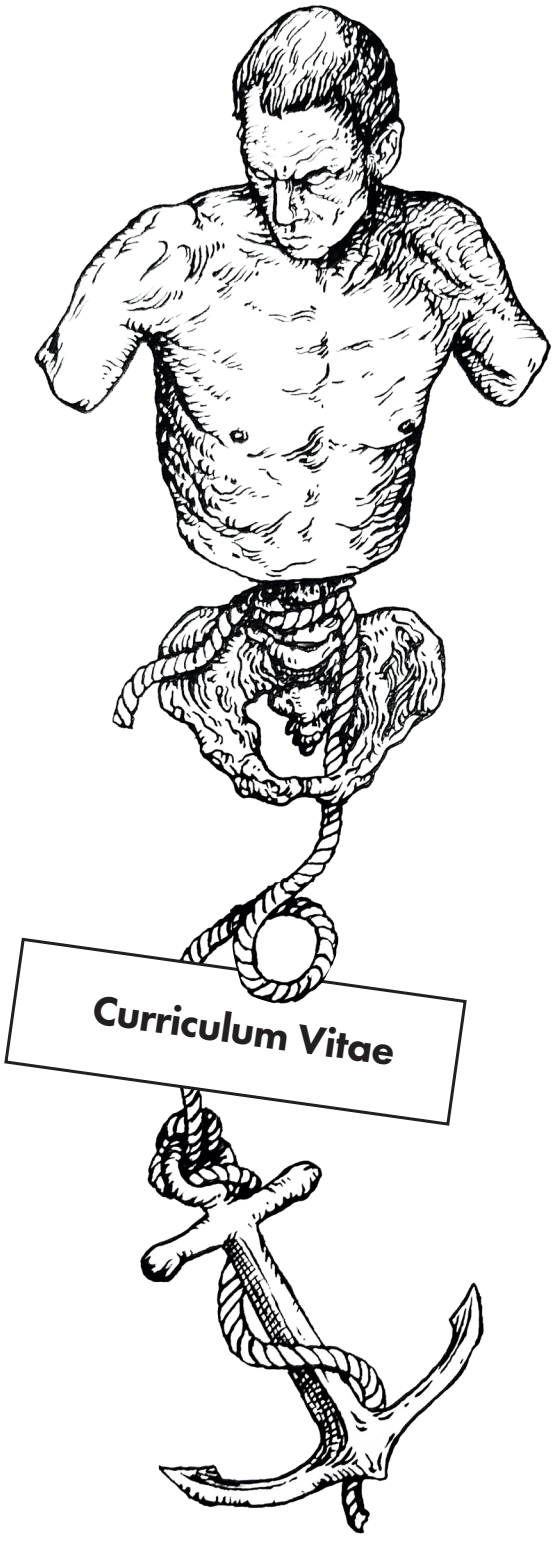
In het tweede hoofdstuk werd de invloed van vermoeidheid op bewegingsvoorbereiding onderzocht door middel van twee experimentele studies uitgevoerd op gezonde volwassen proefpersonen. De studie van vermoeidheid is immers zeer relevant in het kader van het dagelijkse leven van de mens wegens diens mogelijke relatie met blessures, veranderingen in bewegingsperformantie, en LRP. Tot op heden was het echter nog niet volledig duidelijk of en hoe vermoeidheid bewegingsvoorbereiding beïnvloedt en of we differentiële effecten van vermoeidheid kunnen verwachten op basis van verschillende types van vermoeidheids-inducerende inspanningen. Daarom werd de bewegingsvoorbereiding voor rappe armbewegingen zowel op perifeer (spieractiviteit; deel 1) als op centraal vlak (hersenactiviteit; deel 2) beoordeeld na het uitvoeren van enerzijds een fysieke en anderzijds een cognitieve inspanningstaak. Op deze manier konden we indien nodig mogelijke effecten van vermoeidheid meenemen als beïnvloedende factor in de experimentele studie van hoofdstuk III. Gelijkaardige resultaten werden gevonden betreffende beide experimentele studies die in hoofdstuk II besproken werden. Er is namelijk geen evidentie gevonden voor effecten van fysieke noch cognitieve inspanning op zowel centrale als perifere maten voor de bewegingsvoorbereiding van rappe armbewegingen bij gezonde volwassen proefpersonen. Dit leidde tot de hypothese dat de invloed van vermoeidheid op verminderde bewegingsperformantie, die in eerdere studies beschreven werd, mogelijks niet door veranderingen in motorische controle teweeg gebracht wordt, maar eerder door verminderde motivatie. Daarentegen kan het niet uitgesloten worden dat vermoeidheid andere mechanismen die bijdragen aan motorische controle, maar die niet in deze studies onderzocht werden, beïnvloedt. Deze materie vereist dus verder onderzoek. Wanneer we ons baseren op de bevindingen van dit hoofdstuk, kunnen we verder stellen dat de rappe armbewegingstaak die gebruikt werd in deze studies geschikt lijkt om zowel perifere als centrale processen van bewegingsvoorbereiding voor grof motorische bewegingen te meten. Deze taak lijkt immers niet onderhevig aan leereffecten of gevolgen van fysieke noch cognitieve inspanning. Om deze resultaten te kunnen generaliseren naar andere populaties, zoals bijvoorbeeld LRP patiënten, raden we echter aan om eerst gelijkaardig onderzoek uit te voeren in klinische populaties.

Hoofdstuk III. Een biopsychosociaal perspectief omtrent de invloed van angst op bewegingsvoorbereiding bij gezonde personen, RLRP en CLRP patiënten.

Het derde en laatste hoofdstuk had als doel de invloed van experimenteel-geïnduceerde cognitief-affectieve factoren, nl. pijn-gerelateerde angst en verwachtingen, op zowel centrale (corticale) als perifere (rompspiertiming) maten van bewegingsvoorbereiding te onderzoeken voor gezonde personen, evenals RLRP en CLRP patiënten. Op deze manier kon de, door voorgaand onderzoek gesuggereerde, modererende rol van cognitief-affectieve factoren op het chronificatieproces van LRP door middel van veranderingen in (sensori)motorische controle verder toegelicht worden. Bovendien, stelde deze studie ons in staat om na te gaan of de diverse types LRP die bestudeerd werden in dit onderzoek een graduele toename vertonen wat betreft de aanwezigheid van maladaptieve cognitief-affectieve factoren, evenals een progressieve toename van functionele veranderingen qua bewegingsvoorbereiding. De hypothese in dit kader was immers dat de aanwezigheid van dergelijke veranderingen meer uitgesproken zou zijn bij CLRP dan RLRP patiënten, aangezien het klinisch beeld van CLRP een verder gevorderd stadium doet vermoeden. Deze studie toonde aan dat de amplitudo van de 'Contingent Negative Variation' EEG-potentiaal (corticale bewegingsvoorbereiding) tijdens het uitvoeren van rappe armbewegingen verhoogd was in een

context met pijn-gerelateerde angst, maar dat dit onafhankelijk was van de aan-/afwezigheid of de graad van LRP. Deze bevindingen indiceren dat wanneer personen een dreiging van pijn ondervinden ze hun aandacht meer gaan focussen op de bewegingen die gelinkt zijn aan die pijndreiging. De timing van rompspieractivatie tijdens het uitvoeren van rappe armbewegingen was niet onderhevig aan veranderingen ten gevolge van pijngerelateerde angst. Voor deze uitkomstmaat werden echter wel groepsverschillen gevonden die indiceren dat er verschillende perifere mechanismen qua bewegingsvoorbereiding aanwezig zijn bij RLRP ten opzichte van CLRP patiënten. Onze hypothese hieromtrent is dat er mogelijks een adaptief mechanisme in werking treedt bij RLRP patiënten dat hen in staat stelt om (al dan niet tijdelijk) te herstellen van een pijnopstoot, aangezien deze patiënten gelijkaardige spieractivatie vertonen als gezonde personen. Bij CLRP patiënten zien we echter het tegenovergestelde, met eerder vertraagde spieractivatie in de rompspieren van deze patiënten in vergelijking met gezonden en RLRP patiënten. Dit zou kunnen wijzen op een falen van het eerder vermelde adaptieve systeem in CLRP patiënten, wat mogelijks kan verklaren waarom deze niet meer herstellen van een pijnopstoot en persisterende klachten vertonen. Op basis van dit nieuwe inzicht is het alvast aan te raden voor toekomstig onderzoek om beide LRP groepen apart te bestuderen wanneer men geïnteresseerd is in rompspieractivatie, wat in het verleden vaak niet het geval is geweest. Een andere bevinding was dat rompspieractivatie en corticale bewegingsvoorbereiding niet systematisch gerelateerd waren aan elkaar in deze studie. Daarom concluderen we dat dit waarschijnlijk twee afzonderlijke mechanismen zijn in het kader van bewegingsvoorbereiding.

De bevindingen van dit proefschrift dragen bij tot de brede en multi-gefacetteerde kennis omtrent mechanismen en processen die gerelateerd zijn aan LRP en het chronificatieproces daarvan. Er is echter nog steeds nood aan een verdere uitdieping van de huidige bevindingen om het complexe probleem van LRP chronificate verder te kunnen ontrafelen. Voornamelijk longitudinaal onderzoek is aangewezen.



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Member of the organizing and scientific committee of the 'Pain Research Meeting' conference in Antwerp (2017)

SCIENTIFIC PUBLICATIONS

"Does experimentally-included pain-related fear influence central en peripheral movement preparation in healthy people and low back pain patients? Pain. Accepted November 23rd 2019
Stijn Schouppe, Amanda Clauwaert, Jessica Van Oosterwijck, Stefaan Van Damme, Tanneke Palmans, Jan R. Wiersema, Enrique Sanchis-Sanchéz, Lieven Danneels
A1 article, Impact factor (2018): 6.029, categories: Clinical Neurology, ranking: 21/199(Q1); Neurosciences, ranking: 31/667 (Q1); Anesthesiology, ranking 3/31 (Q1)

"Are functional brain alterations present in low back pain? A systematic review of EEG studies." The Journal of Pain. June 28th 2019 [Epub ahead of print]
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Dorien Goubert, Robby De Pauw, Mira Meeus, Tine Willems, Barbara Cagnie, Stijn Schouppe, Jessica Van Oosterwijck, Evy Dhondt, Lieven Danneels
A1 article, Impact factor (2017): 3.119, category: Orthopedics, ranking: 11/77 (Q1).

"Applying an active lumbopelvic control strategy during lumbar extension exercises: effect on muscle recruitment patterns of the lumbopelvic region." Human Movement Science. 54. p.24-33 (2017)
Jessica Van Oosterwijck, Eline De Ridder, Andry Vleeming, Guy Vanderstraeten, Stijn Schouppe, Lieven Danneels
A1 article, Impact factor (2017): 1.840, category: Sport Sciences, ranking: 45/81 (Q3).

"Determining predictive outcome factors for a multimodal treatment program in low back pain patients: a retrospective cohort study." Journal of Manipulative and Physiological Therapeutics. 40(9). p.659-667 (2017)
Rahmat Adnan, Jessica Van Oosterwijck, Barbara Cagnie, Evy Dhondt, Stijn Schouppe, Jens Van Akeleyen, Tine Logghe, Lieven Danneels
A1 article, Impact factor (2017): 1.426 , category: Rehabilitation, ranking: 46/65 (Q3).

PRESENTATIONS

International

"Do fear and attention for pain influence motor function in patients with low back pain: a systematic review?"
Stijn Schouppe, Amanda Clauwaert, Stefaan Van Damme, Lieven Danneels, Geert Crombez, Jessica Van Oosterwijck
Oral presentation at the 18th 'Congress of the World Confederation for Physical Therapy' (WCPT), 2-4 July 2017, Cape Town, South-Africa.

"Determining predictive outcome factors for a Multimodal Treatment Program in Low Back Pain Patients: A retrospective cohort study"
Rahmat Adnan, Jessica Van Oosterwijck, Barbara Cagnie, Evy Dhondt, Stijn Schouppe, Jens Van Akeleyen, Tine Logghe, Lieven Danneels
Oral presentation at the 18th 'Congress of the World Confederation for Physical Therapy' (WCPT), 2-4 July 2017, Cape Town, South-Africa.

"An interdisciplinary study on the relation between fear, attention and sensorimotor control in back pain chronicity: movement-related factors"
Stijn Schouppe, Amanda Clauwaert, Jessica Van Oosterwijck, Stefaan Van Damme, Lieven Danneels
Oral presentation at the 2nd 'Pain Science in Motion International and Interdisciplinary Colloquium on Research Methods in Pain Sciences', 24-25 March 2017, Stockholm, Sweden.

"Active stabilization strategy during lumbar extension exercises: effect on muscle recruitment patterns of the lumbopelvic region"
Stijn Schouppe, Lieven Danneels, Eline De Ridder, Andry Vleeming, Guy Vanderstraeten, Jessica Van Oosterwijck
Poster presentation at the 9th 'Interdisciplinary World Congress on Low Back Pain', 3 November 2016, Singapore, Singapore.

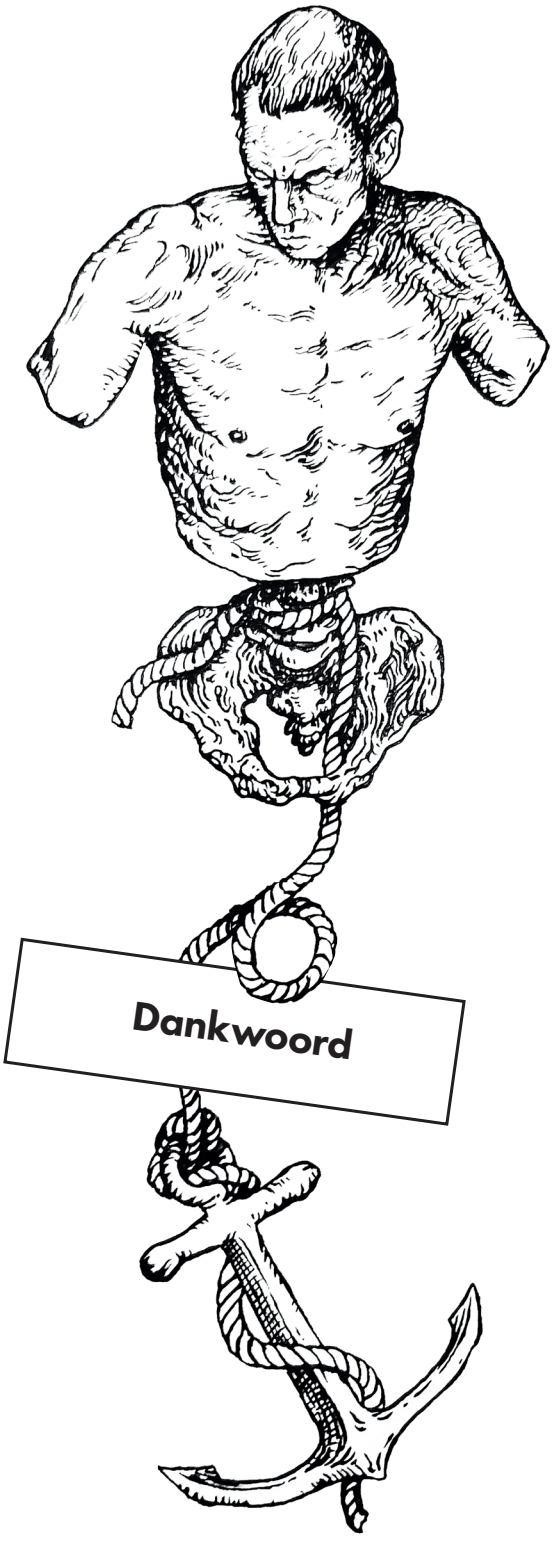
National

"Functional brain alterations in Low back pain: a systematic review of EEG studies."
Stijn Schouppe, Sophie Van Oosterwijck, Lieven Danneels, Stefaan Van Damme, Jessica Van Oosterwijck
Poster presentation at the 9th 'Biennial Congress of the Belgian Back Society (BBS)', 1 December 2018, Brussels, Belgium.

"Beïnvloedt vermoeidheid motorische controle van de rompspieren bij gezonde personen tijdens een rappe armtaak? (voorlopige resultaten)"
Stijn Schouppe, Lieven Danneels, Stefaan Van Damme, Sophie Van Oosterwijck, Tanneke Palmans, Jessica Van Oosterwijck
Poster presentation at the 'Motion in Pain Symposium', 30 May 2018, Antwerp, Belgium.

"An interdisciplinary study on the relation between fear, attention and sensorimotor control in back pain chronicity"
Stijn Schouppe, Amanda Clauwaert, Jessica Van Oosterwijck, Stefaan Van Damme, Lieven Danneels
Oral presentation at the 'PAIN Research Meeting (PRM)', 18-19 September 2017, Antwerp, Belgium.

"Active stabilization strategy during lumbar extension exercises: effect on muscle recruitment patterns of the lumbopelvic region"
Stijn Schouppe, Lieven Danneels, Eline De Ridder, Andry Vleeming, Guy Vanderstraeten, Jessica Van Oosterwijck
Poster presentation at the 6th 'Studenten Onderzoek Symposium Mens & Gezondheid', 26 April 2016, Ghent, Belgium.



Dit doctoraat is voorafgegaan door een 4-jarig proces van vallen en opstaan. Zonder de hulp, raad en ondersteuning van vele mensen die mij zowel direct als indirect de energie hebben gegeven om te blijven doorgaan tot het einde, zou dit doctoraat er nooit gekomen zijn. Mijn oprechte dank gaat dan ook uit naar al deze personen.

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