Medizinische Fakultät

der

Universität Duisburg-Essen

Aus der Klinik für Neurologie

The effect of Open-Label-Placebo on physical functioning in chronic low back pain

I n a u g u r a l - D i s s e r t a t i o n

zur

Erlangung des Doktorgrades der Naturwissenschaften in der Medizin

durch die Medizinische Fakultät

der Universität Duisburg-Essen

Vorgelegt von

Andreas Hellmann

aus Viersen

(2020)

DuEPublico
Duisburg-Essen Publications online

UNIVERSITÄT DUISBURG ESSEN
Offen im Denken

ub universitäts bibliothek

Diese Dissertation wird über DuEPublico, dem Dokumenten- und Publikationsserver der Universität Duisburg-Essen, zur Verfügung gestellt und liegt auch als Print-Version vor.

DOI: 10.17185/duepublico/73732
URN: urn:nbn:de:hbz:464-20210304-091814-6

Alle Rechte vorbehalten.

Dekan: Herr Univ.-Prof. Dr. med. J. Buer

1. Gutachter: Frau Univ.-Prof. Dr. U. Bingel

2. Gutachter: Herr Prof. Dr. med. M. D. Kauther

Tag der mündlichen Prüfung: 05. Oktober 2020

Publikation:

Effects of open-label placebo on pain, functional disability and spine mobility in chronic back pain patients: a randomized controlled trial.

Kleine-Borgmann, J., Schmidt, K., Hellmann, A., Bingel, U.: Pain (2019)

Table of contents

Page

1 Pain

1.1 Definition

In accordance with the International Association for the Study of Pain (IASP) pain is defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage” (Merskey, 1986). In the course of the identification and localization of tissue damaging processes, pain has an essential warning function (Anwar, 2016). It includes an increased arousal, the prioritization of attention to the possible source of pain and avoidance (Vlaeyen et al., 2016) what in consequence forms the foundation for healing processes by preventing tissue micro traumatization. By evaluating the time course, the localization and the quality of pain perception it is possible to link distinctive diseases to characteristic pain signatures, assuming that the tissue damage goes along with a characteristic nociceptive signaling and will disappear with finalization of the recovery process (Elman & Borsook, 2016). But for many patients, approximately 20 - 31%, pain persists beyond the regular recovery process period and will in the end forfeit the physiological nociceptive function (Steingrímsdóttir et al., 2017).

1.2 Acute pain mechanisms

Regular pathways of acute pain mechanisms include the activation of nociceptors and signal transduction via the afferent neurons which are converging at the spinal chord´s root ganglion with their prolongations in afferent spinal and brainstem pathways (Elman & Borsook, 2016). The nociceptive process, which results from a noxious stimulus, can be divided into four stages from transduction over transmission to perception and modulation (Mertens et al., 2015). While the first two phases include the conversion of stimuli into action potentials and the transmission of these potentials to the spinal cord, the perceptional part describes the integration of these signals into cortical levels of the brain. Defined as the sensory-discriminative system, the thalamus receives the nociceptive signal via the spinothalamic tract where third order neurons transmit the signal to the somatosensory cortex for further generating the sensory aspects of pain, the location and intensity (Dickenson, 2016).

The central modulation of pain is demonstrated in patients with similar nature of injuries but different sensory experience of pain. The descending pain modulatory

network can diminish pain through endogenous mechanisms that inhibit or enhance nociceptive traffic (Maier et al., 2017). These descending pain modulating pathways have their origin in the brainstem and are based on serotonergic and noradrenergic neurotransmission and can be triggered by psychological interventions (Yarnitsky, 2015).

1.3 Chronic pain mechanisms

According to the biopsychosocial model of health (Engel, 1979), biophysical, psychological and societal factors play a contributing role in pain perception. For chronic pain patients, pain does not necessarily seem to be a direct consequence of these biophysical and structural processes. Some authors assume, that even an acute preparatory stage is secondary in the development of chronic pain states and that chronification processes are highly individual and influenced by psychological factors, societal and work-related environments (Hartvigsen et al., 2018).

There is accumulating evidence that pain in chronic pain patients is not predominantly driven by peripheral nociceptive signaling but rather pain perception as a result of neuroplastic changes in pain -perception and -modulation associated areas of the central nervous system by associative learning processes (Alleva et al., 2016; Hartvigsen et al., 2018).

1.3.1 Learning pain

These central neuronal restructuring can not only be observed in areas, commonly described to be involved in pain processing, but also in the hippocampal or frontal brain areas (Baliki et al., 2011) which are associated with enhancement of motor sequence performance (Albouy et al., 2015). Activation of these neuronal pathways occurs context specific (Sawangjit et al., 2018). This is interesting because inherently, pain is an unconditioned stimulus. By the simultaneous occurrence of a bodily sensation with pain perception (e.g. forward bending and an acute episode of back pain), this sensation allegedly predicts the development and maintenance of pain (Peuter et al., 2011). As a consequence of persistent pain, novel memory or learning processes are linked to the maintenance or recall of pain states (Mansour et al., 2014). Peuter et al. (2011) state, that there is a preferred conditioning for stimuli within the same body areas or physiological system explaining the development of,

so-called specific pain identities, of chronic pain patients, resulting in avoidance behavior (Crombez et al., 2012). Within a process of operant conditioning avoidance behavior will manifest itself by limiting physical activity as a result of fear (Crombez et al., 2012).

1.3.2 From somatosensory to limbic associated pain

Spontaneous fluctuations of pain, as well as a pain-avoidance-motivated behavior, fear of movement, fear of pain, predictability of pain relief, anxiety, depression, catastrophizing and somatizing are accompanied by changes in activation of forebrain structures (Wiech, 2016). These observations are characterizing the transition from a “somatosensory dimension of pain” to a “limbic dimension” of pain in chronic pain states. Alterations of central pain processing by neuroplastic changes can lead to enhanced pain perception or non-painful peripheral stimuli by cortico-limbic learning mechanisms (Vachon-Presseau et al., 2016). Chronic pain states can be seen as a complex of sensory and emotional experiences that will lead to a modified behavior by rendering the sensory stimulus to become more emotional (Hartvigsen et al., 2018).

Avoidance motivated behavior, specifically prefrontal and limbic circuitry, is associated with a diminished descending modulatory pathway (Geva et al., 2014). As a consequence this can affect the excitability of primary afferent nerve fibers and spinal cord neurons (Mansour et al., 2014). Further a maladaptive avoidance behavior could lead to subsequent musculoskeletal disorders and a new source for nociceptive stimuli (Klinger et al., 2017)

In conclusion, persistent pain can be attributed to psychological factors. Furthermore coping with persistent pain is accompanied by cognitive control, negative emotions and emotional memory processing (Alleva et al., 2016; Steingrímsdóttir et al., 2017; Treede et al., 2019). Thus the maintenance of pain perception, as well as avoidance motivated behavior, can be related to associative learning and emotional learning procedures organized by the mesolimbic network (Vachon-Presseau et al., 2016). This interplay indicates the requirement for a paradigm shift from the mere biomedical point of view to constitute chronic pain as a mechanism, that results in response to perceived individual threats from multiple domains.

2 Chronic low back pain

2.1 Definition of low back pain

Low back pain is defined as pain in the area on the posterior aspect of the body from the lower margin of the twelfth ribs to the lower gluteal folds with or without pain referred into one or both lower limbs that lasts for at least one day (Hurwitz et al., 2018). It is experienced by more than 80% of the population during their lifespan, at any age (Vos et al., 2016). Although there is an existing substantial heterogeneity among the classification of low back pain the most established three categories regarding the development in the course of time are: acute, subacute and chronic low back pain (Vos et al., 2012). Acute lower back pain is defined as low back pain lasting for less than six weeks. Subacute lower back pain lasts between six weeks and three months. If the period of three months is exceeded, lower back pain is no longer defined as a symptom, but a disorder (Vlaeyen et al., 2018). Within 68% of all epidemiological studies Chronic lower back pain (CLBP) is defined as lower back pain persisting for longer than 12 weeks, pain beyond the regular course of healing or pain that intermittently affects an individual over a long period of time (Steingrímsdóttir et al., 2017).

2.2 Prevalence of lower back pain

Lower back pain (LBP) remains to be one of the most crucial clinical challenges and is seen as the number one cause of disability worldwide (Hartvigsen et al., 2018; Vos et al., 2016).

With a multifactorial etiology, the occurrence of LBP can be affected by a number of biophysical, psychological and social dimensions which are accompanied by impaired functional capabilities and social participation (Hartvigsen et al., 2018). In fact, LBP is a multi-dimensional disorder comprised of different conditions that can be connected to the anatomical area round the spine (O'Sullivan et al., 2016). Hence, it can be considered as a reference to a distressing feeling in an anatomical area which is so frequently affected that is has become a paradigm of responses to external and internal stimuli (Vachon-Presseau et al., 2016). Between 1990 and 2016 the Number of Years-lived-with-disability (YLD) increased continuously by 54% (Hartvigsen et al., 2018), resulting in a total amount of YLD in 2016 of 57648

[95% 40820 to 75877 UI (in thousands)] (Vos et al., 2017). LBP constitutes the leading cause of YLD in every geographical high-income region within central and eastern Europe (Hurwitz et al., 2018; Vos et al., 2016). LBP symptoms will improve considerably during the regular course of healing within the first six weeks following the initial onset (Buchbinder & Underwood, 2012) and will result in a return to work rate of 93.3% within the first six months (Wynne-Jones et al., 2014).

2.2.1 Costs and work-related factors

Even if the return to work rate seems high, the percentage of days of incapacity to work, related to the ICD-10 diagnosis “back pain” in Germany is at 5,8 %. Subsequent to respiratory diseases it is the second most common reason for inability to work (Hartvigsen et al., 2018). In 2008 the costs for dorsopathies (ICD 720- 724) exceeded a value of nine billion Euros (Statistisches Bundesamt, 2015), of which 85% were estimated to be caused by a loss of productivity and not directly by the medical treatments (Deutscher Bundestag, 2015). Similar observations are made for the Netherlands, the United Kingdom and Australia (Vlaeyen et al., 2018) indicating a supra-regional economic issue.

2.2.2 Causes of LBP

Without ignoring the fact that most of the structures of the back can contribute to pain by damage or inflammation, evidence suggests that for the majority of the people affected by LBP, it is not possible to accurately identify a specific nociceptive source of symptoms associated with their LBP episode (Hartvigsen et al., 2018). Merely <5% have traumatic or osteoporotic fractures, <1% showed an infection or inflammatory arthritis and <2% exhibited referred pain resulting from pathological visceral conditions (Vlaeyen et al., 2018). This suggests that the majority of pain symptoms are inherently nonorganic in LBP patients. Although nociceptive pain can serve as a valuable signal of a significantly painful event the interplay between physical, psychological, social and lifestyle factors, as well as comorbid disorders and non-modifiable genetic factors seems to play a major role in the development of disabling LBP (Hartvigsen et al., 2018).

Yet, CLBP patients demonstrate primarily biomedically oriented health beliefs perceiving their spine as vulnerable and their pathology as serious (Darlow et al., 2015). Importantly organic pain beliefs are highly related to disability and a decreased

physical activity, which in turn are amongst the most valid risk factors in the development of persisting pain (Vlaeyen et al., 2018).

2.2.3 Definitions of CLBP

The concept of a delayed regular recovery process, indicating a more biomedical approach, may be applicable to pain after surgery, while the nociceptive signaling regarding to the treatment is indicated, but is very difficult to verify for musculoskeletal pain (Treede et al., 2019). Especially for the group of LBP patients it seems not applicable given the fact that in most cases the underlying pathophysiology remains unknown (Hartvigsen et al., 2018; Vlaeyen et al., 2018). Therefore CLBP cannot be seen as a valid indicator for a local tissue pathology or damage (Hartvigsen et al., 2018; O'Sullivan et al., 2016).

For this reason and in consideration of the highly subjective nature of pain, the differentiation between acute and chronic pain states is based on a pure temporal dimension: “Chronic pain is pain, that lasts or recurs for longer than three months" (Treede et al., 2015). Additional to the interplay of the different domains of the biopsychosocial model, the presence and interaction of comorbidities and genetic factors can contribute to the presence of CLBP (Hartvigsen et al., 2018).

2.2.4 Epidemiological signature

Reviewing the epidemiological data CLBP is associated with comorbidities, an age over 30 years, pregnancy (Steingrímsdóttir et al., 2017) and the presence of psychological factors like stress, anxiety and depression (Alleva et al., 2016). Social factors including lower levels of education, a lower household income as well as employment status (Steingrímsdóttir et al., 2017) or geographical and cultural background (Hartvigsen et al., 2018) are associated with the presence of chronic low back pain. Further a strong correlation is found to modifiable factors like characteristics of a so called inferior lifestyle, like obesity (BMI >30kg/m^2) or low levels of physical activity, smoking status and alcohol consumption (Hartvigsen et al., 2018).

2.3 Burdens of impaired function and movement in CLBP

In their activities of daily life (ADL) CLBP patients show a variety of functional impairments like getting dressed, walking stairs, bending and kneeling, heavy housework or lifting and carrying of shopping bags (Stamm et al., 2016). Hence most of

the therapy approaches should focus on the improvement of the functional status (Hartvigsen et al., 2018; Vlaeyen et al., 2018) and quality of life (Sullivan & Ballantyne, 2016).

2.3.1 Movement behavior

LBP has a substantial impact on individuals and their movement behavior. Within the scope of biophysical factors, alterations in muscle size and composition (fatty infiltrations) of the mm. multifidus and the paraspinal muscles are associated with LBP (Goubert et al., 2016; Vlaeyen et al., 2018) as well as motor control which differs from pain free patients which was observed by Ansari and colleagues (2018).

2.3.1.1 Motor Control

Investigations into back muscle fatigue demonstrated a difference between CLBP-patients and healthy controls (da Silva et al., 2015) indicating an adjusted movement pattern in pain states. These results are supported by a reduced movement variability in low back patients (Bauer et al., 2017). The authors assume that movement strategies are limited in pain patients since fatigue states are reached more quickly in consequence of a less complex movement strategy compared to asymptomatic adults. More complex movement strategies could prevent an overload of fatigued tissue. Interestingly muscle fatigue is accompanied by the reduction of prefrontal oxygenation (Rupp et al., 2008), suggesting a direct connection between prefrontal activity and motor output.

There is existing evidence for a connection between structural findings and an impaired ADL-level. Therefore an interaction between Mm. multifidii composition, but not muscle size and functional activity levels in older adults with CLBP was observed Sions et al. (2017). Supporting these findings, lower levels of physical activity are associated with increased risk of fat content in Mm.multifidii and higher disability rates (Teichtahl et al., 2015). In addition an adjusted activity pattern of the lumbar m. erector spinae is observed in contrast to healthy controls during ADL-activities like ‘sit to stand’, ’30-seconds standing’ ‘climbing stairs’ as well as ‘static waist flexion’ (Becker et al., 2018).

Patients with CLBP also adjust their gait patterns, in contrast to healthy controls. To avoid extensive hip and spine movements they show statistically significant alterations in velocity cadence and step length (Barzilay et al., 2016). When asked to

perform a faster walk, they showed adjustments in cadence and not in step length, which supports the idea of hip and spine movement avoidance.

2.3.1.2 Range of Motion

Additionally, there is existing evidence that CLBP patients show a 10% to 15% decrease in range of motion (RoM) and 15% to 30% decrease in movement velocity (VoM) of the lumbar regions compared to asymptomatic controls (Vaisy et al., 2015). The flexion angle deficit could be meaningful in the patients ADL. Hence, patients with a flexion deficit, measured by the peak flexion angles showed an adoption of movement pattern resulting in altered flexion angles during other functional abilities like standing up or stepping up (Christe, Redhead, Jolles-Haeberli, & Favre, 2016). When compared to asymptomatic controls, CLBP patients showed, both alterations in RoM and a decreased VoM of the lumbar spine (Christe, Redhead, Legrand et al., 2016).

It remains unclear why lingering maladaptive motion behavior is observable in CLBP patients, even in absence of nociceptive input. One possible explanation for an altered motor behavior by an impaired motor control is the neuroplastic change, like gray matter density of the primary motor cortex areas associated with CLBP, controlling the paravertebral muscles (Baliki et al., 2011) or the prefrontal cortices, which are crucial for the monitoring and integration of motor abilities.

Further an observed shifted sensorimotor-related brain activation to an overactivation of these brain regions could explain an abnormal pain processing during physical activity. Authors suggest that a reorganized lumbar spine representation in higher-order processing could lead to overgeneralized protective responses (Goossens et al., 2018).

On the other hand a sensorimotor conflict between motion intention and movement (Roussel et al., 2013), highlights the conditioned cognitive dimension of motion alterations in CLBP patients. An inconsistent information situation, in form of a mismatch between intention of motion, the proprioceptive input and a visual resonance leads to an increased symptom severity in chronic pain patients and even induced pain symptoms in healthy controls (Nijs et al., 2017).

2.3.2 CLBP and movement related fears

Mediators of pain resulting in physical impairments and disability are still not fully understood. Existing evidence indicates that self-efficacy, psychological distress, and fear play a pivotal role in this connection for LBP and neck pain patients (Alleva et al., 2016). Studies and the clinically practice demonstrate that CLBP patients fear that specific movements or increased physical performance produce or exacerbate their pain (Darlow et al., 2015). As a result of this cognitive mediated association between motor performance and pain, patients avoid potential harmful body positions or motions. Based on operant learning mechanisms, negative reinforcements leads to maintenance of this pain avoidance behavior (Atlas & Wager, 2013; Fordyce, 1984). The visualization or imagination of a harmful movement evokes an activation of the fear memory center in the brain and leads to pain-development without peripheral nociceptive input (Nijs et al., 2017). Interestingly the association between avoidance and threat is bidirectional. The avoidance of a specific motion (for example forward bending) due to the learned association between a painful event and this motion, leads to stigmatizing the motion as dangerous .

When aiming to improve the motor behavior in patients with CLBP it remains unclear if the instruction about “correct” motion strategies (for example lifting techniques) and training of functional activities would lead to a reduced disability or a decreased pain intensity. Interestingly back and spine exercise courses as a composite of exercise and education about back-saving behavior showed no difference or just a minimal effect in favor of disability or pain levels (Parreira et al., 2017).

There seems to be a large heterogeneity observed in expected burdens, which could be explained by the interaction between different health care systems and individual health requirements (Hurwitz et al., 2018). This and the interaction between psychological, social and mechanical factors due to ADL movement patterns, effects the development and incidence of CLBP (Hartvigsen et al., 2018).

As mentioned above it remains unclear to what extent the alteration of motion capabilities is a concrete consequence of structural findings or whether it is a result of cognitive-psychological-social factors. It stands to reason that CLBP patients are severely restricted in ADL and that these restricted activities are associated with impaired motion capabilities.

2.3.3 From expectations to motor performance

Particularly in the context of expectation and conditioning processes, pain related expectations can predict functional outcomes in CLBP, like pain-related disabilities, especially for work-related activities (Karsdorp et al., 2018). In addition to the fear of movement, pain cognition is strongly associated with disability in CLBP patients and a reduced physical activity level (Hartvigsen et al., 2018) indicates a direct connection between expectations and an altered motor performance (Dubois et al., 2014).

2.4 Therapeutic strategies

2.4.1 Pharmacotherapie

In a recently conducted survey only 33% of the 807 patients who suffer from a monthly episode of LBP considered medical treatments like medication to be effective, while 74% considered physical therapy and sport activity to be effective when treating LBP (Statista, 2017). However medication still remains the first method of choice among 50% of the population aged 30 – 59 and 51% of the population aged 60 years and older (Statista, 2017). Several systemic medications for LBP are associated with small to moderate effects on pain. These effects are observable in research mostly on the short term (Foster et al., 2018). Reviewing the pharmacological impact on chronic low back pain conditions according to the guidelines for LBP (Stochkendahl et al., 2018) suggested administration of paracetamol, skeletal muscle relaxants, selective antiseizure medications and systemic glucocorticoids are not recommended due to the insufficient evidence or an uncertain role in the therapy process (Foster et al., 2018). Non-steroidal anti-inflammatory drugs (NSAIDS) seem to be more effective than a placebo in CLBP in regards to pain control (Chou et al., 2017b) and disability, yet the mean difference is only 0.85 (95% CI -1.30 to -0.40) on a scale from 0 to 24 (Enthoven et al., 2016). Opioids did not alleviate the pain effectively, compared to NSAIDS and showed just a small effect, compared to a placebo (Foster et al., 2018). Effects on the functional capabilities of patients with chronic low back pain should be focused on any option of the medical treatment, so pain medication should be adjunctive to remain active and able to work (Foster et al., 2018). To provide pain relief, reduction of depressive symptoms

and help with sleep disturbance, physicians prescribe antidepressants to CLBP patients. There is no convincing evidence that antidepressants relieve back pain more effectively than placebo (Chou et al., 2017b).

A possible explanation of the inadequate effect of medication is delivered by Koob and colleagues. Based on a neurobiological model of addiction a close connection between reward and stress systems could lead to a decreased function of the psychological reward systems as a result of a repeated drug taking procedure (Koob et al., 2014) and a decreased pain relief from analgesic treatments with increased duration of chronic pain (Du Percie Sert & Rice, 2014). As a result of this disfunction patients show a reduced experience capacity of motivation and an increased subjective experience of stress and aversion (Borsook et al., 2016).

For patients reporting high pain intensity in chronic pain conditions psychological factors seem to play a more important role in the maintenance of pain (Hartvigsen et al., 2018). Therefore, a medical treatment could lead to adverse expectations in patients and clinicians, which in turn could reinforce the pain state (Sullivan & Ballantyne, 2016). Interestingly, a direct consequence of the treatments given to CLBP patients could be a disrupted dopaminergic signaling caused by long-term usage of opioids (Taylor, Castonguay et al., 2016). Assuming the dopaminergic state leads to an altered reward responsivity this connection could modify pain related emotional states like depression or anxiety (Elvemo et al., 2015).

In summary, the pharmacological usage on CLBP patients is accompanied by long term adverse and unintended side effects (Foster et al., 2018), while achieving modest improvements on pain related functional abilities which seems not to be clinically meaningful (Enthoven et al., 2016). Further, surgical interventions are indicated by radiological diagnostics assuming structural findings predicting the development of pain and functional impairments.

2.4.2 Radiological diagnostics

There are many structures surrounding the spine that could be a potential source of low back pain due to their sensory innervation. The intervertebral disc has obtained more and more attention as a potential source of pain. Almost 25% of the working population between the age of 30 – 59 believe that their back pain results from a

herniated disc (Statista, 2017). The gold standard for evaluating a possible relationship between soft tissue and neural structures is the Magnetic Resonance Imaging (MRI) (Sasiadek & Bladowska, 2012). Interestingly the amount of surgical treatments, indicated by imaging technique, seems to be a supply-induced demand, regarding to the timepoint of the imaging. Hence the difference between carrying out an MRI at an earlier stage of pain symptom development versus doing no MRI results in a different amount of surgical treatment. 22% for people who had an MRI at an earlier stage compared to 0,8% of people without MRI in 3264 homogeneous LBP cases (Webster & Cifuentes, 2010).

While the association between disc bulging and LBP seems to be strong for the population younger than 30 year of age (Al-Saeed et al., 2012), this relationship seems to disappear with advancing age, resulting in a prevalence of disc bulging in more than 90% in the whole population (Brinjikji, Luetmer et al., 2015). However it remains questionable whether the radiographic classification is anyway coherent with symptom severity and the functional outcome of low LBP patients (Hartvigsen et al., 2018; Vlaeyen et al., 2018).

In contrast the prevalence of chronic pain conditions increases from 4,2% (aged 24 to 39) to 19,6% (aged 20 to 59) reaching an amount of 25,4% (aged >59) (Meucci et al., 2015). The situation is similar in regards to disc degeneration in which almost 30% - 90% of the asymptomatic population shows anomalies (Brinjikji, Luetmer et al., 2015). It should be pointed out, that in the age under 50 the rate of anomalies in symptomatic patients seems to be higher (>50%) than in asymptomatic patients (>30%) (Brinjikji, Diehn et al., 2015).

Yet, a meta-analysis reveals that annular fissures, high intensity zones (annular disc tears), central canal stenosis and spondylolisthesis highlighted no association between LBP and abnormal findings in the MRI (Brinjikji, Diehn et al., 2015). In addition disc degeneration mentioned above, modic type -1 changes, but not modic changes as a whole (1-3) (Brinjikji, Diehn et al., 2015) and spondylolysis are associated with low back pain (Snyder et al., 2014).

Scientific findings in asymptomatic patients should not exclude the possibility of a structural pain source causing LBP. But even the association of symptom severity

and the lumbar degenerative disc disease. But especially findings on disc degeneration or modic changes could be an indirect consequence of the sociodemographic modalities of LBP patients like low physical activity in leisure time, smoking and high BMI rates which are accompanied by disc degeneration (Hartvigsen et al., 2018). The situation is similar if injection therapy and denervation procedures in CLBP patients (Foster et al., 2018). Reviewing the existing evidence, low to very low-quality evidence is available to support the use of these procedures, which does not necessarily represent the quality of the treatment, but the indication regarding CLBP.

The identification of specific surgical targets in CLBP remains unclear and speculative (Vlaeyen et al., 2018) and evidence suggest that MRI scans and the resulting surgical treatment should not be the first line of treatment for CLBP patients (Foster et al., 2018).

2.4.3 Physical Therapy

In accordance with the guidelines “staying active” is one of the first recommendations for LBP patients, in order to avoid a persisting back pain development (Foster et al., 2018). As a first instance treatment, physical therapy forms one of the most important pillars in the management of LBP due to its ability to intervene and reduce the severity of pain, mobility deficits and activity limitations through exercise therapy or manual therapy treatments (Booth et al., 2017; Chou et al., 2017a; Foster et al., 2018).

In 2016 almost 21,1% of the patients that contacted a physiotherapist due to back pain and thereby formed the largest group of all physical therapy treatments in 2016 with 26,1% (Waltersbacher, 2017). It is widely accepted, that LBP patients benefit from active treatments to build up improved physical activity levels, while there are indications for a u-shaped relationship between physical activity and the presence of low back pain indicating that even too much physical activity is accompanied by LBP (Booth et al., 2017).

A modulated pain perception during exercise in LBP-patients can be explained with inhibitory systems modulated by the central nervous system, like the release of endogenous opioids (Da Silva Santos & Galdino, 2018) while there are still no converging results about the duration, intensity and modality of exercises leading to an

activity induced analgesia which could be a further indication of the u-shaped relationship between pain and physical activity (Da Silva Santos & Galdino, 2018). Interestingly the endogenous inhibition does not differ between LBP patients and healthy controls (Roussel et al., 2013), which is why it should be considered as a recommendation for the inclusion of exercise in the early stage of therapy.

For the group of CLBP patients the data indicates significantly reduced pain levels and disability, among those who participate in exercise therapy when compared to patients who were given no treatment or conservative therapies (Chou et al., 2017a; Geneen et al., 2017; van Middelkoop et al., 2010). Interestingly there are conflicting results regarding the sort of exercise intervention and there are no clear differences between different exercise regimens (Qaseem et al., 2017).

The clinical representation of the patients seems to be very multilateral in contrast to the unilateral diagnosis of CLBP, which would be an explanation for the different requirements applicable to the exercise treatment and the different results in clinical trials. This could be attributed either to the fact that the clinical representation of symptoms is very multifaceted or that psychological and/or neurophysiological factors are common to all investigated exercise programs that have a mediating effect on outcome variables, such as pain severity and function (Booth et al., 2017).

Unanimity exists in the application of a supervised individualized exercise program based on the clinical presentation of the diagnosis and the resulting aims and preferences (Booth et al., 2017). It is widely believed, that improvements in disability and pain are initiated by improvements in physical function and performance like RoM or muscular strength and/or endurance (Steiger et al., 2012). Hence it appears to be impossible to identify one superior exercise modality. However, there are still contradictory results of the research focused on CLBP when it comes to addressing the relationship of improvements in pain and the physical function and disability during an exercise program (Steiger et al., 2012).

Supporting results are found in the recommendations for the manual therapy management in form of manipulative and nonthrust mobilization, as well as hands-on procedures which should be used to improve hip and spine mobility leading to a reduction of pain and disability in patients with CLBP (Hidalgo et al., 2014). Even

though there is existing evidence for spinal manipulation compared to sham manipulation for pain, function and overall-health (Hidalgo et al., 2014), the effects are small and short term. A clear statistically significant difference in pain or function when comparing spinal manipulation and other active treatments is not evident on short- or long term (van Middelkoop et al., 2010). Further, only low quality evidence exists showcasing a benefit in pain and function for patients, which participated in a combination of spinal manipulation and active treatments (Qaseem et al., 2017). There is also low level evidence that highlights no effect for massage therapy on pain intensity and insufficient evidence that could estimate an effect on function (Chou et al., 2017a).

Reviewing the evidence for non-pharmacological treatments against the background of physical functioning and pain intensity in CLBP patients several nonpharmacologic therapies are associated with inconsistently small to moderate, primarily short-term effects to reduce the pain and improve the physical functioning (Chou et al., 2017a; Geneen et al., 2017). In fact, the effect or outcome of a therapy can barely be estimated, when ignoring the responder for the therapy, having considered modifiable factors like health beliefs, lifestyle and patient expectations to the treatment.

3 The Placebo effect in CLBP

3.1 The concept of placebo

Almost any medical treatments can be classified into a specific component (a surgical treatment or a pharmacological substance) and a non- specific component, which is formed by the context, in which the treatment is administered, and by the patient's expectations (Enck et al., 2013). The final therapeutic outcome is a combination of the non-specific and the specific components.

The impact that non-specific factors can have was already shown in the early 18th century when patients received an inert substance shortly before they died to mitigate their symptoms (Raicek et al., 2012). Throughout the course of time and ever since Beecher (1955) established the term of a "powerful placebo", the treatment context and the patients expectations resulting from this, gathered attention to maximize treatment outcomes. Placebo treatments can have a significant impact on clinical outcomes as well as on the physiological state, which is accompanied by a reduction of the patient´s symptoms and an improvement of the patient´s medical condition (Benedetti & Amanzio, 2013; Enck et al., 2013).

3.2 Placebo Effect and Placebo Response

A placebo, as in inert substance or inert procedure, which is mostly used to disentangle non-specific effects in randomized controlled trials assuming that drug and placebo effects are additive. From that point of view, placebo effects are unwanted and undirected incidences even if they can have considerable influence (Enck et al., 2013; Kaptchuk & Miller, 2015).

In contrast to placebo effects, the response to a placebo, as the outcome that follows after the administration can be specific. Mediated via the patient´s cognition, specific neurobiological mechanisms can be triggered which can result not only in an adapted mode of action of the central nervous system, but also in peripheral, physiological and organic changes (Enck et al., 2013). For example, physiological responses like increased blood pressure and resting pulse rates are measurable as a result of an adapted cognition, via a modified mind set (Crum & Langer, 2007). Yet, cardiovascular functions are connected to psychological factors, but there are also

indications for immunological, gastrointestinal, endocrine, respiratory functions, and even motor functions, that may be linked to placebo responses (Enck et al., 2013).

3.3 Placebo analgesia

The mechanisms underlying the placebo response are most robust characterized in the placebo analgesia (Enck et al., 2013). The expectation of a treatment benefit seems to be pivotal for the modulation of pain perception (Geuter et al., 2017). When expecting an opioid, which is known as a powerful drug, the magnitude of a placebo response is enhanced, indicating an association between the expected amount of pain relief and the actual pain relief (Vase et al., 2015). This suggests that an analgesia changes not only the perceived pain intensity but also reduces anxiety and depressive symptoms (Cormier et al., 2016), which are frequent contributors to chronic pain levels.

According to the definition of Ashar et al. (2017), a placebo can be described as a feigned medical treatment, or as a device or drug without pertaining potency. In this context, it is important to note, that a placebo does not necessarily have to be a pain medication. It describes a manipulation or modification of the informational context factors round the medical treatment including social and physical cues, verbal suggestions and treatment history (Enck et al., 2013).

This modification of information by the psychological context around the therapy leads to neural and psychological responses based on the appraisal of future well-being and meaning of the treatment (Ashar et al., 2017; Benedetti & Amanzio, 2013; Vase et al., 2015). In contrast to the placebo effect, nocebo effects describe the induction of a symptom perceived as negative by an inert treatment and/or by the suggestion of negative expectations (Enck et al., 2013). Similarly implicit learning mechanisms lead to recruitment of disease-related processes in the body and even biological markers like immune and allergic responses can be initiated (Zion & Crum, 2018).

In addition to the expectations of the patient, in regards to a treatment benefit, these implicit learning mechanisms form the framework of the placebo analgesia (Benedetti & Amanzio, 2013; Enck et al., 2013; Zion & Crum, 2018).

Imaging studies suggest, that the effect of the placebo analgesia on a neurophysiological level, seems to involve the descending pain modulatory network, with the interacting neural structures of the dorsolateral prefrontal cortex, the anterior cingulate cortex the amygdala, the hypothalamus and the periaqueductal grey (Enck et al., 2013; Geuter et al., 2017). The functional connectivity of these regions is associated with modifications of the endogenous and endocannabinoid system (Geuter et al., 2017) and positively correlated to pain relief (Wiech, 2016). Healthy subjects demonstrated a linear parallel running dopaminergic and opioid activity in the nucleus accumbens, linked to the size of the placebo response, while nocebo effects led to a deactivation of the opioid and dopaminergic release (Scott et al., 2008). On the other hand modifications in dopaminergic and opiodergic function have been observed in chronic pain conditions (Borsook et al., 2010) indicating the role of a suppressed modulatory pain network and associated neuroplastic changes in chronic low back pain (Hartvigsen et al., 2018).

With the aid of PET Imaging Technique, studies demonstrated an association between placebo effects and the release of dopamine in brain areas that are related to reward (Scott et al., 2008). In contrast to this chronic pain conditions lead to a decreased dopaminergic state that impairs motivated behavior (Taylor, Becker et al., 2016).

But these observations are not only limited to a psychological revaluation. In contrast to catastrophizing and fear as contributors to pain sensations, Cormier et al. (2016) showcased that expectations of pain relief are strongly correlated to expected improvements of motor functions.

In lieu of specific nociceptive sources for pain but in the presence of pain sensations in CLBP-Patients, implicit learning mechanisms like classical conditioning and associative learning mechanisms must be considered, in regard to a connection between the psychological revaluation as a possible contributor to the actual health status and the involved pain perception. Summarizing the observations connected to placebo analgesia, triggering the descending pain inhibitory network by a placebo could break the vicious circle of negative revaluation and possible nocebo effects in CLBP patients, which leads to a decreased catastrophizing and fear avoidance behavior, which is in turn associated with an improvement in motor functions.

3.4 The role of expectancy and conditioning in placebo analgesia

The key factors, that are attributed to placebo effects are expectancies (Bingel et al., 2011) and implicit learning mechanisms, like conditioning procedures, observational learning, as well as the therapeutic relationship and verbal information (Enck et al., 2013). Kirsch and colleagues (2018) tried to identify a connection between these key factors. In this model, response expectancy mediates the effects of verbal information, conditioning, and observational learning and conditioning, which alters expectancies (Kirsch et al., 2014).

While expectancies and implicit learning mechanisms are the major contributor to the magnitude of placebo effects, they share similar mechanisms with chronic pain states, but in opposite directions. Whereas chronic pain states lead to a decrease in activation of the descending inhibitory system (Konno & Sekiguchi, 2018), the administration of a placebo leads to an increased activation (Enck et al., 2013; Scott et al., 2007) promoted by the endogenous opioid system (Benedetti & Amanzio, 2013).

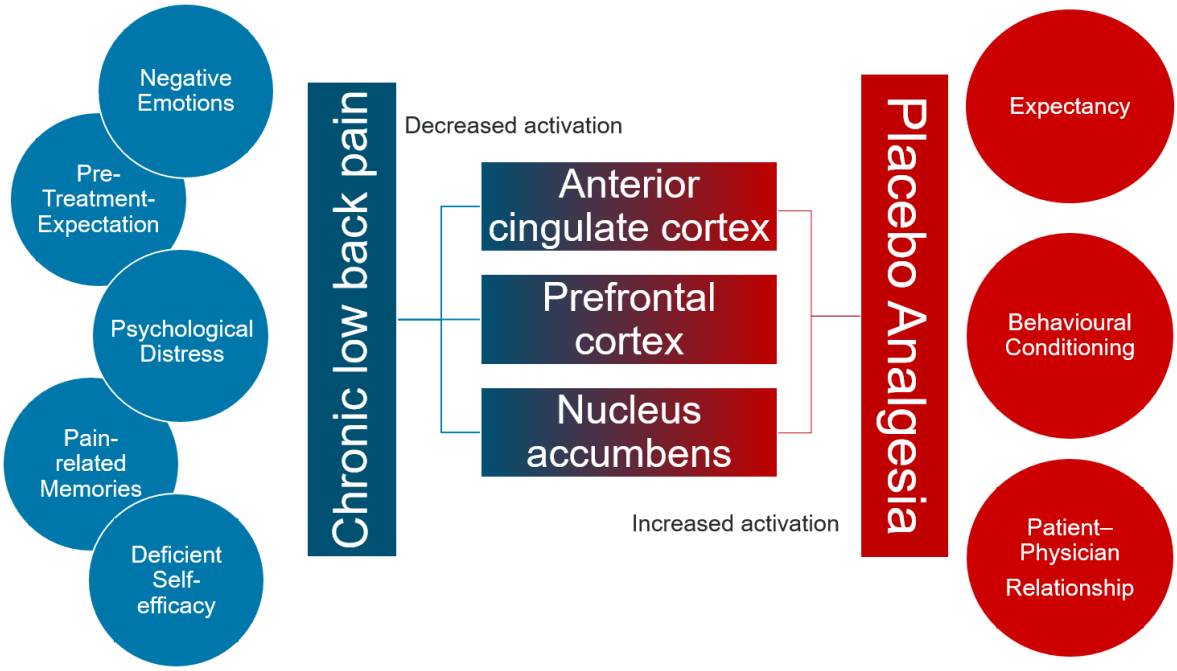

Figure 1: Illustration in accordance with Enck et al. (2013); Konno & Sekiguchi (2018) and Scott et al. (2007)

Aside from the activation of the endogenous opioid system, the release of dopamine seems to be another expectancy-related factor, while the release of endogenous dopamine is higher in patients with a high magnitudes of placebo effects than those who did not benefit from the placebo treatment (Ashar et al., 2017). Interestingly exercise training under placebo conditions resulted in greater motor learning abilities in participants with higher dopamine levels compared to those with lower dopamine levels (Seidler & Carson, 2017), indicating a possible placebo-induced motor performance in CLBP patients.

At present it seems possible to replace the concept of “powerful placebo” with specific biochemical pathways and activities of brain regions associated with placebo analgesia (For review see: Benedetti & Amanzio, 2013)

3.4.1 Placebo Responses in CLBP

As mentioned above, placebo responses are not only limited to pain intensity, but can also affect motor function (Enck et al., 2013). Resulting in a higher release of dopamine in the basal ganglia, patients with Parkinson´s disease showed improvement in motor performance after administration of a placebo (La Fuente-Fernández et al., 2001). Aside from a reduced pain rating patients required substantially less time to complete functional tasks and scored statistically significantly higher in self-reported functional capacity (Klinger et al., 2017).

3.4.2 Hidden vs. open administration of placebos

For a long time, it was assumed that a placebo effect could only be caused by the unawareness of receiving an inert substance. This deception leads to an ethical issue due to the failure of fulfilling information requirements between practitioner and patient, in regards to the background of informed consent and patient´s autonomy (Carvalho et al., 2016).

In the words of the American Medical Association ‘‘the use of a placebo without the patient’s knowledge may undermine trust, compromise the patient physician relationship, and result in medical harm to the patient’’ (American Medical Association, 2006). A non-deceptive administration of placebos could remove the ethical contradiction in clinical practice” (Charlesworth et al., 2017; Kaptchuk et al., 2010).

Recently, a growing body of evidence has been revealed, showcasing studies in which patients across different medical conditions have benefitted from a placebo treatment, even if they received a placebo described as a placebo (Kaptchuk & Miller, 2018). In all these studies, patients received a placebo pill described as an “inert placebo containing no medication”. Addressing the symptom severity, patients demonstrated a placebo effect in statistically significant improved health conditions, despite having been informed about the intake of a placebo.

The manipulation of positive expectations was accompanied by detailed information about the placebo effect which participants received before the randomization into the treatment and control groups (Carvalho et al., 2016; Schaefer et al., 2018). Schaefer and colleagues demonstrated that expectancy could be one of the key factors in the open label placebo effect, demonstrating a mental health sum difference between placebo recipients, whose expectancy was manipulated, and those who were not informed about a possible effect of placebos (Schaefer et al., 2018). Even if the informed consent was different while concealing the inert pill as pain medication or informing about the inactive substance, the pure intake would usually be combined with positive suggestions (Schaefer et al., 2018). For our study, results from the research by Carvalho et al. (2016) were substantial to form the experimental groundwork. They showed a significantly reduced disability, along with reduced pain intensity, in an open label placebo group. However, there is still prevailing uncertainty about an objective increase in motion capabilities. Therefore, we replicated the research question and added a motion capturing system to assess a possible increase in objective motion capabilities. To date, OLP-effects have only been surveyed regarding subjective symptoms (e.g. pain, fatigue, reported disability).

4 Aims of the study

4.1 The effect of an open label placebo on pain intensity and self-reported functional capacity

The aim of this study was to investigate and replicate the existing evidence that OLP in addition to TAU can result in a higher patient-reported functional capacity and a decreased patient-reported pain intensity by regularly adding OLP to a treatment as usual (OLP+TAU). The treatment as usual (TAU) included the individual routine behaviors of the patients, with regards to their personal pain management. By adding an OLP in one group (OLP+TAU) and the comparison to TAU alone, we hypothesized to identify if this could benefit patients with CLBP on the basis of classical conditioning and associative learning processes according to the results of Carvalho et al. (2016). We hypothesized a stronger decrease of pain and self-reported disability in the TAU + OLP group, as compared to the OLP only group.

4.2 The effect of an open label placebo on pain intensity and objective measurement criteria

A further aim was to investigate whether regularly adding OLP to TAU leads to a difference in Range of Motion (RoM) and Velocity of Motion (VoM) between the OLP + TAU and TAU group, assuming a possible connection between self-reported functional capacity and objective measurement criteria by the EPIONICS Spine motion capturing. We hypothesized a strong correlation between pain intensity and objective measurement criteria.

4.3 Relationship between objective and subjective measurement criteria

While it is trivial to assume connection between objective measurement criteria and self-reported functional capacity, we investigated whether this connection was present in the study population by correlating the scores of the EPIONICS spine motion capturing system and the scores of the self-reported functional capacity.

Additionally, as OLP-effects might be very different across individuals (El Brihi et al., 2019), an explorative analysis was conducted, investigating whether there was a

subpopulation which could be identified by subjective data and have a response in objective movement parameters.

5 Materials and Methods

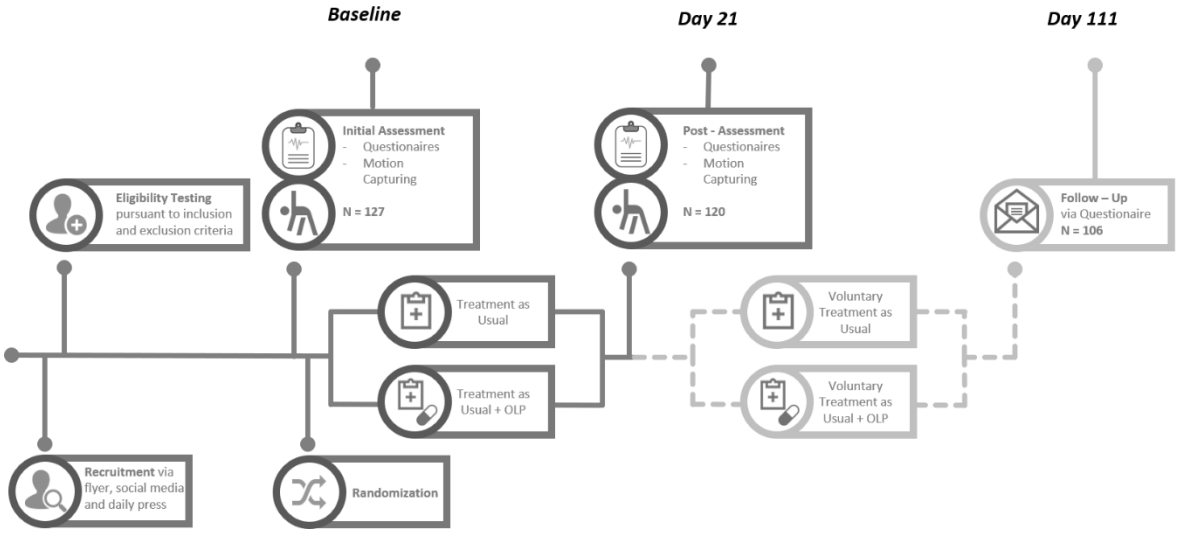

Figure 2: Study design – Randomized controlled, single-blind study: subjective Outcomes were examined at Baseline, day 11, 21 and day 111. Objective motion capturing was executed at Baseline and day 21. Follow up period is characterized by the dashed line.

5.1 Participants and inclusion criteria

Patients were registered and included in this study at the Department of Neurology of the University Hospital Essen. A total of N=127 patients with CLBP (Pain > 12 weeks) were recruited by advertisements in regional newspapers and social media platforms, regionally offered flyers and through the websites of the department of neurology. The sample size estimation is based on a power calculation of similar studies (Wrobel, Wiech, Forkmann, Ritter, & Bingel, 2014) and on an collaborating working group (Carvalho et al., 2016). All subjects received a contribution to expenses of 20€/hour at the laboratory for participation (i.e. approximately 120€/subject) independent of allocation into TAU or OLP+TAU group.

Inclusion criteria comprised the following: an age over 18 years with a confirmed diagnosis of CLBP (persistent back pain of the same quality for more than 12 weeks) and a voluntarily provided consent to participate in the study. Excluded from study population were all subjects with any history of malignancy in the past five years, any severe and - regarding the study objectives - highly influential diagnosis due to the investigator's opinion, neurological deficits (e.g. paralysis), or any severe psychological disorder (e.g. major depressive disorder, personality disorder, psychosis). Further all subjects reporting a clinically not significant pain (referred to as a rating less than 4 on an 11-point numerical rating scale (0-10; "no pain", "worst pain")

during the week prior baseline were excluded from study participation. All women and men who met the inclusion criteria were included in the study for a period of three months. According to the Declaration of Helsinki issued by the World Medical Association the study concept has been approved by the ethics committee at the faculty of medicine of the university of Duisburg-Essen.

5.2 Study Design

The study followed a three-week, randomized design (see **Figure 2**). Between June 2017 and March 2018, N=127 patients with CLBP were involved in a three-week intervention period with two sessions of measurements each. After oral and written information all participants were randomly assigned in two groups (TAU & OLP+TAU).

5.2.1 Randomization and Blinding

The administration of the study medication occurred single-blind in which the assessors were blinded to the assignment of the patient's treatment. The randomization was carried out through a randomly generated numbered list by one of the examiners (Julian Kleine-Borgmann). The RoM and VoM measurements obtained via the Epionics Spine system were carried out by the second examiner (Andreas Hellmann), who did not gain an insight into the randomization list and did not know about the group membership of each of the patients. Patients were asked not to inform the examiners about their study medication or experimental group membership. Accidental unblindings been documented.

5.2.2 OLP+TAU- Intervention

All participating patients were informed about the placebo effect within the framework of an OLP intervention and received the following information from studies that had been carried out previously (Kaptchuk et al., 2010): "the placebo effect is strong and scientifically proven, the human body automatically reacts to a placebo in the sense of a classical conditioning (example: Pavlovian dog). A positive basic setting is helpful, but not essential, pivotal is a regular intake of the pills, however there are no active ingredients in the pill." This information was given in a standardized way by presenting a video. This video consisted of a genuine, audio-translated TV report, informing about open label placebo trials and mechanisms. In regard to possible

bias and false-positive results due to manipulation of positive expectations, all participants were informed at baseline about the “powerful placebo” before randomization. Therefore, any group difference can only be explained by the randomized allocation into TAU and TAO+OLP Group.

The period of placebo intake, additional to their established standard treatment, consisted of 21 days with a dosage of 2 pills per day. Until the follow-up after three months, a voluntary intake of the drug was recommended. The subject documented the duration and frequency of intake themselves.

All placebos that were administered were white gelatin capsules filled with silicon dioxide, titanium dioxide, microcrystalline cellulose from Zeebo Effect, LLC.

5.2.3 TAU - Intervention

The TAU-Group received no open label placebo treatment. To overcome a possible disappointment about allocation to the control group, all TAU-participants had the opportunity to receive the OLP treatment subsequently to the intervention period after 21 days (Visit 2). All outcomes used for statistical analysis have been collected on day 0 (Baseline) and day 21 (Test) (see Table 1).

Table 1: Visit schedule

Baseline (Day 0)	**Test (Day 21)**	**Follow-Up (Day 90)**
Informed consent (30 min)	Information about examination order (30 min)	
Screening Inclusion/ Exclusion criteria	Screening Inclusion/ Exclusion criteria	
Range of motion/ movement velocity - scoring (30 min)	Range of motion/ movement velocity – scoring (30 min)	
Back Performance Scale (15 min)	Back Performance Scale (15 min)	
Questionnaires (30 min	Questionnaires (30 min)	Questionnaires (30 min)

5.3 Outcome Variables

Pain perception is affected by a variety of cognitive factors. To be able to account for these factors the following measurements have been performed:

5.3.1 Pain Intensity

For the detection of a possible difference in pain experience the intensity of low back pain was measured using an 11-point mixed rating scale from a numeric rating scale (NRS) and a visual analogue scale (VAS) ranging from 0 to 10. Using a 16 cm scale on which scores were in regular distance of 1,6 cm each and numbers from 0 to 10, which represent the pain intensity allowed further processing by calculating the arithmetic means. Higher scores indicated a higher pain intensity (0 = no pain, 10 = worst pain possible). The liability and reliability of the VAS has been widely evaluated (Karcioglu et al., 2018). On behalf of a differentiated overview of the subjective pain intensity, situational pain ratings were used. In total three pain ratings were used. In addition to the minimum and maximum pain intensity during the previous week, the average pain intensity during the previous week was captured. For further processing and analysis, a composite score (VAScomp) for pain was computed by the arithmetic mean of all three pain ratings.

5.3.2 VoM and RoM (Epionics SPINE®)

The recording of movement data was carried out by the Epionics SPINE system (Epionics SPINE®, Epionics GmbH, Hamburg, Germany), consisting of two flexible sensors, which are attached to the Spina Iliaca Posterior Superior through attaching hollow plasters to the left and right paravertebral of the lumbar spine. The sensors run parallel to the vertebral column and, in 12 equally sized segments, detect the bends which the sensors experience on the back surface. In addition, acceleration sensors measure the orientation in the gravity field of the earth at both ends of the sensors. This allows, among others, to distinguish between standing and lying positions and movements outside the sagittal plane. The parameters are recorded in real time: 50 times in a second and then stored in a dedicated unit which is connected to the sensor strips and worn by the patient. The motion characteristics contain parameters for RoM, (outputted in degrees) and VoM (outputted in degrees per second) for the following movement directions: flexion, extension, lateroflexion left, lateroflexion right, rotation left and rotation right.

For the creation of composite motion characteristics, we calculated the mean value of the scaled direction and velocity of movement scores. In a standardized procedure, patients were asked to complete six typical movements of the back, each three times. The maximum movement speed and the maximum movement angle were determined as raw variables for each direction of motion as the mean value of the last two repetitions of the measurement. All raw variables were summarized after z-transformation (standardization by MW and SD) as the arithmetic means to the composite score for RoM and VoM. As a reliability analysis, Cronbach's alpha was calculated to assess the internal consistency of the calculated composite scores using the *ltm - package* in R Studio (Rizopoulos, 2006).

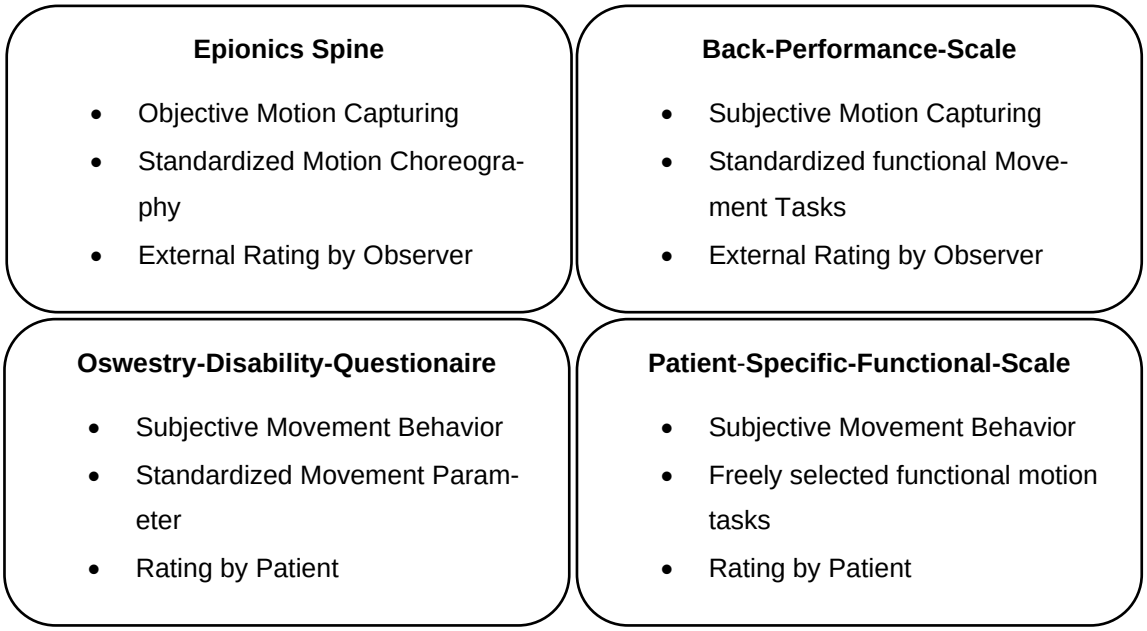

Figure 3: Motion Test Structure used in Study

5.3.3 Oswestry Disability Index

The German version of the Oswestry Disability Index (ODI) (Mannion et al., 2006) is one of the standard diagnostic tools used for the detection of everyday functional limitations in CLBP. The interaction between the perceived pain intensity and the functional capacity of nine different areas of Activities of Daily Living (ADL): personal care, lifting, sitting, standing, sleeping, sexual function, social life and traveling, forms the basis of this assessment. It is conducted as a standardized questionnaire and is considered as an established procedure for the documentation of the subjectively assessed level of activity in situations in which patients may have persistently

severe disabilities (Fairbank & Pynsent, 2000; Mannion et al., 2006; Roland & Fairbank, 2000).

5.3.4 Patient specific functional scale

In addition to the ODI the patients-specific functional scale (PSFS) was used to identify possible functional impairments that are not covered by standardized assessments of functional states, which do not account for individual preferences of patients. The PSFS is a patient-oriented specific measuring instrument in which the subjects themselves evaluate three individually significant activities. The impairment associated with the activity is measured using a numerical rating 11-point scale ranging from 0 to 10 where 0 is unable to perform the activity and 10 means the patient can perform the activity at preinjury level. Lower scores indicate a higher impairment as well as a lower performance capacity of the selected activity. This is characterized by a high degree of responsiveness and sensitivity in the case of milder restrictions on the subjectively acquired potential for movement in CLBP (Heldmann et al., 2015; Horn et al., 2012)

5.3.5 Health related Quality of life (VR -12)

The veterans RAND-12 is a self-administered health survey comprised of 12 questions to gather data on the patient´s health-related quality of life. The 12 questions in the questionnaire including general health perceptions; physical functioning; role limitations due to physical and emotional problems; physical pain; energy-fatigue, social functioning and mental health correspond to eight substantial physical and mental health dimensions. The summation of these 12 Items leads to two different scores, a physical component score (PCS-VR12) and a mental component score (MCS-VR12). This provides an important contrast between the physical and the psychological health status and allows a valid identification of symptom based conditions in CLBP (Selim et al., 2009; Skinner et al., 2005).

5.3.6 Back-performance scale

The back-performance scale (BPS) is a 16-point scale ranging from 0 to 15. Each BPS category is scored from 0 to 3 over the 4-point ordinal scales according to the observed physical performance level. The categories refer to activities of daily life and included a sock-test, a pick-up test, a roll-up test, a lift test, and the fingertip-to-

floor distance. A score of 0 is considered a good performance with no signs of physical impairment, whereas a score of 3 is considered a substantially limited performance. Total score is calculated by the arithmetic mean value of the five different components of the test. The higher the score the more impaired is the physical performance. Each test allows a reliable and valid assessment of a specific trunk mobility and the combined movement patterns in different starting positions of LBP patients (Magnussen et al., 2004)

5.3.7 Psychological Diagnosis Questionnaire

In addition to the questionnaires on back pain diagnostics the following additional survey for the exploratory investigation of psychological factors were conducted. The selection was carried out on the basis of high validity and reliability scores. The depression-anxiety-stress-scale - 21 (DASS-21), for the acquisition of anxiety, depression and stress (Antony et al., 1998), the pain catastrophizing scale (PCS) for the detection of pain-related catastrophizing (Wheeler et al., 2019) and the screening for somatoform disorder (SOMS) for the detection of the level of somatization (Geue et al., 2016).

5.4 Statistical analysis

All statistical evaluations were made using R – Studio (R Core Team, 2018). In all cases, the level of significance was set at $p \leq 0.05$. All calculated tests were two sided and the data were presented in the results section as Mean ± Standard Deviation (SD). From all 127 entrolled patients (Baseline), 122 completed observations (Baseline + Test) were available for analysis of differences.

To increase signal-to-noise ratio and in consideration of possible marginal violation of normality and the different possibilities of motion, in relation to the anatomical planes of the body, we performed a composite score calculation. The composite scores for RoM and VoM were calculated by averaging the standardized raw data across movement directions (flexion, extension, lateroflexion left, lateroflexion right, rotation left and rotation right). Standardization (to zero mean and unit variance) ensured that the composite score is not biased by the variable magnitude across movement directions. The internal consistency of the computed composite scores for motion and velocity Cronbach´s alpha was used (Taber, 2018). Consisting of the

captured and z-transformed movement directions extension, flexion, lateral flexion and rotation, the internal consistency is acceptable with Cronbach's alpha for the comp motion score = 0,83. Almost the same situation appeared for the Velocity – composite score (comp Velocity) with an α = 0,91. Testing the internal reliability of the compositscore for pain,consisting of the non-standardized maximum pain, the minimum pain and the average pain rating during the last week, the internal consistency is acceptable as well, with a Cronbachs Alpha for the compVAS = 0,85. Cronbachs alpha was in every case higher than 0,7, indicating that the combination of items has an acceptable reliability (Taber, 2018).

As an initial step, Shapiro-Wilk normality tests were used to determine whether outcome variables followed a normal distribution. Additional qq-plots were conducted, giving a visual impression of the distributions. To avoid a possibly masked statistical effect pursuant to Lord´s paradox, all variables were visualized in scatterplots comparing the scores of the post assessment with those of the pre-assessment, separately for the TAU and the OLP+TAU group (Wright, 2003). To test for variance homogeneity between the two time periods of pre and post assessment the F-Test was used.

To contrast the results of the motion capabilities of patients at baseline asymptomatic subjects, we compared our RoM and VoM data of CLBP patients to those observed by Consmüller et al. (2012). In their paper 429 healthy volunteers were examined, using the same motion capturing system (Epionics Spine) and a comparable measurement protocol. For the comparison of the means for range of flexion and range of extension, as well as velocity of flexion and extension, sample means and standard deviations (per age groups) were fed into an two-sided unpaired t-test. The population of our study presented an average age of 60.8 ±15.01(SD) at the time of the pre assessment. Hence, we compared the age groups between 36 – 50 years and 51 – 75 years, assuming that no difference between our groups and the Consmüller groups indicates to a regular motion capabilities in CLBP patients.

To assess randomization bias, baseline differences between groups (i.e. before OLP treatment) were tested in the pretest phase for demographics and the outcome variables by two-sample T-tests.

Within the applied pretest – posttest design (Baseline vs. day 21: see **Figure 2**), all conditions were identical for all patients, except the administration of an open label placebo within the OLP+TAU group. According to Dimitrov and Rumrill (2003) two major problems are related to this design, particularly maturation and history for internal validity and interaction of pretesting for external validity of results.

As recommended by Dimitrov and Rumrill, we applied a pretest-posttest difference-based method. Under the assumption that the OLP+TAU treatment shows no effect, the collated pretest-posttest differences(“gain-scores”) of the outcome variables must be approximately equal compared with the TAU group, who received no treatment. As reported by Dimitorv and Rumrill (2003), simple statistical inference on the gain scores (pretest-posttest differences) has satisfying statistical properties pursuant to valid null hypothesis testing in many realistic situations.

The analysis of change was performed by testing the pretest-posttest differences with a Welch-Test of all outcome variables.

In an explorative analysis, we first analyzed relationships across outcome variables by correlation analysis, with the aim of providing further information of the interpretation of any divergence of the OLP-effect across various objective and subjective outcome variables. To reduce the number of comparisons (and, thus, the chance of false positives), variables of the BPFS, the pain intensity composite score (CompVAS), Depression, Anxiety, Stress, ODI, PCS, PSFS and the composite score of motion and the composite score of velocity were used.

Second, as OLP-effects might be very different across individuals (El Brihi et al., 2019), (especially for the objective outcomes), we performed an explorative investigation of interaction-effects, focusing on interactions between the treatment (OLP+TAU and TAU) and the psychological diagnosis subjective outcome results (ODI, BPFS, Depression, Anxiety, Stress, PCS, VAS composite, PSFS) when modelling the composite RoM and VoM gain-scores. Analysis was performed with general linear models on R and consisted of a total of 16 model fits (two outcomes, 8 kinds of interactions).

6 Results

6.1 Patients demographics

In total N=127 subjects met the inclusion criteria and were enrolled. **Table 2** & **Table 3** provide an overview of the sociodemographic data, separately for treatment groups (TAU & OLP+TAU).

Overall, participating patients were predominantly female (n = 79; 62,2%), with an average age of 60.88 ± 14.03 years, with 41.7% of them having had nine years of education, 83.76% being non-smokers and having a BMI (kg/m^2) of 28.32 ± 5.31. A regular drug use due to back pain was observed in 79.97% of all participating patients while 83.46% of the patients considered themselves as healthy when questioned about their general health status as part of the questionnaire (**Table 2**). After having been randomly categorized into Open Label Placebo Group (OLP+TAU) and treatment as usual Group (TAU) both groups of patients did not differ in age, $t(125)=-0.85$, p = 0.394 >.05, gender distribution $\chi 2(1, N = 127) = 2.94$, $p = 0.101$ >.05, Nutrition habits $\chi 2(1, N = 127) = 0.13$, $p = 1{,}00$ >.05, years of education $U = 1949.00$; $z = -0.310$; $p = 0.757$ >.05, smoking behavior (packs per day * years) $t(117)= 0.87$, $p = 0.385$ >,05 alcohol consumption (in g) $t(107)= 0.136$, $p = 0.892$ >.05, regular drug use $\chi 2(1, N = 120) = 0.33$, $p = 1.00$ >.05 and self-assessed health status $\chi 2(1, N = 127) = 0.26$, $p = 0.639$ >.05.

With a mean value of 28,31 ± 5,31, the OLP+TAU group showed a statistically significant higher BMI value compared to the TAU-group (25.64 ± 5.06), $t(125)= -2.887$, $p = 0.005$ <.05 after randomization. This was also the case with regards to the mean values of body weight (OLP+TAU: 85.93 ± 18.85; TAU: 74.36 ± 16.12), $t(125)= -3.696$, $p = 0.000$ <.05 and body height (OLP+TAU: 173.89 ± 10.06; TAU: 170.13 ± 8.50).$t(125)= -2.261$, $p = 0.025$ <.05.

Table 2: Sociodemographical Data of the random sample (n =127) - Distributions and Mean Values (Mean) ± Standard Deviation (SD)

		OLP	**TAU**	**p**
Sex (in %)	Male	14.14 %	23.62%	
		N = 18	N = 30	.101 >.05
	Female	33.07%	29.13%	
		N = 42	N = 37	
Age (in years)	Mean ± SD	60,88 ± 15,01	58,67 ± 14,039	.394 >,05
Weight (in kg)	Mean ± SD	85.93 ± 18.85	74.36 ± 16.12	.000 <.05
Height (in kg)	Mean ± SD	173.89 ± 10.06	170.13 ± 8.50	.025 <.05
BMI (kg/m^2)	Mean ± SD	28.32 ± 5.31	25.65 ± 5.07	.005 <.05
Nutrition habits	Meat	51.18%	45.67%	
		N = 65	N = 58	1.000 >.05
	Vegetarian	1.57%	1.57%	
		N = 2	N = 2	
	Vegan	0%	0%	
		N = 0	N = 0	
Years of Education	Qualifikation	15.08%	10.32%	
	(6 yrs.)	N = 19	13	.757 >.05
	Mittlere Reife	20.63%	21.43%	
	(9 yrs.)	N = 26	N = 27	
	Abitur	7.14%	10.32%	
	(13 yrs.)	N = 9	N = 13	
	Hochschulabschluss	9.52%	5.56%	
	(> 13 yrs.)	N = 12	N = 7	

Table 3: Sociodemographical Data of the random sample (n =127) - Distributions and Mean Values (Mean) ± Standard Deviation (SD)

		OLP	TAU	p
Health Status ("Do you feel healthy?")	Yes	44.88%	38.58%	
	No	N = 57	N = 49	.639 >.05
		7.87%	8.66%	
		N = 10	N = 11	
Regular drug use	Yes	41.64%	38.33%	
	No	N = 50	N = 46	1.000 >.05
		10%	10%	
		N = 12	N = 12	
Smoking	Yes	5.98%	10.26	
	No	n = 7	n = 12	
		45.3%	38.46%	
		n = 53	n = 45	
Smoking behavior (in Pack years)	Mean ± SD	3.3 ± 10,7	5.0 ± 10.8	.385 >.05
Alcohol consumption (In g per week)	Mean ± SD	24.5 ± 29,9	25.5 ± 47.8	.892 >.05

6.2 Effects of OLP on pain intensity and self-reported functional capacity

N=122 patients completed the trial from Baseline to day 21 (N=63 OLP+TAU-group; N=59 TAU-group) and were included in the data analysis of the self-reported functional capacity. Statistically significant differences were detected by using the Welch t-Test on completed observations between the TAU and the OLP+TAU group. With regard to the study protocol the primary outcome pain intensity, depicted by the composite VAS score (VAScomp) ($t(104.3)=-2.649$, $p<.001$) decreased in the OLP+TAU group compared to the TAU group. With respect to functional capacity, as a secondary outcome, the Oswestry Disability Index (ODI) ($t(116.470)=2.574$, $p=.01$), showed a decreased functional impairment in the OLP+TAU group. This also applies to the depression subscale of the Depression-Anxiety-Stress-Scale (DASS) ($t(99.053)=2.247$, $p=.02$) as an explorative outcome, indicating a decreased depression score.

In summary, these results suggest a decrease in pain intensity (VAScomp), functional disability (ODI) and parameters associated with depression (DASS) after OLP+TAU treatment, as compared to the TAU group. These results are consistent with our first hypothesis (see **4.1**), anticipating a stronger decrease of pain and self-reported disability in the TAU + OLP group, as compared to the OLP only group.

No statistically significant differences were detected for the scores of the back-performance scale (BPFS), the subscales of the DASS for anxiety and stress, the pain-catastrophizing scale (PCS) and the patient specific functional scale PSFS. **Table 4** provides an overview of the differences between the TAU and the OLP+TAU groups.

Table 4: Results Differences between TAU and OLP+TAU Group on subjective motion criteria

Behavioral Data	T	df	p-value	CI	95%	Diff [1]-[0]	Cohens d=	r
ODI	2.573700	116.470	**0.01132***	0.9299629	7.1407060	4.0353349	0.457	0.232
BPFS	0.712060	90.763	0.47830	-0.4070133	0.8618473	0.2274170	0.127	0.075
Depression	2.246800	99.053	**0.02687***	0.1549858	2.4972390	1.3261124	0.399	0.220
Anxiety	1.793300	108.740	0.07571	-0.0996768	1.9936162	0.9469697	0.319	0.169
Stress	1.680100	115.000	0.09565	-0.2233626	2.7192642	1.2479510	0.299	0.155
PCS	0.337680	121.330	0.73620	-2.4821570	3.5030560	0.5104493	0.060	0.031
VAS min	2.178700	112.900	**0.03143***	0.0623738	1.3136724	2.0411328	0.387	0.201
VAS max	2.362500	108.710	**0.01993***	0.1326023	1.5141509	1.5333333	0.420	0.221
VAS mean	1.418500	115.070	0.15870	-0.1885258	1.1397523	0.4756132	0.252	0.131
VAS comp	2.6494	104.33	**0.009317***	0.1666108	1.1580645	0.6623377	0.481	0.251
PSFS	-0.252340	112.250	0.80120	-11.692241	0.9050451	0.1320900	-0.045	0.024

6.3 Relationship between open label placebo, subjective and objective measurement criteria

Out of the 127 patients who were part of the motion capturing group during the pre-assessment n=118 were included in the data analysis and n=4 had to be excluded due to interfering artifacts. **Table 5** provides an overview over average RoM and VoM of the participants of the study at the time of the pre assessment and before randomization.

Table 5: Average Range of Motion (RoM) and Velocity (VoM) of the pooled sample at Pre-Assessment (N=127)

Movement Direction	RoM (in °)	SD	VoM (in °/sek)	SD
Flexion	38.0474	10.90373	36.7954	16.43264
Extension	19.5162	10.47477	23.6162	15.85809
Rotation (left)	23.7207	9.52593	36.5514	25.41229
Rotation (right)	24.1908	9.06802	34.8007	22.52836
Lateroflexion (left)	18.2294	6.69876	30.8021	18.41450
Lateroflexion (right)	18.5010	7.13738	31.4413	19.46542

To gain insights into the motion capabilities of patients with CLBP, findings of the motion analysis were compared to the results of a preliminary experiment by Consmüller et al. (2012) of 429 asymptomatic volunteers. The authors used the same motion capturing system and differentiated the groups adjusted by the regular age-related loss of motion capabilities. This opened the possibility to relate our results to an asymptomatic study population. The population of our study presented an average age of 60.8 ±15.01(SD) at the time of the pre assessment. Hence, the logical conclusion was to compare our findings to the findings by Consmüller et al. We compared the age groups between 36 – 50 years and 51 – 75 years, assuming that no difference between our groups and the Consmüller groups indicates regular motion capabilities in CLBP patients. In comparison to the asymptomatic volunteers a statistically significantly difference was detected for range of flexion ($t(271)=-9.889$, $p<=.001$) between our study population and the group of 36 – 50 year old asymptomatic volunteers ($t(271)=-9.889$, $p<=.001$) and extension ($t(271)=-2.344$,

p=.01). For the group of 51 – 75 year old volunteers our study population differed statistically significant in range of flexion (t(219)=4,722, p<=.001), whereas there was no difference in range of extension (t(219)=0.000, p=1.0) (**Figure 4**).

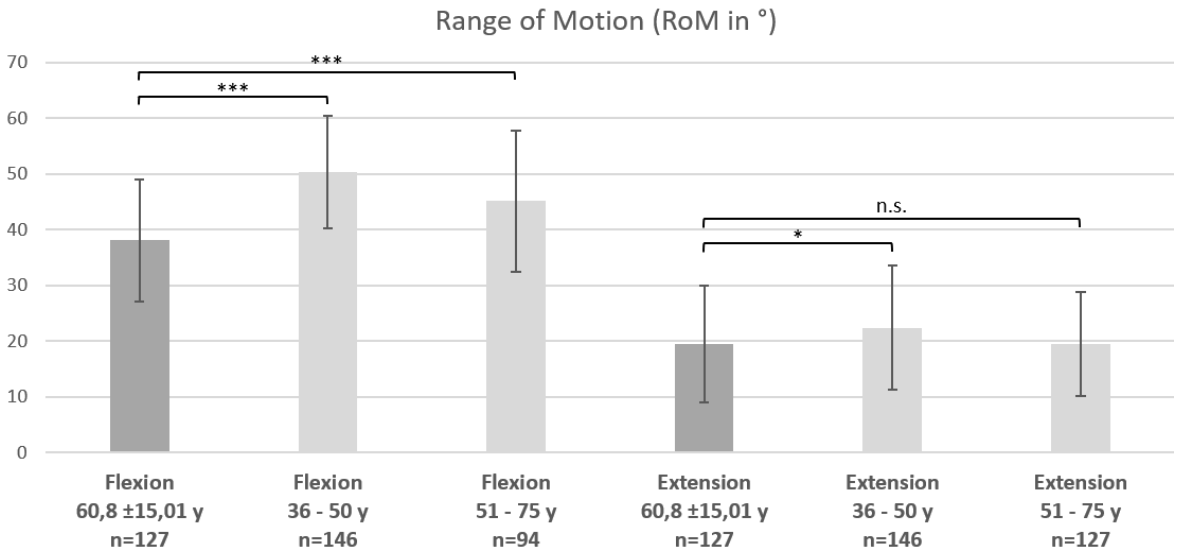

Figure 4: Comparison of Range of Motion between study population (dark grey) and asymptomatic patients of different age groups according to Consmüller (2012).

This indicates a changed range of motion in CLBP, compared to asymptomatic volunteers. Results are similar for the VoM. When comparing these results to the group of 36 – 50 years old participants of, our study population demonstrated a statistically significant difference for velocity of flexion (t(271)=-20.960, p<.001) and extension (t(271)=-13.373 p<.001). The same is also valid for the group of the 51 – 75-year-old asymptomatic participants. Compared to the CLBP patients a statistically significant difference in flexion velocity (t(219)=-14.692, p<.001) and extension velocity (t(219)=-9.373, p<.001) was observed (**Figure 5**).

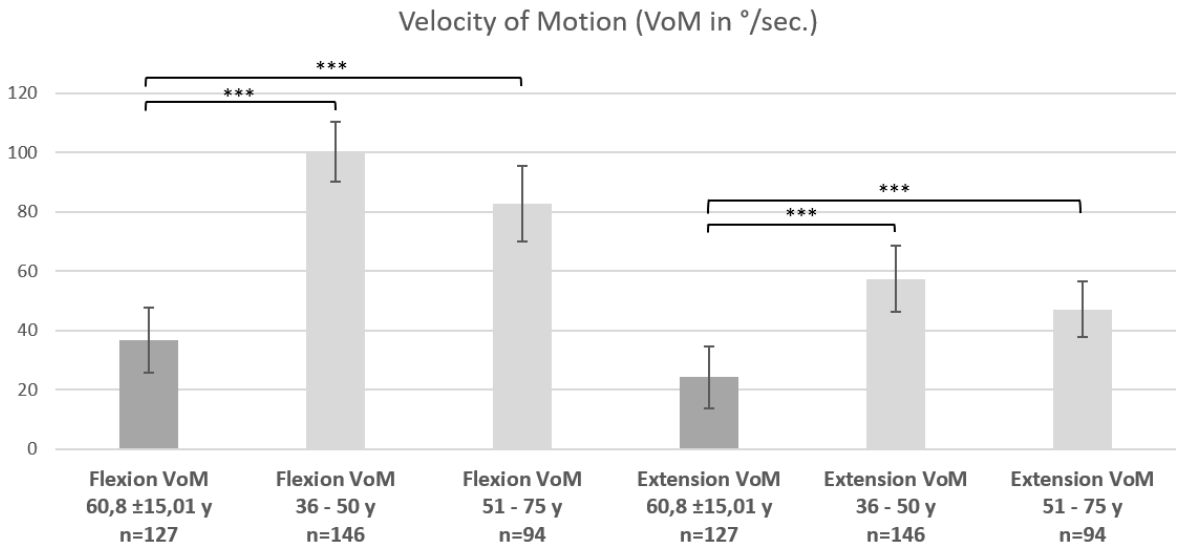

Figure 5: Comparison of Velocity of Motion between study population (dark grey) and asymptomatic patients of different age groups according to Consmüller (2012).

We assessed randomization bias by comparing baseline RoM and VoM measurements between the TAU and OLP+TAU groups. As presented in **Table 6**, a statistically significant difference was detected between the TAU and the OLP+TAU Group on the Range of motion parameter Extension (t(90.811)= 2.0111, p=0.04728). The statistical analysis of OLP-effect revealed no statistically significant difference in objective motion capabilities between the TAU and the OLP+TAU groups (**Table 7** & **Table 8**).

Table 6: Differences of Averaged Motion Scores (RoM &VoM) after randomization into TAU and TAU + OLP Group

Range of Motion	**TAU (in º) N=67**	**SD**	**OLP+TAU (in º) N=60**	**SD**	**T**	**DF**	**P**
Flexion	39.38	10.13	36.84	11.49	1.3213	124.97	.18>.05
Extension	21.52	12.92	17.71	7.29	2.0111	90.811	**.04<.05**
Rotation (left)	23.25	8.97	24.13	10.04	-0.52219	125	.60>.05
Rotation (right)	24.63	9.65	23.79	8.55	0.52016	118.69	.60>.05
Lateroflexion (left)	19.24	6.33	17.32	6.93	1.6317	124.94	.10>.05
Lateroflexion (right)	19.78	6.99	17.35	7.11	1.9374	123.91	.06>.05

Velocity of Motion	TAU (in °/sec.) N=67	SD	OLP+TAU (in °/sec) N=60	SD	T	DF	P
Flexion	37.47	15.22	36.19	17.53	0.43994	124.89	.66>.05
Extension	25.38	18.55	22.02	12.92	1.1714	103.86	.24>.05
Rotation (left)	33.89	20.13	38.92	29.29	-1.1381	117.43	.25>.05
Rotation (right)	33.91	20.77	35.59	24.11	-0.41945	124.82	.67>.05
Lateroflexion (left)	31.49	16.44	30.17	20.11	0.40661	124.01	.68>.05
Lateroflexion (right)	32.90	18.79	30.12	20.09	0.80554	124.76	.42>.05

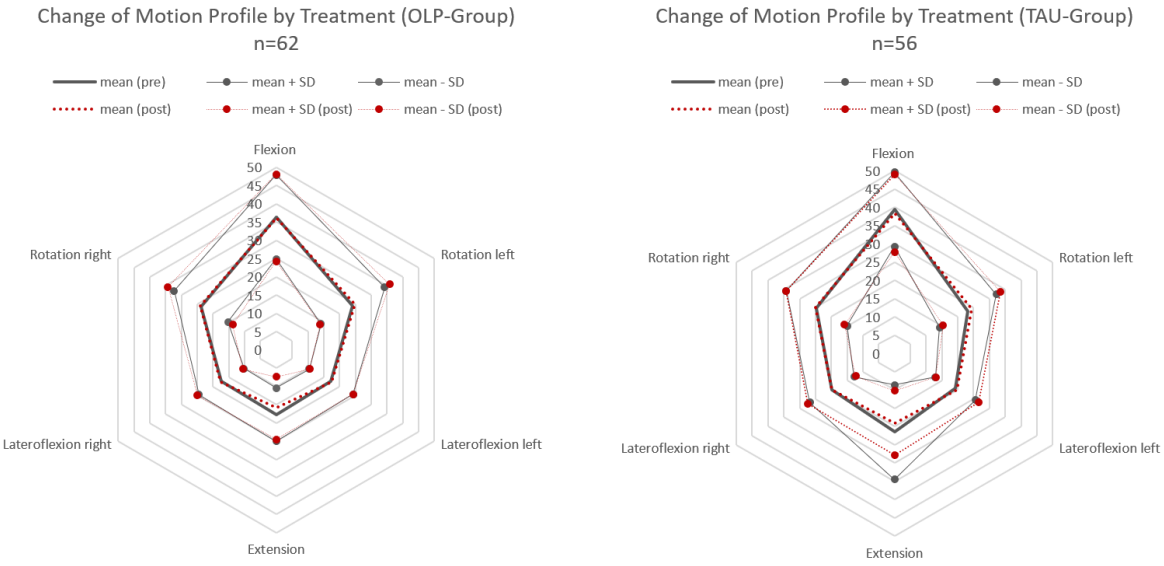

Figure 6: Change of Motion Profile by Treatment – Averaged scores of pre – (dark grey line) and post – test (red dotted line)

Table 7: Welch Test on Pre-Post Differences between OLP+TAU and TAU Group for RoM-Parameters

Range of Motion	T	df	p-value	CI	95%	Diff [1]-[0]	Cohens d=	r
Flexion	-0.573500	115.950	0.56740	-3.7053350	2.0413490	0.8319931	-0.102	0.053
Extension	-0.553890	100.860	0.58090	-4.3949380	2.4763900	0.9592740	-0.098	0.055
Lateral- Flexion (l)	0.129670	114.040	0.89710	-1.4019120	1.5982940	0.0981913	0.023	0.012
Lateral- Flexion (r)	-0.766190	115.890	0.44510	-2.1504910	0.9507905	0.5998502	-0.136	0.071
Rotation (l)	0.201660	113.820	0.84050	-2.6422250	3.2411190	0.2994470	0.036	0.019
Rotation (r)	-0.362750	115.620	0.71750	-3.5665920	2.4624100	0.5520910	-0.064	0.034

Table 8: Welch-Test on Pre-Post Differences between OLP+TAU and TAU Group for VoM-Parameters

Velocity	T	df	p-value	CI	95%	Diff [1]-[0]	Cohens d=	r
Flexion	0.240140	107.470	0.81070	-4.0435210	5.1582450	0.5573617	0.043	0.023
Extension	0.049184	112.290	0.96090	-4.9176600	5.1680280	0.1251843	0.009	0.005
Lateral Flexion (l)	-0.200980	104.430	0.84110	-5.8420260	4.7667720	0.2994470	-0.036	0.020
Lateral Flexion (r)	-0.448670	114.890	0.65450	-6.9396260	4.3764460	2.7613890	-0.080	0.042
Rotation (l)	0.201660	113.820	0.84050	-2.6422250	3.2411190	0.5376270	0.036	0.019
Rotation (r)	-0.748330	114.460	0.45580	-10.071114	4.5483380	1.2815900	-0.133	0.070

6.4 Relationship between objective and subjective measurement criteria

While it is plausible to assume that objective measurement criteria and self-reported functional capacity are complexly related, we investigated whether and how this connection was present in the study population by correlating the composite RoM and VoM scores of the self-reported functional capacity and related questionnaires (BPSF, composite VAS, Depression, Anxiety, Stress, ODI, PCS, PSFS) at Baseline. Specifically, we calculated pairwise Pearson product-moment correlations to examine the relationship between the composite motion characteristics for Range of motion and the behavioral scale scores.

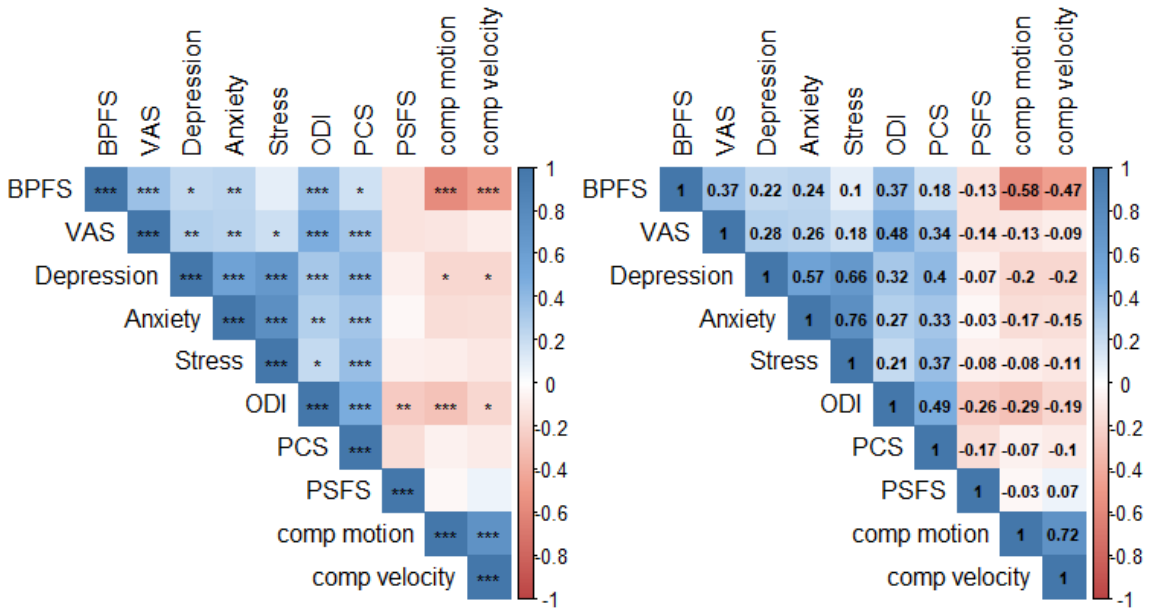

Figure 7: Correlationplot with correlationscoefficents (right) on significancelevel p <0,05 (left)

The highest statistical correlation was found between the Range of motion and the velocity of motion. The relationship was positive, strong and statistically significant (r(125)=0.7237972,p<.001). Moderate negative, statistically significant correlations were found for range of motion and the back performance scale (r(124)=-0.5752337, p<.001). Negative and small, but statistically significant relationships (without correcting for multiple comparisons) were seen between the range of motion and the Depression subscale of the DASS-score (r(123)= -0.1952914,p=.03) and the ODI (r(124)=-0.2927828, p<.001). No further statistically significant correlations were observed (**Table 9**).

Table 9: Pearson Product Moment Correlations between composite Range of Motion Characteristics and scale scores of the behavioral dataset at Baseline

Range of Motion	t	df	p-value	CI	95%	r
Velocity	11.728	125	< 2.2e-16	0.6288822	0.7974558	0.7237972
ODI	-3.4234	125	0.0008366	-0.4443333	-0.1249410	-0.2927828
BPFS	-7.8308	124	1.856e-12	-0.6815666	-0.4451103	-0.5752337
Depression	-2.2084	123	0.02907	-0.35860087	-0.02038294	-0.1952914
Anxiety	-1.8727	122	0.06351	-0.333642393	0.009435485	-0.1671592
Stress	-0.90021	123	0.3698	-0.2529172	0.0960695	-0.0809029
VAS	-1.4139	123	0.1599	-0.29551065	0.05025772	-0.1264659
PCS	-0.77354	125	0.4407	-0.2403468	0.1064727	-0.06902222
PSFS	-0.34858	125	0.728	-0.2042683	0.1438329	-0.0311626

Focusing on the Velocity of motion Characteristics, a positive, strong and statistically significant relationship was observed with the Range of Motion Score, as mentioned above. A small, negative and statistically significant correlation was equally observed between Velocity of Motion and the back performance scale (r(124)= - 0.4685889, p<.001)., the Depression Subscale of the DASS- Score (r(124)= - 0.1963908, p=.03)., as well as the ODI (r(125)= - 0.1935509, p=.03). No further statistically significant correlations were found as seen in **Table 10**.

Table 10: Pearson Product Moment Correlations between composite Velocity of Motion Characteristics and scale scores of the behavioral dataset

Velocity of Motion	t	df	p-value	CI	95%	r
RoM	11.728	125	< 2.2e-16	0.6288822	0.7974558	0.7237972
ODI	-2.2057	125	0.02924	-0.35576918	-0.02001098	-0.1935509
BPFS	-5.9066	124	3.137e-08	-0.5947504	-0.3199008	-0.4685889
Depression	-2.2213	123	0.02816	-0.35959664	-0.02152563	-0.1963908
Anxiety	-1.6859	122	0.09437	-0.3187256	0.0261232	-0.1508884
Stress	-1.2673	123	0.2074	-0.28348869	0.06333713	-0.1135332
VAS	-0.97737	123	0.3303	-0.25939471	0.08919658	-0.08778598

Velocity of Motion	t	df	p-value	CI	95%	r
PCS	-1.0789	125	0.2827	-0.26581704	0.07949443	-0.09605042
PSFS	0.74034	125	0.4605	-0.1094009	0.2375532	0.066073

6.4.1 Interaction of Pain Catastrophizing on Movement speed

As OLP-effects might be very different across individuals (El Brihi et al., 2019), an explorative analysis was conducted, investigating whether there was a subpopulation which could be identified by subjective data and have a response in objective movement parameters. The analysis consisted of systematically modelling the interaction-effect between OLP treatment and subjective outcomes on the objective outcomes (composite RoM, VoM scores).

The interaction term was statistically significant (p=0.003) in one out of the 16 possible models, showing that group differences are significantly influenced by the patients' pain catastrophizing (PCS, see **Figure 8**). Importantly, the observed p-value is considerably low and meets the acceptance level with Bonferroni-correction ($\alpha_{Bonf.}$=0.003).This means that, patients with low pain catastrophizing (at baseline) show an improvement in movement speed in the TAU + OLP group as compared to the TAU condition while patients with high pain catastrophizing tended to show an opposite effect. This resulted in a negligible, statistically not significant main effect, but a statistically significant interaction effect.

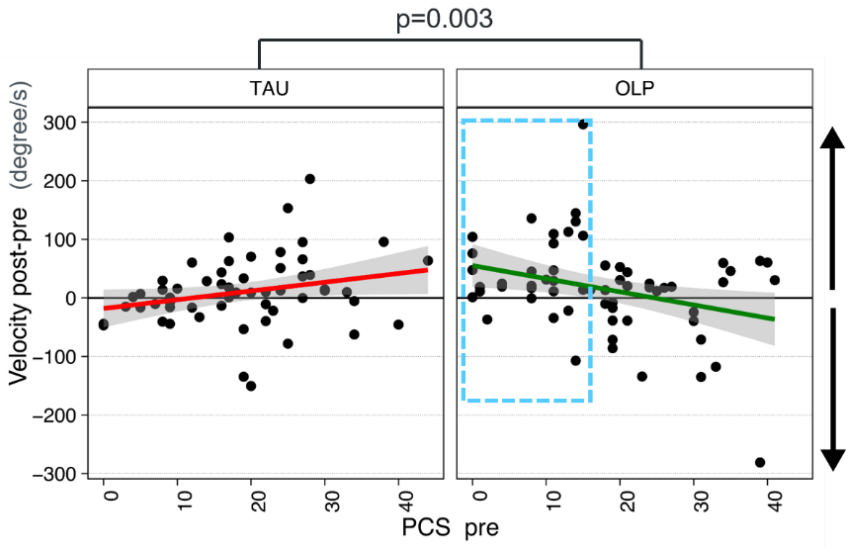

Figure 8: Interaction effect between treatment and pain catastrophising on velocity alteration

7 Discussion

In the present work we investigated the effect of an open-label placebo intervention over a period of 21 days on pain, self-assessed ADL- Impairment and motor performance of chronic low back pain patients. While a previous study has shown improved self-reported disability in chronic low back pain patients as a consequence of an open-label-placebo treatment to our best knowledge, this study is the first to assess the effect of OLP on objective characteristics of motor performance, as measured by a motion capturing system, in form of Range of Motion and Velocity of Motion. To enable comparability to previous investigations, motion capturing was supplemented by Questionnaires for pain intensity, subjective movement behavior and psychological variables. According to the Declaration of Helsinki issued by the World Medical Association the study has been approved by the ethics committee at the faculty of medicine of the university of Duisburg-Essen. A total n=127 patients were included into motion capturing at pre-assessment. A total amount of n=118 patients completed the motion capturing at second time of assessment and n=4 had to be excluded due to interfering artifacts. By providing the OLP as an adjunct treatment, it was ensured that all patients suffering from CLBP were not restricted in individual procedures within the health problem.

Statistically significant differences were marked for the perceived level of disability, depression and pain intensity of chronic low back pain patients (**Table 4**). These findings replicate research by Carvalho et al. (2016) in a greater sample, demonstrating statistically significant improvements in subjective/self-reported measures of motion capacity/disability, pain, as well as depressive symptoms in a group of CLBP patients receiving OLP treatment additional to their regular health related routines (OLP+TAU) as compared to a group with treatment as usual (TAU).

In contrast to the OLP-induced reduction in the subjectively perceived limitation in movement behavior (ODI), no statistically significant difference was found between the two groups for objective motion capabilities.

The lack of objectively measured OLP-induced improvement in motion capabilities somewhat contradicts the results of our exploratory analysis which revealed complex and statistically significant relationships between objective and self-reported

subjective measures of movement behavior (ODI and BPFS) across participants at baseline conditions.

Interestingly, we found that individual pain catastrophizing (at baseline conditions) might modulate the beneficial effect of OLP on objectively measurable motion characteristics. Specifically, an improved movement velocity following the OLP treatment was found only in low pain catastrophizers, which might explain the lack of significant main effect of OLP-treatment on objective measures. While these results, due to the exploratory nature of the interaction-analysis, still have to be replicated by further studies, they suggest that OLP-treatment, next to its known beneficial effects on the patients subjectively perceived movement abilities, might also achieve an objectively measurable improvement in a subgroup of subjects, and thus might serve as a basis for personalized medicine in CLBP.

7.1 Relating results to the current state of research

Relationship between open label placebo, pain intensity and self-reported functional capacity

Existing evidence indicates that adding an open label placebo treatment to the treatment as usual in chronic low back pain patients leads to an decrease in pain intensity and an improvement in functional capacity (Carvalho et al., 2016). In their study 83 adults suffering from persistent low back pain for more than 3 months, presented a statistically significant pain reduction and a reduced disability while randomized into the OLP group, receiving an open-labeled placebo compared to the TAU group, receiving no placebo. The measurement tools that were used included the NRS Score for Pain intensity addressing the minimum, maximum and usual pain and the Roland-Morris-Disability Questionnaire (RMDQ) detecting disability. Within our study we were able to replicate these results, using similar measurement. Addressing the functional impairment, we used the ODI instead of the RMDQ. Reviewing the evidence, measuring functional impairments for nonspecific low back pain patients, both assessments are characterized by high reliability and validity (Roland & Fairbank, 2000) and there are no reasons to prefer one of the two assessments (Chiarotto et al., 2016).

Notwithstanding the fact that the term of pain intensity is often wrongly conflated with the term of suffering of chronic low back pain (Sullivan & Ballantyne, 2016), our

data suggest a robust correlation (r=0,48) between disability (ODI) and pain intensity (VAS), analyzing the n=127 participants before randomization (see **Figure 7**). This forms the framework for the interpretation of the statistically significant difference between the OLP+TAU and TAU Group for pain Intensity after completing the trial.

Nevertheless there is a difference in clinical meaningful and statistically significant difference in pain intensity, we were able to demonstrate not only a statistically significant pain difference in favor of the OLP+TAU group, but also a statistically significant difference in ODI scores and the depression subscale of the DASS. While patients received the OLP treatment additional to their usual treatment, the beneficial effect on pain intensity, disability and depression must be highlighted as an effect driven by the placebo treatment without deception of a possible effect mechanism by a powerful drug. Using a larger sample of CLBP-Patients these results support the results by Carvalho et al.(2016) and stand in line with earlier observations of beneficial effects by an open label placebo treatment (Kaptchuk & Miller, 2018). Results are published in detail (Kleine-Borgmann et al., 2019). Highlighting the observation of a potential interdependence between expectancy and the a placebo effect it is possible, that the pure pill-taking procedure could be sufficient for triggering the analgesic impact in chronic low back pain and a deception by particularly feigning the usage of a powerful drug, is not necessary (Carvalho et al., 2016). By strengthening the expectation of relief, a dynamic cycle could be initiated, whereby adjusted expectations lead to pain relief which in turn could result in a changed motion behavior.

Relationship between open label placebo, pain intensity and objective measurement criteria

It has been suggested that altered spinal kinematics can be considered a possible reason for symptom severity and the persistence of disability in chronic low back pain (Dubois et al., 2014). Reasons for an adapted motor behavior are neuromuscular adaptations that can lead to a different muscular activation pattern in chronic low back pain patients compared to healthy controls (Dubois et al., 2014). In addition to the self-assessed functional capabilities we performed a motion capturing procedure to quantify a hypothesized decreased disability. In analogy to the hypothesis that was presented in chapter 3 4.3, we expected a negative correlation between disability scores and motion capabilities (Range of Motion and Velocity of Motion).

This expectation was substantiated by the comparison of our sample to motion capabilities of healthy adults of comparable demographics, using the same motion capturing system (Consmüller et al., 2012). Here, our sample presented a statistically significant impaired RoM and VoM compared to healthy adults (**Figure 4** & **Figure 5**) indicating to an adapted motor behavior in our study population. This assumption is confirmed by the observed inverse significant correlation between the composite motion score and ODI Scores ($r(124)=-0.2927828$, $p<.001$) at baseline in our study population.

Our observation that motion capturing does not provide any statistically significant differences between the groups (and no difference within the treatment period), while disability ratings, pain intensity and depression ratings showed a statistically significant difference between the groups highlights the complexity of adapted motor behavior of chronic low back pain patients. Notwithstanding the fact that the data used for comparison are not part of our data acquisition, our patients demonstrated an adapted motor behavior by a reduced RoM and VoM in contrast to healthy controls. The underlying reasons for this adaptation may not only be a consequence of pain intensity. One explanation might be that the neuromuscular adaptations, leading to an adapted motion behavior stand in line with health beliefs of harmful motions and a desire of protecting the tissue. Patients consider their back as vulnerable due to its specific design, the use of it and the pathomechanic mechanism which is most probably connected with previous pain events (Darlow et al., 2015). These negative assumptions are leading to an affected information process by misinterpretations and can create fear reactions while typical fear reactions are accompanied by an increased avoidance behaviour (Dubois et al., 2014). The intention to guard the structure and the fear avoidance beliefs relating thereto are affecting the prognosis of chronic low back pain to a large extent (Darlow et al., 2015) and could be a more robust predictor of altered motion characteristics than pain intensity itself.

Another explanation according to recent literature of fMRI studies might be, that there are subgroups within the study population reacting differently to a placebo. Placebo responders were identified by connectivity in specific brain areas like the right midfrontal gyrus of the prefrontal cortex a region associated with high-level executive functions and decision-related processes (Talati & Hirsch, 2005).

Relationship between objective and subjective measurements of spinal movement and functional capacity

The lack of objectively measured OLP-induced improvement in motion capabilities somewhat contradicts the results of our exploratory analysis which revealed complex and statistically significant relationships between objective and self-reported subjective measures of movement behavior (ODI and BPFS) across participants at baseline conditions.

Standardized RoM values were found to be strongly correlated to the back performance scale (r=-0.58), and statistically significant but weak correlated to ODI (r=0.29) (**Figure 7**) indicating for an impact of RoM on functional motion sequences that are rated by an examiner but not on self-assessed disability.

Among each other the results of the BPFS were weakly correlated (r=0,37) to the ODI indicating for different dimensions of disability assessed by the different assessments. Thus, for example negative emotions in connection to depleted coping resources are associated with functional impairment and the level of chronic pain (Gerhart et al., 2018). It stands to reason, that a pure performance aspect, highlighting the motion parameters (BPFS and RoM), are indicators for functional impairments, but not for the level of suffering, unless the emotional and cognitive dimension is excluded from assessment. Possibly functional impairments are not a direct consequence of pain, but more a result of abnormal pain processing brain activation in consequence of functional brain changes that lead to over-responsiveness to sensory inputs that signal potential harm (Goossens et al., 2018).

While we identified statistically significant differences in Pain Intensity and self-assessed impairments (ODI), which potentially covers the dimension of suffering more than the pure motion performance. This raises the question of whether the pain intensity and impairment in motion characteristics both are connected to CLBP, but not connected to each other.

Open label placebo responder analysis

As discussed above, a plausible explanation of the divergent results with subjective and objective outcomes might be that there are subgroups within the study population reacting differently to a placebo.

Our interaction analysis strongly supports this explanation as it shows that individual pain catastrophizing (at baseline conditions) might modulate the beneficial effect of OLP on objectively measurable motion characteristics. Specifically, an improvement in the velocity-of-motion was observed in low pain catastrophizers treated with OLP.

Interestingly, the level of Pain-Catastrophizing has been previously associated with a decreased activation of prefrontal brain structures among persons with chronic pain in fibromyalgia (Gracely et al., 2004). This prefrontal activity has been shown to be crucial for placebo responsiveness and forms an possible explanation for interindividual differences in placebo effects (Enck et al., 2013). Moreover a disrupted functional connectivity in cognitive and sensorimotor networks (Dubois et al., 2014), are linked to brain areas that have also been reported to be relevant in identifying placebo responders (Ashar et al., 2017) highlighting a connection between prefrontal activity and motor function.

While these results, due to the exploratory nature of the interaction-analysis, still have to be replicated by further studies, they suggest that OLP-treatment, next to its known beneficial effects on the patients subjectively perceived movement abilities, might also achieve an objectively measurable improvement in a subgroup of subjects, and thus might serve as a basis for personalized medicine in CLBP.

7.2 Limitations

7.2.1 Is the Open label placebo treatment open?

Referring to the way that patients are informed in OLP-Trials, the explanation by the video that placebo effects may still be powerful although they do not contain any medication could lead to manipulation of the patient expectation. So asking the question whether the open label placebo is really open-labelled and the level of expectation driven by the manipulated patient information situation, evidence suggests that information about the general effect mechanisms of placebos seems not to be necessary to elicit an open-label-placebo-effect in the form of symptom relief (Schaefer et al., 2018). But the exclusion from the placebo treatment in the first instance could lead to a negative effect in the TAU group, while they were informed about the “powerful placebo” but receiving no additional treatment. In one trial the disappointment about allocation to the Control group in smoking cessation led to higher drop-out rates (Lindström et al., 2010).

7.2.2 Motion capturing

After randomization we identified some differences between the groups, which potentially could affect the results and analysis after completing the trial. First the BMI differed statistically significant with higher scores within the OLP+TAU group (**Table 2**). Other studies indicated, that a body weight, body height and BMI play only a secondary role for motion capabilities measured by the Epionics Spine System (Consmüller et al., 2012) suggesting that this difference will not be a decisive factor for potential differences between TAU and OLP+TAU in motion possibilities. The other parameter that differed already at the timepoint after randomization was the score of Extension which showed a statistically significant difference OLP+TAU and TAU group, which could refer to a heterogeneous basis for the comparison. This difference was clinically not meaningful and explainable by the high variance caused by outliers on the Extension Parameter within the TAU (**Figure 9**). Moreover, the observed p-value is close to the alpha-level (α=0.05) and does not survive a Bonferroni correction for the multiple comparisons, therefore it is most probably a false positive result.

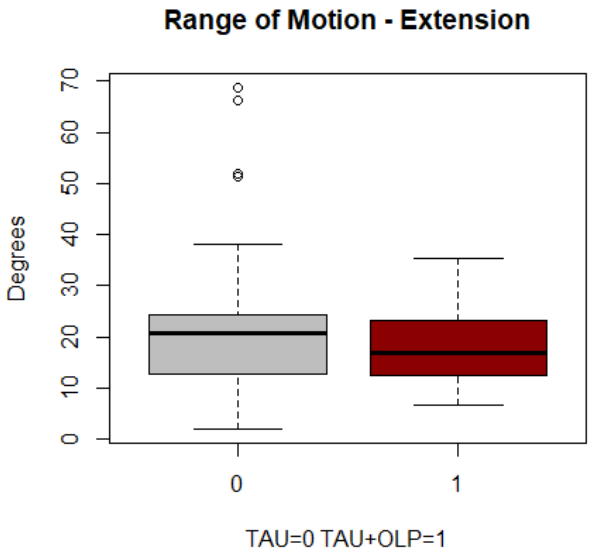

Figure 9: Boxplot of the grouped Range of Extension after randomization

7.2.3 Questionnaires

The questionnaire survey we used predominantly consisted of extensively validated national and international studies (Fairbank & Pynsent, 2000; Heldmann et al., 2015; Horn et al., 2012; Karcioglu et al., 2018; Mannion et al., 2006; Selim et al., 2009). Furthermore, the questionnaires were selected with a view to ensuring that we were able to evaluate possible contributing factors of function, related to chronic low back pain in comparison to previous investigations (Carvalho et al., 2016). It was found, that particularly the "*Deutscher Schmerzfragebogen"* for the Inventory of causes of pain has been problematic, because of the relatively high amount of items (Core questionnaire: 24 questions, Module S - social-security components: 8 ques-

tions, Module L – Health related quality of life: 12 questions, Module D – Demography: 17 questions). In connection to the other used questionnaires (ODI, PSFS) the processing period varied strongly and exceeded the planned period. So, it is possible that this interferes the feeling of redundancy in participating patients. In further studies it will be important to reduce the processing period to maintain the participants motivation since the length of a questionnaire is related to the response of participants (Edwards et al., 2009). Further the usage of numeric pain intensity ratings should be called into question against the background of habituation effect and social desirability in chronic pain states. Patients demonstrated considerable experience with numeric rating scales which could indicate, that this is a conditioned status and not the representation of the actual pain intensity. Consistent to these findings, other authors reported that chronic pain patients report a higher self-estimated percentage improvement of pain compared to the value calculated from their pain scores (Cushman et al., 2015).

7.3 Outlook

Our study replicates previous results of research by Carvalho et al. (2016) in a greater sample, demonstrating statistically significant improvements in subjective/self-reported measures of motion capacity/disability, pain, as well as depressive symptoms in a group of CLBP patients receiving OLP treatment additional to their regular health related routines (OLP+TAU) as compared to a group with treatment as usual (TAU). and indicates a separation between actual and perceived movement capacity and highlights the necessity to functional therapy management of chronic low back pain patients. Similar conclusions were obtained with cognition based physical therapy in contrast to manual therapy and exercise.

Our finding that individual pain catastrophizing (at baseline conditions) might modulate the beneficial effect of OLP on objectively measurable motion characteristics, due to the exploratory nature of the interaction-analysis, still has to be confirmed by future studies.

The improved movement velocity we found to be present only in low pain catastrophizers suggest that OLP-treatment, next to its known beneficial effects on the patients' subjectively perceived movement abilities, might also achieve an objectively

measurable improvement in a subgroup of subjects, and thus might serve as a basis for novel personalized medicine approaches in CLBP.

8 Summary

In the present work we investigated the effect of an open-label placebo (OLP) intervention over a period of 21 days on pain, self-assessed activities of daily life (ADL) - Impairment and motor performance of chronic low back pain (CLBP) patients. To our best knowledge, this study is the first to assess the effect of OLP on objective characteristics of motor performance, as measured by a motion capturing system, in form of Range of Motion (RoM) and Velocity of Motion (VoM). To enable comparability to previous investigations, motion capturing was supplemented by Questionnaires for pain intensity, subjective movement behavior and psychological variables.

A total amount of n=127 patients were included into motion capturing at pre-assessment. A total amount of n=118 patients completed the motion capturing at second time of assessment and n=4 had to be excluded due to interfering artifacts. By providing the OLP as an adjunct treatment, it was ensured that all patients suffering from CLBP were not restricted in individual procedures within the health problem.

Statistically significant differences were marked for the perceived level of disability, depression and pain intensity of chronic low back pain patients but no differences for objective motion capabilities (RoM & VoM). These findings demonstrating statistically significant improvements in subjective/self-reported measures of motion capacity/disability, pain, as well as depressive symptoms in a group of CLBP patients receiving OLP treatment additional to their regular health related routines (OLP+TAU) as compared to a group with treatment as usual (TAU).

As an additional finding the individual pain catastrophizing (at baseline conditions) might modulate the beneficial effect of OLP on objectively measurable motion characteristics. Specifically, an improved movement velocity following the OLP treatment was found only in low pain catastrophizers, which might explain the lack of significant main effect of OLP-treatment on objective measures. suggest that OLP-treatment, next to its known beneficial effects on the patients subjectively perceived movement abilities, might also achieve an objectively measurable improvement in a subgroup of subjects, and thus might serve as a basis for personalized medicine in CLBP.

9 Bibliography

1. Albouy, G., Fogel, S., King, B. R., Laventure, S., Benali, H., Karni, A., Carrier, J., Robertson, E. M., Doyon, J. (2015): Maintaining vs. enhancing motor sequence memories: respective roles of striatal and hippocampal systems. NeuroImage 108, 423–434. doi:10.1016/j.neuroimage.2014.12.049

2. Alleva, J., Hudgins, T., Belous, J., Kristin Origenes, A. (2016): Chronic low back pain. Disease-a-month : DM 62. (9), 330–333. doi:10.1016/j.disamonth.2016.05.012

3. Al-Saeed, O., Al-Jarallah, K., Raeess, M., Sheikh, M., Ismail, M., Athyal, R. (2012): Magnetic resonance imaging of the lumbar spine in young arabs with low back pain. Asian spine journal 6. (4), 249–256. doi:10.4184/asj.2012.6.4.249

4. American Medical Association: Placebo Use in Clinical Practice: CEJA Report 2-I-2006. (2006). Online-Publikation; https://www.ama-assn.org/delivering-care/ethics/use-placebo-clinical-practice/ 19.08.2019.

5. Ansari, B., Bhati, P., Singla, D., Nazish, N., Hussain, M. E. (2018): Lumbar Muscle Activation Pattern During Forward and Backward Walking in Participants With and Without Chronic Low Back Pain: An Electromyographic Study. Journal of chiropractic medicine 17. (4), 217–225. doi:10.1016/j.jcm.2018.03.008

6. Antony, M. M., Bieling, P. J., Cox, B. J., Enns, M. W., Swinson, R. P. (1998): Psychometric properties of the 42-item and 21-item versions of the Depression Anxiety Stress Scales in clinical groups and a community sample. Psychological Assessment 10. (2), 176–181. doi:10.1037/1040-3590.10.2.176

7. Anwar, K. (2016): Pathophysiology of pain. Disease-a-month : DM 62. (9), 324–329. doi:10.1016/j.disamonth.2016.05.015

8. Ashar, Y. K., Chang, L. J., Wager, T. D. (2017): Brain Mechanisms of the Placebo Effect: An Affective Appraisal Account. Annual review of clinical psychology 13, 73–98. doi:10.1146/annurev-clinpsy-021815-093015

9. Atlas, L. Y., Wager, T. (2013): Expectancies and beliefs: insights from cognitive neuroscience: Oxford University Press.

10. Baliki, M. N., Schnitzer, T. J., Bauer, W. R., Apkarian, A. V. (2011): Brain morphological signatures for chronic pain. PloS one 6. (10), e26010. doi:10.1371/journal.pone.0026010

11. Barzilay, Y., Segal, G., Lotan, R., Regev, G., Beer, Y., Lonner, B. S., Mor, A., Elbaz, A. (2016): Patients with chronic non-specific low back pain who reported reduction in pain and improvement in function also demonstrated an improvement in gait pattern. European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society 25. (9), 2761–2766. doi:10.1007/s00586-015-4004-0

12. Bauer, C. M., Rast, F. M., Ernst, M. J., Meichtry, A., Kool, J., Rissanen, S. M., Suni, J. H., Kankaanpää, M. (2017): The effect of muscle fatigue and low back pain on lumbar movement variability and complexity. Journal of electromyography and kinesiology : official journal of the International Society of Electrophysiological Kinesiology 33, 94–102. doi:10.1016/j.jelekin.2017.02.003

13. Becker, S., Bergamo, F., Schnake, K. J., Schreyer, S., Rembitzki, I. V., Disselhorst-Klug, C. (2018): The relationship between functionality and erector spinae activity in patients with specific low back pain during dynamic and static movements. Gait & posture 66, 208–213. doi:10.1016/j.gaitpost.2018.08.042

14. BEECHER, H. K. (1955): The powerful placebo. Journal of the American Medical Association 159. (17), 1602–1606. doi:10.1001/jama.1955.02960340022006

15. Benedetti, F., Amanzio, M. (2013): Mechanisms of the placebo response. Pulmonary pharmacology & therapeutics 26. (5), 520–523. doi:10.1016/j.pupt.2013.01.006

16. Bingel, U., Wanigasekera, V., Wiech, K., Ni Mhuircheartaigh, R., Lee, M. C., Ploner, M., Tracey, I. (2011): The effect of treatment expectation on drug efficacy: imaging the analgesic benefit of the opioid remifentanil. Science translational medicine 3. (70), 70ra14. doi:10.1126/scitranslmed.3001244

17. Booth, J., Moseley, G. L., Schiltenwolf, M., Cashin, A., Davies, M., Hübscher, M. (2017): Exercise for chronic musculoskeletal pain: A biopsychosocial approach. Musculoskeletal care 15. (4), 413–421. doi:10.1002/msc.1191

18. Borsook, D., Linnman, C., Faria, V., Strassman, A. M., Becerra, L., Elman, I. (2016): Reward deficiency and anti-reward in pain chronification. Neuroscience and biobehavioral reviews 68, 282–297. doi:10.1016/j.neubiorev.2016.05.033

19. Borsook, D., Upadhyay, J., Chudler, E. H., Becerra, L. (2010): A key role of the basal ganglia in pain and analgesia—insights gained through human functional imaging. Molecular pain 6, 27. doi:10.1186/1744-8069-6-27

20. Brinjikji, W., Diehn, F. E., Jarvik, J. G., Carr, C. M., Kallmes, D. F., Murad, M. H., Luetmer, P. H. (2015): MRI Findings of Disc Degeneration are More Prevalent in Adults with Low Back Pain than in Asymptomatic Controls: A Systematic Review and Meta-Analysis. AJNR. American journal of neuroradiology 36. (12), 2394–2399. doi:10.3174/ajnr.A4498

21. Brinjikji, W., Luetmer, P. H., Comstock, B., Bresnahan, B. W., Chen, L. E., Deyo, R. A., Halabi, S., Turner, J. A., Avins, A. L., James, K., Wald, J. T., Kallmes, D. F., Jarvik, J. G. (2015): Systematic literature review of imaging features of spinal degeneration in asymptomatic populations. AJNR. American journal of neuroradiology 36. (4), 811–816. doi:10.3174/ajnr.A4173

22. Buchbinder, R., Underwood, M. (2012): Prognosis in people with back pain. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne 184. (11), 1229–1230. doi:10.1503/cmaj.120627

23. Carvalho, C., Caetano, J. M., Cunha, L., Rebouta, P., Kaptchuk, T. J., Kirsch, I. (2016): Open-label placebo treatment in chronic low back pain: A randomized controlled trial. Pain 157. (12), 2766–2772. doi:10.1097/j.pain.0000000000000700

24. Charlesworth, J. E. G., Petkovic, G., Kelley, J. M., Hunter, M., Onakpoya, I., Roberts, N., Miller, F. G., Howick, J. (2017): Effects of placebos without deception compared with no treatment: A systematic review and meta-analysis. Journal of evidence-based medicine 10. (2), 97–107. doi:10.1111/jebm.12251

25. Chiarotto, A., Maxwell, L. J., Terwee, C. B., Wells, G. A., Tugwell, P., Ostelo, R. W. (2016): Roland-Morris Disability Questionnaire and Oswestry Disability Index: Which Has Better Measurement Properties for Measuring Physical Functioning in Nonspecific Low Back Pain? Systematic Review and Meta-Analysis. Physical Therapy 96. (10), 1620–1637. doi:10.2522/ptj.20150420

26. Chou, R., Deyo, R., Friedly, J., Skelly, A., Hashimoto, R., Weimer, M., Fu, R., Dana, T., Kraegel, P., Griffin, J., Grusing, S., Brodt, E. D. (2017 a): Nonpharmacologic Therapies for Low Back Pain: A Systematic Review for an American College of Physicians Clinical Practice Guideline: A Systematic Review for an American College of Physicians Clinical Practice Guideline. Annals of internal medicine 166. (7), 493–505. doi:10.7326/M16-2459

27. Chou, R., Deyo, R., Friedly, J., Skelly, A., Weimer, M., Fu, R., Dana, T., Kraegel, P., Griffin, J., Grusing, S. (2017 b): Systemic Pharmacologic Therapies for Low Back Pain: A Systematic Review for an American College of Physicians Clinical Practice Guideline. Annals of internal medicine 166. (7), 480–492. doi:10.7326/M16-2458

28. Christe, G., Redhead, L., Jolles-Haeberli, B., Favre, J. (2016): Correlation of regional lumbar kinematics between forward flexion and functional activities in patients with chronic low back pain. Manual Therapy 25, e78. doi:10.1016/j.math.2016.05.127

29. Christe, G., Redhead, L., Legrand, T., Jolles, B. M., Favre, J. (2016): Multisegment analysis of spinal kinematics during sit-to-stand in patients with chronic low back pain. Journal of biomechanics 49. (10), 2060–2067. doi:10.1016/j.jbiomech.2016.05.015

30. Consmüller, T., Rohlmann, A., Weinland, D., Druschel, C., Duda, G. N., Taylor, W. R. (2012): Velocity of lordosis angle during spinal flexion and extension. PloS one 7. (11), e50135. doi:10.1371/journal.pone.0050135

31. Cormier, S., Lavigne, G. L., Choinière, M., Rainville, P. (2016): Expectations predict chronic pain treatment outcomes. Pain 157. (2), 329–338. doi:10.1097/j.pain.0000000000000379

32. Crombez, G., Eccleston, C., van Damme, S., Vlaeyen, J. W. S., Karoly, P. (2012): Fear-avoidance model of chronic pain: the next generation. The Clinical journal of pain 28. (6), 475–483. doi:10.1097/AJP.0b013e3182385392

33. Crum, A. J., Langer, E. J. (2007): Mind-set matters: Exercise and the placebo effect. Psychological science 18. (2), 165–171. doi:10.1111/j.1467-9280.2007.01867.x

34. Cushman, D., McCormick, Z., Casey, E., Plastaras, C. T. (2015): Discrepancies in describing pain: is there agreement between numeric rating scale scores and pain reduction percentage reported by patients with musculoskeletal pain after corticosteroid injection? Pain medicine (Malden, Mass.) 16. (5), 870–876. doi:10.1111/pme.12669

35. da Silva, R. A., Vieira, E. R., Cabrera, M., Altimari, L. R., Aguiar, A. F., Nowotny, A. H., Carvalho, A. F., Oliveira, M. R. (2015): Back muscle fatigue of younger and older adults with and without chronic low back pain using two protocols: A case-control study. Journal of electromyography and kinesiology : official journal of the International Society of Electrophysiological Kinesiology 25. (6), 928–936. doi:10.1016/j.jelekin.2015.10.003

36. Da Silva Santos, R., Galdino, G. (2018): Endogenous systems involved in exercise-induced analgesia. Journal of physiology and pharmacology : an official journal of the Polish Physiological Society 69. (1), 3–13. doi:10.26402/jpp.2018.1.01

37. Darlow, B., Dean, S., Perry, M., Mathieson, F., Baxter, G. D., Dowell, A. (2015): Easy to Harm, Hard to Heal: Patient Views About the Back. Spine 40. (11), 842–850. doi:10.1097/BRS.0000000000000901

38. Deutscher Bundestag. (2015): Technikfolgenabschätzung (TA) - Technischer Fortschritt im Gesundheitswesen: Quelle für Kostensteigerungen oder Chance für Kostensenkungen. Berlin. Online-Publikation; http://dip21.bundestag.de/dip21/btd/18/042/1804283.pdf/.

39. Dickenson, A. (2016): The neurobiology of chronic pain states. Anaesthesia & Intensive Care Medicine 17. (9), 436–439. doi:10.1016/j.mpaic.2016.06.010

40. Dimitrov, D. M., Rumrill, P. D. (2003): Pretest-posttest designs and measurement of change. Work (Reading, Mass.) 20. (2), 159–165.

41. Du Percie Sert, N., Rice, A. S. C. (2014): Improving the translation of analgesic drugs to the clinic: animal models of neuropathic pain. British journal of pharmacology 171. (12), 2951–2963. doi:10.1111/bph.12645

42. Dubois, J.-D., Abboud, J., St-Pierre, C., Piché, M., Descarreaux, M. (2014): Neuromuscular adaptations predict functional disability independently of clinical pain and psychological factors in patients with chronic non-specific low back pain. Journal of electromyography and kinesiology : official journal of the International Society of Electrophysiological Kinesiology 24. (4), 550–557. doi:10.1016/j.jelekin.2014.04.012

43. Edwards, P. J., Roberts, I., Clarke, M. J., Diguiseppi, C., Wentz, R., Kwan, I., Cooper, R., Felix, L. M., Pratap, S. (2009): Methods to increase response to postal and electronic questionnaires. The Cochrane database of systematic reviews, (3), MR000008. doi:10.1002/14651858.MR000008.pub4

44. El Brihi, J., Horne, R., Faasse, K. (2019): Prescribing Placebos: An Experimental Examination of the Role of Dose, Expectancies, and Adherence in Open-Label Placebo Effects. Annals of behavioral medicine : a publication of the Society of Behavioral Medicine 53. (1), 16–28. doi:10.1093/abm/kay011

45. Elman, I., Borsook, D. (2016): Common Brain Mechanisms of Chronic Pain and Addiction. Neuron 89. (1), 11–36. doi:10.1016/j.neuron.2015.11.027

46. Elvemo, N. A., Landrø, N. I., Borchgrevink, P. C., Håberg, A. K. (2015): Reward responsiveness in patients with chronic pain. European journal of pain (London, England) 19. (10), 1537–1543. doi:10.1002/ejp.687

47. Enck, P., Bingel, U., Schedlowski, M., Rief, W. (2013): The placebo response in medicine: minimize, maximize or personalize?: Minimize, maximize or personalize? Nature reviews. Drug discovery 12. (3), 191–204. doi:10.1038/nrd3923

48. Engel, G. L. (1979): The biopsychosocial model and the education of health professionals. General hospital psychiatry 1. (2), 156–165. doi:10.1111/j.1749-6632.1978.tb22070.x

49. Enthoven, W. T. M., Roelofs, P. D. D. M., Deyo, R. A., van Tulder, M. W., Koes, B. W. (2016): Non-steroidal anti-inflammatory drugs for chronic low back pain. The Cochrane database of systematic reviews 2, CD012087. doi:10.1002/14651858.CD012087

50. Fairbank, J. C. T., Pynsent, P. B. (2000): The Oswestry Disability Index. Spine 25. (22), 2940–2953. doi:10.1097/00007632-200011150-00017

51. Fordyce, W. E. (1984): Behavioural science and chronic pain. Postgraduate Medical Journal 60. (710), 865–868. doi:10.1136/pgmj.60.710.865

52. Foster, N. E., Anema, J. R., Cherkin, D., Chou, R., Cohen, S. P., Gross, D. P., Ferreira, P. H., Fritz, J. M., Koes, B. W., Peul, W., Turner, J. A., Maher, C. G. (2018): Prevention and treatment of low back pain: evidence, challenges, and promising directions. Lancet (London, England) 391. (10137), 2368–2383. doi:10.1016/S0140-6736(18)30489-6

53. Geneen, L. J., Moore, R. A., Clarke, C., Martin, D., Colvin, L. A., Smith, B. H. (2017): Physical activity and exercise for chronic pain in adults: an overview of Cochrane Reviews. The Cochrane database of systematic reviews 4, CD011279. doi:10.1002/14651858.CD011279.pub3

54. Gerhart, J. I., Burns, J. W., Bruehl, S., Smith, D. A., Post, K. M., Porter, L. S., Schuster, E., Buvanendran, A., Fras, A. M., Keefe, F. J. (2018): Variability in negative emotions among individuals with chronic low back pain: relationships with pain and function. Pain 159. (2), 342–350. doi:10.1097/j.pain.0000000000001102

55. Geue, K., Strauß, B., Brähler, E. (2016): Diagnostische Verfahren in der Psychotherapie. 3., überarb. und erw. Aufl. Diagnostik für Klinik und Praxis: Vol. 1. Göttingen: Hogrefe.

56. Geuter, S., Koban, L., Wager, T. D. (2017): The Cognitive Neuroscience of Placebo Effects: Concepts, Predictions, and Physiology. Annual review of neuroscience 40, 167–188. doi:10.1146/annurev-neuro-072116-031132

57. Geva, N., Pruessner, J., Defrin, R. (2014): Acute psychosocial stress reduces pain modulation capabilities in healthy men. Pain 155. (11), 2418–2425. doi:10.1016/j.pain.2014.09.023

58. Goossens, N., Rummens, S., Janssens, L., Caeyenberghs, K., Brumagne, S. (2018): Association Between Sensorimotor Impairments and Functional Brain Changes in Patients With Low Back Pain: A Critical Review. American journal of physical medicine & rehabilitation 97. (3), 200–211. doi:10.1097/PHM.0000000000000859

59. Goubert, D., van Oosterwijck, J., Meeus, M., Danneels, L. (2016): Structural Changes of Lumbar Muscles in Non-Specific Low Back Pain // Structural Changes of Lumbar Muscles in Non-specific Low Back Pain: A Systematic Review. Pain physician 19. (7), E985-E1000.

60. Gracely, R. H., Geisser, M. E., Giesecke, T., Grant, M. A. B., Petzke, F., Williams, D. A., Clauw, D. J. (2004): Pain catastrophizing and neural responses to pain among persons with fibromyalgia. Brain : a journal of neurology 127. (Pt 4), 835–843. doi:10.1093/brain/awh098

61. Hartvigsen, J., Hancock, M. J., Kongsted, A., Louw, Q., Ferreira, M. L., Genevay, S., Hoy, D., Karppinen, J., Pransky, G., Sieper, J., Smeets, R. J., Underwood, M. (2018): What low back pain is and why we need to pay attention. Lancet (London, England) 391. (10137), 2356–2367. doi:10.1016/S0140-6736(18)30480-X

62. Heldmann, P., Schöttker-Königer, T., Schäfer, A. (2015): Cross-cultural Adaption and Validity of the “Patient Specific Functional Scale” / Kulturelle Adaption und Validierung der deutschen Version der “Patient Specific Functional Scale”. International Journal of Health Professions 2. (1). doi:10.1515/ijhp-2015-0002

63. Hidalgo, B., Detrembleur, C., Hall, T., Mahaudens, P., Nielens, H. (2014): The efficacy of manual therapy and exercise for different stages of non-specific low back pain: an update of systematic reviews. The Journal of manual & manipulative therapy 22. (2), 59–74. doi:10.1179/2042618613Y.0000000041

64. Horn, K. K., Jennings, S., Richardson, G., van Vliet, D., Hefford, C., Abbott, J. H. (2012): The patient-specific functional scale: Psychometrics, clinimetrics, and application as a clinical outcome measure. The Journal of orthopaedic and sports physical therapy 42. (1), 30–42. doi:10.2519/jospt.2012.3727

65. Hurwitz, E. L., Randhawa, K., Yu, H., Côté, P., Haldeman, S. (2018): The Global Spine Care Initiative: a summary of the global burden of low back and neck pain studies: A summary of the global burden of low back and neck pain studies. European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society. doi:10.1007/s00586-017-5432-9

66. Kaptchuk, T. J., Friedlander, E., Kelley, J. M., Sanchez, M. N., Kokkotou, E., Singer, J. P., Kowalczykowski, M., Miller, F. G., Kirsch, I., Lembo, A. J. (2010): Placebos without deception: A randomized controlled trial in irritable bowel syndrome. PloS one 5. (12), e15591. doi:10.1371/journal.pone.0015591

67. Kaptchuk, T. J., Miller, F. G. (2015): Placebo Effects in Medicine. The New England journal of medicine 373. (1), 8–9. doi:10.1056/NEJMp1504023

68. Kaptchuk, T. J., Miller, F. G. (2018): Open label placebo: can honestly prescribed placebos evoke meaningful therapeutic benefits? BMJ (Clinical research ed.) 363, k3889. doi:10.1136/bmj.k3889

69. Karcioglu, O., Topacoglu, H., Dikme, O., Dikme, O. (2018): A systematic review of the pain scales in adults: Which to use? The American journal of emergency medicine 36. (4), 707–714. doi:10.1016/j.ajem.2018.01.008

70. Karsdorp, P. A., Schrooten, M. G. S., Geenen, R. (2018): Attentional control and the competition between nonpain goals and the threat of pain. European journal of pain (London, England) 22. (1), 181–190. doi:10.1002/ejp.1114

71. Kirsch, I. (2018): Response Expectancy and the Placebo Effect. International review of neurobiology 138, 81–93. doi:10.1016/bs.irn.2018.01.003

72. Kirsch, I., Kong, J., Sadler, P., Spaeth, R., Cook, A., Kaptchuk, T., Gollub, R. (2014): Expectancy and Conditioning in Placebo Analgesia: Separate or Connected Processes? Psychology of consciousness (American Psychological Association) 1. (1), 51–59. doi:10.1037/cns0000007

73. Kleine-Borgmann, J., Schmidt, K., Hellmann, A., Bingel, U. (2019): Effects of open-label placebo on pain, functional disability and spine mobility in chronic back pain patients: a randomized controlled trial. Pain. doi:10.1097/j.pain.0000000000001683

74. Klinger, R., Kothe, R., Schmitz, J., Kamping, S., Flor, H. (2017): Placebo effects of a sham opioid solution: A randomized controlled study in patients with chronic low back pain. Pain 158. (10), 1893–1902. doi:10.1097/j.pain.0000000000000977

75. Konno, S., Sekiguchi, M. (2018): Association between brain and low back pain. Journal of orthopaedic science : official journal of the Japanese Orthopaedic Association 23. (1), 3–7. doi:10.1016/j.jos.2017.11.007

76. Koob, G. F., Buck, C. L., Cohen, A., Edwards, S., Park, P. E., Schlosburg, J. E., Schmeichel, B., Vendruscolo, L. F., Wade, C. L., Whitfield, T. W., George, O. (2014): Addiction as a stress surfeit disorder. Neuropharmacology 76 Pt B, 370–382. doi:10.1016/j.neuropharm.2013.05.024

77. La Fuente-Fernández, R. de, Ruth, T. J., Sossi, V., Schulzer, M., Calne, D. B., Stoessl, A. J. (2001): Expectation and dopamine release: mechanism of the placebo effect in Parkinson's disease. Science (New York, N.Y.) 293. (5532), 1164–1166. doi:10.1126/science.1060937

78. Lindström, D., Sundberg-Petersson, I., Adami, J., Tönnesen, H. (2010): Disappointment and drop-out rate after being allocated to control group in a smoking cessation trial. Contemporary clinical trials 31. (1), 22–26. doi:10.1016/j.cct.2009.09.003

79. Magnussen, L., Strand, L. I., Lygren, H. (2004): Reliability and validity of the back performance scale: Observing activity limitation in patients with back pain. Spine 29. (8), 903–907.

80. Maier, C., Diener, H.-C., & Bingel, U. (Eds.). (2017). German Medical Collection: Vol. 34: Schmerzmedizin: Interdisziplinäre Diagnose- und Behandlungsstrategien (5. Auflage). München, Deutschland: Urban & Fischer.

81. Mannion, A. F., Junge, A., Fairbank, J. C. T., Dvorak, J., Grob, D. (2006): Development of a German version of the Oswestry Disability Index. Part 1: Cross-cultural adaptation, reliability, and validity. European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society 15. (1), 55–65. doi:10.1007/s00586-004-0815-0

82. Mansour, A. R., Farmer, M. A., Baliki, M. N., Apkarian, A. V. (2014): Chronic pain: the role of learning and brain plasticity. Restorative neurology and neuroscience 32. (1), 129–139. doi:10.3233/RNN-139003

83. Merskey, H. (1986): Classification of chronic pain: Descriptions of chronic pain syndromes and definitions of pain terms. Pain Suppl 3, 226.

84. Mertens, P., Blond, S., David, R., Rigoard, P. (2015): Anatomy, physiology and neurobiology of the nociception: a focus on low back pain (part A). Neuro-Chirurgie 61 Suppl 1, S22-34. doi:10.1016/j.neuchi.2014.09.001

85. Meucci, R. D., Fassa, A. G., Faria, N. M. X. (2015): Prevalence of chronic low back pain: Systematic review. Revista de saude publica 49. doi:10.1590/S0034-8910.2015049005874

86. Nijs, J., Clark, J., Malfliet, A., Ickmans, K., Voogt, L., Don, S., den Bandt, H., Goubert, D., Kregel, J., Coppieters, I., Dankaerts, W. (2017): In the spine or in the brain? Recent advances in pain neuroscience applied in the intervention for low back pain. Clinical and experimental rheumatology 35 Suppl 107. (5), 108–115.

87. O'Sullivan, P., Caneiro, J. P., O'Keeffe, M., O'Sullivan, K. (2016): Unraveling the Complexity of Low Back Pain. The Journal of orthopaedic and sports physical therapy 46. (11), 932–937. doi:10.2519/jospt.2016.0609

88. Parreira, P., Heymans, M. W., van Tulder, M. W., Esmail, R., Koes, B. W., Poquet, N., Lin, C.-W. C., Maher, C. G. (2017): Back Schools for chronic non-specific low back pain. The Cochrane database of systematic reviews 8, CD011674. doi:10.1002/14651858.CD011674.pub2

89. Peuter, S. de, van Diest, I., Vansteenwegen, D., van den Bergh, O., Vlaeyen, J. W. S. (2011): Understanding fear of pain in chronic pain: interoceptive fear conditioning as a novel approach. European journal of pain (London, England) 15. (9), 889–894. doi:10.1016/j.ejpain.2011.03.002

90. Qaseem, A., Wilt, T. J., McLean, R. M., Forciea, M. A. (2017): Noninvasive Treatments for Acute, Subacute, and Chronic Low Back Pain: A Clinical Practice Guideline From the American College of Physicians. Annals of internal medicine 166. (7), 514–530. doi:10.7326/M16-2367

91. R Core Team: R: A language and environment for statistical computing. (2018). Online-Publikation; https://www.R-project.org//.

92. Raicek, J. E., Stone, B. H., Kaptchuk, T. J. (2012): Placebos in 19th century medicine: a quantitative analysis of the BMJ. BMJ (Clinical research ed.) 345, e8326. doi:10.1136/bmj.e8326

93. Rizopoulos, D. (2006): ltm: An R package for Latent Variable Modelling and Item Response Theory Analyses. Journal of Statistical Software 17. (5), 1–25.

94. Roland, M., Fairbank, J. (2000): The Roland–Morris Disability Questionnaire and the Oswestry Disability Questionnaire. Spine 25. (24), 3115–3124. doi:10.1097/00007632-200012150-00006

95. Roussel, N. A., Nijs, J., Meeus, M., Mylius, V., Fayt, C., Oostendorp, R. (2013): Central sensitization and altered central pain processing in chronic low back pain: fact or myth? The Clinical journal of pain 29. (7), 625–638. doi:10.1097/AJP.0b013e31826f9a71

96. Rupp, T., Thomas, R., Perrey, S., Stephane, P. (2008): Prefrontal cortex oxygenation and neuromuscular responses to exhaustive exercise. European journal of applied physiology 102. (2), 153–163. doi:10.1007/s00421-007-0568-7

97. Sasiadek, M. J., Bladowska, J. (2012): Imaging of degenerative spine disease—the state of the art. Advances in clinical and experimental medicine : official organ Wroclaw Medical University 21. (2), 133–142.

98. Sawangjit, A., Oyanedel, C. N., Niethard, N., Salazar, C., Born, J., Inostroza, M. (2018): The hippocampus is crucial for forming non-hippocampal long-term memory during sleep. Nature 564. (7734), 109–113. doi:10.1038/s41586-018-0716-8

99. Schaefer, M., Sahin, T., Berstecher, B. (2018): Why do open-label placebos work? A randomized controlled trial of an open-label placebo induction with and without extended information about the placebo effect in allergic rhinitis. PloS one 13. (3), e0192758. doi:10.1371/journal.pone.0192758

100. Scott, D. J., Stohler, C. S., Egnatuk, C. M., Wang, H., Koeppe, R. A., Zubieta, J.-K. (2007): Individual differences in reward responding explain placebo-induced expectations and effects. Neuron 55. (2), 325–336. doi:10.1016/j.neuron.2007.06.028

101. Scott, D. J., Stohler, C. S., Egnatuk, C. M., Wang, H., Koeppe, R. A., Zubieta, J.-K. (2008): Placebo and nocebo effects are defined by opposite opioid and dopaminergic responses. Archives of general psychiatry 65. (2), 220–231. doi:10.1001/archgenpsychiatry.2007.34

102. Seidler, R. D., Carson, R. G. (2017): Sensorimotor Learning: Neurocognitive Mechanisms and Individual Differences. Journal of neuroengineering and rehabilitation 14. (1), 74. doi:10.1186/s12984-017-0279-1

103. Selim, A. J., Rogers, W., Fleishman, J. A., Qian, S. X., Fincke, B. G., Rothendler, J. A., Kazis, L. E. (2009): Updated U.S. population standard for the Veterans RAND 12-item Health Survey (VR-12). Quality of Life Research 18. (1), 43–52. doi:10.1007/s11136-008-9418-2

104. Sions, J. M., Coyle, P. C., Velasco, T. O., Elliott, J. M., Hicks, G. E. (2017): Multifidi Muscle Characteristics and Physical Function Among Older Adults With and Without Chronic Low Back Pain. Archives of physical medicine and rehabilitation 98. (1), 51–57. doi:10.1016/j.apmr.2016.07.027

105. Skinner, K. M., Miller, D. R., Lincoln, E., Lee, A., Kazis, L. E. (2005): Concordance between respondent self-reports and medical records for chronic conditions: Experience from the Veterans Health Study. The Journal of ambulatory care management 28. (2), 102–110.

106. Snyder, L. A., Shufflebarger, H., O'Brien, M. F., Thind, H., Theodore, N., Kakarla, U. K. (2014): Spondylolysis outcomes in adolescents after direct screw repair of the pars interarticularis. Journal of neurosurgery. Spine 21. (3), 329–333. doi:10.3171/2014.5.SPINE13772

107. Stamm, T. A., Pieber, K., Crevenna, R., Dorner, T. E. (2016): Impairment in the activities of daily living in older adults with and without osteoporosis, osteoarthritis and chronic back pain: a secondary analysis of population-based health survey data. BMC musculoskeletal disorders 17, 139. doi:10.1186/s12891-016-0994-y

108. Statista: Statista-Umfrage Volksleiden & OTC 2017. Zitiert nach de.statista.com. (2017): 10.08.2018.

109. Statistisches Bundesamt (Destatis): Gesundheit: Krankheitskosten 2002, 2004, 2006 und 2008: Krankheitskosten 2002 bis 2008 in Deutschland nach Diagnosen, Einrichtungen, Alter und Geschlecht. (2015). Online-Publikation; https://www.destatis.de/DE/Publikationen/Thematisch/Gesundheit/Krankheitskosten/Krankheitskosten.html/ 29.09.2017.

110. Steiger, F., Wirth, B., Bruin, E. D. de, Mannion, A. F. (2012): Is a positive clinical outcome after exercise therapy for chronic non-specific low back pain contingent upon a corresponding improvement in the targeted aspect(s) of performance? A systematic review. European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society 21. (4), 575–598. doi:10.1007/s00586-011-2045-6

111. Steingrímsdóttir, Ó. A., Landmark, T., Macfarlane, G. J., Nielsen, C. S. (2017): Defining chronic pain in epidemiological studies: a systematic review and meta-analysis. Pain 158. (11), 2092–2107. doi:10.1097/j.pain.0000000000001009

112. Stochkendahl, M. J., Kjaer, P., Hartvigsen, J., Kongsted, A., Aaboe, J., Andersen, M., Andersen, M. Ø., Fournier, G., Højgaard, B., Jensen, M. B., Jensen, L. D., Karbo, T., Kirkeskov, L., Melbye, M., Morsel-Carlsen, L., Nordsteen, J., Palsson, T. S., Rasti, Z., Silbye, P. F., Steiness, M. Z., Tarp, S., Vaagholt, M. (2018): National Clinical Guidelines for non-surgical treatment of patients with recent onset low back pain or lumbar radiculopathy. European Spine Journal 27. (1), 60–75. doi:10.1007/s00586-017-5099-2

113. Sullivan, M. D., Ballantyne, J. C. (2016): Must we reduce pain intensity to treat chronic pain? Pain 157. (1), 65–69. doi:10.1097/j.pain.0000000000000336

114. Taber, K. S. (2018): The Use of Cronbach's Alpha When Developing and Reporting Research Instruments in Science Education. Res Sci Educ 48. (6), 1273–1296. doi:10.1007/s11165-016-9602-2

115. Talati, A., Hirsch, J. (2005): Functional specialization within the medial frontal gyrus for perceptual go/no-go decisions based on "what," "when," and "where" related information: an fMRI study. Journal of cognitive neuroscience 17. (7), 981–993. doi:10.1162/0898929054475226

116. Taylor, A. M. W., Becker, S., Schweinhardt, P., Cahill, C. (2016): Mesolimbic dopamine signaling in acute and chronic pain: implications for motivation, analgesia, and addiction. Pain 157. (6), 1194–1198. doi:10.1097/j.pain.0000000000000494

117. Taylor, A. M. W., Castonguay, A., Ghogha, A., Vayssiere, P., Pradhan, A. A. A., Xue, L., Mehrabani, S., Wu, J., Levitt, P., Olmstead, M. C., Koninck, Y. de, Evans, C. J., Cahill, C. M. (2016): Neuroimmune Regulation of GABAergic Neurons Within the Ventral Tegmental Area During Withdrawal from Chronic Morphine. Neuropsychopharmacology 41. (4), 949–959. doi:10.1038/npp.2015.221

118. Teichtahl, A. J., Urquhart, D. M., Wang, Y., Wluka, A. E., O'Sullivan, R., Jones, G., Cicuttini, F. M. (2015): Physical inactivity is associated with narrower lumbar intervertebral discs, high fat content of paraspinal muscles and low back pain and disability. Arthritis research & therapy 17, 114. doi:10.1186/s13075-015-0629-y

119. Treede, R.-D., Rief, W., Barke, A., Aziz, Q., Bennett, M. I., Benoliel, R., Cohen, M., Evers, S., Finnerup, N. B., First, M. B., Giamberardino, M. A., Kaasa, S., Korwisi, B., Kosek, E., Lavand'homme, P., Nicholas, M., Perrot, S., Scholz, J., Schug, S., Smith, B. H., Svensson, P., Vlaeyen, J. W. S., Wang, S.-J. (2019): Chronic pain as a symptom or a disease: the IASP Classification of Chronic Pain for the International Classification of Diseases (ICD-11). Pain 160. (1), 19–27. doi:10.1097/j.pain.0000000000001384

120. Treede, R.-D., Rief, W., Barke, A., Aziz, Q., Bennett, M. I., Benoliel, R., Cohen, M., Evers, S., Finnerup, N. B., First, M. B., Giamberardino, M. A., Kaasa, S., Kosek, E., Lavand'homme, P., Nicholas, M., Perrot, S., Scholz, J., Schug, S., Smith, B. H., Svensson, P., Vlaeyen, J. W. S., Wang, S.-J. (2015): A classification of chronic pain for ICD-11. Pain 156. (6), 1003–1007. doi:10.1097/j.pain.0000000000000160

121. Vachon-Presseau, E., Centeno, M. V., Ren, W., Berger, S. E., Tétreault, P., Ghantous, M., Baria, A., Farmer, M., Baliki, M. N., Schnitzer, T. J., Apkarian, A. V. (2016): The Emotional Brain as a Predictor and Amplifier of Chronic Pain. Journal of dental research 95. (6), 605–612. doi:10.1177/0022034516638027

122. Vaisy, M., Gizzi, L., Petzke, F., Consmüller, T., Pfingsten, M., Falla, D. (2015): Measurement of Lumbar Spine Functional Movement in Low Back Pain. The Clinical journal of pain 31. (10), 876–885. doi:10.1097/AJP.0000000000000190

123. van Middelkoop, M., Rubinstein, S. M., Verhagen, A. P., Ostelo, R. W., Koes, B. W., van Tulder, M. W. (2010): Exercise therapy for chronic nonspecific low-back pain. Best practice & research. Clinical rheumatology 24. (2), 193–204. doi:10.1016/j.berh.2010.01.002

124. Vase, L., Vollert, J., Finnerup, N. B., Miao, X., Atkinson, G., Marshall, S., Nemeth, R., Lange, B., Liss, C., Price, D. D., Maier, C., Jensen, T. S., Segerdahl, M. (2015): Predictors of the placebo analgesia response in randomized controlled trials of chronic pain: a meta-analysis of the individual data from nine industrially sponsored trials. Pain 156. (9), 1795–1802. doi:10.1097/j.pain.0000000000000217

125. Vlaeyen, J. W. S., Crombez, G., Linton, S. J. (2016): The fear-avoidance model of pain. Pain 157. (8), 1588–1589. doi:10.1097/j.pain.0000000000000574

126. Vlaeyen, J. W. S., Maher, C. G., Wiech, K., van Zundert, J., Meloto, C. B., Diatchenko, L., Battié, M. C., Goossens, M., Koes, B., Linton, S. J. (2018): Low back pain. Nature Reviews Disease Primers 4. (1), 52. doi:10.1038/s41572-018-0052-1

127. Vos, T., Abajobir, A. A., Abate, K. H., Abbafati, C., Abbas, K. M., Abd-Allah, F., Abdulkader, R. S., Abdulle, A. M., Abebo, T. A., Abera, S. F., Aboyans, V., Abu-Raddad, L. J., Ackerman, I. N., Adamu, A. A., Adetokunboh, O., Afarideh, M., Afshin, A., Agarwal, S. K., Aggarwal, R., Agrawal, A., Agrawal, S., Ahmadieh, H., Ahmed, M. B., Aichour, M. T. E., Aichour, A. N., Aichour, I., Aiyar, S., Akinyemi, R. O., Akseer, N., Al Lami, F. H., Alahdab, F., Al-Aly, Z., Alam, K., Alam, N., Alam, T., Alasfoor, D., Alene, K. A., Ali, R., Alizadeh-Navaei, R., Alkerwi, A., Alla, F., Allebeck, P., Allen, C., Al-Maskari, F., Al-Raddadi, R., Alsharif, U., Alsowaidi, S., Altirkawi, K. A., Amare, A. T., Amini, E., Ammar, W., Amoako, Y. A., Andersen, H. H., Antonio, C. A. T., Anwari, P., Ärnlöv, J., Artaman, A., Aryal, K. K., Asayesh, H., Asgedom, S. W., Assadi, R., Atey, T. M., Atnafu, N. T., Atre, S. R., Avila-Burgos, L., Avokphako, E. F. G. A., Awasthi, A., Bacha, U., Badawi, A., Balakrishnan, K., Banerjee, A., Bannick, M. S., Barac, A., Barber, R. M., Barker-Collo, S. L., Bärnighausen, T., Barquera, S., Barregard, L., Barrero, L. H., Basu, S., Battista, B., Battle, K. E., Baune, B. T., Bazargan-Hejazi, S., Beardsley, J., Bedi, N., Beghi, E., Béjot, Y., Bekele, B. B., Bell, M. L., Bennett, D. A., Bensenor, I. M., Benson, J., Berhane, A., Berhe, D. F., Bernabé, E., Betsu, B. D., Beuran, M., Beyene, A. S., Bhala, N., Bhansali, A., Bhatt, S., Bhutta, Z. A., Biadgilign, S., Bicer, B. K., Bienhoff, K., Bikbov, B., Birungi, C., Biryukov, S., Bisanzio, D., Bizuayehu, H. M., Boneya, D. J., Boufous, S., Bourne, R. R. A., Brazinova, A., Brugha, T. S., Buchbinder, R., Bulto, L. N. B., Bumgarner, B. R., Butt, Z. A., Cahuana-Hurtado, L., Cameron, E., Car, M., Carabin, H., Carapetis, J. R., Cárdenas, R., Carpenter, D. O., Carrero, J. J., Carter, A., Carvalho, F., Casey, D. C., Caso, V., Castañeda-Orjuela, C. A., Castle, C. D., Catalá-López, F., Chang, H.-Y., Chang, J.-C., Charlson, F. J., Chen, H., Chibalabala, M., Chibueze, C. E., Chisumpa, V. H., Chitheer, A. A., Christopher, D. J., Ciobanu, L. G., Cirillo, M., Colombara, D., Cooper, C., Cortesi, P. A., Criqui, M. H., Crump, J. A., Dadi, A. F., Dalal, K., Dandona, L., Dandona, R., das Neves, J., Davitoiu, D. V., Courten, B. de, Leo, D. de, Defo, B. K., Degenhardt, L., Deiparine, S., Dellavalle, R. P., Deribe, K., Des Jarlais, D. C., Dey, S., Dharmaratne, S. D., Dhillon, P. K., Dicker, D., Ding, E. L., Djalalinia, S., Do, H. P., Dorsey, E. R., dos Santos, K. P. B., Douwes-Schultz, D., Doyle, K. E., Driscoll, T. R., Dubey, M., Duncan, B. B., El-Khatib, Z. Z., Ellerstrand, J., Enayati, A., Endries, A. Y., Ermakov, S. P., Erskine, H. E., Eshrati, B., Eskandarieh, S., Esteghamati, A., Estep, K., Fanuel, F. B. B., Farinha, C. S. e. S., Faro, A., Farzadfar, F., Fazeli, M. S., Feigin, V. L., Fereshtehnejad, S.-M., Fernandes, J. C., Ferrari, A. J., Feyissa, T. R., Filip, I., Fischer, F., Fitzmaurice, C., Flaxman, A. D., Flor, L. S., Foigt, N., Foreman, K. J., Franklin, R. C., Fullman, N., Fürst, T., Furtado, J. M., Futran, N. D., Gakidou, E., Ganji, M., Garcia-Basteiro, A. L., Gebre, T., Gebrehiwot, T. T., Geleto, A., Gemechu, B. L., Gesesew, H. A., Gething, P. W., Ghajar, A., Gibney, K. B., Gill, P. S., Gillum, R. F., Ginawi, I. A. M., Giref, A. Z., Gishu, M. D., Giussani, G., Godwin, W. W., Gold, A. L., Goldberg, E. M., Gona, P. N., Goodridge, A., Gopalani, S. V., Goto, A., Goulart, A. C., Griswold, M., Gugnani, H. C., Gupta, R., Gupta, R., Gupta, T., Gupta, V., Hafezi-Nejad, N., Hailu, G. B., Hailu, A. D., Hamadeh, R. R., Hamidi, S., Handal, A. J., Hankey, G. J., Hanson, S. W., Hao, Y., Harb, H. L., Hareri, H. A., Haro, J. M., Harvey, J., Hassanvand, M. S., Havmoeller, R., Hawley, C., Hay, S. I., Hay, R. J., Henry, N. J., Heredia-Pi, I. B., Hernandez, J. M., Heydarpour, P., Hoek, H. W., Hoffman, H. J., Horita, N., Hosgood, H.

D., Hostiuc, S., Hotez, P. J., Hoy, D. G., Htet, A. S., Hu, G., Huang, H., Huynh, C., Iburg, K. M., Igumbor, E. U., Ikeda, C., Irvine, C. M. S., Jacobsen, K. H., Jahanmehr, N., Jakovljevic, M. B., Jassal, S. K., Javanbakht, M., Jayaraman, S. P., Jeemon, P., Jensen, P. N., Jha, V., Jiang, G., John, D., Johnson, S. C., Johnson, C. O., Jonas, J. B., Jürisson, M., Kabir, Z., Kadel, R., Kahsay, A., Kamal, R., Kan, H., Karam, N. E., Karch, A., Karema, C. K., Kasaeian, A., Kassa, G. M., Kassaw, N. A., Kassebaum, N. J., Kastor, A., Katikireddi, S. V., Kaul, A., Kawakami, N., Keiyoro, P. N., Kengne, A. P., Keren, A., Khader, Y. S., Khalil, I. A., Khan, E. A., Khang, Y.-H., Khosravi, A., Khubchandani, J., Kiadaliri, A. A., Kieling, C., Kim, Y. J., Kim, D., Kim, P., Kimokoti, R. W., Kinfu, Y., Kisa, A., Kissimova-Skarbek, K. A., Kivimaki, M., Knudsen, A. K., Kokubo, Y., Kolte, D., Kopec, J. A., Kosen, S., Koul, P. A., Koyanagi, A., Kravchenko, M., Krishnaswami, S., Krohn, K. J., Kumar, G. A., Kumar, P., Kumar, S., Kyu, H. H., Lal, D. K., Lalloo, R., Lambert, N., Lan, Q., Larsson, A., Lavados, P. M., Leasher, J. L., Lee, P. H., Lee, J.-T., Leigh, J., Leshargie, C. T., Leung, J., Leung, R., Levi, M., Li, Y., Li, Y., Li Kappe, D., Liang, X., Liben, M. L., Lim, S. S., Linn, S., Liu, P. Y., Liu, A., Liu, S., Liu, Y., Lodha, R., Logroscino, G., London, S. J., Looker, K. J., Lopez, A. D., Lorkowski, S., Lotufo, P. A., Low, N., Lozano, R., Lucas, T. C. D., Macarayan, E. R. K., Magdy Abd El Razek, H., Magdy Abd El Razek, M., Mahdavi, M., Majdan, M., Majdzadeh, R., Majeed, A., Malekzadeh, R., Malhotra, R., Malta, D. C., Mamun, A. A., Manguerra, H., Manhertz, T., Mantilla, A., Mantovani, L. G., Mapoma, C. C., Marczak, L. B., Martinez-Raga, J., Martins-Melo, F. R., Martopullo, I., März, W., Mathur, M. R., Mazidi, M., McAlinden, C., McGaughey, M., McGrath, J. J., McKee, M., McNellan, C., Mehata, S., Mehndiratta, M. M., Mekonnen, T. C., Memiah, P., Memish, Z. A., Mendoza, W., Mengistie, M. A., Mengistu, D. T., Mensah, G. A., Meretoja, T. J., Meretoja, A., Mezgebe, H. B., Micha, R., Millear, A., Miller, T. R., Mills, E. J., Mirarefin, M., Mirrakhimov, E. M., Misganaw, A., Mishra, S. R., Mitchell, P. B., Mohammad, K. A., Mohammadi, A., Mohammed, K. E., Mohammed, S., Mohanty, S. K., Mokdad, A. H., Mollenkopf, S. K., Monasta, L., Montico, M., Moradi-Lakeh, M., Moraga, P., Mori, R., Morozoff, C., Morrison, S. D., Moses, M., Mountjoy-Venning, C., Mruts, K. B., Mueller, U. O., Muller, K., Murdoch, M. E., Murthy, G. V. S., Musa, K. I., Nachega, J. B., Nagel, G., Naghavi, M., Naheed, A., Naidoo, K. S., Naldi, L., Nangia, V., Natarajan, G., Negasa, D. E., Negoi, R. I., Negoi, I., Newton, C. R., Ngunjiri, J. W., Nguyen, T. H., Le Nguyen, Q., Nguyen, C. T., Nguyen, G., Nguyen, M., Nichols, E., Ningrum, D. N. A., Nolte, S., Nong, V. M., Norrving, B., Noubiap, J. J. N., O'Donnell, M. J., Ogbo, F. A., Oh, I.-H., Okoro, A., Oladimeji, O., Olagunju, T. O., Olagunju, A. T., Olsen, H. E., Olusanya, B. O., Olusanya, J. O., Ong, K., Opio, J. N., Oren, E., Ortiz, A., Osgood-Zimmerman, A., Osman, M., Owolabi, M. O., PA, M., Pacella, R. E., Pana, A., Panda, B. K., Papachristou, C., Park, E.-K., Parry, C. D., Parsaeian, M., Patten, S. B., Patton, G. C., Paulson, K., Pearce, N., Pereira, D. M., Perico, N., Pesudovs, K., Peterson, C. B., Petzold, M., Phillips, M. R., Pigott, D. M., Pillay, J. D., Pinho, C., Plass, D., Pletcher, M. A., Popova, S., Poulton, R. G., Pourmalek, F., Prabhakaran, D., Prasad, N. M., Prasad, N., Purcell, C., Qorbani, M., Quansah, R., Quintanilla, B. P. A., Rabiee, R. H. S., Radfar, A., Rafay, A., Rahimi, K., Rahimi-Movaghar, A., Rahimi-Movaghar, V., Rahman, M. H. U., Rahman, M., Rai, R. K., Rajsic, S., Ram, U., Ranabhat, C. L., Rankin, Z., Rao, P. C., Rao, P. V., Rawaf, S., Ray, S. E., Reiner, R. C., Reinig, N., Reitsma, M. B., Remuzzi, G.,

Renzaho, A. M. N., Resnikoff, S., Rezaei, S., Ribeiro, A. L., Ronfani, L., Roshandel, G., Roth, G. A., Roy, A., Rubagotti, E., Ruhago, G. M., Saadat, S., Sadat, N., Safdarian, M., Safi, S., Safiri, S., Sagar, R., Sahathevan, R., Salama, J., Saleem, H. O. B., Salomon, J. A., Salvi, S. S., Samy, A. M., Sanabria, J. R., Santomauro, D., Santos, I. S., Santos, J. V., Santric Milicevic, M. M., Sartorius, B., Satpathy, M., Sawhney, M., Saxena, S., Schmidt, M. I., Schneider, I. J. C., Schöttker, B., Schwebel, D. C., Schwendicke, F., Seedat, S., Sepanlou, S. G., Servan-Mori, E. E., Setegn, T., Shackelford, K. A., Shaheen, A., Shaikh, M. A., Shamsipour, M., Shariful Islam, S. M., Sharma, J., Sharma, R., She, J., Shi, P., Shields, C., Shifa, G. T., Shigematsu, M., Shinohara, Y., Shiri, R., Shirkoohi, R., Shirude, S., Shishani, K., Shrime, M. G., Sibai, A. M., Sigfusdottir, I. D., Silva, D. A. S., Silva, J. P., Silveira, D. G. A., Singh, J. A., Singh, N. P., Sinha, D. N., Skiadaresi, E., Skirbekk, V., Slepak, E. L., Sligar, A., Smith, D. L., Smith, M., Sobaih, B. H. A., Sobngwi, E., Sorensen, R. J. D., Sousa, T. C. M., Sposato, L. A., Sreeramareddy, C. T., Srinivasan, V., Stanaway, J. D., Stathopoulou, V., Steel, N., Stein, M. B., Stein, D. J., Steiner, T. J., Steiner, C., Steinke, S., Stokes, M. A., Stovner, L. J., Strub, B., Subart, M., Sufiyan, M. B., Sunguya, B. F., Sur, P. J., Swaminathan, S., Sykes, B. L., Sylte, D. O., Tabarés-Seisdedos, R., Taffere, G. R., Takala, J. S., Tandon, N., Tavakkoli, M., Taveira, N., Taylor, H. R., Tehrani-Banihashemi, A., Tekelab, T., Terkawi, A. S., Tesfaye, D. J., Tesssema, B., Thamsuwan, O., Thomas, K. E., Thrift, A. G., Tiruye, T. Y., Tobe-Gai, R., Tollanes, M. C., Tonelli, M., Topor-Madry, R., Tortajada, M., Touvier, M., Tran, B. X., Tripathi, S., Troeger, C., Truelsen, T., Tsoi, D., Tuem, K. B., Tuzcu, E. M., Tyrovolas, S., Ukwaja, K. N., Undurraga, E. A., Uneke, C. J., Updike, R., Uthman, O. A., Uzochukwu, B. S. C., van Boven, J. F. M., Varughese, S., Vasankari, T., Venkatesh, S., Venketasubramanian, N., Vidavalur, R., Violante, F. S., Vladimirov, S. K., Vlassov, V. V., Vollset, S. E., Wadilo, F., Wakayo, T., Wang, Y.-P., Weaver, M., Weichenthal, S., Weiderpass, E., Weintraub, R. G., Werdecker, A., Westerman, R., Whiteford, H. A., Wijeratne, T., Wiysonge, C. S., Wolfe, C. D. A., Woodbrook, R., Woolf, A. D., Workicho, A., Xavier, D., Xu, G., Yadgir, S., Yaghoubi, M., Yakob, B., Yan, L. L., Yano, Y., Ye, P., Yimam, H. H., Yip, P., Yonemoto, N., Yoon, S.-J., Yotebieng, M., Younis, M. Z., Zaidi, Z., Zaki, M. E. S., Zegeye, E. A., Zenebe, Z. M., Zhang, X., Zhou, M., Zipkin, B., Zodpey, S., Zuhlke, L. J., Murray, C. J. L. (2017): Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. The Lancet 390. (10100), 1211–1259. doi:10.1016/S0140-6736(17)32154-2

128. Vos, T., Allen, C., Arora, M., Barber, R. M., Bhutta, Z. A., Brown, A., Carter, A., Casey, D. C., Charlson, F. J., Chen, A. Z., Coggeshall, M., Cornaby, L., Dandona, L., Dicker, D. J., Dilegge, T., Erskine, H. E., Ferrari, A. J., Fitzmaurice, C., Fleming, T., Forouzanfar, M. H., Fullman, N., Gething, P. W., Goldberg, E. M., Graetz, N., Haagsma, J. A., Hay, S. I., Johnson, C. O., Kassebaum, N. J., Kawashima, T., Kemmer, L., Khalil, I. A., Kinfu, Y., Kyu, H. H., Leung, J., Liang, X., Lim, S. S., Lopez, A. D., Lozano, R., Marczak, L., Mensah, G. A., Mokdad, A. H., Naghavi, M., Nguyen, G., Nsoesie, E., Olsen, H., Pigott, D. M., Pinho, C., Rankin, Z., Reinig, N., Salomon, J. A., Sandar, L., Smith, A., Stanaway, J., Steiner, C., Teeple, S., Thomas, B. A., Troeger, C., Wagner, J. A., Wang, H., Wanga, V., Whiteford, H. A., Zoeckler, L., Abajobir, A. A., Abate, K. H., Abbafati, C., Abbas, K. M., Abd-Allah, F., Abraham, B., Abubakar, I., Abu-Raddad, L. J., Abu-Rmeileh, N. M. E., Ackerman, I. N., Adebiyi, A. O., Ademi, Z., Adou, A. K., Afanvi, K. A., Agardh, E. E., Agarwal, A., Kiadaliri, A. A., Ahmadieh, H., Ajala, O. N., Akinyemi, R. O., Akseer, N., Al-Aly, Z., Alam, K., Alam, N. K. M., Aldhahri, S. F., Alegretti, M. A., Alemu, Z. A., Alexander, L. T., Alhabib, S., Ali, R., Alkerwi, A., Alla, F., Allebeck, P., Al-Raddadi, R., Alsharif, U., Altirkawi, K. A., Alvis-Guzman, N., Amare, A. T., Amberbir, A., Amini, H., Ammar, W., Amrock, S. M., Andersen, H. H., Anderson, G. M., Anderson, B. O., Antonio, C. A. T., Aregay, A. F., Ärnlöv, J., Artaman, A., Asayesh, H., Assadi, R., Atique, S., Avokpaho, E. F. G. A., Awasthi, A., Quintanilla, B. P. A., Azzopardi, P., Bacha, U., Badawi, A., Balakrishnan, K., Banerjee, A., Barac, A., Barker-Collo, S. L., Bärnighausen, T., Barregard, L., Barrero, L. H., Basu, A., Bazargan-Hejazi, S., Beghi, E., Bell, B., Bell, M. L., Bennett, D. A., Bensenor, I. M., Benzian, H., Berhane, A., Bernabé, E., Betsu, B. D., Beyene, A. S., Bhala, N., Bhatt, S., Biadgilign, S., Bienhoff, K., Bikbov, B., Biryukov, S., Bisanzio, D., Bjertness, E., Blore, J., Borschmann, R., Boufous, S., Brainin, M., Brazinova, A., Breitborde, N. J. K., Brown, J., Buchbinder, R., Buckle, G. C., Butt, Z. A., Calabria, B., Campos-Nonato, I. R., Campuzano, J. C., Carabin, H., Cárdenas, R., Carpenter, D. O., Carrero, J. J., Castañeda-Orjuela, C. A., Rivas, J. C., Catalá-López, F., Chang, J.-C., Chiang, P. P.-C., Chibueze, C. E., Chisumpa, V. H., Choi, J.-Y. J., Chowdhury, R., Christensen, H., Christopher, D. J., Ciobanu, L. G., Cirillo, M., Coates, M. M., Colquhoun, S. M., Cooper, C., Cortinovis, M., Crump, J. A., Damtew, S. A., Dandona, R., Daoud, F., Dargan, P. I., das Neves, J., Davey, G., Davis, A. C., Leo, D. de, Degenhardt, L., Gobbo, L. C. D., Dellavalle, R. P., Deribe, K., Deribew, A., Derrett, S., Des Jarlais, D. C., Dharmaratne, S. D., Dhillon, P. K., Diaz-Torné, C., Ding, E. L., Driscoll, T. R., Duan, L., Dubey, M., Duncan, B. B., Ebrahimi, H., Ellenbogen, R. G., Elyazar, I., Endres, M., Endries, A. Y., Ermakov, S. P., Eshrati, B., Estep, K., Farid, T. A., Farinha, C. S. e. S., Faro, A., Farvid, M. S., Farzadfar, F., Feigin, V. L., Felson, D. T., Fereshtehnejad, S.-M., Fernandes, J. G., Fernandes, J. C., Fischer, F., Fitchett, J. R. A., Foreman, K., Fowkes, F. G. R., Fox, J., Franklin, R. C., Friedman, J., Frostad, J., Fürst, T., Futran, N. D., Gabbe, B., Ganguly, P., Gankpé, F. G., Gebre, T., Gebrehiwot, T. T., Gebremedhin, A. T., Geleijnse, J. M., Gessner, B. D., Gibney, K. B., Ginawi, I. A. M., Giref, A. Z., Giroud, M., Gishu, M. D., Giussani, G., Glaser, E., Godwin, W. W., Gomez-Dantes, H., Gona, P., Goodridge, A., Gopalani, S. V., Gotay, C. C., Goto, A., Gouda, H. N., Grainger, R., Greaves, F., Guillemin, F., Guo, Y., Gupta, R., Gupta, R., Gupta, V., Gutiérrez, R. A., Haile, D., Hailu, A. D., Hailu, G. B., Halasa, Y. A., Hamadeh, R. R., Hamidi,

S., Hammami, M., Hancock, J., Handal, A. J., Hankey, G. J., Hao, Y., Harb, H. L., Harikrishnan, S., Haro, J. M., Havmoeller, R., Hay, R. J., Heredia-Pi, I. B., Heydarpour, P., Hoek, H. W., Horino, M., Horita, N., Hosgood, H. D., Hoy, D. G., Htet, A. S., Huang, H., Huang, J. J., Huynh, C., Iannarone, M., Iburg, K. M., Innos, K., Inoue, M., Iyer, V. J., Jacobsen, K. H., Jahanmehr, N., Jakovljevic, M. B., Javanbakht, M., Jayaraman, S. P., Jayatilleke, A. U., Jee, S. H., Jeemon, P., Jensen, P. N., Jiang, Y., Jibat, T., Jimenez-Corona, A., Jin, Y., Jonas, J. B., Kabir, Z., Kalkonde, Y., Kamal, R., Kan, H., Karch, A., Karema, C. K., Karimkhani, C., Kasaeian, A., Kaul, A., Kawakami, N., Keiyoro, P. N., Kemp, A. H., Keren, A., Kesavachandran, C. N., Khader, Y. S., Khan, A. R., Khan, E. A., Khang, Y.-H., Khera, S., Khoja, T. A. M., Khubchandani, J., Kieling, C., Kim, P., Kim, C., Kim, D., Kim, Y. J., Kissoon, N., Knibbs, L. D., Knudsen, A. K., Kokubo, Y., Kolte, D., Kopec, J. A., Kosen, S., Kotsakis, G. A., Koul, P. A., Koyanagi, A., Kravchenko, M., Defo, B. K., Bicer, B. K., Kudom, A. A., Kuipers, E. J., Kumar, G. A., Kutz, M., Kwan, G. F., Lal, A., Lalloo, R., Lallukka, T., Lam, H., Lam, J. O., Langan, S. M., Larsson, A., Lavados, P. M., Leasher, J. L., Leigh, J., Leung, R., Levi, M., Li, Y., Li, Y., Liang, J., Liu, S., Liu, Y., Lloyd, B. K., Lo, W. D., Logroscino, G., Looker, K. J., Lotufo, P. A., Lunevicius, R., Lyons, R. A., Mackay, M. T., Magdy, M., Razek, A. E., Mahdavi, M., Majdan, M., Majeed, A., Malekzadeh, R., Marcenes, W., Margolis, D. J., Martinez-Raga, J., Masiye, F., Massano, J., McGarvey, S. T., McGrath, J. J., McKee, M., McMahon, B. J., Meaney, P. A., Mehari, A., Mejia-Rodriguez, F., Mekonnen, A. B., Melaku, Y. A., Memiah, P., Memish, Z. A., Mendoza, W., Meretoja, A., Meretoja, T. J., Mhimbira, F. A., Millear, A., Miller, T. R., Mills, E. J., Mirarefin, M., Mitchell, P. B., Mock, C. N., Mohammadi, A., Mohammed, S., Monasta, L., Hernandez, J. C. M., Montico, M., Mooney, M. D., Moradi-Lakeh, M., Morawska, L., Mueller, U. O., Mullany, E., Mumford, J. E., Murdoch, M. E., Nachega, J. B., Nagel, G., Naheed, A., Naldi, L., Nangia, V., Newton, J. N., Ng, M., Ngalesoni, F. N., Le Nguyen, Q., Nisar, M. I., Pete, P. M. N., Nolla, J. M., Norheim, O. F., Norman, R. E., Norrving, B., Nunes, B. P., Ogbo, F. A., Oh, I.-H., Ohkubo, T., Olivares, P. R., Olusanya, B. O., Olusanya, J. O., Ortiz, A., Osman, M., Ota, E., PA, M., Park, E.-K., Parsaeian, M., Azeredo Passos, V. M. de, Caicedo, A. J. P., Patten, S. B., Patton, G. C., Pereira, D. M., Perez-Padilla, R., Perico, N., Pesudovs, K., Petzold, M., Phillips, M. R., Piel, F. B., Pillay, J. D., Pishgar, F., Plass, D., Platts-Mills, J. A., Polinder, S., Pond, C. D., Popova, S., Poulton, R. G., Pourmalek, F., Prabhakaran, D., Prasad, N. M., Qorbani, M., Rabiee, R. H. S., Radfar, A., Rafay, A., Rahimi, K., Rahimi-Movaghar, V., Rahman, M., Rahman, M. H. U., Rahman, S. U., Rai, R. K., Rajsic, S., Ram, U., Rao, P., Refaat, A. H., Reitsma, M. B., Remuzzi, G., Resnikoff, S., Reynolds, A., Ribeiro, A. L., Blancas, M. J. R., Roba, H. S., Rojas-Rueda, D., Ronfani, L., Roshandel, G., Roth, G. A., Rothenbacher, D., Roy, A., Sagar, R., Sahathevan, R., Sanabria, J. R., Sanchez-Niño, M. D., Santos, I. S., Santos, J. V., Sarmiento-Suarez, R., Sartorius, B., Satpathy, M., Savic, M., Sawhney, M., Schaub, M. P., Schmidt, M. I., Schneider, I. J. C., Schöttker, B., Schwebel, D. C., Scott, J. G., Seedat, S., Sepanlou, S. G., Servan-Mori, E. E., Shackelford, K. A., Shaheen, A., Shaikh, M. A., Sharma, R., Sharma, U., Shen, J., Shepard, D. S., Sheth, K. N., Shibuya, K., Shin, M.-J., Shiri, R., Shiue, I., Shrime, M. G., Sigfusdottir, I. D., Silva, D. A. S., Silveira, D. G. A., Singh, A., Singh, J. A., Singh, O. P., Singh, P. K., Sivonda, A., Skirbekk, V., Skogen, J. C., Sligar, A., Sliwa, K., Soljak, M., Søreide, K., Sorensen, R. J.

D., Soriano, J. B., Sposato, L. A., Sreeramareddy, C. T., Stathopoulou, V., Steel, N., Stein, D. J., Steiner, T. J., Steinke, S., Stovner, L., Stroumpoulis, K., Sunguya, B. F., Sur, P., Swaminathan, S., Sykes, B. L., Szoeke, C. E. I., Tabarés-Seisdedos, R., Takala, J. S., Tandon, N., Tanne, D., Tavakkoli, M., Taye, B., Taylor, H. R., Ao, B. J. T., Tedla, B. A., Terkawi, A. S., Thomson, A. J., Thorne-Lyman, A. L., Thrift, A. G., Thurston, G. D., Tobe-Gai, R., Tonelli, M., Topor-Madry, R., Topouzis, F., Tran, B. X., Truelsen, T., Dimbuene, Z. T., Tsilimbaris, M., Tura, A. K., Tuzcu, E. M., Tyrovolas, S., Ukwaja, K. N., Undurraga, E. A., Uneke, C. J., Uthman, O. A., van Gool, C. H., Varakin, Y. Y., Vasankari, T., Venketasubramanian, N., Verma, R. K., Violante, F. S., Vladimirov, S. K., Vlassov, V. V., Vollset, S. E., Wagner, G. R., Waller, S. G., Wang, L., Watkins, D. A., Weichenthal, S., Weiderpass, E., Weintraub, R. G., Werdecker, A., Westerman, R., White, R. A., Williams, H. C., Wiysonge, C. S., Wolfe, C. D. A., Won, S., Woodbrook, R., Wubshet, M., Xavier, D., Xu, G., Yadav, A. K., Yan, L. L., Yano, Y., Yaseri, M., Ye, P., Yebyo, H. G., Yip, P., Yonemoto, N., Yoon, S.-J., Younis, M. Z., Yu, C., Zaidi, Z., Zaki, M. E. S., Zeeb, H., Zhou, M., Zodpey, S., Zuhlke, L. J., Murray, C. J. L. (2016): Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. The Lancet 388. (10053), 1545–1602. doi:10.1016/S0140-6736(16)31678-6

129. Vos, T., Flaxman, A. D., Naghavi, M., Lozano, R., Michaud, C., Ezzati, M., Shibuya, K., Salomon, J. A., Abdalla, S., Aboyans, V., Abraham, J., Ackerman, I., Aggarwal, R., Ahn, S. Y., Ali, M. K., AlMazroa, M. A., Alvarado, M., Anderson, H. R., Anderson, L. M., Andrews, K. G., Atkinson, C., Baddour, L. M., Bahalim, A. N., Barker-Collo, S., Barrero, L. H., Bartels, D. H., Basáñez, M.-G., Baxter, A., Bell, M. L., Benjamin, E. J., Bennett, D., Bernabé, E., Bhalla, K., Bhandari, B., Bikbov, B., Abdulhak, A. B., Birbeck, G., Black, J. A., Blencowe, H., Blore, J. D., Blyth, F., Bolliger, I., Bonaventure, A., Boufous, S., Bourne, R., Boussinesq, M., Braithwaite, T., Brayne, C., Bridgett, L., Brooker, S., Brooks, P., Brugha, T. S., Bryan-Hancock, C., Bucello, C., Buchbinder, R., Buckle, G., Budke, C. M., Burch, M., Burney, P., Burstein, R., Calabria, B., Campbell, B., Canter, C. E., Carabin, H., Carapetis, J., Carmona, L., Cella, C., Charlson, F., Chen, H., Cheng, A. T.-A., Chou, D., Chugh, S. S., Coffeng, L. E., Colan, S. D., Colquhoun, S., Colson, K. E., Condon, J., Connor, M. D., Cooper, L. T., Corriere, M., Cortinovis, M., Vaccaro, K. C. de, Couser, W., Cowie, B. C., Criqui, M. H., Cross, M., Dabhadkar, K. C., Dahiya, M., Dahodwala, N., Damsere-Derry, J., Danaei, G., Davis, A., Leo, D. de, Degenhardt, L., Dellavalle, R., Delossantos, A., Denenberg, J., Derrett, S., Des Jarlais, D. C., Dharmaratne, S. D., Dherani, M., Diaz-Torne, C., Dolk, H., Dorsey, E. R., Driscoll, T., Duber, H., Ebel, B., Edmond, K., Elbaz, A., Ali, S. E., Erskine, H., Erwin, P. J., Espindola, P., Ewoigbokhan, S. E., Farzadfar, F., Feigin, V., Felson, D. T., Ferrari, A., Ferri, C. P., Fèvre, E. M., Finucane, M. M., Flaxman, S., Flood, L., Foreman, K., Forouzanfar, M. H., Fowkes, F. G. R., Franklin, R., Fransen, M., Freeman, M. K., Gabbe, B. J., Gabriel, S. E., Gakidou, E., Ganatra, H. A., Garcia, B., Gaspari, F., Gillum, R. F., Gmel, G., Gosselin, R., Grainger, R., Groeger, J., Guillemin, F., Gunnell, D., Gupta, R., Haagsma, J., Hagan, H., Halasa, Y. A., Hall, W., Haring, D., Haro, J. M., Harrison, J. E., Havmoeller, R., Hay, R. J., Higashi, H., Hill, C., Hoen, B., Hoffman, H., Hotez, P. J., Hoy, D., Huang, J. J., Ibeanusi, S. E., Jacobsen, K. H., James, S. L., Jarvis, D., Jasrasaria, R., Jayaraman, S., Johns, N., Jonas, J. B., Karthikeyan, G., Kassebaum, N., Kawakami, N., Keren, A., Khoo, J.-P., King, C. H., Knowlton, L. M., Kobusingye, O., Koranteng, A., Krishnamurthi, R., Lalloo, R., Laslett, L. L., Lathlean, T., Leasher, J. L., Lee, Y. Y., Leigh, J., Lim, S. S., Limb, E., Lin, J. K., Lipnick, M., Lipshultz, S. E., Liu, W., Loane, M., Ohno, S. L., Lyons, R., Ma, J., Mabweijano, J., MacIntyre, M. F., Malekzadeh, R., Mallinger, L., Manivannan, S., Marcenes, W., March, L., Margolis, D. J., Marks, G. B., Marks, R., Matsumori, A., Matzopoulos, R., Mayosi, B. M., McAnulty, J. H., McDermott, M. M., McGill, N., McGrath, J., Medina-Mora, M. E., Meltzer, M., Memish, Z. A., Mensah, G. A., Merriman, T. R., Meyer, A.-C., Miglioli, V., Miller, M., Miller, T. R., Mitchell, P. B., Mocumbi, A. O., Moffitt, T. E., Mokdad, A. A., Monasta, L., Montico, M., Moradi-Lakeh, M., Moran, A., Morawska, L., Mori, R., Murdoch, M. E., Mwaniki, M. K., Naidoo, K., Nair, M. N., Naldi, L., Narayan, K. V., Nelson, P. K., Nelson, R. G., Nevitt, M. C., Newton, C. R., Nolte, S., Norman, P., Norman, R., O'Donnell, M., O'Hanlon, S., Olives, C., Omer, S. B., Ortblad, K., Osborne, R., Ozgediz, D., Page, A., Pahari, B., Pandian, J. D., Rivero, A. P., Patten, S. B., Pearce, N., Padilla, R. P., Perez-Ruiz, F., Perico, N., Pesudovs, K., Phillips, D., Phillips, M. R., Pierce, K., Pion, S., Polanczyk, G. V., Polinder, S., Pope, C. A., Popova, S., Porrini, E., Pourmalek, F., Prince, M., Pullan, R. L., Ramaiah, K. D., Ranganathan, D., Razavi, H., Regan, M., Rehm, J. T., Rein, D. B., Remuzzi, G., Richardson, K.,

Rivara, F. P., Roberts, T., Robinson, C., Leòn, F. R. de, Ronfani, L., Room, R., Rosenfeld, L. C., Rushton, L., Sacco, R. L., Saha, S., Sampson, U., Sanchez-Riera, L., Sanman, E., Schwebel, D. C., Scott, J. G., Segui-Gomez, M., Shahraz, S., Shepard, D. S., Shin, H., Shivakoti, R., Silberberg, D., Singh, D., Singh, G. M., Singh, J. A., Singleton, J., Sleet, D. A., Sliwa, K., Smith, E., Smith, J. L., Stapelberg, N. J. C., Steer, A., Steiner, T., Stolk, W. A., Stovner, L. J., Sudfeld, C., Syed, S., Tamburlini, G., Tavakkoli, M., Taylor, H. R., Taylor, J. A., Taylor, W. J., Thomas, B., Thomson, W. M., Thurston, G. D., Tleyjeh, I. M., Tonelli, M., Towbin, J. A., Truelsen, T., Tsilimbaris, M. K., Ubeda, C., Undurraga, E. A., van der Werf, M. J., van Os, J., Vavilala, M. S., Venketasubramanian, N., Wang, M., Wang, W., Watt, K., Weatherall, D. J., Weinstock, M. A., Weintraub, R., Weisskopf, M. G., Weissman, M. M., White, R. A., Whiteford, H., Wiersma, S. T., Wilkinson, J. D., Williams, H. C., Williams, S. R. M., Witt, E., Wolfe, F., Woolf, A. D., Wulf, S., Yeh, P.-H., Zaidi, A. K. M., Zheng, Z.-J., Zonies, D., Lopez, A. D., Murray, C. J. L. (2012): Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. The Lancet 380. (9859), 2163–2196. doi:10.1016/S0140-6736(12)61729-2

130. Waltersbacher, A.: Heilmittelbericht 2017. (2017). Online-Publikation; http://www.wido.de/fileadmin/wido/downloads/pdf_heil_hilfsmittel/wido_hei_hmb17_aktualisierte_fassung_1217.pdf/ 03.09.018.

131. Webster, B. S., Cifuentes, M. (2010): Relationship of early magnetic resonance imaging for work-related acute low back pain with disability and medical utilization outcomes. Journal of occupational and environmental medicine 52. (9), 900–907. doi:10.1097/JOM.0b013e3181ef7e53

132. Wheeler, C. H. B., C Williams, A. C. de, Morley, S. J. (2019): Meta-analysis of the psychometric properties of the Pain Catastrophizing Scale and associations with participant characteristics. Pain. doi:10.1097/j.pain.0000000000001494

133. Wiech, K. (2016): Deconstructing the sensation of pain: The influence of cognitive processes on pain perception. Science (New York, N.Y.) 354. (6312), 584–587. doi:10.1126/science.aaf8934

134. Wright, D. B. (2003): Making friends with your data: Improving how statistics are conducted and reported1. British Journal of Educational Psychology 73. (1), 123–136. doi:10.1348/000709903762869950

135. Wynne-Jones, G., Cowen, J., Jordan, J. L., Uthman, O., Main, C. J., Glozier, N., van der Windt, D. (2014): Absence from work and return to work in people with back pain: a systematic review and meta-analysis. Occupational and environmental medicine 71. (6), 448–456. doi:10.1136/oemed-2013-101571

136. Yarnitsky, D. (2015): Role of endogenous pain modulation in chronic pain mechanisms and treatment. Pain 156 Suppl 1, S24-31. doi:10.1097/01.j.pain.0000460343.46847.58

137. Zion, S. R., Crum, A. J. (2018): Mindsets Matter: A New Framework for Harnessing the Placebo Effect in Modern Medicine. International review of neurobiology 138, 137–160. doi:10.1016/bs.irn.2018.02.002

10 List of Figures

11 List of Tables

12 List of Abbrevations

ADL	Activities of Daily Living
BMI	Body Mass Index
BPS	Back Performance Scale
CLBP	Chronic low back pain
DASS-21	Depression Anxiety Stress Scale
EDTA	Ethylenediamine Tetraacetic Acid
IASP	International Association for the Study of Pain
ICD	International Statistical Classification of Diseases and Related Health Problems
LBP	Low back pain
m.	Musculus
MCS	Mental Component Score
Mm.	Musculi
MRI	Magnetic Resonance Imaging
NSAIDS	Non steroidal anti inflammatory drugs
ODI	Oswestry Disability Index
PCS	Physical Component Score, Pain Catastrophizing Scale
PSFS	Patient Specific Functional Scale
RoM	Range of Motion
SD	Standard Deviation
SOMS	Screening for somatoform Disorder
TAU	Treatment as Usual
VAS	Visual Analogue Scale
VAScomp	Composition Score of the Visual Analogue Scale
VoM	Velocity of Motion
VR -12	Veterans Rand 12 Questionaire

YLD	Years lived with disability

13 Appendix

Table 11:

Behavioral Data	t	df	p-value	CI	95%	Diff [1]-[0]	Cohens d=	r
ODI	2,573700	116,470	0,01132*	0,9299629	7,1407060	4,0353349	0,457	0,232
BPFS	0,712060	90,763	0,47830	-0,4070133	0,8618473	0,2274170	0,127	0,075
Depression	2,246800	99,053	0,02687*	0,1549858	2,4972390	1,3261124	0,399	0,220
Anxiety	1,793300	108,740	0,07571	-0,0996768	1,9936162	0,9469697	0,319	0,169
Stress	1,680100	115,000	0,09565	-0,2233626	2,7192642	1,2479510	0,299	0,155
PCS	0,337680	121,330	0,73620	-2,4821570	3,5030560	0,5104493	0,060	0,031
VAS min	2,178700	112,900	0,03143*	0,0623738	1,3136724	2,0411328	0,387	0,201
VAS max	2,362500	108,710	0,01993*	0,1326023	1,5141509	1,5333333	0,420	0,221
VAS mean	1,418500	115,070	0,15870	-0,1885258	1,1397523	0,4756132	0,252	0,131
VAS comp	2,6494	104,33	0,009317*	0.1666108	1.1580645	0.6623377	0,481	
PSFS	-0,252340	112,250	0,80120	-11,692241	0,9050451	0,1320900	-0,045	0,024

Table 12:

Range of Motion	F	df	Denom df	p-value	95%	CI	Ratio of variance
Flexion	0,92637	126	117	0,6725	0,6471181	1,3229531	0,9263699
Extension	1,4264	126	117	0,0523	0,9964471	2,0371131	1,426445
Lateral- Flexion (l)	0,94453	126	117	0,752	0,6598068	1,3488935	0,9445342
Lateral- Flexion (r)	0,92797	126	117	0,6794	0,6482325	1,3252313	0,9279652
Rotation (l)	0,89142	126	117	0,5259	0,622707	1,273048	0,8914247
Rotation (r)	0,86526	126	117	0,4248	0,6044301	1,2356827	0,8652607

Table 13:

Velocity of Motion	F	df	Denom df	p-value	95%	CI	Ratio of variance
Flexion	0,8417	126	117	0,3422	0,5879743	1,2020407	0,8417036
Extension	1,1384	126	117	0,4781	0,7952398	1,6257696	1,138411
Lateral- Flexion (l)	0,68307	126	117	**0,0361**	0,4771588	0,9754922	0,6830678
Lateral- Flexion (r)	0,69058	126	117	**0,04176**	0,4824068	0,9862211	0,6905805
Rotation (l)	0,79404	126	117	0,204	0,5546755	1,1339656	0,7940354
Rotation (r)	0,69779	126	117	**0,04781**	0,4874465	0,9965242	0,697795

Table 14:

Velocity of Motion	F	df	Denom df	p-value	95%	CI	Ratio of variance
ODI	1.0344	126	119	0.8531	0.7239501	1.4753670	1.034433
BPFS	1.0835	125	117	0.6615	0.7564745	1.5486670	1.083534
Depression	1.1255	124	117	0.5189	0.7853316	1.6100091	1.125517
Anxiety	1.4879	123	116	**0.03127**	1.036625	2.131638	1.487942
Stress	1.2799	124	117	0.1783	0.8930626	1.8308686	1.279914
PCS	1.0064	126	123	0.9722	0.7068415	1.4318331	1.006404
VAS min	1.0215	124	118	0.9084	0.7133961	1.4602219	1.021467
VAS max	1.0419	124	118	0.8232	0.7276333	1.4893634	1.041852
VAS mean	1.0779	124	118	0.682	0.7527893	1.5408543	1.077872
VAS comp	0.99081	124	118	0.9584	0.6919853	1.4163970	0.9908103
PSFS	0.49329	126	117	**0.0001118**	0.3445870	0.7044656	0.4932872

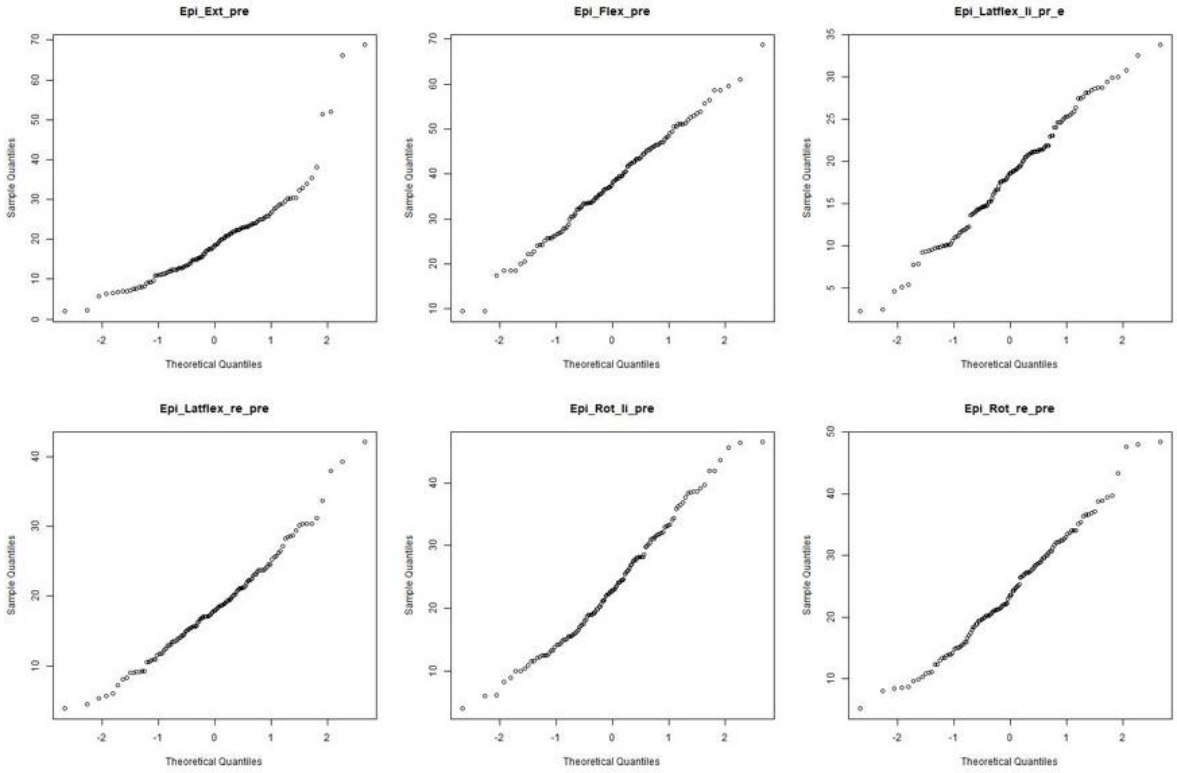

Figure 10: Results of the normality testing for Range of motion raw dataset during pre-assessment.

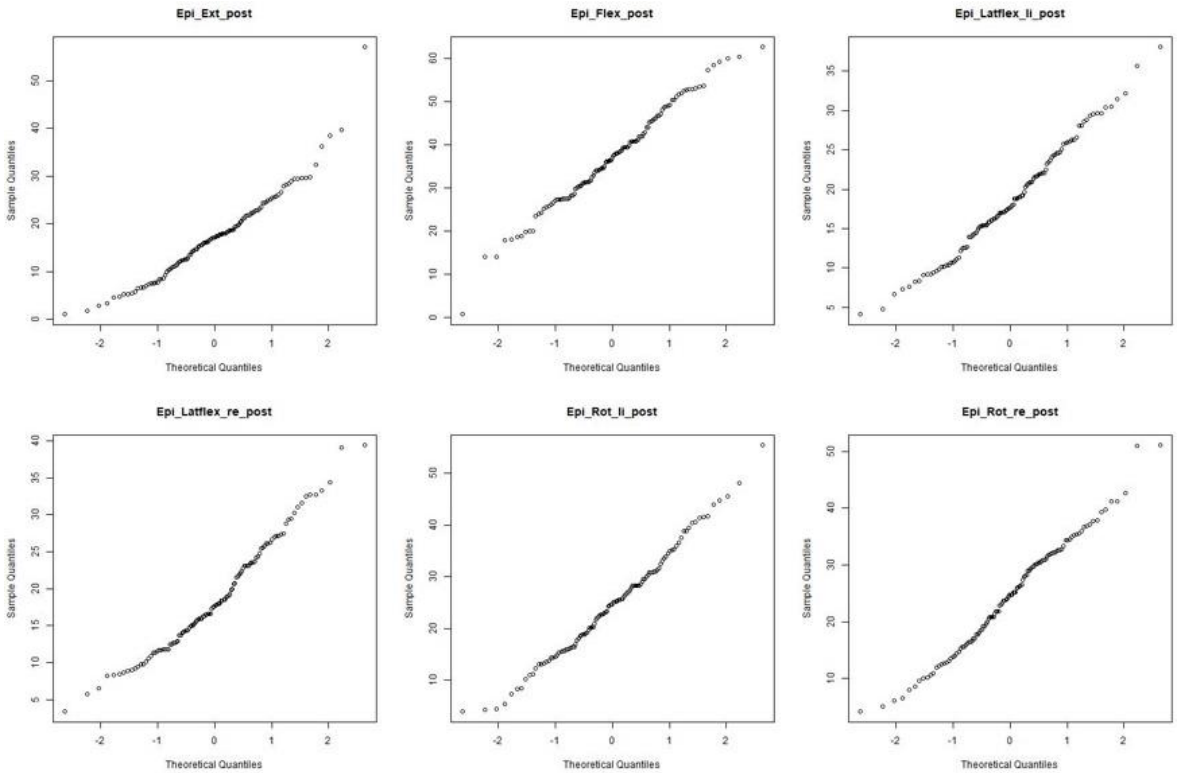

Figure 11: Results of the normality testing for Range of Motion raw dataset during post-assessment.

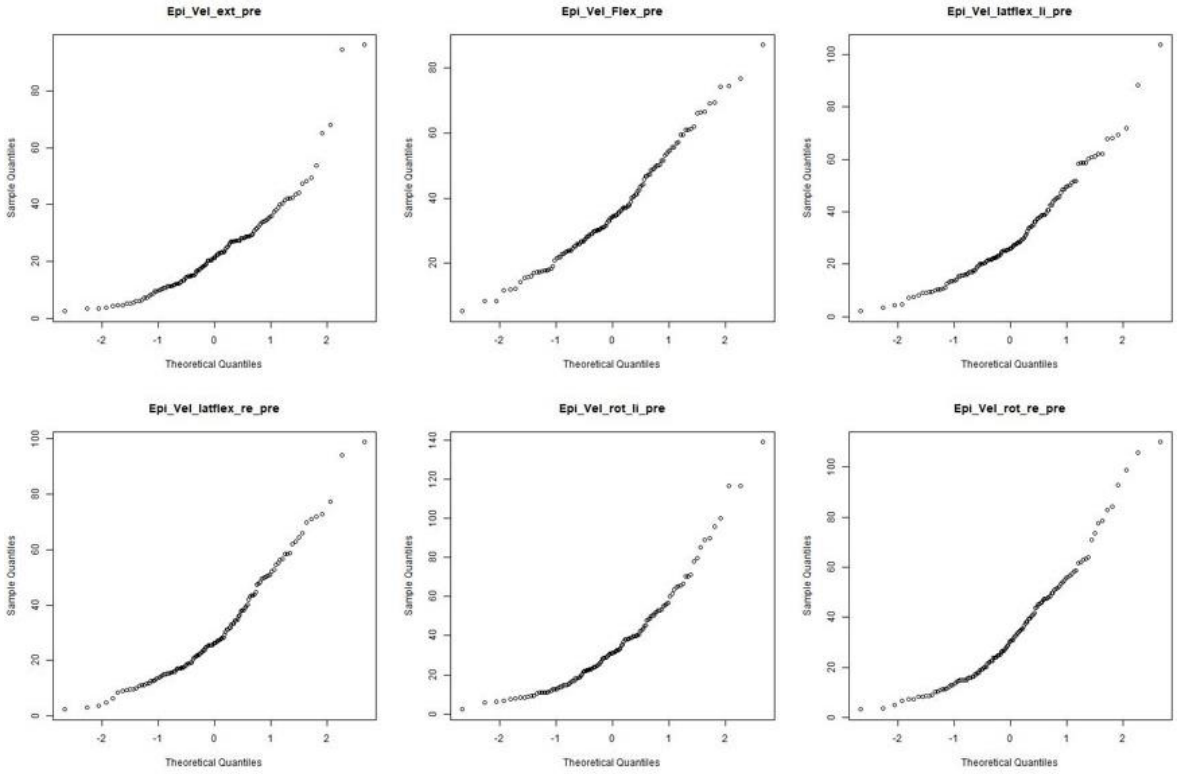

Figure 12 Results of the normality testing for Velocity of Motion raw dataset during pre-assessment

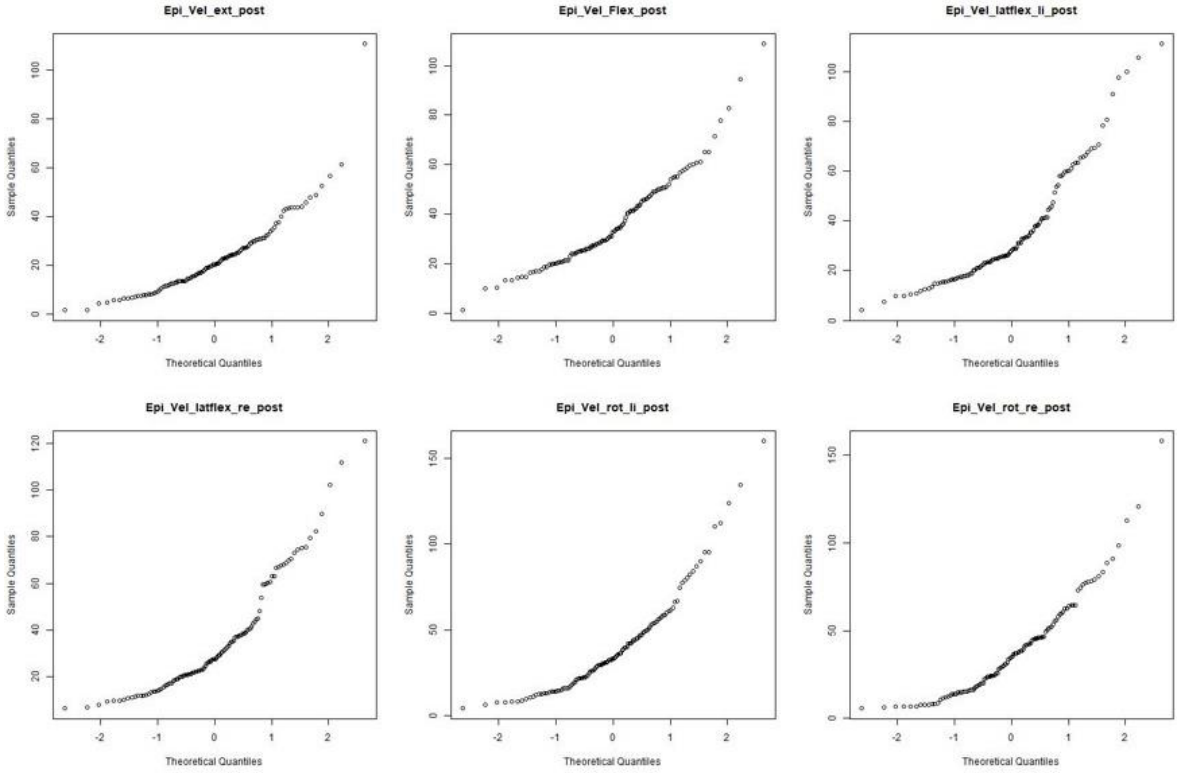

Figure 13: Results of the normality testing for Velocity of Motion dataset during post-assessment.

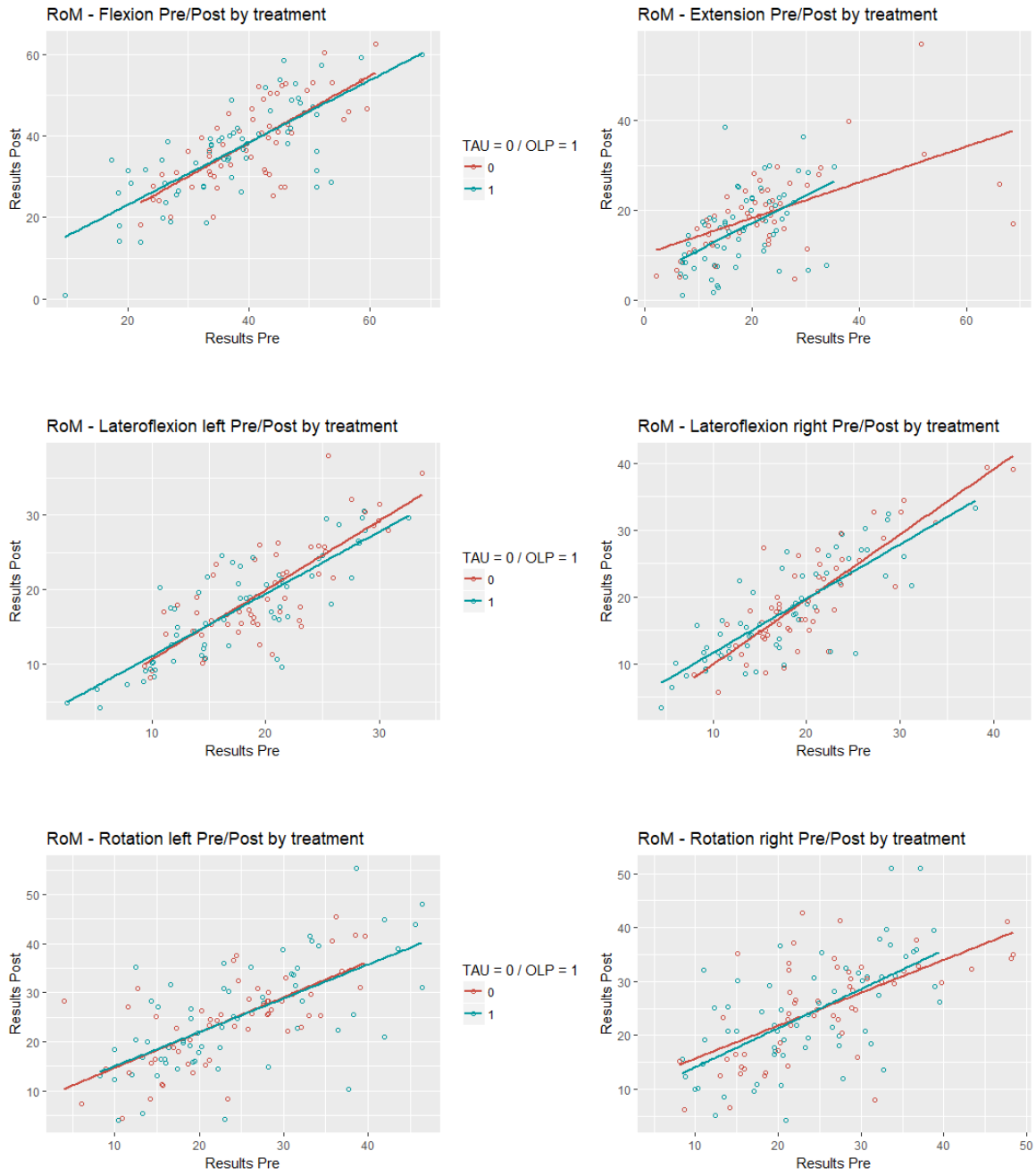

Figure 14: Comparison of the Range of motion (RoM) scores at Post- Measurement with those at Pre Measurement for the Open-Label-Placebo-Group (1) and the Treatment as Usual-Group (0).

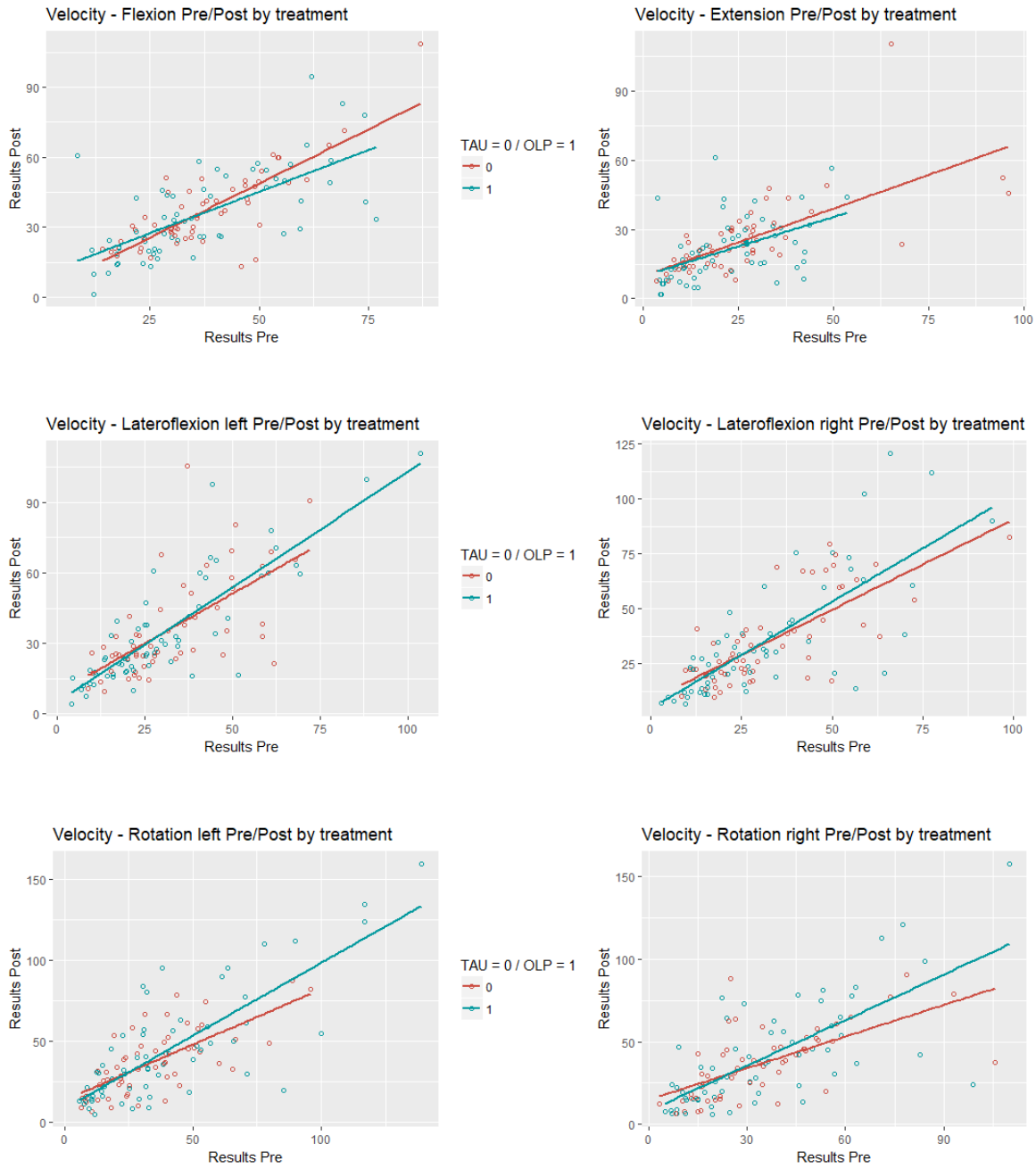

Figure 15: Comparison of the Velocity scores at Post- Measurement with those at Pre Measurement for the Open-Label-Placebo-Group (1) and the Treatment as Usual-Group (0).

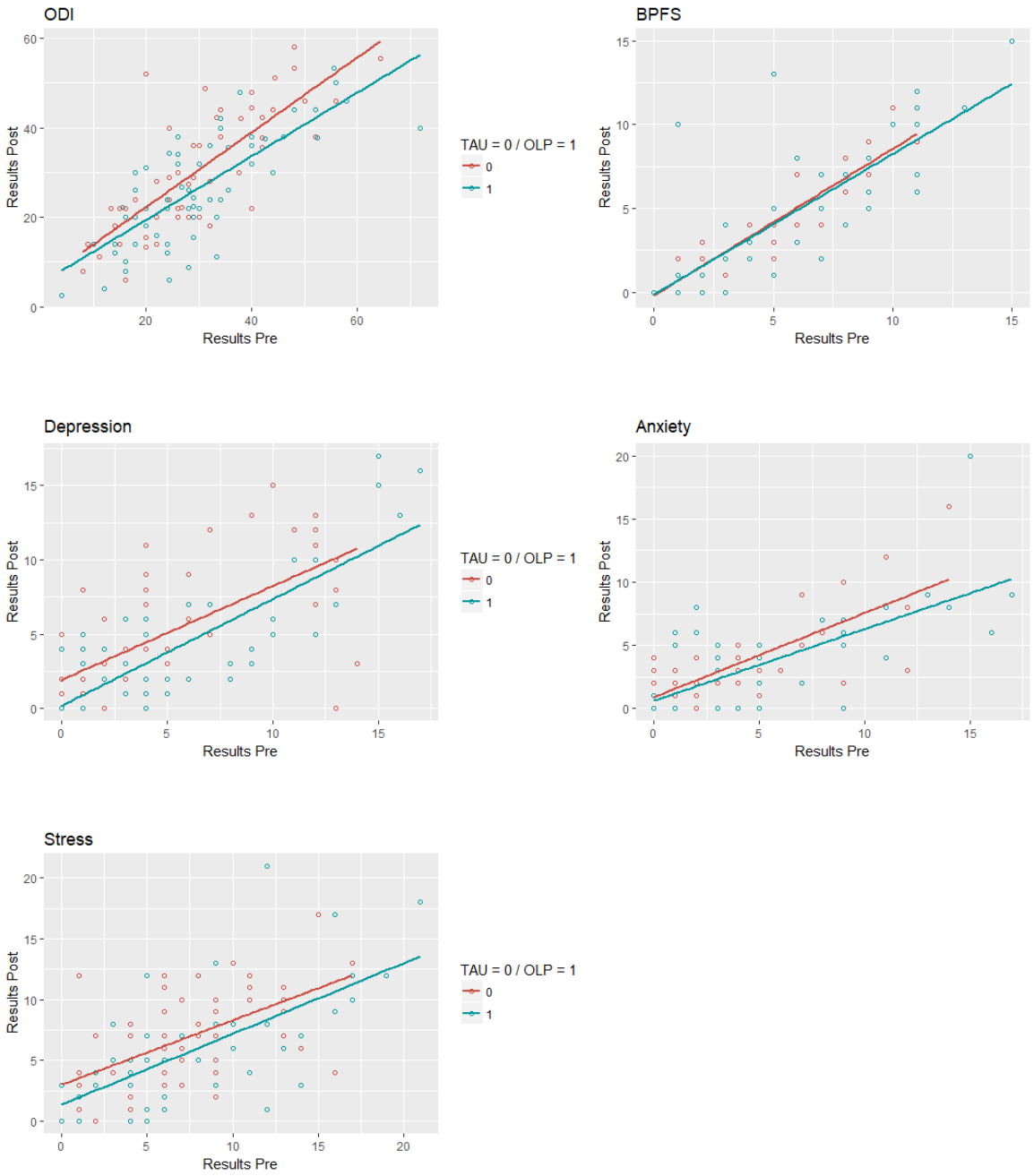

Figure 16: Comparison of the Behavioural Scores (Oswestry Disability Questionaire=ODI; Back Performance Scale=BPFS; Depression, Anxiety, Stress =DASS) at Post- Measurement with those at Pre Measurement for the Open-Label-Placebo-Group (1) and the Treatment as Usual-Group.

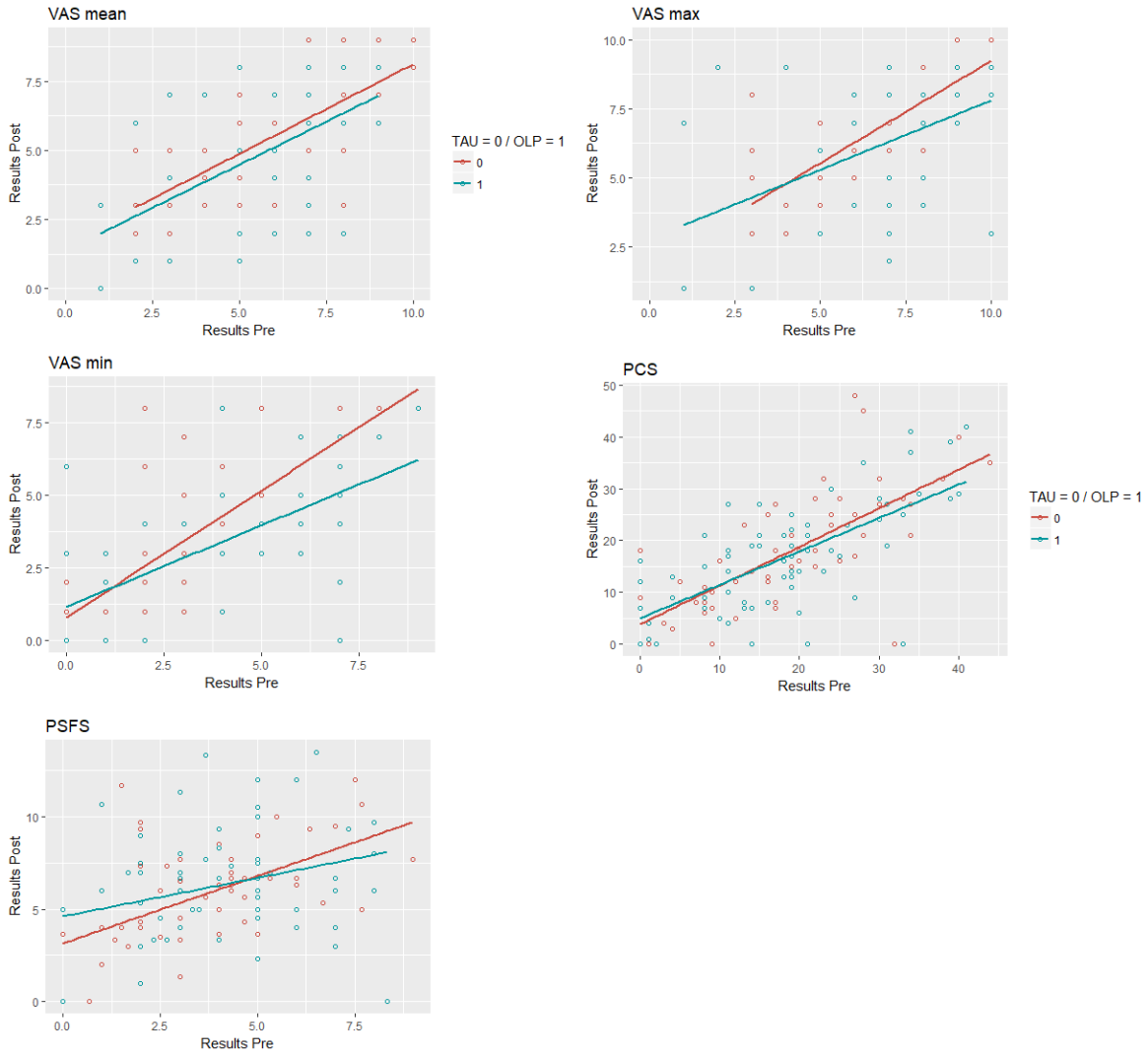

Figure 17: Comparison of the Behavioral Scores (lowest Pain Intensity during the last two weeks =VASmin; highest Pain Intensity during the last two weeks =VASmax, mean Pain Intensity during the last two weeks= VASmean; Pain Catastrophizing Scale = PCS; Patient Specific Functional Scale_ PSFS) at Post- Measurement with those at Pre Measurement for the Open-Label-Placebo-Group (1) and the Treatment as Usual-Group.

14 Acknowledgements

An dieser Stelle möchte ich Allen danken, die mir die Vollendung meiner Promotion ermöglichten: Frau Professor Dr. Ulrike Bingel danke ich für die Möglichkeit, in ihrer Arbeitsgruppe meine Promotionsarbeit anfertigen zu dürfen. Hern Dr. Tamas Spisak möchte ich für die hervorragende Betreuung und die Fortbildungen in Datenanalytik und seine stete Hilfsbereitschaft danken. Herrn Dr. Julian Kleine-Borgmann danke ich für die Zusammanarbeit an der anspruchsvollen und interessanten Promotions-Thematik. Auch meiner Arbeitsgruppe möchte ich hier nicht versäumen zu danken, für die angenehme und hilfsbereite Arbeitsatmosphäre. Insbesondere gilt hierbei mein Dank Frau Dr. Katharina Schmidt für die Unterstützung und Durchsicht dieser Arbeit und Frau Silke Bourdin für den organisatorischen Rahmen der Arbeitsprozesse.

Für viele fruchtbare Gespräche und Anregungen danke ich sehr Herrn Dr. Lars Jäger, der auch immer wieder als Sparring Partner herhalten durfte.

Ganz besonders danke ich natürlich meinen Eltern, die mich jederzeit unterstützten, sowie meiner Freundin Jana, die meiner Arbeit viel Verständnis und Geduld entgegenbrachte. Außerdem danke ich Herrn Andre Kwiatek der Firma EPIONICS für die stets unkomplizierte Zusammenarbeit.

15 Curriculum Vitae

Der Lebenslauf ist in der Online-Version aus Gründen des Datenschutzes nicht enthalten.

Der Lebenslauf ist in der Online-Version aus Gründen des Datenschutzes nicht enthalten.