UHASSELT

KNOWLEDGE IN ACTION

Faculteit Revalidatiewetenschappen

master in de revalidatiewetenschappen en de kinesitherapie

Masterthesis

The effects of mirror therapy, motor imagery and action observation on pain in neurological conditions

Anna-Lisa Nulens
Jessica Thenaers

Eerste deel van het scriptie ingediend tot het behalen van de graad van master in de revalidatiewetenschappen en de kinesitherapie

PROMOTOR :

Prof. dr. Peter FEYS

BEGELEIDER :

Mevrouw Cigdem YILMAZER

2020
2021

UHASSELT
KNOWLEDGE IN ACTION

www.uhasselt.be
Universiteit Hasselt
Campus Hasselt:
Martelarenlaan 42 | 3500 Hasselt
Campus Diepenbeek:
Agoralaan Gebouw D | 3590 Diepenbeek

UHASSELT

KNOWLEDGE IN ACTION

Faculteit Revalidatiewetenschappen

master in de revalidatiewetenschappen en de kinesitherapie

Masterthesis

The effects of mirror therapy, motor imagery and action observation on pain in neurological conditions

Anna-Lisa Nulens
Jessica Thenaers

Eerste deel van het scriptie ingediend tot het behalen van de graad van master in de revalidatiewetenschappen en de kinesitherapie

PROMOTOR :

Prof. dr. Peter FEYS

BEGELEIDER :

Mevrouw Cigdem YILMAZER

The effects of mirror therapy, motor imagery and action observation on pain in neurological conditions: A systematic review

Highlights:

- The included pathologies in this review are CRPS after stroke, spinal cord injury and Parkinson's Disease.
- Mirror therapy is an effective intervention to reduce pain in CRPS after stroke. A small study proved its pain reducing effects on spinal cord injury patients.
- The evidence for motor imagery is contradictory in SCI patients, some studies claim it reduces pain, while others state it could evoke pain.
- Graded motor imagery and virtually enhanced mirror therapy are both shown to be successful for reducing pain in CRPS after stroke patients. While virtually enhanced mirror therapy has pain reducing effects on spinal cord injury patients.
- New studies should be done to conclude the effect of mirror therapy, (graded) motor imagery on other neurological populations such as multiple sclerosis, amyotrophic lateral sclerosis, and traumatic brain injury.

Promotor: Prof. dr. Peter Feys

Mentor: dra. Cigdem Yilmazer

Students: Anna-Lisa Nulens and Jessica Thenaers

1st master rehabilitation sciences and physiotherapy 2020-2021

Context of the master thesis

This master thesis fits in the research domain of neurological rehabilitation.

Pain decreases health-related quality of life (HRQOL) and affects emotional, physical and social functioning, sleep, and productivity negatively. Chronic pain is one of the most prevalent, disabling, and costly public health conditions. (Thieme, Morkisch, Rietz, Dohle, &Borgetto, 2015).

More specifically, the literature study of the master thesis focused on the following research question: what is the effect of mirror therapy, motor imagery and action observation on pain in neurological conditions? While reviewing, the different types of pain were considered (neuropathic or nociceptive).

This master thesis part 1 was conducted as a part of the first master year at the University of Hasselt (UHasselt). In Part 2, according to the results of Part 1, the most suitable and promising intervention of the above-mentioned ones will be applied for the MS population. Primary outcome measures will be pain, secondary ones will be depression, quality of life (QoL), activity of daily life (ADL). There will be a collaboration with Noorderhart (Overpelt) and the National MS Center (Melsbroek). This review will be contributing to the PhD project of C. Yilmazer: “Pain in Multiple Sclerosis”.

For this duo-master’s thesis, the central format was applied. The students chose the research question in consultation with the promoter and mentor based on what was relevant for the PhD-project of C. Yilmazer and the clinical practice. The screening of the articles, quality assessment and the data extraction were evaluated independently by the two students.

Furthermore, the master students were required to formulate a new research question regarding the reviewed topics in this paper. The task was to detect which protocol would provide the most clinically relevant outcome. In accordance with this mindset, the following research question was asked: “What is the effect of mirror therapy on pain in patients with MS”. This therapy will be compared to conventional

therapy after a six week training program through a prospective, experimental, longitudinal study.

Table of contents

Part 1: Overview of the literature

1.1 Abstract

Introduction

Pain is an underestimated, yet one of the most prevalent symptoms in neurological conditions. The interventions of mirror therapy (MT), motor imagery (MI), and action observation (AO) are mostly known for their effects on improving motor function. Mirror therapy reduces pain in phantom limb pain. Hence, the objective of this review is to summarize the evidence on the effectiveness of MT, MI and AO on reducing pain in neurological conditions.

Methods

The databases Pubmed and Web of Science were used for this review. After meeting the selection criteria, data was collected by two independent reviewers. The methodological quality of the included randomized controlled trials, clinical trials, case studies, pilot study, and preliminary report were evaluated with the PEDro scale.

Results

The findings suggest that MT is an effective intervention for reducing pain in CRPS after stroke patients. A smaller study showed a positive effect on pain in SCI patients. However, the results of MI were contradictory. Graded motor imagery was proven to be effective to reduce pain in CRRS in stroke patients. The release of pain was even maintained at a follow up after six months. Virtually enhanced mirror therapy has shown to reduce pain in SCI patients. However, the combination of virtually enhanced mirror therapy with transcranial direct current stimulation might be superior to the single treatment.

Discussion and conclusion

To summarize, MT can be an effective treatment option for reducing pain in CRPS after stroke patients. New studies are still needed to show the effects on pain in SCI, MS, ALS, Parkinson's disease, and TBI patients. MI shouldn't be recommended for reducing pain in SCI patients. There can't be drawn any conclusion on the effect of this intervention on other neurological conditions. Graded motor imagery and virtually enhanced mirror therapy seemed effective for reducing pain in CRPS after stroke patients, while virtually enhanced mirror therapy reduced pain in SCI patients.

Purpose of the protocol

The aim is to evaluate whether MT has a reducing effect on pain in multiple sclerosis.

Operationalization of the protocol

This master's thesis is part of a broader research project, "Pain in Multiple Sclerosis", a PhD project of Dra C. Yilmazer under the supervision of Prof. Dr. P. Feys in collaboration with Noorderhart in Pelt and the National MS Center in Melsbroek (Belgium).

Most important keywords

Pain, mirror therapy, motor/mental imagery, action observation, neurological disorders, multiple sclerosis, spinal cord injury, complex regional pain syndrome, Parkinson's disease, amyotrophic lateral sclerosis, traumatic brain injury.

1.2 Introduction

Pain is an underestimated, yet one of the most prevalent symptoms in neurological conditions. It can be classified based on its duration and the underlying mechanisms. When pain lasts for over 3 months, it's called chronic pain (Ehde, Osborne, Hanley, Jensen, &Kraft, 2006; Treede et al., 2019). The underlying mechanisms determine whether it's classified as neuropathic, nociceptive or neuroplastic. These forms could be mixed as well. According to the International Association for the study of Pain (IASP), nociceptive pain is defined as "Pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors" (Terminology, 2019). Nociceptive pain is the result of a noxious insult to non-neural tissue that triggers nociceptors. This information is passed on by the medial and lateral nociceptive pathways through the spinal cord to the somatosensory cortex and the thalamus. When there's a direct injury to the central or the peripheral nervous system, it's called neuropathic pain. This gives electrical sensations and a burning feeling. (Kandel, Mack, Jessell, Schwartz, Siegelbauwm, &Hudspeth, 2013). Neuropathic pain can be divided into peripheral and central neuropathic pain according to the location of the injury or disease (Terminology, 2019). Nociplastic pain is defined by the IASP as "Pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain" (Terminology, 2019). Pain can be mixed; this is a combination of different types of pain (nociceptive, neuropathic and nociplastic) and located in the same area.

Thirty-three percent of all patients with complete spinal cord injury (SCI) suffer from neuropathic pain (Siddall, McClelland, Rutkowkski, &Cousins, 2003) while 65% report chronic pain (Siddal, Yezierski, &Loeser, 2002). The pain is located diffusely below the level of the injury, in the region of sensory loss (Gustin, Wrigley, Gandevia, Middleton, Henderson, &Siddall, 2008). Neuropathic pain is the most treatment-resistant pain in SCI (Cruz-Almeida, Felix, Martinez-Arizala, &Widerström-Noga, 2009).
Complex regional pain syndrome (CRPS) affects one to five percent of patients after stroke. The pain in CRPS is characterized by sensory disturbances, such as a burning

pain with allodynia and hyperalgesia and is caused by a mismatch between proprioceptive feedback and motor action (Siddall et al., 2003). “Stroke often causes impairment in movement control. It can affect perception as well. Alterations of stimulus integration are common after a stroke, with variable reported prevalence ranging from 11 to 85%. Sometimes these alterations of perception result in pain” (Yekutiel, 2000).

Chronic pain is one of the most common non-motor symptoms of Parkinson’s disease (PD) (Zangrando, Piccinini, Pelliccioni, Saraceni, &Paolucci, 2015).

Pain is an important symptom in multiple sclerosis (MS) (29-86%) as well (O’Connor et al., 2008). It remains unclear what the underlying mechanism of the pain in MS could be. The pain in MS could be neuropathic, nociceptive or mixed (Yilmazer et al., 2020). These patients could suffer from continuous burning sensations in the lower limbs, painful tonic spasms, back pain, headaches, or visceral pain (O’Connor, Schwid, Herrmann, Markman, &Dworkin, 2008; Truini et al., 2012).

Patients with amyotrophic lateral sclerosis (ALS) frequently suffer from pain. It was reported in 78% of patients with ALS in a study of Hanish, Skudlarek, Berndt, &Kornhuber (2015). Pain can occur at any stage of ALS and the severity of pain isn’t correlated with the stage of the disease.

Patients with traumatic brain injury (TBI) usually suffer from acute pain due to tissue damage. This typically resolves after several weeks. However, once the brain has healed, chronic pain may arise (Irvine, &Clark, 2017). It’s unclear whether this pain is primarily caused by the brain injury itself, to injuries suffered concurrently with the brain injury or to psychological factors. Despite pain in TBI being very common, our understanding of the causes and consequences of pain after TBI is limited (Khoury, &Benavides, 2017).

In the literature, various types of interventions targeting pain exist. However, in this literature review, the effectiveness of the relatively novel interventions action observation (AO), mirror therapy (MT) and mental imagery (MI) on pain was being investigated. These interventions have mainly been investigated for their motor aspect so far, less for the effect on pain. In some studies, pain is included as one of the secondary outcome measures. It’s rarely the primary measure. These three

interventions are cheap, easy and practical. The patient could be doing these exercises at home or wherever they want when given the right instructions. Only for mirror therapy, a mirror box is recommended over a normal mirror. This is easily found online starting at the price of €50.

The mechanism behind these interventions is the mirror neuron system. The observation of other actions activates a complex network of visual areas, such as the occipital, temporal and parietal cortex, and of two motor areas, being the parietal (inferior parietal lobule) and the frontal cortex (ventral premotor cortex and inferior frontal gyrus). Watching a movement can facilitate execution of a (known) movement and thereby facilitates neuroplasticity (Heremans, Helsen, De Poel, Alaerts, Meyns, &Feys, 2009).

In MT, the patients move the unaffected limb while watching its mirror reflection. The affected limb is hiding behind the mirror and out of sight. Hereby creating a visual illusion of moving the affected limb. This generates positive feedback to the motor cortex, which could interrupt the pain cycle. (Stevens, &Stoykov, 2003)

MI is a process of internally representing movements without actually performing the movement. There's no contraction of the muscles. It's closely connected to action execution, as it's proven with neuroimaging results that MI stimulates the neural structures largely overlapping with those involved in actually performing the movement, mostly the pre-motor areas, the left intraparietal sulcus and the subcortical structures such as the basal ganglia and cerebellum (Decety, 1996).

Taken together, AO, MI and MT could be effective for treating pain. However, currently no published reviews investigated these modalities in a neurological population to this date. Therefore, the objective of this study was to review the published clinical trials about the effectiveness of these interventions on pain in neurological patients.

1.3 Methods

1.3.1 Research question

The main research question for this literature search is: “What are the effects of mirror therapy, motor imagery and action observation on pain in neurological diseases?”

The PICO (Population, Intervention, Comparison, Outcome) was used to make a search strategy. The population included patients with a neurological disease such as TBI, SCI, PD, MS, ALS, or stroke who were suffering from pain. The interventions MT, AO, and MI were used with the primary or secondary outcome of pain.

1.3.2 Literature search

The databases Pubmed and Web of Science (WOS) were searched. Key words and MESH terms were ‘’mirror therapy’ OR ‘motor imagery’ OR ‘action observation’ AND ‘traumatic brain injury’ OR ‘spinal cord injury’ OR ‘Parkinson’s disease’ OR ‘multiple sclerosis’ OR ‘amyotrophic lateral sclerosis’ OR ‘stroke’ AND ‘pain’ with their synonyms. If no MeSH-term existed, selection was made according to 'Title/abstract'. In WOS the key terms were searched by 'topic'. The full search strategy used for Pubmed and Web of Science is shown in table 1. The yielded articles were screened for relevance based on title and abstract. If there was uncertainty about whether to include an article or not, PF and CY were consulted to decide. The included articles were published between 2004 and 2020. There were randomized controlled trials, clinical trials, one pilot study, one preliminary report and three case studies included in this study. A full list of included articles can be found in the list of references. The long list of excluded articles contains 1548 studies and is therefore a requestable appendix.

1.3.3 Selection criteria

The following inclusion criteria were used to select the articles: a) population including a neurological disease such as TBI, SCI, PD, MS, ALS or stroke; b) rehabilitative interventions such as AO, MT or (graded) MI, whether or not augmented by virtual reality; c) pain as primary or secondary outcome measure; d) participants over 18 years old; e) articles in English.

The exclusion criteria were: a) age under 18 years; b) non-neurological populations, Alzheimer disease or dementia; c) no outcome measure for pain; d) language other than English; e) studies which are not published in peer reviewed journals and theses.

1.3.4 Quality assessment

The PEDro scale (de Morton, 2009) was used to assess the quality and risk of bias of all included studies. Two reviewers (AN and JT) independently scored the studies. Table 3 shows the quality assessments of the included studies.

1.3.5 Data extraction

A data extraction form created to collect the information on the participants characteristics (witch neurological condition), method (study design and sample size), intervention characteristics (the type of intervention, control conditions and duration intervention) and the results (pain outcome, type of pain, main pain outcome at baseline, main pain outcome after treatment, intervention vs. control and main results). Data were extracted by two independent reviewers and compared. The outcome of interest was pain whether it was reported as primary or secondary.

1.4 Results

1.4.1 Results study selection

Database searching identified 1594 articles. After removing duplicates, a total of 1586 articles screened based on title and abstract and 1548 articles were excluded. Inclusion criteria such as population, age, intervention, outcome, and language were taken into account. Thirty-eight articles were selected from the first screening and were assessed by full text. As a result of full-text reading, 19 articles were excluded. The reasons for exclusion were: 13 articles did not investigate pain, two articles had an intervention that was not one of the three included interventions, three articles had another population and one article was a review. This showed a final result of 19 relevant articles where the inclusion and exclusion criteria met. Figure 1 shows the flowchart of the search process. The overview of the excluded articles is covered in table 2.

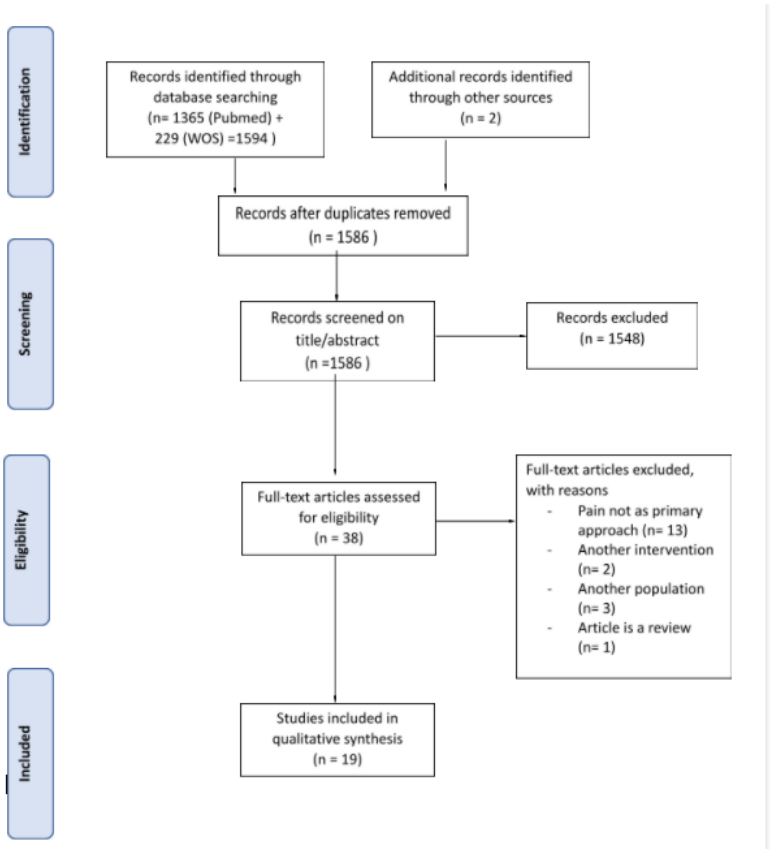


Figure 1
Flow chart in- and excluded articles

Most of the articles that resulted from the search strategy were related to musculoskeletal disorders or the intervention was medication. Therefore, a lot of these articles could not be included into this review. The articles often included a population of patients with heart disease. A recurring population was patients suffering from phantom pain with mirror therapy as intervention of interest. This is no neurological disorder. As a result of our inclusion and exclusion criteria, these studies were excluded. Cannabinoid and cannabis were often used as a treatment within the population of neurological disorders, especially in multiple sclerosis. In view of our selection criteria, these studies have been added to the exclusion list. In several cases, pain was not a primary outcome. However, we did include these articles, as their information could still be relevant. A full text was available for each study.

Included studies

The design of most studies were Randomized Controlled trials (RCTs), Case Reports, and Clinical Trials. One Pilot Study and one Preliminary Report were included.

Interventions

The articles who met the inclusion and exclusion criteria (n = 19) consisted of several different interventions and neurological disorders. Mirror therapy was discussed in the studies of: Cacchio, De Blassis, De Blasis, Santilli, &Spacca (2009a), Cacchio, De blasis, Necozione, Orio, &Santilli (2009b), Corbetta, Sarasso, Agosta, Filippi, &Gatti (2018), Michielsen et al. (2011), Mosely (2004), Sumitani et al. (2008) and Pervane Vural, Nakipoglu Yuzer, Sezgin Ozcan, Demir Ozbudak, &Ozgirgin (2016). (Graded) motor imagery was used in the following studies: Cacchio et al. (2009b), Gustin, Wrigley, Henderson, &Siddall (2010), Gustin et al. (2008), Hasan, Fraser, Conway, Allan, &Vučković (2016), Kaur, Ghosh, Sahani, &Sinha (2020), Mosely (2004), Mosely (2006), Polli et al. (2017), Sumitani et al. (2008), Walz, Usichenko, Moseley, &Lotze (2013) and Zangrando et al. (2015). No study investigated action observation. Some studies had multiple interventions. The studies of Mosely (2007) and Özkul, Kılınç, Yıldırım, Topçuoğlu, &Akyüz (2015) investigated visual walking. Soler et al. (2010) investigated visual illusion, while Sato et al. (2010) looked at virtual reality visual feedback therapy. These interventions are further explained in the results of the data extraction.

Population

Eight studies investigated an intervention on patients with SCI. The following studies included this population: Gustin et al. (2010), Gustin et al. (2008), Hasan et al. (2016), Kaur et al. (2020), Mosely (2007), Özkul et al. (2015), Soler et al. (2010) and Sumitani et al. (2008).

Ten studies included patients with (CRPS after) stroke (Cacchio et al. (2009a); Cacchio et al. (2009b); Corbetta et al. (2018); Michielsen et al. (2011); Mosely (2004); Mosely (2006); Polli et al. (2017); Sato et al. (2010); Pervane Vural et al. (2016) and Walz et al. (2013)).

Only one study included a Parkinson's Disease patient (Zangrando et al., 2015). No studies investigated the effectiveness of action observation. Furthermore, no studies included MS, ALS, or TBI patients.

Table 2

Overview of excluded articles

Article	Excluded + reason
Aggarwal N. K. (2013). Mirror therapy for facial paralysis in traditional South Asian Islamic medicine. *Journal of the history of the neurosciences*, 22(1), 1–5. https://doi.org/10.1080/0964704X.2011.649137	Excluded No pain outcome
Andritoi, D., Corciovă, C., Luca, C., Matei, D., & Ciorap, R. (2017). Heart Rate Dynamics Study on the Impact of "Mirror Therapy" in Patients with Stroke. *Springer International Publishing*, 59, 21-24. DOI: 10.1007/978-3-319-52875-5_5	Excluded No pain outcome
Bartur, G., Pratt, H., Frenkel-Toledo, S., & Soroker, N. (2018). Neurophysiological effects of mirror visual feedback in stroke patients with unilateral hemispheric damage. *Brain research*, 1700, 170–180. https://doi.org/10.1016/j.brainres.2018.09.003	Excluded No pain outcome
Bolognini, N., Russo, C., & Vallar, G. (2015). Crossmodal illusions in neurorehabilitation. *Frontiers in behavioral neuroscience*, *9*, 212. https://doi.org/10.3389/fnbeh.2015.00212	Excluded Review
Mirela Cristina, L., Matei, D., Ignat, B., & Popescu, C. D. (2015). Mirror therapy enhances upper extremity motor recovery in stroke patients. *Acta neurologica Belgica*, 115(4), 597–603. https://doi.org/10.1007/s13760-015-0465-5	Excluded No pain outcome
Crosby, L. D., Marrocco, S., Brown, J., & Patterson, K. K. (2016). A novel bilateral lower extremity mirror therapy intervention for individuals with stroke. *Heliyon*, 2(12), e00208. https://doi.org/10.1016/j.heliyon.2016.e00208	Excluded No pain outcome
Diers, M., Kamping, S., Kirsch, P., Rance, M., Bekrater-Bodmann, R., Foell, J., Trojan, J., Fuchs, X., Bach, F., Maaß, H., Cakmak, H., & Flor, H. (2015). Illusion-related brain activations: a new virtual reality mirror box system for use during functional magnetic resonance imaging. *Brain research*, 1594, 173–182. https://doi.org/10.1016/j.brainres.2014.11.001	Excluded No neurological population Healthy subjects
Ding, L., Wang, X., Guo, X., Chen, S., Wang, H., Cui, X., Rong, J., & Jia, J. (2019). Effects of camera-based mirror visual feedback therapy for patients who had a stroke and the neural mechanisms involved: protocol of a multicentre randomised control study. *BMJ open*, 9(3), e022828. https://doi.org/10.1136/bmjopen-2018-022828	Excluded No pain outcome

Fardo, F., Allen, M., Jegindø, E. M., Angrilli, A., & Roepstorff, A. (2015). Neurocognitive evidence for mental imagery-driven hypoalgesic and hyperalgesic pain regulation. *NeuroImage*, 120, 350–361. https://doi.org/10.1016/j.neuroimage.2015.07.008	Excluded No neurological population
Fukumori, S., Gofuku, A., Isatake, K., & Sato, K. (2015). Mirror thrapy system based virtual reality for chronic pain in home use*. Graduate School of Natural Science and Technology,* 4034-4039. DOI:10.1109/IECON.2014.7049106	Excluded No neurological population
Guo, J., Qian, S., Wang, Y., & Xu, A. (2019). Clinical study of combined mirror and extracorporeal shock wave therapy on upper limb spasticity in poststroke patients. International journal of rehabilitation research. Internationale Zeitschrift fur Rehabilitationsforschung. *Revue internationale de recherches de readaptation*, 42(1), 31–35. https://doi.org/10.1097/MRR.0000000000000316	Excluded No pain outcome
Hoermann, S., Ferreira Dos Santos, L., Morkisch, N., Jettkowski, K., Sillis, M., Devan, H., Kanagasabai, P. S., Schmidt, H., Krüger, J., Dohle, C., Regenbrecht, H., Hale, L., & Cutfield, N. J. (2017). Computerised mirror therapy with Augmented Reflection Technology for early stroke rehabilitation: clinical feasibility and integration as an adjunct therapy. *Disability and rehabilitation*, 39(15), 1503–1514. https://doi.org/10.1080/09638288.2017.1291765	Excluded No pain outcome
Noh, J. S., Lim, J. H., Choi, T. W., Jang, S. G., & Pyun, S. B. (2019). Effects and safety of combined rTMS and action observation for recovery of function in the upper extremities in stroke patients: A randomized controlled trial. *Restorative neurology and neuroscience*, 37(3), 219–230. https://doi.org/10.3233/RNN-180883	Excluded No pain outcome
Osinski, T., Martinez, V., Bensmail, D., Hatem, S., & Bouhassira, D. (2020). Interplay between body schema, visuospatial perception and pain in patients with spinal cord injury. *European journal of pain (London, England),* 24(7), 1400–1410. https://doi.org/10.1002/ejp.1600	Excluded Other intervention
Radajewska, A., Opara, J. A., Kucio, C., Błaszczyszyn, M., Mehlich, K., & Szczygiel, J. (2013). The effects of mirror therapy on arm and hand function in subacute stroke in patients. International journal of rehabilitation research. Internationale Zeitschrift fur Rehabilitationsforschung. *Revue internationale de recherches de readaptation*, 36(3), 268–274. https://doi.org/10.1097/MRR.0b013e3283606218	Excluded No pain outcome

Scandola, M., Aglioti, S. M., Avesani, R., Bertagnoni, G., Marangoni, A., & Moro, V. (2017). Corporeal illusions in chronic spinal cord injuries. *Consciousness and cognition*, 49, 278–290. https://doi.org/10.1016/j.concog.2017.01.010	Excluded Other intervention
Vučković, A., Jarjees, M., Abul Hasan, M., Miyakoshi, M., & Fraser, M. (2018). Central neuropathic pain in paraplegia alters movement related potentials. Clinical neurophysiology : official journal of the International Federation of *Clinical Neurophysiology*, 129(8), 1669–1679. https://doi.org/10.1016/j.clinph.2018.05.020	Excluded No pain outcome
Yavuzer, G., Selles, R., Sezer, N., Sütbeyaz, S., Bussmann, J. B., Köseoğlu, F., Atay, M. B., & Stam, H. J. (2008). Mirror therapy improves hand function in subacute stroke: a randomized controlled trial. *Archives of physical medicine and rehabilitation*, 89(3), 393–398. https://doi.org/10.1016/j.apmr.2007.08.162	Excluded No pain outcome

1.4.2 Quality assessment

The quality assessment of the included articles by using the PEDro scale is covered in table 3. An overview of the strengths and weaknesses of the included articles is available in table 4.

The PEDro scale was developed by the Physiotherapy Evidence Database to determine the quality of the clinical trials. A PEDro score between six and ten is considered 'high quality', between four and five 'fair quality' and a score less than or equal to three 'poor quality'.

Five studies scored low quality, namely the studies of: Corbetta et al. (2018), Mosely (2007), Sato et al. (2010), Walz et al. (2013) and Zangrando et al. (2015). The following five studies of Cacchio et al. (2009a), Gustin et al. (2010), Gustin et al. (2008), Hasan et al. (2016) and Sumitani et al. (2008) scored a fair quality. The remaining nine studies scored a high quality: Cacchio et al. (2009b), Kaur et al. (2020), Michielsen et al. (2011), Mosely (2004), Mosely (2006), Özkul et al. (2015), Polli et al. (2017), Soler et al. (2010) and Pervane Vural et al. (2016).

Table 3
The PEDRO scale

	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	PEDro score
Cacchio et al. (AUG 2009) (RCT)	No	Yes	No	No	No	No	No	Yes	Yes	Yes	No	4
Cacchio et al. (OCT 2009) (RCT)	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	8
Corbetta et al. (2018) (Case report)	No	No	No	No	No	No	No	Yes	Yes	No	No	2
Gustin et al. (2010)	No	No	No	No	No	No	No	Yes	Yes	Yes	Yes	4
Gustin et al. (2008)	No	No	No	No	No	No	No	Yes	Yes	Yes	Yes	4
Hasan et al. (2016)	Yes	No	No	Yes	No	No	No	Yes	Yes	Yes	No	4
Kaur et al. (2020) (RCT)	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	7
Michielsen et al. (2011) (RCT)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	8
Mosely et al. (2004) (RCT)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	8
Mosely et al. (2006) (RCT)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	8
Mosely et al. (2007)	No	No	No	No	No	No	No	Yes	Yes	No	Yes	3
Özkul et al. (2015) (RCT)	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	7
Pervane Vural et al. (2016) (RCT)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	8
Polli et al. (2017) (n-RCT)	Yes	No	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	7
Sato et al. (2010) (pilot study)	No	No	No	No	No	No	No	Yes	Yes	No	No	2
Soler et al. (2010)(RCT)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	10
Sumitani et al. (2008) (preliminary repo	No	No	No	No	No	No	No	Yes	Yes	Yes	Yes	4
Walz et al. (2013) (case study)	No	No	No	No	No	No	No	Yes	Yes	No	No	2
Zangrando et al. (2015) (Case report)	No	No	No	No	No	Yes	No	Yes	Yes	No	No	3

Table 4

Strengths and weakness of the included studies

Title and author	Strengths	Limitations
Cacchio et al. (2009a)	• Cross over to another intervention group • Progression in the active-mirror group (also after the cross-over)	• Small sample size (n= 24) • No follow-up • No control group • No description on how they randomized the groups: selection bias
Cacchio et al. (2009b)	• Inclusion and exclusion criteria are clearly described • Characteristics of the patients are clearly descirbed • Control group • Long-term follow up (6 months) • No statistically significant differences between the groups in the baseline	• No description on how they randomized the groups: selection bias • The lack of direct evidence of brain reorganization after mirror therapy using imaging techniques
Corbetta et al. (2018)	• Characteristics of the patient are clearly described • The intervention was supervised • The baseline was one month before starting MT • Long-term follow up (12 months) • Progression in the therapy	• Small sample size (n=1 → a case report) • No control group • Short treatment duration (2 weeks) • No generalization: one single subject
Gustin et al. (2010)	• Control group • Progression in the exercise group • The intervention was supervised	• Small sample size (n=11) • No gender equality (9 males) • No description on how they randomized the groups: selection bias • No follow-up

Gustin et al. (2008)	• Characteristics of the patients are clearly described • The intervention was supervised	• Small sample size (n=15) • No gender equality (all men) • No control group • No follow-up
Hasan et al. (2016)	• Inclusion and exclusion criteria are clearly described • Characteristics of the patient are clearly described • Control group • All groups followed the same protocol	• Small sample size (n=25, patients with pain n=5) • No gender equality (n=21 males) • No follow-up
Kaur et al. (2020)	• Inclusion and exclusion criteria are clearly described • Large sample size (n=44) • Characteristics of the patients are clearly described • The samples were randomized by a computer-generated randomization sequence by a blinded person • Control group • Progression in the exercise group	• 2 drop-outs • No follow-up • SCI is a multi-faceted condition with a number of associated conditions so differ ences in variables such as the level of injury, chronicity and degree of impairments can influence the results
Michielsen et al. (2011)	• Inclusion and exclusion criteria are clearly described • Characteristics of the patients are clearly described • Large sample size (n= 40)	• Blinding of the patients or the physiotherapist was not possible because of the nature of the therapy • 8 drop-outs • The sample consisted mainly of nondominant hemisphere stroke

	• All participants were randomly assigned to either the experimental group receiving mirror therapy or the control group • Once a week under the supervision of a physiotherapist • Long-term follow-up (6 months)	
Moseley (2004)	• Inclusion and exclusion criteria are clearly described • Characteristics of the patients are clearly described • Control group cross-over • Patients were randomized by an independent investigator to the 6-week MIP treatment group or to ongoing medical management (control) using a random number table • All assessments were made by a separate investigator who was blind to experimental group and measurement occasion	• Small sample size (n=13) • The generalisability of findings to the wider CRPS1 population may be limited • It was not possible to blind patients to treatment group and there may have been a systematic effect introduced by simply participating in a research experiment, particularly considering the novel nature of the treatment and the volume of training involved • The follow-up period may not have been sufficient to determine the long-term effect of the treatment and did not permit evaluation of the MIP on work status or long-term quality of life
Moseley (2006)	• Inclusion and exclusion criteria are clearly described • Characteristics of the patients are clearly described (on the Neurology Web site at www.neurology.org)	• 1 drop-out • Short treatment duration (2 weeks)

	• Control group • Long-term follow-up (6 months) • Large sample size (n=51) • Patients were randomized via random number generation by an independent investigator, to a graded motor imagery program (experimental group) or to standard medical and physiotherapy care (control group), using a random numbers table • Prior to randomization, an independent investigator obtained several assessments	
Moseley (2007)	• Long-term follow-up (3 months) • Characteristics of the patients are clearly described	• Small sample size (n=5) • No control group • No gender equality (all men)
Özkul et al. (2015)	• Inclusion and exclusion criteria are clearly described • The patients were divided into two groups using a table of random numbers (group A, group B) • Cross-over after two weeks, with 1 week break	• Small sample size (n=24) • No gender equality (n=18 males) • No control group • No follow-up • Short treatment duration (2 weeks) • The limited numbers of patients, the diversity and heterogeneity of samples in terms of gender, age, level of injury, duration of injury, duration of pain could not be achieved
Pervane Vural et al. (2016)	• Inclusion and exclusion criteria are clearly described • Characteristics of the patients are clearly described	• Don’t use brain imaging techniques to reveal neuroplasticity precipitated by mirror therapy • They evaluated the clinical outcome scales only twice, before and 4 weeks after the therapy, and did not include follow-up evaluation

	• Large sample size (n=38) • Single-blinded, randomized controlled design • Patients were randomly assigned to the mirror therapy group or the control group using computer-generated random numbers • The assessments were performed by the same investigator, who was blinded to group allocation • Long-term follow-up (6 months)	• The effect of mirror therapy on other common symptoms of CRPS (eg, edema, allodynia) was also lacking • Couldn't evaluate the psychological signs of the patients and the psychological aspects of additional mirror therapy
Polli et al. (2017)	• Inclusion and exclusion criteria are clearly described • Two therapists were in charge of all the assessments, before and after intervention, and were blinded to treatments • The control treatment program was based on current standard practice protocols • No patients were lost during the protocol	• No follow-up • Small sample size (n=28) • No gender equality (n=21 males)
Sato et al. (2010)	• Characteristics of the patients are clearly described • A Personal computer-based desktop virtual reality system was developed for MVF therapy	• Small sample size (n=5) • No gender equality (n=4 females) • No follow-up • The design of the present study is an open-label case series with no control conditions
Soler et al. (2010)	• Inclusion and exclusion criteria are clearly described • Characteristics of the patients are clearly described • Large sample size (n=40)	• No gender equality (n= 31 males) • Short treatment duration (2 weeks)

	• Follow-up (12 weeks) • The one researcher, who was blind to the treatment interventions, performed all clinical evaluations • The other researcher, who applied the interventions, remained blind to the findings of the clinical evaluation • Assignment of the patients to the treatment interventions was random, and patients remained blinded to their treatment condition and the specific hypotheses of the study • Double-blind, placebo-controlled trial: patients were randomly assigned to one of four treatment groups • A computer-generated list was used as randomization strategy • They assessed patient blinding at the end of the trial by asking each patient to guess which treatment they believed to have received	
Sumitani et al. (2008)	• Characteristics of the patients are clearly described • Follow-up	• Small sample size (n=22) • No description on how they randomized the groups: selection bias
Walz et al. (2013)	• Long treatment duration (6 weeks) • Long-term follow-up (6 months) • This single-case design is strengthened by having a comparison participant, which controls for habituation to the testing and scanning but	• Small sample size (n=1) • No control group

	not for the many other aspects of an intervention that may have an effect	
Zangrando et al. (2015)	• Long treatment duration (3 months) • Long term follow-up (12 weeks) • Characteristics of the patients are clearly described • Data were collected by a blinded tester specialist in physical medicine and rehabilitation at the beginning of treatment (T0), at the end of treatment (3 months) (T1), and at the 3- month follow-up (T2)	• Small sample size (n=1) • Second outcome is pain • No control group

Table 5. Overview of studies						
Study	**Design**	**Sample size**	**Population**	**Intervention**	**Control conditions**	**Duration intervention**
Cacchio et al. (august 2009)	RCT	24	CRPS in stroke patiënts	MT + MI for arms	Covered MT for arms	4 weeks, 30 min daily
Cacchio et al. (october 2009)	RCT	48	CRPS in stroke patiënts	MT for upper limbs + conventional stroke rehabilitation program	Placebo-MI for upper limbs + conventional stroke rehabilitation program	4 weeks: First 2 weeks 30 min, last 2 weeks 1h sessions, 5x/week
Corbetta et al. (2018)	Case Report	1	Stroke	MT for left arm	N/A	45 mins, 5x/week, 2 weeks
Gustin et al. (2010)	Clinical Trail	30	SCI	MI for feet	N/A	7 days, 3x/day, 8 min
Gustin et al. (2008)	Clinical trial	15	SCI	MI for feet	N/A	7 days, 3x/day, 8min
Hasan et al. (2016)	Clinical Trial	5	SCI	MI + neurofeedback training	N/A	20-40 sessions (no time mentioned)
Kaur et al. (2020)	RCT	44	SCI	MI	To perform random addition task of 1-digit numbers through the software + listen to music of their choice	4 weeks, 5x/week, 30min
Michielsen et al. (2011)	RCT	40	Stroke (chronic)	MT	Exercise therapy with affected arm in sight	6 weeks, 5x/day, 1h + once a week
Mosely et al. (2004)	RCT	13	CRPS in stroke patiënts	Graded MI	Ongoing medical management	6 weeks: 2 weeks recognition of hand laterality (3x/waking hour), 2 weeks MI (3x/waking hour), MT (1x/waking hour)
Mosely et al. (2006)	RCT	51	CRPS in stroke patiënts + phantom limb pain	Graded MI	Standard medical and physiotherapy care	6 weeks: 2 weeks recognition of hand laterality, 2 weeks MI, 2 weeks MT all 2x/day
Mosely et al. (2007)	Clinical trial	5	SCI	Visual walking	Guided imagery + watching a film	3 weeks, 5x/week, 10min

Table 5. (Part 2) Overview of studies						
Study	**Design**	**Sample size**	**Population**	**Intervention**	**Control conditions**	**Duration intervention**
Özkul et al. (2015)	RCT	24	SCI	Visual walking	TENS	2 weeks, 5x/week, 15min
Pervane Vural et al. (2016)	RCT	30	CRPS in stroke patiënts	MT + conventional rehabilitation for stroke	Conventional rehabilitation for stroke	4 weeks, 5x/week, 2-4h/day conventional stroke rehabilitation + additional mirror therapy program for 30min/day
Polli et al. (2017)	RCT	28	Stroke	Graded MI for upper limbs	Conventional rehabilitation	4 weeks, 5x/week, 1h
Sato et al. (2010)	Pilot Study	5	CRPS in stroke patiënts	Virtual reality visual feedback therapy	N/A	5-8 weeks, once a week
Soler et al. (2010)	RCT	39	SCI	tDCS + visual illusion	Control illusion (movie)	2 weeks, 5x/week
Sumitani et al. (2008)	Preliminary Report	22	SCI (2) + single limb amputation (11) + brachial plexus lesion (6) + malignant tumour (1) + traumatic periferal nerve lesions (2)	MT	N/A	Mean 20.4 weeks, once a day, 10min (duration of weeks depended upon an individual basis)
Walz et al. (2013)	Case Report	1	CRPS in stroke patiënts	Graded MI	N/A	6 weeks: 2 weeks recognition of hand laterality (each waking hour), 2 weeks MI (each waking hour), MT (each waking hour) for 5-10min
Zangrando et al. (2015)	Case Report	1	PD	MI	N/A	3 months, 2x/week, 1h

Table 5. (Part 3) Overview of studies						
Study	**Pain outcome**	**Type of pain**	**Main pain outcome at baseline**	**Main pain outcome after treatment**	**Intervention vs control (>=<)**	**Main results**
Cacchio et al. (august 2009)	VAS (0-100mm)	CRPS	64mm	MT: 13mm MI: 81mm	MT intervention > Control MI intervention < Control	**MT has shown to be a succesful therapy for pain reduction in patients with CRPS1. However, MI was not.**
Cacchio et al. (october 2009)	VAS (0-10cm)	CRPS	At rest: 7.6cm On movement: 8.7cm Tactile allodynia: 6.8cm	At rest: 4.3cm On movement: 5.1 Tactile allodynia: 3.8	Intervention > Control	**Mirror therapy has shown to be succesful in the management of CRPS1 to relieve pain.**
Corbetta et al. (2018)	VAS (0-10cm)	Central neuropathic pain	Shoulder: 6.7cm Hand: 5.3cm	Shoulder: 5.5 Hand: 0.8	N/A	**After the two weeks of MT, the patient demonstrated a reduction in VAS pain score of the hand at rest and during a maximal squeeze hand contraction. At one-year follow-up, pain reduction was maintained and also extended to the shoulder.**
Gustin et al. (2010)	VAS (0-10cm)	Neuropathic pain	3.2cm	5.2cm	N/A	**MI either evoked pain in a previously non-painful region or evoked an increase in pain within the region of on-going pain in SCI patients.**
Gustin et al. (2008)	VAS (0-10cm)	Neuropathic pain	2.9cm	5cm	N/A	**MI may increase neuropathic pain and other sensations following SCI and may even induce pain in those who are otherwise symptom free.**
Hasan et al. (2016)	VNS (0 - 10)	Central neuropathic pain	7.4	4.8	N/A	**Reduction of CNP is accompanied by reduced cortical over-activity during movement imagination.**
Kaur et al. (2020)	NRS (0 - 10) + VAS	Neuropathic pain	NRS: 6.9 VAS: 5.5cm	NRS: 3.4 VAS: 2.8cm	Intervention > Control	**MI is an effective rehabilitative approach in improving central neuropathic pain in SCI.**
Michielsen et al. (2011)	VAS (0-100mm)	CRPS	9.3mm	8.8mm	Intervention = Control (both not significantly improved)	**MT-group improved on VAS, but not significantly. (Secundary outcome)**
Mosely et al. (2004)	NPS	Neuropathic pain	46	6 weeks: 20 12 weeks: 22	Intervention > Control	**The NPS-score reduced with 20 points after 6 weeks of the intervention.**
Mosely et al. (2006)	VAS	CRPS	/	-23.4mm	Intervention > Control	**The mean decrease in pain between pre- and post-treatment (100 mm visual analogue scale) was 23.4 mm for the motor imagery group and 10.5 mm for the control group. Improvement in function was similar and gains were maintained at 6-month follow-up.**
Mosely et al. (2007)	VAS (0-100mm)	Neuropathic pain	/	-42mm	Intervention > Control	**Virtual walking can be used in paraplegic patients to reduce pain.**

Table 5. (Part 4) Overview of studies						
Study	**Pain outcome**	**Type of pain**	**Main pain outcome at baseline**	**Main pain outcome after treatment**	**Intervention vs control (>=<)**	**Main results**
Özkul et al. (2015)	VAS (10cm)	Neuropathic pain	5,3cm	4,9cm	Intervention < Control	**Improvement rate of the two groups were similar after the treatments. The post-treatment pain intensity values were significantly lower than pre-treatment values in both groups all the treatment days. After the 6th session, TENS was superior to VI treatment. After 2 weeks, pain values were reduced in TENS group, but not significantly in the VI group.**
Pervane Vural et al. (2016)	VAS	CRPS	6cm	3cm	Intervention > Control	**In patients with stroke and simultaneous complex regional pain syndrome type 1, addition of mirror therapy to a conventional stroke rehabilitation program provides more improvement in motor functions of the upper limb and pain perception than conventional therapy without mirror therapy.**
Polli et al. (2017)	VAS (0-10cm) + FMA (pain section)	CRPS	VAS: 3.74 Pain-FMA: 19,6	VAS: 3.7 Pain-FMA: 21,9	Intervention > Control	**GMi is a feasible treatment for stroke patients with better outcomes than conventional therapy.**
Sato et al. (2010)	VAS (0-100mm)	CRPS	64mm		N/A	**Four of the five patients showed >50% reduction in pain intensity. Two of these patients ended their visits to the pain clinic after five sessions.**
Soler et al. (2010)	NRS	Neuropathic pain	tDCS + VI: 7.5 tDCS: 6.3 VI: 7.2 Placebo: 7.1	tDCS + VI: 5.2 (significant) tDCS: 5.3 VI: 6.4 (significant) Placebo: 6.6	Combined intervention > VI > tDCS > control	**The combination of transcranial direct current stimulation and visual illusion reduced the intensity of neuropathic pain significantly more than any of the single interventions. Patients receiving transcranial direct current stimulation and visual illusion experienced a significant improvement in all pain subtypes, while patients in the visual illusion group improved only in continuous pain and dysaesthesias. At 12 weeks after treatment, the combined treatment group still presented significant improvement on the overall pain intensity perception, whereas no improvements were reported in the other three groups.**
Sumitani et al. (2008)	NRS	Neuropathic pain	6.3	3.2	N/A	**The decrease in pain rating (NRS) of the patients with the MT was more than that of the patients without the MT**
Walz et al. (2013)	VAS (0-10cm)	CRPS	Movement evoked pain: 9.4cm Pain at rest: 8.5cm	Both movement evoked pain and pain at rest: <1cm after 6 weeks <5cm after 6 month follow-up	N/A	**Pain intensity decreased over the course of GMI, and relief was maintained at follow-up.**
Zangrando et al. (2015)	VAS	Central neuropathic pain	7cm	1.7cm after treatment 0.5 after 3 month follow-up	N/A	**Rehabilitation with motor imagery (MI) was proposed to bring back coherence between afferences at central level, which is needed to rebuild the body self and relieve the pain**

CRPS = complex regional pain syndome, SCI = spinal cord injury, PD = Parkinson's disease, MT = mirror therapy, MI = motor imagerty, tDCS = transcranial dirrect current stimulation, TENS = transcutaneous electrical nerve stimulation, VAS = visual analogue scale, VNS = visual numeric scale, NRS = numeric rating scale, FMA = Fugl-Meyer Assessment, NPS = neuropathic pain scale, VI = visual illusion, CNP: central neuropathic pain

1.4.3 Results data extraction

Mirror Therapy (MT)

Five studies investigating the effect of mirror therapy on patients with stroke were included. CRPS and central neuropathic pain were two types of investigated pain. The baseline characteristics were similar and there were no significant differences between the groups.

Cacchio et al. (2009a) prescribed an active-mirror therapy with a training of 30 minutes daily for four weeks. Participants of the study of Cacchio et al. (2009b) received an additional 30 minute training for the first two weeks on top of conventional physiotherapy. The last two weeks, the mirror therapy duration went up to one hour per session, five times a week. A 45 minute session, five days a week for two weeks is administered in the study of Corbetta et al. (2018). All patients participated in a six week training program, once a week under the supervision of a physiotherapist and practiced five times a week and one hour a day at home (Michielsen et al., 2011). A four week training program, five times a week for two to four hours (Pervane Vural et al., 2016). The protocol is not the same in each study. Cacchio and colleagues seated patients on a chair with a mirror, which is 70 x 120 cm, positioned between the upper limb perpendicular to the midline of the subject with the unaffected upper limb facing the reflective surface (Cacchio et al., 2009b). In the study of Pervane Vural et al. (2016), the patients were sitting on a chair close to a table. The mirror (35 x 35 cm) was vertically placed between the patient's upper limbs on a table. The unaffected limb was placed in front of the mirror. According to these findings, the set-up of the environment in each study was similar.

The study of Cacchio et al. (2009a) had three groups: the active-mirror group, the mental-imagery group and the covered-mirror group. In the covered-mirror group, patients had to perform the same exercises as the active mirror group, without being able to see the reflection of the non-painful arm. The baseline scores for pain were similar among the groups. After four weeks, the active-mirror group differed significantly from the other two groups in terms of pain. Patients switched to active

mirror therapy from either the covered-mirror group or the mental-imagery group after four weeks. This resulted in a significant reduction in pain. Before crossover, there was little reduction in pain. Mirror therapy reduced arm pain effectively in patients with stroke and chronic CRPS. Cacchio et al. (2009b) had a mirror group and a control group where the baseline characteristics were not significantly different between the groups. There were significant differences between the study and control groups after treatment. When the same parameter was compared before and after treatment within each group, a statistically significant reduction emerged in the mirror group both after treatment and at the 6-month follow-up. The results of this study supported the hypothesis that using a mirror can reduce the perception of pain in stroke patients with upper limb CRPSt1.

The study of Corbetta et al. (2018) examined one patient. After the mirror training, the patient showed a decrease in pain intensity during rest and maximal voluntary contraction of the trained hand. Michielsen et al. (2011) showed a slight improvement in pain on the VAS scores, yet these improvements were not significant. The study by Pervane Vural et al. (2016) worked with a mirror group and a control group. Both the mirror- as the control group, showed a significant improvement for VAS. Nonetheless, the mirror group scores improved more than those of the control group.

Motor Imagery (MI)

Ten studies were included with (graded) motor imagery as intervention. Study populations differed: spinal cord injury (Gustin et al. 2010; Gustin et al. 2008; Hasan et al. 2016; Kaur et al. 2020 and Sumitani et al. 2008), stroke (Mosely 2004; Mosely 2006; Polli et al. 2017 and Walz et al. 2013) and Parkinson's disease (Zangrando et al., 2015). In the study of Gustin et al. (2010) and Gustin et al. (2008), the patients had to train seven days a week, three times a day. The study of Hasan et al. (2016) prescribed 20 to 40 sessions. The study of Kaur et al. (2020) had a duration of 30 minutes for five days a week for four weeks. Patients of the studies of Mosely (2010) and Mosely (2004) had to train for six weeks. Twenty sessions of one hour over a four-week period is recommended in the study of Polli et al. (2017). Zangrando et al. (2015) had a

similar training duration, being 20 sessions for one hour, twice a week. In Sumitani et al. (2008), the patients trained for ten minutes every day.

The study of Gustin et al. (2010) and Gustin et al. (2008) had the same protocol. The patients had to imagine their right ankle moving as if they were stepping on the gas pedal of a car while listening to a recording of a car accelerating. There were strict instructions for the patients before the start of the training to imagine, yet not to attempt to move the foot. Pain was located below the neurological level of the spinal cord lesion in each patient (Gustin et al. 2010). Movement imagery evoked pain in eight out of 30 subjects. After the intervention, the pain decreased to baseline levels. Two patients reported no change in pain intensity during the imagery task. Most of them reported that they experienced pain in the areas of their bodies where they usually experience on-going pain. The groups in the study of Gustin et al. (2008) were similar in age (43 years old), level of SCI (T6) and time since injury (13 years). Six of the seven subjects with chronic pain had an increase in pain located within the area where their on-going pain usually occurred. Movement imagery evoked a greater increase in non-painful areas during the task than actually performing it.

The study of Hasan et al. (2016) had three groups: SCI patients with central neuropathic pain, SCI patients with no chronic pain, and able-bodied volunteers with no chronic pain. All groups followed the same protocol. However, the SCI patients with central neuropathic pain followed the intervention twice. The patients were seated 1,5 m in front of a computer monitor. They were then instructed to look at the monitor's center and respond to a series of visual cues. The first one was a readiness cue, which asked participants to stand still for four seconds. The second one was an initiation cue, which asked participants to point to the right, to the left or down and indicate the imagination of the right or left hand. They were then asked to perform the imaginary movements for three seconds. After 20-40 sessions, the pain, measured by the visual numeric scale (VNS) (0-10), dropped significantly from 7,4 to 4,8.

Kaur et al. (2020) had two groups, a mental imagery group and a control group. To prepare for the training, the participants were seated with their hands on the armrest of their chair or their lap. They were asked to place their feet on the footrest of their wheelchair or the floor. The software used for the laterality training was presented to the participants where they had to respond to stimuli according to the directions shown on the screen. Next, the guided imagery session started. Participants were asked to sit down and listen to a prerecorded audio script. They were told to close their eyes and follow the instructions carefully. After 4 weeks of intervention, significant changes were seen in patients' pain scores on the numeric rating scale and the visual analogue scale. The results showed that the mean total score of neuropathic pain symptoms decreased significantly in the group that received the intervention. Fifty-five percent of the patients in the mental imagery group reported that pain had greatly improved, 10% of the SCI patients reported maximal improvement in pain. However, 15% had no change in pain after the treatment.

The study of Mosely (2004) had two groups: the motor imagery treatment group and the control group. The protocol had three stages: recognition of hand laterality, imagined hand movements and mirror therapy. For the recognition of hand laterality task, 42 photos of a right hand were digitally mirrored to create an identical picture of a left hand. The images were then presented in random order in front of a monitor. Participants were asked to respond by pressing a button to indicate whether they recognized the hand. To perform imagined hand movements, patients were asked to place their hand in a random order and pretend to move it using the posture shown in a picture. The task was performed several times a day for 30 minutes. For the mirror movement, the patient was instructed to place their unaffected hand in front of the mirror and slowly adopt a posture that was shown in the pictures. They were asked to stop if they experienced an increase in pain. There were no differences in the pre-treatment status of groups. However, there were significant reductions in all three variables after the motor imagery program. The effect of the treatment on these measures remained for at least 6 weeks after the motor imagery program. Mosely (2006) had a control group and a graded motor imagery group; the protocol was the

same as Mosely (2004). For the graded motor imagery group, the mean decrease in pain over the last two days was 23,4 mm on the 100 mm VAS.

A control and experimental group were used in the study of Polli et al. (2017). There were three interventions: the implicit motor imagery, the explicit motor imagery, and mirror therapy. For the implicit motor imagery, the task involved the presentation of 60 images of right and left hands. The patients were required to select which hand they saw as a right or left one by clicking the respective buttons on a computer mouse. For the explicit motor imagery, they used the KVIQ. This is a series of movements that have to be imagined by the patient. The protocol of the mirror therapy intervention was identical to the study of Cacchio et al. (2009b). No significant correlation was found between implicit motor imagery and explicit motor imagery. The improvement in the Fugl-Meyer Assessment (FMA) pain section was statistically significant.

The intervention motor imagery by mirror visual feedback is used in the study of Sumitani et al. (2008). The patients were asked to look at the mirror and see if the image of their unaffected limb was reflected in the mirror. For ten minutes, they were asked to exercise their affected limb at their discretion. The subjective pain intensity of all patients was significantly reduced after the visuomotor imagery. The patients who had visuomotor imagery were significantly less likely to experience pain than those without it.

The study of Zangrando et al. (2015) was a case report which researched one Parkinson's disease patient. The patient needed to envision herself transitioning from a seated position to a standing position, to stride and stance phase, start of gait and gait on different paths and grounds. After performing these movements, the patient had to compare the imagined movements with the executed movements, so she could identify and correct the possible errors. Rehabilitation with movement imagery was proposed to bring back coherence between afferences at central level, which is needed to rebuild the body and relieve the pain.

Visual illusion

Three studies used the intervention 'visual illusion' with a population of spinal cord injury patients. The patients performed ten minutes of virtual walking during three weeks on 15 consecutive weekdays (Mosely, 2007). In the study of Özkul et al. (2015), the patients practiced a training of ten sessions for 15 minutes a day, five days a week for two weeks. The study of Soler et al. (2010) used the same training, although using slightly longer sessions, being 20 minutes. The protocol of all three studies is the same. While sitting in wheelchairs, normal chairs, or beds, the patients were asked to sit in front of a vertical mirror (150 cm x 52 cm) that was placed 2,5 meters away. A projector was used to show a film of an actor as he walked on a treadmill. The patients were then asked to watch the film of the actor as they moved their upper body according to the rhythm. It appeared to the patient as if they were watching themselves walk. (Mosely 2007; Özkul et al. 2015; Soler et al. 2010).

In the study of Mosely 2007 the patients performed three interventions for ten-minutes: virtual walking, guided imagery and watching an animated comedy film. The pain was not recorded during the guided imagery. The VAS during virtual walking decreased by ~65% (or 42 mm) (Mosely, 2007). During guided imagery the pain decreased by 18 mm and by 4 mm while watching the film (Mosely, 2007). Virtual walking had a greater effect than guided imagery in this study. In the study of Özkul et al. 2015 there were two groups. The first group performed a visual illusion intervention and the second got a TENS intervention. This study was a five-week cross-over study where group A underwent visual illusion for the first two weeks and group B got TENS applications for two weeks first. Then both groups have a one-week wash-out period and switched interventions for another two weeks. As a result, both groups underwent virtual illusion and TENS treatment. The results showed that the post-treatment pain intensity values were significantly lower than pre-treatment values in both groups all the treatment days. There is a significant decrease in pain intensity immediately after the application of TENS and virtual illusion in patients with SCI. In the study of Soler et al. 2010, the patients were randomized in four treatment groups: transcranial DCS + visual illusion group, transcranial DCS + control illusion group, transcranial DCS sham + visual illusion group and transcranial DCS sham + control

illusion group. The baseline measurements of pain intensity were similar in the four groups. The score for pain was significantly reduced after the last day of treatment for transcranial DCS and visual illusion patients. At the first follow-up visit, the pain scores were significantly lower in the transcranial DCS + visual illusion group. The sham intervention failed to produce these results. There was no difference between groups at the second follow up. The percentage of improvement was significantly different between the groups at the last follow-up. In the transcranial DCS + visual illusion group, a significant reduction of pain scores was found at the last day of treatment in comparison to baseline values. After the last day of treatment, the patients in the visual illusion group showed significant improvements in neuropathic pain intensity. The effect was not maintained at the follow-up. There were no significant changes in the placebo group and transcranial DCS group.

Virtual reality mirror visual feedback therapy

Exceptionally, the study of Sato et al. (2010) used the intervention virtual reality mirror visual feedback therapy. The included participants were stroke patients with complex regional pain syndrome. The intervention happened once a week for five to eight sessions. The imposed exercises were target-oriented motor control tasks. The exercises involved the movements of the affected side of the virtual hand. The subjects were then instructed to focus on the virtual hand's motion on the PC monitor. The patients aimed to close the fingers of the virtual hand around the target and got visual feedback. After that, the non-affected hand controlled the virtual hand's motion. The movements were made synchronously with both hands. The proprioception of the affected side was only returned when the hand was turned. It should be the same underlying mechanism as the original mirror box therapy. When using a mirror box, visual feedback comes from the reflected image in the mirror. When using the virtual reality mirror visual feedback therapy, however, the feedback comes from the computer screen.

All the patients reported spontaneous pain that increased with movement in the affected limb at baseline. The severity of the pain was assessed using the VAS score. In

four out of five patients, the pre-treatment value dropped by 50% (Sato et al., 2010). After eight treatment sessions, 80% of patients showed a 50% reduction in pain intensity (Sato et al., 2010). This level of effectiveness was achieved after the third treatment session.

The studies used the following pain measures VAS, VNS, NPS, NRS or FMA (pain section). The data extraction is covered in table 5.

1.5 Discussion

1.5.1 Reflection on the quality of the included studies

Quality assessments were made using the 'PEDro scale' (table 3). As discussed in section 1.4.2. Quality Assessment, most of the included articles scored a 'high quality' according to the PEDro scale. Only five articles scored 'fair quality' and the other five articles scored 'low quality'.

All of the included studies said 'yes' to items eight and nine in the PEDro scale. This meant that the measures of at least one key outcome in every study were obtained from more than 85% of the subjects initially allocated to groups and that all subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by "intention to treat".

Subjects were only randomly allocated to groups in nine studies (Cacchio et al. 2009a; Cacchio et al. 2009b; Kaur et al. 2020; Michielsen et al. 2011; Mosely 2004; Mosely 2006; Özkul et al. 2015; Soler et al. 2010 and Pervane Vural et al. 2016). The internal validity of the other studies was negatively affected. They had an increased risk of allocation bias. Some studies did not include a control group. Naturally, there was no concealed allocation. The allocation was concealed, however, in seven studies (Kaur et al. 2020; Michielsen et al. 2011; Mosely 2004; Mosely 2006; Özkul et al. 2015; Soler et al. 2010 and Pervane Vural et al. 2016).

Cacchio et al. (2009b), Hasan et al. (2016), Kaur et al. (2020), Michielsen et al. (2011), Mosely (2004), Mosely (2006), Özkul et al. (2015), Polli et al. (2017), Soler et al. (2010) and Pervane Vural et al. (2016) were studies where the groups were similar at baseline regarding the most important prognostic indicators.

Only in the study of Cacchio et al. (2009b) and Soler et al. (2010), there was blinding of all subjects. Polli et al. (2017), Soler et al. (2010) and Zangrando et al. (2015) had

blinding of all therapists who administered the therapy. In the studies of Cacchio et al. (2009b), Michielsen et al. (2011), Mosely (2004), Mosely (2006), Polli et al. (2017), Soler et al. (2010) and Pervane Vural et al. (2016), there was blinding of all assessors who measured at least one key outcome. In the remaining studies, the assessors were unblinded or they failed to mention blinding. This could result in a detection bias, which could jeopardize the internal validity of these studies.

The results of between-group statistical comparisons were not reported for at least one key outcome in the studies of Corbetta et al. (2018), Mosely (2007), Sato et al. (2010), Walz et al. (2013) and Zangrando et al. (2015). The studies did not provide both point measures and measures of variability for at least one key outcome (Cacchio et al. 2009a; Corbetta et al. 2018; Hasan et al. 2016; Sato et al. 2010; Walz et al. 2013 and Zangrando et al. 2015). This increased the risk of confounding bias and could negatively affect the ability to make the results interpretable.

1.5.2 Reflection on the findings in function of the research question

General findings

In this study, the effect of mirror therapy, (graded) motor imagery (possibly augmented by virtual reality) on pain in neurological conditions such as SCI, stroke, and Parkinson's Disease was studied. Nineteen studies were included using the search strategy. None of these studies had a population of TBI-, MS- or ALS-patients, or included action observation as an intervention. There was only one study found on Parkinson's disease, which was a case report. Therefore, there is no conclusion to be made about action observation or those three neurological conditions.

MT was only investigated on a population with SCI, stroke and/or CRPS. Hence, there cannot be a conclusion about the effectiveness of MT or MI on other neurological populations. All these studies on MT found a significant improvement in pain, except for the study of Michielsen et al. (2011). They detected an improvement in pain. Yet, this was not significant. One study even found the results to last up to the one-year-

follow-up. The pain reduction, originally intended for the hand, extended to the shoulder (Corbetta et al., 2018).

In the articles investigating MI, the population consisted of patients with CRPS, SCI and PD. According to a pilot study, MI could be an efficient way to reduce neuropathic pain in PD (Zangrado et al., 2015). However, not in CRPS (Cacchio et al., 2009a). The results were contradictory about the effect of MI on patients with SCI. The studies of Gustin et al. (2010) and Gustin et al. (2008) actually found MI to make pain worse in SCI. However, the studies of Hasan et al. (2016) and Kaur et al. (2020) found MI to be effective in reducing pain for patients with SCI, and these studies have a higher scientific level of evidence than the studies that report an increase in pain.

Graded motor imagery (GMI) was only studied in stroke patients with CRPS. All studies agreed that GMI was a feasible intervention to reduce pain for CRPS/stroke patients better than conventional therapy. Two studies showed that the release of pain was maintained at a follow-up after six months (Mosely, 2006; Walz et al., 2013)

The methods of the virtually enhanced mirror therapy were the same in the studies of Mosely 2007, Özkul et al. 2015 and Soler et al., 2010. These interventions focused on the lower extremities on SCI patients while the study of Sato et al. (2010) investigated the effect on the upper extremities in CRPS patients. Mosely (2007) and Sato et al. (2010) found these virtually enhanced mirror therapy interventions to have a reducing effect on pain in SCI and CRPS patients. Özkul et al. (2019) found that TENS had a better effect on pain in patients with SCI than the virtually enhanced mirror therapy. Soler et al. (2010) concluded that the combination of the virtually enhanced MT with transcranial direct current stimulation (tDCS) is superior to single treatments or the control group for patients with SCI.

There were no articles discussing the effect of AO on pain in any neurological disease.

1.5.3 Reflection on the strengths and weaknesses of the literature study

The literature study conducted for the master's thesis has its strengths and weaknesses. In terms of strengths, this is the first review on the effect of MI, MT and AO in neurological populations. Cuenca-Martínez are currently investigating the effect on pain of the interventions. However, they include a broader population where the neurological population is only part of it.

When looking at the limitations of this study, it is noted that the research question describes a broad neurological population. However, nothing was found about MS-, TBI- and ALS-patients. Only one study was found on Parkinson's disease, which is limited. The included studies with low scientific evidence such as case reports, clinical trials, pilot studies, preliminary reports and case studies did not have a control group. A final limitation of this study could be that some of the included studies contained combined interventions. Yet, all of the studies that combined different interventions published their results on pain separately for each intervention (Cacchio et al. 2009b; Hasan et al. 2016; Solet et al. 2010). Therefore, this should not compromise the results for the interventions of our interest.

1.5.4 Recommendations for further research

Further research is needed on the long-term effects of mirror therapy, motor imagery and action observation on pain in neurological conditions. Studies should be done on this topic with a larger sample size, higher quality and rigorous methods. Sufficient power will be needed to demonstrate differences in groups. There should not only be control groups, but attention controls or sham interventions. Possibly with another, more subjective outcome measure, such as pressure pain. The VAS scale is known for its subjectivity (which is also a strength), however this makes it difficult to measure, as it is strongly influenced by contextual factors and placebo. It would be interesting to have studies on a specific neurological population that have not been researched before, such as ALS, MS of TBI.

1.6 Conclusion

The current literature suggested that MT is an adequate way to reduce pain in patients with CRPS after stroke or with SCI. Graded MI has proven to be efficient for reducing pain in patients with CRPS after stroke. However, the literature was contradictory about whether normal MI helps limit or even provokes pain in SCI or CRPS. Virtually enhanced MT improved pain in patients with SCI and CRPS, but for SCI patients, TENS or the combination of the virtually enhanced MT and tDCS may work better to reduce pain.

1.7 List of references

- Cruz-Almeida, Y., Felix, E. R., Martinez-Arizala, A., & Widerström-Noga, E. G. (2009). Pain Symptom Profiles in Persons with Spinal Cord Injury. *Pain Medicine*, *10*(7), 1246–1259. https://doi.org/10.1111/j.1526-4637.2009.00713.x
- Decety J. (1996). Neural representations for action. *Reviews in the neurosciences*, *7*(4), 285–297. https://doi.org/10.1515/revneuro.1996.7.4.285
- Ehde, D., Osborne, T., Hanley, M., Jensen, M., & Kraft, G. (2006). The scope and nature of pain in persons with multiple sclerosis. *Multiple Sclerosis*. Published. https://doi.org/10.1191/1352458506ms1292oa
- Hanisch, F., Skudlarek, A., Berndt, J., & Kornhuber, M. E. (2015). Characteristics of pain in amyotrophic lateral sclerosis. *Brain and Behavior*, *5*(3). https://doi.org/10.1002/brb3.296
- Heremans, E., Helsen, W. F., De Poel, H. J., Alaerts, K., Meyns, P., & Feys, P. (2009). Facilitation of motor imagery through movement-related cueing. *Brain Research*, *1278*, 50–58. https://doi.org/10.1016/j.brainres.2009.04.041
- Irvine, K. A., & Clark, J. D. (2017). Chronic Pain After Traumatic Brain Injury: Pathophysiology and Pain Mechanisms. *Pain Medicine*, *19*(7), 1315–1333. https://doi.org/10.1093/pm/pnx153
- Kandel, E. R., Mack, S., Jessell, T. M., Schwartz, J. H., Siegelbaum, S. A., & Hudspeth, A. J. (2013). *Principles of Neural Science, Fifth Edition*. McGraw-Hill Education.
- Khoury, S., & Benavides, R. (2018). Pain with traumatic brain injury and psychological disorders. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *87*, 224–233. https://doi.org/10.1016/j.pnpbp.2017.06.007
- O'Connor, A. B., Schwid, S. R., Herrmann, D. N., Markman, J. D., & Dworkin, R. H. (2008). Pain associated with multiple sclerosis: Systematic review and proposed classification. *Pain*, *137*(1), 96–111. https://doi.org/10.1016/j.pain.2007.08.024

- Siddal P, Yezierski RP, Loeser JD. Taxonomy and epidemiology of spinal cord injury pain. In: Yezierski BKJR, editor. Progress in pain research and management 2002;vol. 23. Seattle: IASP Press; 2002. p. 9–23.
- Siddall, P. J., McClelland, J. M., Rutkowski, S. B., & Cousins, M. J. (2003). A longitudinal study of the prevalence and characteristics of pain in the first 5 years following spinal cord injury. *Pain*, *103*(3), 249–257. https://doi.org/10.1016/s0304-3959(02)00452-9
- Stevens, J. A., & Stoykov, M. E. (2003). Using motor imagery in the rehabilitation of hemiparesis. *Archives of physical medicine and rehabilitation*, *84*(7), 1090–1092. https://doi.org/10.1016/s0003-9993(03)00042-x
- Terminology I. International Association for the Study of Pain, https://www.iasp-pain.org/Education/ Content.aspx?ItemNumber=1698&navItemNumber= 576#Pain (2019, accessed 20 September 2019).
- Thieme, H., Morkisch, N., Rietz, C., Dohle, C., & Borgetto, B. (2016). The Efficacy of Movement Representation Techniques for Treatment of Limb Pain—A Systematic Review and Meta-Analysis. *The Journal of Pain*, *17*(2), 167–180. https://doi.org/10.1016/j.jpain.2015.10.015
- 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., . . . 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. https://doi.org/10.1097/j.pain.0000000000001384
- Truini, A., Galeotti, F., La Cesa, S., Di Rezze, S., Biasiotta, A., Di Stefano, G., Tinelli, E., Millefiorini, E., Gatti, A., & Cruccu, G. (2012). Mechanisms of pain in multiple sclerosis: A combined clinical and neurophysiological study. *Pain*, *153*(10), 2048–2054. https://doi.org/10.1016/j.pain.2012.05.024
- Yekutiel, M. (2000). *Sensory Re-Education of the Hand after Stroke*. Wiley.

- Yilmazer, C., Lamers, I., Solaro, C., & Feys, P. (2020). Clinical perspective on pain in multiple sclerosis. *Multiple Sclerosis Journal*, 135245852095201. https://doi.org/10.1177/1352458520952015

Articles included from the literature search

(*) Included in review

- Aggarwal, N. K. (2013). Mirror Therapy for Facial Paralysis in Traditional South Asian Islamic Medicine. *Journal of the History of the Neurosciences*, *22*(1), 1–5. https://doi.org/10.1080/0964704x.2011.649137
- Andriţoi, D., Corciovă, C., Luca, C., Matei, D., & Ciorap, R. (2017). Heart Rate Dynamics Study on the Impact of “Mirror Therapy” in Patients with Stroke. *International Conference on Advancements of Medicine and Health Care through Technology; 12th - 15th October 2016, Cluj-Napoca, Romania*, 21–24. https://doi.org/10.1007/978-3-319-52875-5_5
- Bartur, G., Pratt, H., Frenkel-Toledo, S., & Soroker, N. (2018). Neurophysiological effects of mirror visual feedback in stroke patients with unilateral hemispheric damage. *Brain Research*, *1700*, 170–180. https://doi.org/10.1016/j.brainres.2018.09.003
- Bolognini, N., Russo, C., & Vallar, G. (2015). Crossmodal illusions in neurorehabilitation. *Frontiers in Behavioral Neuroscience*, *9*. https://doi.org/10.3389/fnbeh.2015.00212
- (*) Cacchio, A., De Blasis, E., De Blasis, V., Santilli, V., & Spacca, G. (2009a). Mirror Therapy in Complex Regional Pain Syndrome Type 1 of the Upper Limb in Stroke Patients. *Neurorehabilitation and Neural Repair*, *23*(8), 792–799. https://doi.org/10.1177/1545968309335977
- (*) Cacchio, A., De Blasis, E., Necozione, S., Orio, F. D., & Santilli, V. (2009b). Mirror Therapy for Chronic Complex Regional Pain Syndrome Type 1 and Stroke. *New England Journal of Medicine*, *361*(6), 634–636. https://doi.org/10.1056/nejmc0902799
- (*) Corbetta, D., Sarasso, E., Agosta, F., Filippi, M., & Gatti, R. (2018). Mirror therapy for an adult with central post-stroke pain: a case report. *Archives of Physiotherapy*, *8*(1). https://doi.org/10.1186/s40945-018-0047-y

- Crosby, L. D., Marrocco, S., Brown, J., & Patterson, K. K. (2016). A novel bilateral lower extremity mirror therapy intervention for individuals with stroke. *Heliyon*, *2*(12), e00208. https://doi.org/10.1016/j.heliyon.2016.e00208
- de Morton N. A. (2009). The PEDro scale is a valid measure of the methodological quality of clinical trials: a demographic study. *The Australian journal of physiotherapy*, *55*(2), 129–133. https://doi.org/10.1016/s0004-9514(09)70043-1
- Diers, M., Kamping, S., Kirsch, P., Rance, M., Bekrater-Bodmann, R., Foell, J., Trojan, J., Fuchs, X., Bach, F., Maaß, H., Çakmak, H., & Flor, H. (2015). Illusion-related brain activations: A new virtual reality mirror box system for use during functional magnetic resonance imaging. *Brain Research*, *1594*, 173–182. https://doi.org/10.1016/j.brainres.2014.11.001
- Ding, L., Wang, X., Guo, X., Chen, S., Wang, H., Cui, X., Rong, J., & Jia, J. (2019). Effects of camera-based mirror visual feedback therapy for patients who had a stroke and the neural mechanisms involved: protocol of a multicentre randomised control study. *BMJ Open*, *9*(3), e022828. https://doi.org/10.1136/bmjopen-2018-022828
- Fardo, F., Allen, M., Jegindø, E. M. E., Angrilli, A., & Roepstorff, A. (2015). Neurocognitive evidence for mental imagery-driven hypoalgesic and hyperalgesic pain regulation. *NeuroImage*, *120*, 350–361. https://doi.org/10.1016/j.neuroimage.2015.07.008
- Fukumori, S., Gofuku, A., Isatake, K., & Sato, K. (2014). Mirror thrapy system based virtual reality for chronic pain in home use. *IECON 2014 - 40th Annual Conference of the IEEE Industrial Electronics Society*. Published. https://doi.org/10.1109/iecon.2014.7049106
- Guo, J., Qian, S., Wang, Y., & Xu, A. (2019). Clinical study of combined mirror and extracorporeal shock wave therapy on upper limb spasticity in poststroke patients. *International Journal of Rehabilitation Research*, *42*(1), 31–35. https://doi.org/10.1097/mrr.0000000000000316
- (*) Gustin, S. M., Wrigley, P. J., Gandevia, S. C., Middleton, J. W., Henderson, L. A., & Siddall, P. J. (2008). Movement imagery increases pain in people with

neuropathic pain following complete thoracic spinal cord injury. *Pain*, *137*(2), 237–244. https://doi.org/10.1016/j.pain.2007.08.032

- (*) Gustin, S. M., Wrigley, P. J., Henderson, L. A., & Siddall, P. J. (2010). Brain circuitry underlying pain in response to imagined movement in people with spinal cord injury. *Pain*, *148*(3), 438–445. https://doi.org/10.1016/j.pain.2009.12.001
- (*) Hasan, M. A., Fraser, M., Conway, B. A., Allan, D. B., & Vučković, A. (2016). Reversed cortical over-activity during movement imagination following neurofeedback treatment for central neuropathic pain. *Clinical Neurophysiology*, *127*(9), 3118–3127. https://doi.org/10.1016/j.clinph.2016.06.012
- Hoermann, S., Ferreira dos Santos, L., Morkisch, N., Jettkowski, K., Sillis, M., Devan, H., Kanagasabai, P. S., Schmidt, H., Krüger, J., Dohle, C., Regenbrecht, H., Hale, L., & Cutfield, N. J. (2017). Computerised mirror therapy with Augmented Reflection Technology for early stroke rehabilitation: clinical feasibility and integration as an adjunct therapy. *Disability and Rehabilitation*, *39*(15), 1503–1514. https://doi.org/10.1080/09638288.2017.1291765
- (*) Kaur, J., Ghosh, S., Sahani, A. K., & Sinha, J. K. (2020). Mental Imagery as a Rehabilitative Therapy for Neuropathic Pain in People With Spinal Cord Injury: A Randomized Controlled Trial. *Neurorehabilitation and Neural Repair*, *34*(11), 1038–1049. https://doi.org/10.1177/1545968320962498
- (*) Michielsen, M. E., Selles, R. W., van der Geest, J. N., Eckhardt, M., Yavuzer, G., Stam, H. J., Smits, M., Ribbers, G. M., & Bussmann, J. B. (2010). Motor Recovery and Cortical Reorganization After Mirror Therapy in Chronic Stroke Patients. *Neurorehabilitation and Neural Repair*, *25*(3), 223–233. https://doi.org/10.1177/1545968310385127
- Mirela Cristina, L., Matei, D., Ignat, B., & Popescu, C. D. (2015). Mirror therapy enhances upper extremity motor recovery in stroke patients. *Acta Neurologica Belgica*, *115*(4), 597–603. https://doi.org/10.1007/s13760-015-0465-5
- (*) Moseley, G. L. (2006). Graded motor imagery for pathologic pain: A randomized controlled trial. *Neurology*, *67*(12), 2129–2134. https://doi.org/10.1212/01.wnl.0000249112.56935.32

- (*) Moseley, L. G. (2004). Graded motor imagery is effective for long-standing complex regional pain syndrome: a randomised controlled trial. *Pain*, *108*(1), 192–198. https://doi.org/10.1016/j.pain.2004.01.006
- (*) Moseley, L. G. (2007). Using visual illusion to reduce at-level neuropathic pain in paraplegia. *Pain*, *130*(3), 294–298. https://doi.org/10.1016/j.pain.2007.01.007
- Noh, J. S., Lim, J. H., Choi, T. W., Jang, S. G., & Pyun, S. B. (2019). Effects and safety of combined rTMS and action observation for recovery of function in the upper extremities in stroke patients: A randomized controlled trial. *Restorative Neurology and Neuroscience*, *37*(3), 219–230. https://doi.org/10.3233/rnn-180883
- Osinski, T., Martinez, V., Bensmail, D., Hatem, S., & Bouhassira, D. (2020). Interplay between body schema, visuospatial perception and pain in patients with spinal cord injury. *European Journal of Pain*, *24*(7), 1400–1410. https://doi.org/10.1002/ejp.1600
- (*) Özkul, A., Kılınç, M., Yıldırım, S. A., Topçuoğlu, E. Y., & Akyüz, M. (2015). Effects of visual illusion and transcutaneous electrical nerve stimulation on neuropathic pain in patients with spinal cord injury: A randomised controlled cross-over trial. *Journal of Back and Musculoskeletal Rehabilitation*, *28*(4), 709–719. https://doi.org/10.3233/bmr-140573
- (*) Pervane Vural, S., Nakipoglu Yuzer, G. F., Sezgin Ozcan, D., Demir Ozbudak, S., & Ozgirgin, N. (2016). Effects of Mirror Therapy in Stroke Patients With Complex Regional Pain Syndrome Type 1: A Randomized Controlled Study. *Archives of Physical Medicine and Rehabilitation*, *97*(4), 575–581. https://doi.org/10.1016/j.apmr.2015.12.008
- (*) Polli, A., Moseley, G. L., Gioia, E., Beames, T., Baba, A., Agostini, M., Tonin, P., & Turolla, A. (2017). Graded motor imagery for patients with stroke: a non-randomized controlled trial of a new approach. *European journal of physical and rehabilitation medicine*, *53*(1), 14–23. https://doi.org/10.23736/S1973-9087.16.04215-5
- Radajewska, A., Opara, J., Małecki, A., & Szczygieł, J. (2013). The effects of mirror therapy on arm and hand function in subacute stroke inpatients. *Journal*

of the Neurological Sciences, *333*, e563. https://doi.org/10.1016/j.jns.2013.07.1974

- (*) Sato, K., Fukumori, S., Matsusaki, T., Maruo, T., Ishikawa, S., Nishie, H., Takata, K., Mizuhara, H., Mizobuchi, S., Nakatsuka, H., Matsumi, M., Gofuku, A., Yokoyama, M., & Morita, K. (2010). Nonimmersive Virtual Reality Mirror Visual Feedback Therapy and Its Application for the Treatment of Complex Regional Pain Syndrome: An Open-Label Pilot Study. *Pain Medicine*, *11*(4), 622–629. https://doi.org/10.1111/j.1526-4637.2010.00819.x
- Scandola, M., Aglioti, S. M., Avesani, R., Bertagnoni, G., Marangoni, A., & Moro, V. (2017). Corporeal illusions in chronic spinal cord injuries. *Consciousness and Cognition*, *49*, 278–290. https://doi.org/10.1016/j.concog.2017.01.010
- Scandola, M., Aglioti, S. M., Pozeg, P., Avesani, R., & Moro, V. (2016). Motor imagery in spinal cord injured people is modulated by somatotopic coding, perspective taking, and post-lesional chronic pain. *Journal of Neuropsychology*, *11*(3), 305–326. https://doi.org/10.1111/jnp.12098
- (*) Soler, M. D., Kumru, H., Pelayo, R., Vidal, J., Tormos, J. M., Fregni, F., Navarro, X., & Pascual-Leone, A. (2010). Effectiveness of transcranial direct current stimulation and visual illusion on neuropathic pain in spinal cord injury. *Brain*, *133*(9), 2565–2577. https://doi.org/10.1093/brain/awq184
- (*) Sumitani, M., Miyauchi, S., McCabe, C. S., Shibata, M., Maeda, L., Saitoh, Y., Tashiro, T., & Mashimo, T. (2008). Mirror visual feedback alleviates deafferentation pain, depending on qualitative aspects of the pain: a preliminary report. *Rheumatology*, *47*(7), 1038–1043. https://doi.org/10.1093/rheumatology/ken170
- Vučković, A., Jarjees, M., Abul Hasan, M., Miyakoshi, M., & Fraser, M. (2018). Central neuropathic pain in paraplegia alters movement related potentials. *Clinical Neurophysiology*, *129*(8), 1669–1679. https://doi.org/10.1016/j.clinph.2018.05.020
- (*) Walz, A. D., Usichenko, T., Moseley, G. L., & Lotze, M. (2013). Graded Motor Imagery and the Impact on Pain Processing in a Case of CRPS. *The Clinical Journal of Pain*, *29*(3), 276–279. https://doi.org/10.1097/ajp.0b013e318250f4e8

- Yavuzer, G., Selles, R., Sezer, N., Sütbeyaz, S., Bussmann, J. B., Köseoğlu, F., Atay, M. B., & Stam, H. J. (2008). Mirror Therapy Improves Hand Function in Subacute Stroke: A Randomized Controlled Trial. *Archives of Physical Medicine and Rehabilitation*, *89*(3), 393–398. https://doi.org/10.1016/j.apmr.2007.08.162
- (*) Zangrando, F., Piccinini, G., Pelliccioni, A., Saraceni, V. M., & Paolucci, T. (2015). Neurocognitive Rehabilitation in Parkinson's Disease with Motor Imagery: A Rehabilitative Experience in a Case Report. *Case Reports in Medicine*, *2015*, 1–4. https://doi.org/10.1155/2015/670385

Articles excluded from the literature search

Requestable appendix.

1.8 Appendices

Appendix 1: Search strategy

Table 1.

Search strategy

Keywords in the search bar	# hits in PubMed
Intervention	
Title/abstract	
Motor imagery	3294
Action observation	1490
Mirror therapy	407
Outcome	
MeSH terms	
Pain	421783
Title/abstract	
Pain	700618
Population	
MeSH terms	
Spinal cord injury	1649
Sclerosis*	9129
Tbi traumatic brain injury	3563
Parkinson disease	71796
Brain infarction	40528
Cerebral hemorrhage	35797
Cerebral hematoma	64098
Cva cerebrovascular accident	393569
Title/abstract	
Spinal cord injury	392020
Sclerosis*	154807
Stroke	275580
Cerebral infarction	16056
Brain infarction	2651
Cerebral hemorrhage	7651
Cerebral hematoma	210
Complete literature search	

(("motor imagery"[Title/Abstract]) OR ("action observation"[Title/Abstract])) OR ("mirror therapy"[Title/Abstract])) AND ("pain"[MeSH Terms]) OR ("pain"[Title/Abstract]) AND ((((((((((((spinal cord injury[MeSH Terms]) OR (sclerosis*[MeSH Terms])) OR (tbi traumatic brain injury[MeSH Terms])) OR (parkinson disease[MeSH Terms])) OR (brain infarction[MeSH Terms])) OR (cerebral hemorrhage[MeSH Terms])) OR (cerebral hematoma[MeSH Terms])) OR (cva cerebrovascular accident[MeSH Terms])) OR (spinal cord injury[Title/Abstract])) OR (sclerosis*[Title/Abstract])) OR (stroke[Title/Abstract])) OR (cerebral infarction[Title/Abstract])) OR (brain infarction[Title/Abstract])) OR (cerebral hemorrhage[Title/Abstract]) OR (cerebral hematoma[Title/Abstract])	1367
Keywords in the search bar	# hits in WOS
Intervention	
Topic	
Motor imagery	8364
Action observation	42603
Mirror therapy	3773
Outcome	
Topic	
Pain	670268
Population	
Topic	
Spinal cord injury	71727
Sclerosis*	210705
Tbi	29146
Traumatic brain injury	66933
Parkinson disease	129194
Brain infarction	24280
Cerebral hemorrhage	40900
Cerebral hematoma	5263
Cva	3801
Cerebrovascular accident	7307
Stroke	375947
Cerebral infarction	34723
Complete literature search	
(((TS= motor imagery OR TS= action observation OR TS= mirror therapy) AND (TS= pain) AND (TS= spinal cord injury OR TS= sclerosis* OR TS= tbi OR TS= traumatic brain injury OR TS= parkinson disease OR TS= brain infarction OR TS= cerebral hemorrhage OR TS= cerebral hematoma OR TS= cva OR TS= cerebrovascular accident OR TS= stroke OR TS= cerebral infarction)))	229

Appendix 2: PEDro scale

PEDro scale

1.	eligibility criteria were specified	no ❑ yes ❑ where:
2.	subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received)	no ❑ yes ❑ where:
3.	allocation was concealed	no ❑ yes ❑ where:
4.	the groups were similar at baseline regarding the most important prognostic indicators	no ❑ yes ❑ where:
5.	there was blinding of all subjects	no ❑ yes ❑ where:
6.	there was blinding of all therapists who administered the therapy	no ❑ yes ❑ where:
7.	there was blinding of all assessors who measured at least one key outcome	no ❑ yes ❑ where:
8.	measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups	no ❑ yes ❑ where:
9.	all subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by "intention to treat"	no ❑ yes ❑ where:
10.	the results of between-group statistical comparisons are reported for at least one key outcome	no ❑ yes ❑ where:
11.	the study provides both point measures and measures of variability for at least one key outcome	no ❑ yes ❑ where:

The PEDro scale is based on the Delphi list developed by Verhagen and colleagues at the Department of Epidemiology, University of Maastricht (*Verhagen AP et al (1998). The Delphi list: a criteria list for quality assessment of randomised clinical trials for conducting systematic reviews developed by Delphi consensus. Journal of Clinical Epidemiology, 51(12):1235-41*). The list is based on "expert consensus" not, for the most part, on empirical data. Two additional items not on the Delphi list (PEDro scale items 8 and 10) have been included in the PEDro scale. As more empirical data comes to hand it may become possible to "weight" scale items so that the PEDro score reflects the importance of individual scale items.

The purpose of the PEDro scale is to help the users of the PEDro database rapidly identify which of the known or suspected randomised clinical trials (ie RCTs or CCTs) archived on the PEDro database are likely to be internally valid (criteria 2-9), and could have sufficient statistical information to make their results interpretable (criteria 10-11). An additional criterion (criterion 1) that relates to the external validity (or "generalisability" or "applicability" of the trial) has been retained so that the Delphi list is complete, but this criterion will not be used to calculate the PEDro score reported on the PEDro web site.

The PEDro scale should not be used as a measure of the "validity" of a study's conclusions. In particular, we caution users of the PEDro scale that studies which show significant treatment effects and which score highly on the PEDro scale do not necessarily provide evidence that the treatment is clinically useful. Additional considerations include whether the treatment effect was big enough to be clinically worthwhile, whether the positive effects of the treatment outweigh its negative effects, and the cost-effectiveness of the treatment. The scale should not be used to compare the "quality" of trials performed in different areas of therapy, primarily because it is not possible to satisfy all scale items in some areas of physiotherapy practice.

Last amended June 21st, 1999

Notes on administration of the PEDro scale:

All criteria	**Points are only awarded when a criterion is clearly satisfied**. If on a literal reading of the trial report it is possible that a criterion was not satisfied, a point should not be awarded for that criterion.
Criterion 1	This criterion is satisfied if the report describes the source of subjects and a list of criteria used to determine who was eligible to participate in the study.
Criterion 2	A study is considered to have used random allocation if the report states that allocation was random. The precise method of randomisation need not be specified. Procedures such as coin-tossing and dice-rolling should be considered random. Quasi-randomisation allocation procedures such as allocation by hospital record number or birth date, or alternation, do not satisfy this criterion.
Criterion 3	*Concealed allocation* means that the person who determined if a subject was eligible for inclusion in the trial was unaware, when this decision was made, of which group the subject would be allocated to. A point is awarded for this criteria, even if it is not stated that allocation was concealed, when the report states that allocation was by sealed opaque envelopes or that allocation involved contacting the holder of the allocation schedule who was "off-site".
Criterion 4	At a minimum, in studies of therapeutic interventions, the report must describe at least one measure of the severity of the condition being treated and at least one (different) key outcome measure at baseline. The rater must be satisfied that the groups' outcomes would not be expected to differ, on the basis of baseline differences in prognostic variables alone, by a clinically significant amount. This criterion is satisfied even if only baseline data of study completers are presented.
Criteria 4, 7-11	*Key outcomes* are those outcomes which provide the primary measure of the effectiveness (or lack of effectiveness) of the therapy. In most studies, more than one variable is used as an outcome measure.
Criterion 5-7	*Blinding* means the person in question (subject, therapist or assessor) did not know which group the subject had been allocated to. In addition, subjects and therapists are only considered to be "blind" if it could be expected that they would have been unable to distinguish between the treatments applied to different groups. In trials in which key outcomes are self-reported (eg, visual analogue scale, pain diary), the assessor is considered to be blind if the subject was blind.
Criterion 8	This criterion is only satisfied if the report explicitly states *both* the number of subjects initially allocated to groups *and* the number of subjects from whom key outcome measures were obtained. In trials in which outcomes are measured at several points in time, a key outcome must have been measured in more than 85% of subjects at one of those points in time.
Criterion 9	An *intention to treat* analysis means that, where subjects did not receive treatment (or the control condition) as allocated, and where measures of outcomes were available, the analysis was performed as if subjects received the treatment (or control condition) they were allocated to. This criterion is satisfied, even if there is no mention of analysis by intention to treat, if the report explicitly states that all subjects received treatment or control conditions as allocated.
Criterion 10	A *between-group* statistical comparison involves statistical comparison of one group with another. Depending on the design of the study, this may involve comparison of two or more treatments, or comparison of treatment with a control condition. The analysis may be a simple comparison of outcomes measured after the treatment was administered, or a comparison of the change in one group with the change in another (when a factorial analysis of variance has been used to analyse the data, the latter is often reported as a group × time interaction). The comparison may be in the form hypothesis testing (which provides a "p" value, describing the probability that the groups differed only by chance) or in the form of an estimate (for example, the mean or median difference, or a difference in proportions, or number needed to treat, or a relative risk or hazard ratio) and its confidence interval.
Criterion 11	A *point measure* is a measure of the size of the treatment effect. The treatment effect may be described as a difference in group outcomes, or as the outcome in (each of) all groups. *Measures of variability* include standard deviations, standard errors, confidence intervals, interquartile ranges (or other quantile ranges), and ranges. Point measures and/or measures of variability may be provided graphically (for example, SDs may be given as error bars in a Figure) as long as it is clear what is being graphed (for example, as long as it is clear whether error bars represent SDs or SEs). Where outcomes are categorical, this criterion is considered to have been met if the number of subjects in each category is given for each group.

Part 2: Research protocol

2.1 Introduction

People with multiple sclerosis (pwMS) report their pain as one of the most irritating symptoms of their disease (Harrison, Bogosian, Silber, McCracken, &Moss-Morris, 2015; Rae-Grant, Eckert, Bartz, &Reed, 1999). It is an underestimated symptom of multiple sclerosis (MS), while being a chronic unpleasant feeling (Brola, Motisek-Szewcyk, &Opara, 2014). It additionally meddles with activity of daily living (ADL), quality of life (QoL), sleep and work ability in MS (Beiske, Pedersen, Czujko, &Myhr, 2004; Svendsen, Jensen, Overad, Hansen, Koch-Hendriksen, &Bach, 2003; O'Connor, Schwid, Herrmann, Markman, &Dworkin, 2008; Shahrbanian, Auais, Duquette, Andersen, &Mayo, 2013).

Pain is classified as nociceptive, neuropathic, nociplastic and mixed, based on underlying mechanisms (Yilmazer, Lamers, Solaro, &Feys, 2020). Nociceptive pain is defined by the International Association for the Study of Pain (IASP) as "Pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors." (Terminology., 2019). A noxious insult to non-neural tissue stimulates nociceptors in nociceptive pain. Through the lateral and medial nociceptive pathways, the stimulation is carried through the spinal cord to the thalamus and mainly to the somatosensory cortex. A direct injury to the central or peripheral nervous system is present in neuropathic pain. Usually with a feeling of burning and electrical sensations accompany (Kandel, Schwartz, &Jessell., 2013). Neuropathic pain is defined as "Pain caused by a lesion or disease of the somatosensory nervous system." (Terminology., 2019). According to the disease or the location of the lesion, neuropathic pain can be divided into two types, namely peripheral or central neuropathic pain (Terminology., 2019). The binary classification, nociceptive and neuropathic, of pain doesn't cover all circumstances (Kosek et al., 2016). Nociplastic pain is defined by IASP as ""Pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral

nociceptors or evidence for disease or lesion of the somatosensory system causing the pain." (Terminology., 2019). The combination of multiple types of pain is mixed pain (nociceptive, neuropathic and nociplastic). It is seen in the same body area (Freynhagen et al., 2019). However, none of the pain classifications of the IASP have been investigated in MS yet (Yilmazer et al., 2020).

Mirror therapy (MT) is a kind of mental practice. It activates the primary motor cortex and brings out movement of the affected side as patients see movement of the non-affected side in the mirror (Garry, Loftus, &Summers, 2005). Each time an individual sees another individual perform a movement, neurons that are responsible for that movement are activated in the observer's premotor cortex (Rizzolatti, &Craighero, 2004).

MT in rehabilitation is increasingly being investigated in recent studies. The effectiveness of MT on pain has been proven to be efficient in patients with CRPS after stroke and a small study including SCI patients shows some promising results for the effect of MT on pain in this population. It is well known as an effective way to treat phantom pain as well. Yet, there is no scientific evidence about the results of MT on pwMS (Tekeoglu Tosun, Ipek, Razak Ozdincler, &Saip, 2021).

No study has examined pain after MT in MS patients. In the previous literature review, five studies on MT were discussed. The results of our systematic review showed that MT is the only intervention that gave a reduction in pain consistently. The population of these studies only consisted of SCI- and stroke patients. Pain within MS is common, hence this study with MS patients as a population and with the intervention of MT. It will be performed in patients with pain in the upper limbs, because no studies were found on MT in the lower extremities. If MT has a significant positive effect on pain of MS patients, there is a possibility to do further research for lower limbs.

2.2 Aim of the study

2.2.1 Research question

The aim of this study is to investigate the effect of MT on neuropathic pain in pwMS. A secondary objective is to observe whether mirror therapy and the potential reduction in pain could influence the quality of life (QoL) in pwMS. Another outcome will be whether MT will reduce the influence of MS on these patient's daily life.

Research question: What is the effect of mirror therapy on neuropathic pain in patients with multiple sclerosis?

2.2.2 Hypothesis

Significant reductions in neuropathic pain in patients with CRPS after stroke who have undergone MT have already been established in several studies (Cacchio, De Blasis, E., De Blasis, V., Santilli, &Spacca, 2009a; Cacchio, De Blasis, Necozione, Orio, &Santilli, 2009b; Corbetta, Sarasso, Agosta, Filippi, &Gatti, 2018; Pervane Vural, Nakipoglu Yuzer, Sezgin Ozcan, Demir Ozbudak, &Ozgirgin, 2016).
Based on these results, we expect MT to reduce neuropathic pain in pwMS.

As of yet, no studies have been performed on the effect of MT on pain in MS. The little number of studies investigating MT in pwMS, focus on the motor aspect of the intervention, which seem to be promising.

2.3 Methods

2.3.1 Research design

A prospective, observational, longitudinal study will be set up to investigate the research question. Randomization is not applicable because there is only one intervention and no control group. As of yet, there is no evidence on the effect of mirror therapy on neuropathic pain in pwMS, so this will be a first study about this subject. Therefore, no specific information is available to calculate the effect size in this population. According to Cohen (1988), 0,5 is a moderate effect size (Cohen, 1988). When using a paired t-test with an alpha level of 0,05, power of 80%, a moderate effect size and considering a drop-out rate of 10%, the sample size of the study should be 38 participants.

2.3.2 Participants

The participants with MS will be recruited at pre-selected hospitals and rehabilitation centers: Noorderhart (Pelt) and National MS Center (Melsbroek).

2.3.2.1 Inclusion criteria

Patients that will be participating in the study should satisfy the following criteria:

- Diagnosis of multiple sclerosis
- Minimal age of 18 years
- Neuropathic pain in upper limb

2.3.2.2 Exclusion criteria

Patients meeting the following criteria will be excluded from the study:

- Cognitive impairment (MMSE > 23)
- Unstable medical status
- Changes in medication over the last six months
- Visual impairments or neglect

- Prior surgery or injections to either the shoulder or neck region
- Shoulder subluxation

2.3.2.3 Patient recruitment

The goal is to include 38 patients in the study. There will be a collaboration with Noorderhart (Overpelt) and National MS Center (Melsbroek). Twenty patients will be included from each hospital.

2.3.3 Medical ethics

Approval for this study (including the informed consent document) will be obtained from the Medical Ethics Committee of the UHasselt and the local ethical committees at Noorderhart and Melsbroek.

2.3.4 Intervention

Measurements will be taken immediately before the intervention (baseline) and immediately after the intervention (posttreatment), to determine after treatment whether or not the possible differences are significant. The two measurements will be done by an investigator who will be blinded to the statistical analysis.

Only one experimental group is used. The patients will follow a MT program in addition to their conventional therapy for a period of six weeks, for five days a week. Each session will last 30 minutes. Figure 2 gives an overview of the study design.

Fig. 2
Study design

During the mirror therapy program, the patient will be seated near a table with a mirror situated between the patient's upper limbs. The unaffected arm is going to be placed before the mirror, while the affected arm will be put in an appropriate box, which makes it undetectable (Figure 3). Patients were asked to perform different movements of the unaffected side: flexion and extension of the elbow, wrist, and fingers; supination and pronation of the lower arm; abduction, adduction, and opposition of the fingers. The patients are instructed to look in the mirror continuously during the activity and imagine that the reflection is related to the affected side. Patients are advised to attempt to do similar developments with the unaffected side. All sessions will be under the supervision of similar specialists. (Pervane Vural et al., 2016)

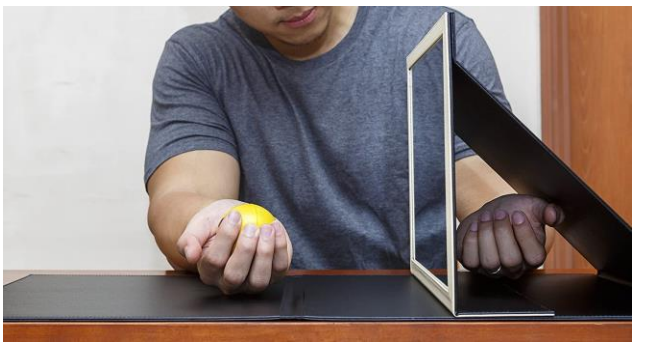


Fig. 3
Example of upper limb movements performed by a patient during the mirror therapy training.

2.3.5 Outcome measures

2.3.5.1 Primary outcomes

The primary outcome of this study will be the effect of MT on pain in MS, measured by the visual analogue scale (VAS). The VAS is used to assess the severity of pain. The scale is a 100mm scale, for which zero indicates no pain at all and 100 indicates the worst pain imaginable. Patients are asked to indicate the position on the scale that represents the level of their current pain.

Based on the outcome of a study of Haefel and Elfering (2006), VAS should be the best way to measure differences in pain over time in general. Therefore, this will be the only form of measuring pain in this protocol. A change on the VAS of 20% between

two time-points of an assessment is regarded as being clinically significant (Haefel, &Elfering, 2006).

2.3.5.2 Secondary outcomes

The Multiple Sclerosis Quality of Life-54 (MSQOL-54) will be used to measure the QoL of the patients. It is a multidimensional health-related quality of life measure that joins both generic and MS-explicit items into a single measurement instrument (Vickrey, Hays, Harooni, Myers, &Ellison, 1995; Vickrey, Hays, Genovese, Myers, &Ellison, 1997). The subscales are: physical function, cognitive function, role limitations-physical, pain, emotional well-being, health perceptions, social function, energy, role limitations-emotional, health distress, overall quality of life, and sexual function. The summary scores are the physical health composite summary and the mental health composite summary. The single item measures are fulfillment with sexual capacity and change in health. The MSQOL-54 is a structured and self-report questionnaire. The patient can generally complete the questionnaire with little or no assistance.

The Multiple Sclerosis Impact Scale (MSIS-29) questionnaire will be used to identify how the condition of multiple sclerosis (MS) affects the daily life of the patient in the past 2 weeks. The higher the scores, the more the condition has affected daily functioning. The questionnaire consists of 29 items, divided into two subscales: physical scale (20 items) and psychological scale (nine items). There is a five-point scale (one to five) for each item, ranging from one-not at all to five-extremely. For each subscale, the score ranges from zero to 100. In the physical scale, the scores from item one to 20 are added together. In the psychological scale, the scores of items 21 to 29 are added together. The final score is the result of the scores on the subscales that are converted to a zero to 100 scale with the following formulas:

- Physical scale: $\frac{(100*(subscale\ score-20))}{(100-20)}$
- Psychological scale: $\frac{(100*(subscale\ score-9))}{(45-9)}$

2.3.6 Data analysis

The program JMP will be used to perform the data analysis. The visual analogue scale is a continuous variable. The scores of the questionnaires MSQOL-54 and MSIS-29 are continuous variables as well.

For comparison of outcomes pre- and posttreatment, a paired t-test with 0,05 alpha level and 80% power will be used.

2.4 Time planning

The approval for this study, including the informed consent document, will be obtained from the Medical Ethics Committee of Hasselt University and the local ethics committees of Noorderhart and the National MS Center Melsbroek in July 2021.
The participants will enter the study between October 2020 and December 2021. The baseline measurements of the participants will be in October. The training period starts exactly one week after the baseline measurements. This training period lasts six weeks. After the last session, measurements will be taken again. In January 2022, the static analysis of all measurements will be performed. Finally, the results will be published in March 2022.

2.5 List of references

- Beiske, A. G., Pedersen, E. D., Czujko, B., & Myhr, K. M. (2004). Pain and sensory complaints in multiple sclerosis. *European journal of neurology*, *11*(7), 479–482. https://doi.org/10.1111/j.1468-1331.2004.00815.x
- Brola, W., Mitosek-Szewczyk, K., & Opara, J. (2014). Symptomatology and pathogenesis of different types of pain in multiple sclerosis. *Neurologia i neurochirurgia polska*, *48*(4), 272–279. https://doi.org/10.1016/j.pjnns.2014.07.009
- Cacchio, A., De Blasis, E., De Blasis, V., Santilli, V., & Spacca, G. (2009a). Mirror Therapy in Complex Regional Pain Syndrome Type 1 of the Upper Limb in Stroke Patients. *Neurorehabilitation and Neural Repair*, *23*(8), 792–799. https://doi.org/10.1177/1545968309335977
- Cacchio, A., De Blasis, E., Necozione, S., Orio, F. D., & Santilli, V. (2009b). Mirror Therapy for Chronic Complex Regional Pain Syndrome Type 1 and Stroke. *New England Journal of Medicine*, *361*(6), 634–636. https://doi.org/10.1056/nejmc0902799
- Cohen, J. (1988). *Statistical Power Analysis for the Behavioral Sciences* (2nd New edition). Taylor & Francis.
- Corbetta, D., Sarasso, E., Agosta, F., Filippi, M., & Gatti, R. (2018). Mirror therapy for an adult with central post-stroke pain: a case report. *Archives of Physiotherapy*, *8*(1). https://doi.org/10.1186/s40945-018-0047-y
- Freynhagen, R., Parada, H. A., Calderon-Ospina, C. A., Chen, J., Rakhmawati Emril, D., Fernández-Villacorta, F. J., Franco, H., Ho, K. Y., Lara-Solares, A., Li, C. C., Mimenza Alvarado, A., Nimmaanrat, S., Dolma Santos, M., & Ciampi de Andrade, D. (2019). Current understanding of the mixed pain concept: a brief narrative review. *Current medical research and opinion*, *35*(6), 1011–1018. https://doi.org/10.1080/03007995.2018.1552042
- Garry, M. I., Loftus, A., & Summers, J. J. (2005). Mirror, mirror on the wall: viewing a mirror reflection of unilateral hand movements facilitates ipsilateral M1 excitability. *Experimental brain research*, *163*(1), 118–122. https://doi.org/10.1007/s00221-005-2226-9

- Haefeli, M., & Elfering, A. (2006). Pain assessment. *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 Suppl 1*(Suppl 1), S17–S24. https://doi.org/10.1007/s00586-005-1044-x
- Harrison, A. M., Bogosian, A., Silber, E., McCracken, L. M., & Moss-Morris, R. (2015). 'It feels like someone is hammering my feet': understanding pain and its management from the perspective of people with multiple sclerosis. *Multiple sclerosis (Houndmills, Basingstoke, England)*, *21*(4), 466–476. https://doi.org/10.1177/1352458514544538
- Kandel ER, Schwartz JH, Jessell TM, et al. Principles of neural science. 5th ed. New York: McGraw-Hill, 2013.
- Kosek, E., Cohen, M., Baron, R., Gebhart, G. F., Mico, J. A., Rice, A., Rief, W., & Sluka, A. K. (2016). Do we need a third mechanistic descriptor for chronic pain states?. *Pain*, *157*(7), 1382–1386. https://doi.org/10.1097/j.pain.0000000000000507
- O'Connor, A. B., Schwid, S. R., Herrmann, D. N., Markman, J. D., & Dworkin, R. H. (2008). Pain associated with multiple sclerosis: systematic review and proposed classification. *Pain*, *137*(1), 96–111. https://doi.org/10.1016/j.pain.2007.08.024
- Pervane Vural, S., Nakipoglu Yuzer, G. F., Sezgin Ozcan, D., Demir Ozbudak, S., & Ozgirgin, N. (2016). Effects of Mirror Therapy in Stroke Patients With Complex Regional Pain Syndrome Type 1: A Randomized Controlled Study. *Archives of Physical Medicine and Rehabilitation*, *97*(4), 575–581. https://doi.org/10.1016/j.apmr.2015.12.008
- Rae-Grant, A. D., Eckert, N. J., Bartz, S., & Reed, J. F. (1999). Sensory symptoms of multiple sclerosis: a hidden reservoir of morbidity. *Multiple sclerosis (Houndmills, Basingstoke, England)*, *5*(3), 179–183. https://doi.org/10.1177/135245859900500307
- Riazi, A., Hobart, J. C., Lamping, D. L., Fitzpatrick, R., & Thompson, A. J. (2002). Multiple Sclerosis Impact Scale (MSIS-29): reliability and validity in hospital

based samples. *Journal of neurology, neurosurgery, and psychiatry*, 73(6), 701–704. https://doi.org/10.1136/jnnp.73.6.701

- Rizzolatti, G., & Craighero, L. (2004). The mirror-neuron system. *Annual review of neuroscience*, *27*, 169–192. https://doi.org/10.1146/annurev.neuro.27.070203.144230
- Shahrbanian, S., Auais, M., Duquette, P., Andersen, K., & Mayo, N. E. (2013). Does pain in individuals with multiple sclerosis affect employment? A systematic review and meta-analysis. *Pain research & management*, *18*(5), e94–e100. https://doi.org/10.1155/2013/829464
- Svendsen, K. B., Jensen, T. S., Overvad, K., Hansen, H. J., Koch-Henriksen, N., & Bach, F. W. (2003). Pain in patients with multiple sclerosis: a population-based study. *Archives of neurology*, *60*(8), 1089–1094. https://doi.org/10.1001/archneur.60.8.1089
- Tekeoglu Tosun, A., Ipek, Y., Razak Ozdincler, A., & Saip, S. (2021). The efficiency of mirror therapy on drop foot in Multiple Sclerosis Patients. *Acta neurologica Scandinavica*, 143(5), 545–553. https://doi.org/10.1111/ane.13385
- Terminology I. International Association for the Study of Pain, https://www.iasp-pain.org/Education/ Content.aspx?ItemNumber=1698&navItemNumber= 576#Pain (2019, accessed 20 September 2019).
- Vickrey, B. G., Hays, R. D., Harooni, R., Myers, L. W., & Ellison, G. W. (1995). A health-related quality of life measure for multiple sclerosis. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation,* 4(3), 187–206. https://doi.org/10.1007/BF02260859
- Vickrey, B. G., Hays, R. D., Genovese, B. J., Myers, L. W., & Ellison, G. W. (1997). Comparison of a generic to disease-targeted health-related quality-of-life measures for multiple sclerosis. *Journal of clinical epidemiology*, 50(5), 557–569. https://doi.org/10.1016/s0895-4356(97)00001-2
- Yilmazer, C., Lamers, I., Solaro, C., & Feys, P. (2020). Clinical perspective on pain in multiple sclerosis. Multiple Sclerosis Journal, 135245852095201. https://doi.org/10.1177/1352458520952015

www.uhasselt.be
Campus Hasselt | Martelarenlaan 42 | BE-3500 Hasselt
Campus Diepenbeek | Agoralaan gebouw D | BE-3590 Diepenbeek
T + 32(0)11 26 81 11 | E-mail: info@uhasselt.be

UHASSELT
KNOWLEDGE IN ACTION

CONTRACT WETENSCHAPPELIJKE STAGE DEEL 1

Datum: 7/11/2020

Student(e)1: Jessica Thenaers

Student(e) 2: Anna-Lisa Nulens

Promotor: Peter Feys

Copromotor: Cigdem Yilmazer

Situering masterproef:

☐ Vormt onderdeel van lopend onderzoeksproject, nl. ……

☐ **Vormt onderdeel van opstartend onderzoeksproject, nl. "Effectiveness of mirror therapy/action observation/mental imagery on pain in MS"**

☐ Individuele studie

☐ Andere, nl. ……

Nederlandstalige werktitel masterproef:

/……

Engelstalige werktitel masterproef (indien van toepassing)

/……

Voorlopige onderzoeksvraag literatuurstudie (indien gekend)

/……

Formatkeuze van format MP1

X **Centrale format** (conform met masterproefrichtlijnen)

☐ Alternatieve format (zie richtlijnen alternatieve format), nl.

……

……

……

……

……

……

www.uhasselt.be
Campus Hasselt | Martelarenlaan 42 | BE-3500 Hasselt
Campus Diepenbeek | Agoralaan gebouw D | BE-3590 Diepenbeek
T + 32(0)11 26 81 11 | E-mail: info@uhasselt.be

Uitsluitend van toepassing indien CENTRAL FORMATKEUZE

Doelstelling	Akkoord	Niet akkoord	NVT
1. De student(e) formuleert (in samenspraak met de promotor) een duidelijke vraag in functie van de literatuurstudie. Duid NVT aan indien de vraagstelling voor de literatuurstudie volledig door de promotor wordt aangereikt en formuleer een doelstelling voor de student(e): ……	☐	☐	☐
2. De student(e) voert een literatuurstudie uit conform de richtlijnen MP deel 1.	☐	☐	
3. De student(e) schrijft de literatuurstudie uit in academische taal conform met de richtlijnen MP deel 1.	☐	☐	
4. De student(e) formuleert, op grond van de gerealiseerde literatuurstudie een onderzoeksvraag voor het eigenlijke wetenschappelijke onderzoek (MP 2). Duid NVT aan indien de student(e) deelneemt aan een lopend onderzoeksproject en de onderzoeksvraag al geformuleerd is en formuleer een doelstelling voor de student(e): ……..	☐	☐	☐
5. De student(e) kiest een onderzoeksdesign en maakt een kritische keuze van de te hanteren methodologie en materialen. Duid NVT aan indien de student(e) gebruik maakt van een uitgewerkt onderzoeksdesign (lopend onderzoeksproject) en formuleer een doelstelling voor de student(e) ……..	☐	☐	☐
6. De student(e) schrijft de methodologiesectie van zijn/haar onderzoek uit conform de richtlijnen MP deel 1. Duid NVT aan indien de student(e) gebruik maakt van een uitgewerkt onderzoeksprotocol (lopend onderzoeksproject) en formuleer een doelstelling voor de student(e) ……	☐	☐	☐
7. De student(e) schrijft het onderzoeksprotocol uit in academische taal conform met de richtlijnen MP1.	☐	☐	
8. De student(e) voert reeds in deze fase (een deel van) de data acquisitie uit. Duid NVT aan indien de data-acquisitie voltooid wordt/werd zonder inbreng van de student(e) en formuleer een doelstelling voor de student(e)……	☐	☐	☐
9. De student(e) voert reeds in deze fase (een deel van) de data verwerking uit. Duid NVT aan indien de dataverwerking voltooid wordt/werd zonder inbreng van de student(e) en formuleer een doelstelling voor de student(e)……	☐	☐	☐
10. Bijkomende afspraken: ✔ Mogelijk reeds datacollectie in AJ 2020-2021 ✔	☐	☐	☐

Datum & handtekening student(e)(**Datum & handtekening promotor**

www.uhasselt.be
Campus Hasselt | Martelarenlaan 42 | BE-3500 Hasselt
Campus Diepenbeek | Agoralaan gebouw D | BE-3590 Diepenbeek
T + 32(0)11 26 81 11 | E-mail: info@uhasselt.be

UHASSELT
KNOWLEDGE IN ACTION

7/11/2020

Nulens A.

Peter Feys

08/11/2020

Type text here

Maak een kopie van het ondertekende contract voor de student(e), de promotor en het studentensecretariaat.

De kopie voor het studentesecretariaat wordt ter attentie van mevrouw Vicky Vanhille (gebouw D) ingediend.

www.uhasselt.be
Campus Hasselt | Martelarenlaan 42 | BE-3500 Hasselt
Campus Diepenbeek | Agoralaan gebouw D | BE-3590 Diepenbeek
T + 32(0)11 26 81 11 | E-mail: info@uhasselt.be

UHASSELT
KNOWLEDGE IN ACTION

Uitsluitend van toepassing indien ALTERNATIEVE FORMATKEUZE

(Zie voorwaarden in masterproef MP 1 richtlijnen).

☐ Alternatieve format (beschrijving van format)

.....
.....
.....
.....
.....
.....
.....
.....
.....

Richtlijnen alternatieve format:

.....
.....
.....
.....
.....
.....
.....
.....
.....
.....
.....
.....
.....
.....
.....
.....
.....

Beoordelingscriteria alternatieve format:

.....
.....
.....
.....
.....
.....
.....
.....
.....
.....
.....
.....
.....

Goedkeuring alternatieve format door masterproefcoördinator en Leerlijn Wetenschappelijk Onderzoek in Kinesitherapie (WOK) onder coördinatie van Prof. R. Meesen op datum van: .....

Datum & handtekening student(e)
7/11/2020

Nulens A.

Datum & handtekening promotor

Therapeia

Maak een kopie van het ondertekende contract voor de student(e)(e), de promotor en het studentensecretariaat.
De kopie voor het studentesecretariaat wordt ter attentie van mevrouw Vicky Vanhille (gebouw D) ingediend.

Verklaring op Eer

Ondergetekende, student aan de Universiteit Hasselt (UHasselt), faculteit Revalidatiewetenschappen aanvaardt de volgende voorwaarden en bepalingen van deze verklaring:

1. Ik ben ingeschreven als student aan de UHasselt in de opleiding revalidatiewetenschappen en kinesitherapie, waarbij ik de kans krijg om in het kader van mijn opleiding mee te werken aan onderzoek van de faculteit Revalidatiewetenschappen aan de UHasselt. Dit onderzoek wordt beleid door Peter Feys en kadert binnen het opleidingsonderdeel Wetenschappelijke stage/masterproef deel 1. Ik zal in het kader van dit onderzoek creaties, schetsen, ontwerpen, prototypes en/of onderzoeksresultaten tot stand brengen in het domein van "Effectiveness of mirror therapy/action observation/mental imagery on pain in MS" (hierna: "De Onderzoeksresultaten").

2. Bij de creatie van De Onderzoeksresultaten doe ik beroep op de achtergrondkennis, vertrouwelijke informatie[1], universitaire middelen en faciliteiten van UHasselt (hierna: de "Expertise").

3. Ik zal de Expertise, met inbegrip van vertrouwelijke informatie, uitsluitend aanwenden voor het uitvoeren van hogergenoemd onderzoek binnen UHasselt. Ik zal hierbij steeds de toepasselijke regelgeving, in het bijzonder de Algemene Verordening Gegevensbescherming (EU 2016-679), in acht nemen.

4. Ik zal de Expertise (i) voor geen enkele andere doelstelling gebruiken, en (ii) niet zonder voorafgaande schriftelijke toestemming van UHasselt op directe of indirecte wijze publiek maken.

5. Aangezien ik in het kader van mijn onderzoek beroep doe op de Expertise van de UHasselt, draag ik hierbij alle bestaande en toekomstige intellectuele eigendomsrechten op De Onderzoeksresultaten over aan de UHasselt. Deze overdracht omvat alle vormen van intellectuele eigendomsrechten, zoals onder meer – zonder daartoe beperkt te zijn – het auteursrecht, octrooirecht, merkenrecht, modellenrecht en knowhow. De overdracht geschiedt in de meest volledige omvang, voor de gehele wereld en voor de gehele beschermingsduur van de betrokken rechten.

6. In zoverre De Onderzoeksresultaten auteursrechtelijk beschermd zijn, omvat bovenstaande overdracht onder meer de volgende exploitatiewijzen, en dit steeds voor de hele beschermingsduur, voor de gehele wereld en zonder vergoeding:

   - het recht om De Onderzoeksresultaten vast te (laten) leggen door alle technieken en op alle dragers;
   - het recht om De Onderzoeksresultaten geheel of gedeeltelijk te (laten) reproduceren, openbaar te (laten) maken, uit te (laten) geven, te (laten) exploiteren en te (laten) verspreiden in eender welke vorm, in een onbeperkt aantal exemplaren;

[1] Vertrouwelijke informatie betekent alle informatie en data door de UHasselt meegedeeld aan de student voor de uitvoering van deze overeenkomst, inclusief alle persoonsgegevens in de zin van de Algemene Verordening Gegevensbescherming (EU 2016/679), met uitzondering van de informatie die (a) reeds algemeen bekend is; (b) reeds in het bezit was van de student voor de mededeling ervan door de UHasselt; (c) de student verkregen heeft van een derde zonder enige geheimhoudingsplicht; (d) de student onafhankelijk heeft ontwikkeld zonder gebruik te maken van de vertrouwelijke informatie van de UHasselt; (e) wettelijk of als gevolg van een rechterlijke beslissing moet worden bekendgemaakt, op voorwaarde dat de student de UHasselt hiervan schriftelijk en zo snel mogelijk op de hoogte brengt.

- het recht om De Onderzoeksresultaten te (laten) verspreiden en mee te (laten) delen aan het publiek door alle technieken met inbegrip van de kabel, de satelliet, het internet en alle vormen van computernetwerken;
- het recht De Onderzoeksresultaten geheel of gedeeltelijk te (laten) bewerken of te (laten) vertalen en het (laten) reproduceren van die bewerkingen of vertalingen;
- het recht De Onderzoeksresultaten te (laten) bewerken of (laten) wijzigen, onder meer door het reproduceren van bepaalde elementen door alle technieken en/of door het wijzigen van bepaalde parameters (zoals de kleuren en de afmetingen).

De overdracht van rechten voor deze exploitatiewijzen heeft ook betrekking op toekomstige onderzoeksresultaten tot stand gekomen tijdens het onderzoek aan UHasselt, eveneens voor de hele beschermingsduur, voor de gehele wereld en zonder vergoeding.

Ik behoud daarbij steeds het recht op naamvermelding als (mede)auteur van de betreffende Onderzoeksresultaten.

7. Ik zal alle onderzoeksdata, ideeën en uitvoeringen neerschrijven in een "laboratory notebook" en deze gegevens niet vrijgeven, tenzij met uitdrukkelijke toestemming van mijn UHasseltbegeleider Peter Feys.

8. Na de eindevaluatie van mijn onderzoek aan de UHasselt zal ik alle verkregen vertrouwelijke informatie, materialen, en kopieën daarvan, die nog in mijn bezit zouden zijn, aan UHasselt terugbezorgen.

Gelezen voor akkoord en goedgekeurd,

Naam: Anna-Lisa Nulens

Adres: Spurkerweg 63b, 3740 Bilzen

Geboortedatum en –plaats : 03/12/1998 te Tongeren

Datum: 07/11/2020

Handtekening:

Verklaring op Eer

Ondergetekende, student aan de Universiteit Hasselt (UHasselt), faculteit Revalidatiewetenschappen aanvaardt de volgende voorwaarden en bepalingen van deze verklaring:

1. Ik ben ingeschreven als student aan de UHasselt in de opleiding revalidatiewetenschappen en kinesitherapie, waarbij ik de kans krijg om in het kader van mijn opleiding mee te werken aan onderzoek van de faculteit Revalidatiewetenschappen aan de UHasselt. Dit onderzoek wordt beleid door Peter Feys en kadert binnen het opleidingsonderdeel Wetenschappelijke stage/masterproef deel 1. Ik zal in het kader van dit onderzoek creaties, schetsen, ontwerpen, prototypes en/of onderzoeksresultaten tot stand brengen in het domein van "Effectiveness of mirror therapy/action observation/mental imagery on pain in MS" (hierna: "De Onderzoeksresultaten").

2. Bij de creatie van De Onderzoeksresultaten doe ik beroep op de achtergrondkennis, vertrouwelijke informatie[1], universitaire middelen en faciliteiten van UHasselt (hierna: de "Expertise").

3. Ik zal de Expertise, met inbegrip van vertrouwelijke informatie, uitsluitend aanwenden voor het uitvoeren van hogergenoemd onderzoek binnen UHasselt. Ik zal hierbij steeds de toepasselijke regelgeving, in het bijzonder de Algemene Verordening Gegevensbescherming (EU 2016-679), in acht nemen.

4. Ik zal de Expertise (i) voor geen enkele andere doelstelling gebruiken, en (ii) niet zonder voorafgaande schriftelijke toestemming van UHasselt op directe of indirecte wijze publiek maken.

5. Aangezien ik in het kader van mijn onderzoek beroep doe op de Expertise van de UHasselt, draag ik hierbij alle bestaande en toekomstige intellectuele eigendomsrechten op De Onderzoeksresultaten over aan de UHasselt. Deze overdracht omvat alle vormen van intellectuele eigendomsrechten, zoals onder meer – zonder daartoe beperkt te zijn – het auteursrecht, octrooirecht, merkenrecht, modellenrecht en knowhow. De overdracht geschiedt in de meest volledige omvang, voor de gehele wereld en voor de gehele beschermingsduur van de betrokken rechten.

6. In zoverre De Onderzoeksresultaten auteursrechtelijk beschermd zijn, omvat bovenstaande overdracht onder meer de volgende exploitatiewijzen, en dit steeds voor de hele beschermingsduur, voor de gehele wereld en zonder vergoeding:

   - het recht om De Onderzoeksresultaten vast te (laten) leggen door alle technieken en op alle dragers;
   - het recht om De Onderzoeksresultaten geheel of gedeeltelijk te (laten) reproduceren, openbaar te (laten) maken, uit te (laten) geven, te (laten) exploiteren en te (laten) verspreiden in eender welke vorm, in een onbeperkt aantal exemplaren;

[1] Vertrouwelijke informatie betekent alle informatie en data door de UHasselt meegedeeld aan de student voor de uitvoering van deze overeenkomst, inclusief alle persoonsgegevens in de zin van de Algemene Verordening Gegevensbescherming (EU 2016/679), met uitzondering van de informatie die (a) reeds algemeen bekend is; (b) reeds in het bezit was van de student voor de mededeling ervan door de UHasselt; (c) de student verkregen heeft van een derde zonder enige geheimhoudingsplicht; (d) de student onafhankelijk heeft ontwikkeld zonder gebruik te maken van de vertrouwelijke informatie van de UHasselt; (e) wettelijk of als gevolg van een rechterlijke beslissing moet worden bekendgemaakt, op voorwaarde dat de student de UHasselt hiervan schriftelijk en zo snel mogelijk op de hoogte brengt.

- het recht om De Onderzoeksresultaten te (laten) verspreiden en mee te (laten) delen aan het publiek door alle technieken met inbegrip van de kabel, de satelliet, het internet en alle vormen van computernetwerken;
- het recht De Onderzoeksresultaten geheel of gedeeltelijk te (laten) bewerken of te (laten) vertalen en het (laten) reproduceren van die bewerkingen of vertalingen;
- het recht De Onderzoeksresultaten te (laten) bewerken of (laten) wijzigen, onder meer door het reproduceren van bepaalde elementen door alle technieken en/of door het wijzigen van bepaalde parameters (zoals de kleuren en de afmetingen).

De overdracht van rechten voor deze exploitatiewijzen heeft ook betrekking op toekomstige onderzoeksresultaten tot stand gekomen tijdens het onderzoek aan UHasselt, eveneens voor de hele beschermingsduur, voor de gehele wereld en zonder vergoeding.

Ik behoud daarbij steeds het recht op naamvermelding als (mede)auteur van de betreffende Onderzoeksresultaten.

7. Ik zal alle onderzoeksdata, ideeën en uitvoeringen neerschrijven in een "laboratory notebook" en deze gegevens niet vrijgeven, tenzij met uitdrukkelijke toestemming van mijn UHasseltbegeleider Peter Feys.

8. Na de eindevaluatie van mijn onderzoek aan de UHasselt zal ik alle verkregen vertrouwelijke informatie, materialen, en kopieën daarvan, die nog in mijn bezit zouden zijn, aan UHasselt terugbezorgen.

Gelezen voor akkoord en goedgekeurd,

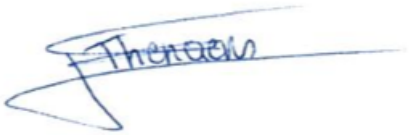
Naam: Jessica Thenaers

Adres: Vijverstraat 15, 3581 Beverlo

Geboortedatum en –plaats : 15/05/1998 te Heusden-Zolder

Datum: 7/11/2020

Handtekening:



www.uhasselt.be
Campus Hasselt | Martelarenlaan 42 | BE-3500 Hasselt
Campus Diepenbeek | Agoralaan gebouw D | BE-3590 Diepenbeek
T + 32(0)11 26 81 11 | E-mail: info@uhasselt.be

UHASSELT
KNOWLEDGE IN ACTION

VOORTGANGSFORMULIER WETENSCHAPPELIJKE STAGE DEEL 1

DATUM	INHOUD OVERLEG	HANDTEKENINGEN
04/11/2020	Kennismaking Onderzoeksvraag	Promotor: Peter Feys Copromotor/begeleider: Cigdem Yilmazer Student(e): Anna-Lisa Nulens Student(e): Jessica Thenaers
10/11/2020	Onderzoeksvraag Inclusie- en exclusiecriteria	Promotor: Peter Feys Copromotor/begeleider: Cigdem Yilmazer Student(e): Anna-Lisa Nulens Student(e): Jessica Thenaers
17/11/2020	Checklist Deadlines	Promotor: Peter Feys Copromotor/begeleider: Cigdem Yilmaze Student(e): Anna-Lisa Nulens Student(e): Jessica Thenaers
24/11/2020	Zoekstrategie	Promotor: Afwezig Copromotor/begeleider: Cigdem Yilmazer Student(e): Anna-Lisa Nulens Student(e): Jessica Thenaers
01/12/2020	Team meeting: voorstelling zoekstrategie	Promotor: Peter Feys Copromotor/begeleider: Cigdem Yilmazer (Ilse Lamers, Ines Noukpo, Joke Raats, Lisa Tabone, Lousin Moumdjian, Mieke Goetschalckx) Student(e): Anna-Lisa Nulens Student(e): Afwezig (Jessica)
26/02/2021	Resultaten zoekstrategie	Promotor: Peter Feys Copromotor/begeleider: Cigdem Yilmazer Student(e): Anna-Lisa Nulens Student(e): Jessica Thenaers
27/04	Data-extractie + feedback tabel Kwaliteitsbeoordeling	Promotor: Peter Feys Copromotor/begeleider: Cigdem Yilmazer Student(e): Anna-Lisa Nulens Student(e): Jessica Thenaers

J.T A.N Peter Feys C.Y.

Type text here

31/5/21	Protocol	Promotor: / Copromotor/begeleider: Cigdem Yilmaz Student(e): Anna-Lisa Student(e): Jessica
		Promotor: Copromotor/begeleider: Student(e): Student(e):
	Niet-bindend advies: De promotor verleent hierbij het advies om de masterproef WEL/NIET te verdedigen.	Promotor: Copromotor/begeleider: Student(e): Student(e):

Cigdem Yilmaz

Jessica Thenaers

Anna-Lisa Nulens

Peter Feys

05/06/2021

www.uhasselt.be
Campus Hasselt | Martelarenlaan 42 | BE-3500 Hasselt
Campus Diepenbeek | Agoralaan gebouw D | BE-3590 Diepenbeek
T + 32(0)11 26 81 11 | E-mail: info@uhasselt.be

UHASSELT
KNOWLEDGE IN ACTION

BEOORDELING VAN DE WETENSCHAPPELIJKE STAGE-DEEL 1

Wetenschappelijke stage deel 1 (Masterproef deel 1- MP1) van de Master of Science in de revalidatiewetenschappen en de kinesitherapie bestaat uit **twee delen**:

1) De literatuurstudie volgens een welomschreven methodiek.
2) Het opstellen van het onderzoeksprotocol ter voorbereiding van masterproef deel 2.

Omschrijving van de **evaluatie**:

1) 80% van het eindcijfer wordt door de promotor in samenspraak met de copromotor gegeven op grond het product en van het proces dat de student doorliep om de MP1 te realiseren, met name het zelfstandig uitvoeren van de literatuurstudie en het zelfstandig opstellen van het onderzoeksprotocol, alsook de kwaliteit van academisch schrijven.
2) 20% van het eindcijfer wordt door de interne jury gegeven op grond van het ingeleverde product en de mondelinge presentatie waarin de student zijn/haar proces toelicht.

In de beoordeling dient onderscheid gemaakt te worden tussen studenten die, in samenspraak met de promotor, een nieuw onderzoek uitwerkten en studenten die instapten in een lopend onderzoek of zich baseren op voorgaande masterproeven of onderzoeksprojecten. Van deze laatste worden bijkomende inspanningen verwacht zoals bv. het bijsturen van de eerder geformuleerde onderzoeksvraag, de kritische reflectie over het onderzoeksdesign, het uitvoeren van een pilotexperiment.

Beoordelingskader:

Beoordelingskader: criteria op 20	
18-20	Excellente modelmasterproef
16-17	Zeer goede masterproef
14-15	Goede masterproef
12-13	Voldoende masterproef
10-11	Zwakke masterproef
≤ 9	Onvoldoende masterproef die niet aan de minimumnormen voldoet

ZELFEVALUATIERAPPORT

Onderstaand zelfevaluatierapport is een hulpmiddel om je wetenschappelijke stage -deel 1 zelfstandig te organiseren. Bepaal zelf je deadlines, evalueer en reflecteer over je werkwijze en over de diepgang van je werk. Check de deadlines regelmatig. Toets ze eventueel af bij je (co)promotor. Succes!

www.uhasselt.be
Campus Hasselt | Martelarenlaan 42 | BE-3500 Hasselt
Campus Diepenbeek | Agoralaan gebouw D | BE-3590 Diepenbeek
T + 32(0)11 26 81 11 | E-mail: info@uhasselt.be

UHASSELT
KNOWLEDGE IN ACTION

ZELFEVALUATIERAPPORT **WETENSCHAPPELIJKE STAGE - DEEL 1** **RWK**

LITERATUURSTUDIE	Gestelde deadline	Behaald op	Reflectie
De belangrijkste concepten en conceptuele kaders van het onderzoekdomein uitdiepen en verwerken	30/10/2020	17/10/2020	/
De belangrijkste informatie opzoeken als inleiding op de onderzoeksvraag van de literatuurstudie	5/11/2020	30/10/2020	/
De opzoekbare onderzoeksvraag identificeren en helder formuleren in functie van de literatuurstudie	10/12/2020	17/11/2020	Stage zorgde voor vertraging.
De zoekstrategie op systematische wijze uitvoeren in relevante databanken	15/12/2020	6/12/2020	/
De kwaliteitsbeoordeling van de artikels diepgaand uitvoeren	11/04/2021	15/04/2021	/
De data-extractie grondig uitvoeren	11/04/2021	15/04/2021	Stage zorgde voor vertraging.
De bevindingen ïntegreren tot een synthese	17/04/2021	20/04/2021	Stage zorgde voor vertraging.

ONDERZOEKSPROTOCOL	Gestelde deadline	Behaald op	Reflectie
De onderzoeksvraag in functie van het onderzoeksprotocol identificeren	31/05/2021	31/05/2021	/
Het onderzoeksdesign bepalen en/of kritisch reflecteren over bestaande onderzoeksdesign	31/05/2021	31/05/2021	/
De methodesectie (participanten, interventie, uitkomstmaten, data-analyse) uitwerken	03/06/2021	03/06/2021	/

ACADEMISCHE SCHRIJVEN	Gestelde deadline	Behaald op	Reflectie
Het abstract tot he point schrijven	1/06/2021	28/05/2021	/
De inleiding van de literatuurstudie logisch opbouwen	9/05/2021	14/05/2021	Met groepsopdrachten bezig.
De methodesectie van de literatuurstudie transparant weergegeven	25/04/2021	23/04/2021	/
De resultatensectie afstemmen op de onderzoeksvragen	20/05/2021	25/05/2021	Met groepsopdrachten bezig.
In de discussiesectie de bekomen resultaten in een wetenschappelijke tekst integreren en synthetiseren	25/05/2021	28/05/2021	Met groepsopdrachten bezig.
Het onderzoeksprotocol deskundig technisch uitschrijven	5/06/2021	3/06/2021	/
Referenties correct en volledig weergeven	6/06/2021	4/06/2021	/

ZELFSTUREND EN WETENSCHAPPELIJK DENLEN EN HANDELEN	Aanvangsfase	Tussentijdse fase	Eindfase
Een realistische planning opmaken, deadlines stellen en opvolgen	17/11/2020	07/04/2021	03/06/2021
Initiatief en verantwoordelijkheid opnemen ten aanzien van de realisatie van de wetenschappelijke stage	27/10/2020	26/02/2021	03/06/2021
Kritisch wetenschappelijk denken	10/11/2020	26/02/2021	03/06/2021
De contacten met de promotor voorbereiden en efficiënt benutten	27/10/2020	26/02/2021	27/04/2021
De richtlijnen van de wetenschappelijke stage autonoom opvolgen en toepassen	17/11/2020	07/04/2021	03/06/2021
De communicatie met de medestudent helder en transparant voeren	22/09/2020	26/02/2021	03/06/2021
De communicatie met de promotor/copromotor helder en transparant voeren	27/10/2020	26/02/2021	24/04/2021
Andere verdiensten:	/	/	/