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Faculteit Revalidatiewetenschappen

master in de revalidatiewetenschappen en de kinesitherapie

Masterthesis

The adjuvant effect of tDCS on the rehabilitation of the upper limb and aphasia following stroke

Nathalie Van den Eede
Ellen Van der Veken

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

PROMOTOR :
Prof. dr. Raf MEESEN

COPROMOTOR :
dr. Ilse LAMERS

2018
2019

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The adjuvant effect of tDCS on the rehabilitation of the upper limb and aphasia following stroke.

"What is the additional value of anodal transcranial direct current stimulation (a-tDCS), cathodal tDCS (c-tDCS) or bihemispheric tDCS (b-tDCS) on the rehabilitation of the upper limb and aphasia of adults after stroke?"

- A large heterogeneity of outcome measures is present in recent literature.
- Interventions in the subacute stage of aphasia have promising effects, but the additional tDCS does not ameliorate these effects.
- Current evidence indicates a promising adjuvant value of tDCS for the rehabilitation of the upper limb function.
- None of the different forms of tDCS seemed to be superior over each other.
- Further research is necessary to gain more evidence about the adjuvant effects of tDCS on the rehabilitation of upper extremity and aphasia.

Promotor: Prof. dr. R. Meesen

Co-promotor: dr. I. Lamers

Students: Nathalie Van den Eede

Ellen Van der Veken

Research context

This systematic review takes place as part one, within a two-part master thesis which was conducted at the Faculty of Rehabilitation Sciences at Hasselt University. This review belongs to the domain Neurorehabilitation and was coordinated and supervised by prof. dr. Raf Meesen and dr. Ilse Lamers.

The first part is a systematic review investigating the adjuvant effect of transcranial direct current stimulation (tDCS) on the rehabilitation of stroke. tDCS is a relatively new type of treatment and therefore sufficient evidence is needed if it is to be implemented in clinical practice.

The second part contains the protocol for next year's thesis. This is a new research project led by dr. Ilse Lamers, which will investigate the long-term effects of anodal tDCS on the rehabilitation of stroke survivors where a plateau in rehabilitation is reached. This research will be conducted at the Rehabilitation and MS-Centre Overpelt.

A certain proportion of stroke survivors never regain full independence in activities of daily living. This results in a large societal cost to provide these people with both material and human aid. Regaining functionality could greatly reduce healthcare costs and could indirectly provide extra resources when patients can resume their former profession or become less dependent on help from others (Dewilde et al., 2017; Joo, George, Fang, & Wang, 2014).

This systematic review is the result of an equal contribution of both authors. Both review authors were involved in the screening of the articles, quality assessment, writing of the method section, discussion and conclusion. VN was responsible for writing the introduction and the protocol. VE was responsible for the data extraction, the result section and the research context. Every single part of the review was independently controlled and adjusted by both authors.

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Part 1: Literature study

The adjuvant effect of tDCS on the rehabilitation of the upper limb and aphasia following stroke.

Van den Eede N., Van der Veken E.

1 Abstract

Background: Stroke is one of the leading causes of adult-onset disability, only 25% of the stroke survivors return to their previous level of physical functioning and everyday participation. Recent research states the possibility of transcranial direct current stimulation (tDCS) to facilitate the emphasis on reorganisation, compensation and neuroplasticity. Implementation in future rehabilitation is still unsure, but promising.

Methods: Articles were retrieved between December 2018 and May 2019, using two databases, PubMed and Web of Science. The PEDro Checklist was used to assess quality.

Results: Of the 135 studies, 20 fully met the eligibility criteria. 11 studies demonstrated a significance in favour of the real tDCS on the upper limb function especially on WMFT. For aphasia, no significant between group differences were found.

Conclusion: Further research containing larger sample sizes is necessary to draw conclusions about the efficacy of tDCS on the rehabilitation of aphasia and upper limb function and the eventual superiority of one type of tDCS to the other.

Purpose: The aim of this systematic review is to determine the additional value of anodal tDCS (a-tDCS), cathodal tDCS (c-tDCS) or bihemispheric tDCS (b-tDCS) on the rehabilitation of the upper extremity and aphasia of adults after stroke.

Research question: What is the additional value of tDCS on the rehabilitation of the upper limb and aphasia of adults following stroke? Secondly, what are the differences in effectiveness of a-tDCS, c-tDCS and b-tDCS and which one is the most effective?

Keywords: Stroke; transcranial direct current stimulation (tDCS); upper extremity; aphasia; rehabilitation; review

2 Introduction

Stroke is one of the leading causes of adult-onset disability (Dobkin, 2004), only 25% of the stroke survivors return to their previous level of physical functioning and everyday participation (Dobkin, 2005). Most of the recovery occurs within the first two to three months, at this point we also see in the conventional rehabilitation a transition from cure to care. Beyond this point, in the chronic stage, stroke survivors benefit less from conventional rehabilitation treatment techniques (Ilic et al., 2016). Recent research gives room to a more positive view that puts the emphasis on reorganization, compensation and neuroplasticity. Transcranial direct current stimulation (tDCS) can facilitate these mechanisms, it is a technique which was introduced by Antal, Nitsche, and Paulus (2001) and initially was used to treat or modify psychiatric disease, depression in particular (Nitsche et al., 2008). Later on it was utilized for multiple causes, including rehabilitation after stroke. Schlaug, Renga, and Nair (2008) were the first to develop specific stimulation protocols for stroke survivors.

Transcranial direct current stimulation is a non-invasive brain stimulation technique that delivers low-intensity, direct current to cortical areas and its purpose is to facilitate or inhibit spontaneous neuronal activity (Brunoni et al., 2012). The current intensity is usually ranging from 0,5 to 2 mA (Tortella et al., 2015). Compared to transcranial magnetic stimulation (TMS), which is known for a longer time, it is less expensive, easier to use and its use is more convenient for the patient. It can be applied at home by the patient itself, while TMS can only be carried out in a clinical setting by skilled medical personnel (Hummel et al., 2008). The tDCS device is a small box powered by batteries with two electrodes placed over the scalp (Chang, Kim, & Park, 2015). Because no serious adverse events have been reported, it is a popular application in rehabilitative programs (Russo, Souza Carneiro, Bolognini, & Fregni, 2017).

After a focal lesion, the balance of interhemispheric communication is disrupted and the output from the lesioned hemisphere is reduced. Based on this hypothesis, contralesional and ipsilesional plastic changes may be induced by cortical stimulation after stroke, which could lead to a shift of this imbalance (Marquez, van Vliet, McElduff, Lagopoulos, & Parsons, 2015). To promote adaptive neuroplasticity, the activity of the perilesional region is stimulated, whereas the activity of the homologous area of the contralesional hemisphere is inhibited (Lefaucheur et al., 2017). Because cathodal tDCS hyperpolarises neurons, it diminishes the

excitability of the underlying cortex. Anodal tDCS causes neuronal hypopolarisation, which leads to increased excitability (Nitsche & Paulus, 2000). Bihemispheric tDCS is a combination of both: it uses cathodal tDCS over the non-lesioned cortex and anodal tDCS over the lesioned cortex (Lee, Cheon, Yoon, Chang, & Kim, 2013). These changes in cortical excitability are often measured and evaluated by TMS.

Following stroke, patients encounter many impairments which affect various aspects of their activities of daily living. A common deficit after stroke is impairment of the upper limb. Many rehabilitation techniques have been described, yet 30% to 66% of stroke survivors do not restore the function of the affected arm (van der Lee et al., 1999) and 15% to 30% of the survivors experience a permanent disability (Rosamond et al., 2008). Therefore a more effective therapy that results in better outcomes for stroke survivors and a lower cost of therapy and care is needed (Blank, French, Pehlivan, & O'Malley, 2014).

Another frequent functional impairment is aphasia. Of all stroke patients, 33% have aphasia (Nouwens et al., 2015) which affects their ability to communicate and their quality of life. Besides the spontaneous recovery in the acute and subacute phase, some interventions (such as speech-language therapy) have been presented to enhance language functions (Brady, Kelly, Godwin, & Enderby, 2012). Nevertheless, when it comes to chronic aphasia there still is a limited rehabilitative potential (Zhang et al., 2017). Therefore, treatment of aphasia was ranked third in the top 10 priorities in stroke research in a large survey of caregivers and health professionals (Pollock, St George, Fenton, & Firkins, 2014).

This literature study is limited to the upper limb and aphasia for the reason that the topography of Broca's centre and the representation of the hand and arm on the motor cortex are easier to reach with TMS, a neurologic measurement tool which gives us inside in the underlying mechanisms. In addition, Broca's centre is located near the motor cortex, which makes it interesting to combine both impairments. A closer look is taken at the effect of tDCS on the upper limb and aphasia and whether it is more or less effective than conventional therapy alone. Secondly, this review investigates what the differences are in effectiveness of anodal, cathodal and bihemispheric tDCS and which one is the most effective.

3 Methods

3.1 Purpose

The aim of this systematic review, is to determine the additional value of anodal transcranial direct current stimulation (a-tDCS), cathodal tDCS (c-tDCS) or bihemispheric tDCS (b-tDCS) on the rehabilitation of the upper extremity and aphasia of adults after stroke. A sub question is the following: what are the differences in effectiveness of a-tDCS, c-tDCS and b-tDCS and which one is the most effective?

3.2 Literature search

Studies were systematically searched (up to May 2019) using two databases: PubMed and Web of Science (WOS). The following keywords were included: (1) stroke, (2) rehabilitation, (3) transcranial direct current stimulation, (4) anodal transcranial direct current stimulation, (5) cathodal transcranial direct current stimulation, (6) dual transcranial direct current stimulation, (7) bihemispheric transcranial direct current stimulation, (8) upper limb, (9) upper extremity and (10) aphasia. Boolean operators AND and OR were used. If there was no existing Mesh-term, 'Title/Abstract' was used in the search builder. Furthermore, the search was specified using the filters 'randomized controlled trial', 'adults 19+' and 'humans'. In WOS, the term 'topic' (TS) and filter 'article' was selected. Duplicates were removed through hand search and studies were selected if they met the following eligibility criteria.

Details from the search strategy can be found in table 1 and 2.

Table 1

Literature search PubMed

	MeSH-terms and keywords in PubMed	Hits December 2018	Hits June 2019
1	Stroke[MeSH]	5023	5190
2	Rehabilitation[MeSH]	23609	24589
3	Transcranial direct current stimulation[MeSH]	391	405
4	Anodal transcranial direct current stimulation[Title/Abstract]	92	93
5	Cathodal transcranial direct current stimulation[Title/Abstract]	30	30
6	Dual transcranial direct current stimulation[Title/Abstract]	6	6
7	Bihemispheric transcranial direct current stimulation[Title/Abstract]	3	3
8	Upper limb[MeSH Terms]	4730	4812
9	Upper extremity[MeSH Terms]	4730	4812
10	Aphasia[MeSH Terms]	176	178
11	#3 OR #4 OR #5 OR # 6 OR # 7	546	560
12	#8 OR #9 OR #10	4961	4988
13	#1 AND #2 AND #11	68	68
14	#12 AND #13	31	31

Table 2

Literature search Web of Science

	Keywords in Web of Science	Hits December 2018	Hits June 2019
1	Stroke (topic)	207616	213851
2	Rehabilitation (topic)	136008	140442
3	Transcranial direct current stimulation (topic)	2948	3139
4	Anodal transcranial direct current stimulation (topic)	1553	1649
5	Cathodal transcranial direct current stimulation (topic)	901	943
6	Dual transcranial direct current stimulation (topic)	81	89
7	Bihemispheric transcranial direct current stimulation (topic)	43	47
8	Upper limb (topic)	27215	28062
9	Upper extremity (topic)	23316	23963
10	Aphasia (topic)	13523	13791
11	#3 OR #4 OR #5 OR # 6 OR # 7	2948	3139
12	#8 OR #9 OR #10	57981	59594
13	#1 AND #2 AND #11	247	259
14	#12 AND #13	104	128

3.3 Eligibility criteria

Inclusion criteria were (1) randomized controlled study design, (2) study on humans, (3) adults over 19 years old, (4) diagnosis of stroke and (5) tDCS used as an intervention. Exclusion criteria were (1) study contains TMS, (2) comparison with healthy participants, (3) electrical stimulation only, (4) no conventional therapy, (5) combined intervention (tDCS plus another kind of stimulation) and (6) cross-over design. The screening was done by two researchers (VE and VN).

3.4 Quality assessment

The quality of the included studies was analysed using the Physiotherapy Evidence Database (PEDro) scale. This scale provides a more comprehensive measure of methodological quality of the stroke literature (Bhogal, Teasell, Foley, & Speechley, 2005) and consists of 11 quality ratings regarding the external, internal and statistical validity of the study, each receiving a yes (1) or no (0) score. Since the first item (a measure of external validity) is not used for the final score, there's a maximum possible score of 10, which is obtained by summation (Bucur & Papagno, 2018). As described in Foley, Teasell, Bhogal, and Speechley (2003), a higher score indicates a greater quality: 9-10: excellent; 6-8: good; 4-5: fair; <4: poor.

The table used for analysing the level of evidence of the included studies was found in Portney (2008). Furthermore, all the included studies were screened for different biases.

3.5 Data extraction

The following data were collected from the included studies: sample size, gender of the participants (% women), disability, mean age of the sample (years ± SD) and recovery stages. The recovery stages were set at zero to two weeks for the acute stage, two weeks to six months for the subacute stage and more than six months for the chronic stage. This was done to ensure that the articles were evaluated in the right context. Looking at the intervention, the parameters (intensity, duration and electrode size), positioning of the active electrode and reference electrode, total intervention duration and the used conventional or control treatment were collected. Furthermore, all the used outcome measures, matching results and the maximum follow-up time were gathered.

4 Results

4.1 Results of literature search

The performed literature search resulted in 136 publications on Web of Science and 31 publications on PubMed. Duplicates were removed and a total of 135 publications were screened based on title and abstract. 60 articles were found relevant for further reading. Studies which compared with healthy participants (n = 2) and studies with participants age <19 years (n = 1) were excluded. Furthermore, studies not comparing with sham transcranial direct current stimulation (tDCS) (n = 1) or without conventional therapy (n = 2) and studies which contained transcranial magnetic stimulation (TMS) (n = 1) or electrical stimulation only (n = 13) were also excluded. Cross-over studies (n = 6), studies with irrelevant outcome measures (n = 3) or studies which were not Randomized Controlled Trials (RCT) (n = 7) were excluded as well. At last one full text was not available. Finally, 23 articles were included.

You can the find selection process flowchart in figure 1. Excluded articles are listed in table 3 and table 4.

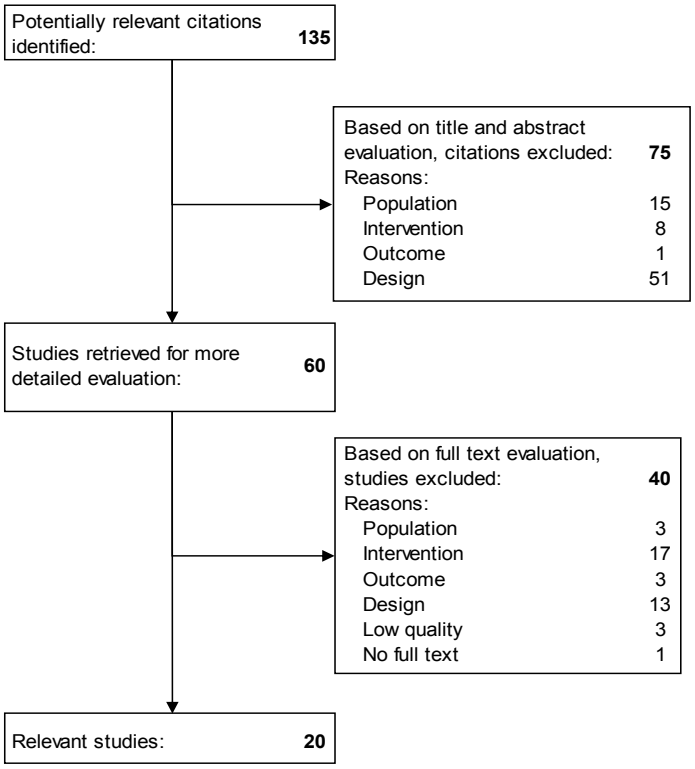

Figure 1. Flowchart: selection process

Table 3

Summary of excluded articles and reason of exclusion based on Title/ Abstract

Reason of exclusion	Number of articles (n = 75)	References
Design		
No RCT	48	(Alsharidah et al., 2018), (Bin Pai, Terranova, Simis, Fregni, & Battistella, 2018), (Bradnam, Stinear, & Byblow, 2013), (Fuentes Calderon, Miralles, Pimienta, Estella, & Ledesma, 2019), (Cappa, 2011), (Cappon, Jahanshahi, & Bisiacchi, 2016), (Carson, Kennedy, Linden, & Britton, 2008), (Chen & Schlaug, 2016), (Cherney et al., 2013), (Chrysikou & Hamilton, 2011), (Crinion, 2016), (Crosson et al., 2015), (Darkow & Floel, 2016), (de Souza et al., 2019), (De Tommaso et al., 2017), (Edwardson, Lucas, Carey, & Fetz, 2013), (Feng & Belagaje, 2013), (Fleming, Pavlou, Newham, Sztriha, & Teo, 2017), (Friel et al., 2017), (Galletta et al., 2015), (Harvey & Stinear, 2010), (Heiss, 2016), (Hesse et al., 2007), (Hodics et al., 2012), (Holland & Crinion, 2012), (Kang, Weingart, & Cauraugh, 2018), (Kasashima-Shindo et al., 2015), (Levin et al., 2018), (Liepert & Breitenstein, 2016), (Middleton, Fritz, Liuzzo, Newman-Norlund, & Herter, 2014), (Montenegro, Alvarez-Montesinos, Estudillo, & Garcia-Orza, 2017), (Murdoch & Barwood, 2013), (Nanji, Cardoso, Costa, & Vaz-Carneiro, 2015), (Nowak, Bosl, Podubecka, & Carey, 2010), (Otal et al., 2016), (Pavlova et al., 2017), (Peters, Pisegna, Faieta, & Page, 2017), (Plow et al., 2013), (Plow, Cunningham, Varnerin, & Machado, 2015), (Rosso, Arbizu, Dhennain, Lamy, & Samson, 2018), (Spielmann, van de Sandt-Koenderman, Heijenbrok-Kal, & Ribbers, 2016), (Sunderland & Tuke, 2005), (Tanaka, Sandrini, & Cohen, 2011), (Tanaka, Takeda, et al., 2011), (Triccas et al., 2018), (Ulanov, Shtyrov, & Stroganova, 2018), (Van de Winckel et al., 2018), (Wu, Wang, & Yuan, 2015)
Study protocol	3	(Andrade et al., 2016), (Thiel et al., 2015), (Welsby, Ridding, Hillier, & Hordacre, 2018)
Intervention		
Electrical stimulation only	1	(Bao, Wong, Leung, & Tong, 2019)
Contains TMS	4	(Cotelli et al., 2011), (D'Agata et al., 2016), (Kwon, Park, Kang, Chang, & Kim, 2016), (Santos et al., 2017)
Combined intervention	3	(Koh, Lin, Jeng, Huang, & Hsieh, 2017), (Shaheiwola, Zhang, Jia, & Zhang, 2018), (Takebayashi, Takahashi, Moriwaki, Sakamoto, & Domen, 2017)
Population		
No stroke	9	(Cattaneo, Pisoni, & Papagno, 2011), (Clemens, Jung, Zvyagintsev, Domahs, & Willmes, 2013), (Cortes et al., 2017), (Cotelli et al., 2014), (Fan, Voisin, Milot, Higgins, & Boudrias, 2017), (Inguaggiato, Bolognini, Fiori, & Cioni, 2019), (McCambridge, Bradnam, Stinear, & Byblow, 2011), (Potter-Baker et al., 2018), (Yozbatiran et al., 2016)
Comparison with healthy participants	6	(Darkow, Martin, Wurtz, Floel, & Meinzer, 2017), (Hong et al., 2017), (Kim et al., 2014), (Naros et al., 2016), (Turkeltaub, Swears, D'Mello, & Stoodley, 2016), (Zheng, Dai, Alsop, & Schlaug, 2016)
Outcome		
Irrelevant outcome measures	1	(van der Vliet, Ribbers, Vandermeeren, Frens, & Selles, 2017)

Table 4

Summary of excluded articles and reason of exclusion based on full text

Reason of exclusion	Number of articles (n = 40)	References
Design		
No RCT	7	(Black & Gaebler-Spira, 2018), (Branscheidt, Hoppe, Zwitserlood, & Liuzzi, 2018), (Dmochowski et al., 2013), (Fuentes et al., 2018), (Marangolo et al., 2011), (Spielmann, Van De Sandt-Koenderman, Heijenbrok-Kal, & Ribbers, 2018), (Zheng & Schlaug, 2015)
Cross-over design	6	(de Aguiar et al., 2015), (Dehem et al., 2018), (Fusco et al., 2014), (Keser et al., 2017), (Pestalozzi et al., 2018), (Woodhead et al., 2018),
Intervention		
Electrical stimulation only	13	(Achacheluee et al., 2018), (Au-Yeung, Wang, Chen, & Chua, 2014), (da Silva, Mac-Kay, Chao, dos Santos, & Gagliadi, 2018), (Del Felice, Daloli, Masiero, & Manganotti, 2016), (Lefebvre et al., 2014), (Marangolo, Fiori, Caltagirone, Pisano, & Priori, 2018), (Marquez et al., 2017), (McCambridge, Stinear, & Byblow, 2018), (Menezes et al., 2018), (Oveisgharan, Organji, & Ghorbani, 2018), (Tahtis, Kaski, & Seemungal, 2014), (You, Kim, Chun, Jung, & Park, 2011), (Zimerman et al., 2012)
Contains TMS	1	(Nicolo et al., 2018)
No conventional therapy	2	(Ochi, Saeki, Oda, Matsushima, & Hachisuka, 2013), (Saruco et al., 2017)
No comparison with sham tDCS	1	(S. J. Lee & Chun, 2014)
Population		
< 19 years	1	(Wu et al., 2013)
Comparison with healthy participants	2	(Kasashima et al., 2012), (Marangolo et al., 2013)
Outcome		
Irrelevant outcome measures	3	(Hamoudi et al., 2018), (Klomjai et al., 2018), (Manji et al., 2018)
Other		
Low quality (≤ 4/10)	3	(D. G. Lee & Lee, 2015), (Lindenberg, Zhu, & Schlaug, 2012), (Silva, Mac-Kay, Chao, Santos, & Gagliadi, 2018)
No full text available	1	(Sik, Dursun, Dursun, Sade, & Sahin, 2015)

4.2 Results quality assessment

Studies with a score of 4/10 or less on the PEDro scale were excluded (n = 3) because of their poor quality (Lee & Lee, 2015; Lindenberg, Zhu, & Schlaug, 2012; Silva, Mac-Kay, Chao, Santos, & Gagliadi, 2018). This resulted in a total of 20 studies eligible for data-analysis.

According to the PEDro Checklist, 12 studies achieved an excellent quality (Allman et al., 2016; Edwards et al., 2019; Figlewski et al., 2017; Goodwill, Teo, Morgan, Daly, & Kidgell, 2016; Hesse et al., 2011; Ilic et al., 2016; Kim et al., 2010; Mortensen, Figlewski, & Andersen, 2016; Polanowska, Lesniak, Seniow, Czepiel, & Czlonkowska, 2013; Rocha et al., 2016; Spielmann, van de Sandt-Koenderman, Heijenbrok-Kal, & Ribbers, 2018; Viana et al., 2014). The other eight were of good quality (Bolognini et al., 2011; Cunningham et al., 2015; Fusco et al., 2014; Lindenberg, Renga, Zhu, Nair, & Schlaug, 2010; Nair, Renga, Lindenberg, Zhu, & Schlaug, 2011; Polanowska, Lesniak, Seniow, & Czlonkowska, 2013; Rabadi & Aston, 2017; Triccas et al., 2015). Of the included studies, none scored less than good and all had a level of evidence of 1B. For more information about the scores, see table 5.

Table 5

Quality assessment of included studies

	Eligibility criteria were specified	Randomization participants	Allocation was concealed	The groups were similar at baseline regarding the most important prognostic indicators	Blinding of all participants	Blinding of all therapists who administrated the therapy	Blinding of all assessors who measured at least one key outcome	Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups	All participants 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"	The results of between-group statistical comparisons are reported for at least one key outcome	The study provides both point measures and measures of variability for at least one key outcome	Score /10	LoE
(Allman et al., 2016)	✓	✓	✓	✓	✓	✓	✓	✓	✗	✓	✓	9	1 B
(Bolognini et al., 2011)	✓	✓	✗	✓	✓	✓	✓	✓	✗	✓	✓	8	1 B
(Cunningham et al., 2015)	✓	✓	✗	✓	✓	✗	✓	✓	✗	✓	✓	7	1 B
(Edwards et al., 2019)	✓	✓	✓	✓	✓	✓	✓	✓	✗	✓	✓	9	1 B
(Figlewski et al., 2017)	✓	✓	✓	✓	✓	✓	✓	✓	✗	✓	✓	9	1 B
(Fusco, Assenza, et al., 2014)	✓	✓	✗	✓	✓	✓	✓	✗	✗	✓	✓	7	1 B
(Goodwill, Teo, Morgan, Daly, & Kidgell, 2016)	✓	✓	✓	✓	✓	✓	✓	✓	✗	✓	✓	9	1 B
(Hesse et al., 2011)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	10	1 B
(Ilic et al., 2016)	✓	✓	✓	✓	✓	✓	✓	✓	✗	✓	✓	9	1 B
(Kim et al., 2010)	✓	✓	✓	✓	✓	✓	✓	✓	✗	✓	✓	9	1 B
(Lindenberg, Renga, Zhu, Nair, & Schlaug, 2010)	✓	✓	✗	✓	✓	✓	✗	✓	✗	✓	✓	7	1 B
(Mortensen, Figlewski, & Andersen, 2016)	✓	✓	✗	✓	✓	✓	✓	✓	✓	✓	✓	9	1 B
(Nair, Renga, Lindenberg, Zhu, & Schlaug, 2011)	✓	✓	✗	✓	✓	✓	✓	✗	✗	✓	✓	7	1 B
(Polanowska, Lesniak, Seniow, & Czlonkowska, 2013)	✓	✓	✗	✓	✓	✗	✗	✓	✗	✓	✓	6	1 B
(Polanowska, Lesniak, Seniow, Czepiel, & Czlonkowska, 2013)	✓	✓	✓	✓	✓	✓	✓	✓	✗	✓	✓	9	1 B
(Rabadi & Aston, 2017)	✓	✓	✓	✓	✓	✓	✗	✗	✓	✓	✓	8	1 B
(Rocha et al., 2016)	✓	✓	✓	✓	✓	✓	✓	✗	✓	✓	✓	9	1 B
(Spielmann, van de Sandt-Koenderman, Heijenbrok-Kal, & Ribbers, 2018b)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	10	1 B
(Triccas et al., 2015)	✓	✓	✓	✓	✓	✗	✓	✓	✗	✓	✓	8	1 B
(Viana et al., 2014)	✓	✓	✓	✓	✓	✓	✓	✓	✗	✓	✓	9	1 B

Potential biases are listed in table 6. The most prevalent bias was the wrong sample size bias (Allman et al., 2016; Bolognini et al., 2011; Cunningham et al., 2015; Fusco et al., 2014; Goodwill et al., 2016; Hesse et al., 2011; Ilic et al., 2016; Kim et al., 2010; Lindenberg et al., 2010; Mortensen et al., 2016; Nair et al., 2011; Polanowska, Lesniak, Seniow, & Czlonkowska, 2013; Polanowska, Lesniak, Seniow, Czepiel, et al., 2013; Rabadi & Aston, 2017; Rocha et al., 2016; Spielmann et al., 2018; Triccas et al., 2015; Viana et al., 2014). The other potential biases were the performance bias (therapist blinding) (Cunningham et al., 2015; Rabadi & Aston, 2017; Triccas et al., 2015), allocation concealment bias (Bolognini et al., 2011; Cunningham et al., 2015; Fusco et al., 2014; Lindenberg et al., 2010; Mortensen et al., 2016; Nair et al., 2011; Polanowska, Lesniak, Seniow, & Czlonkowska, 2013) and selection bias (Allman et al., 2016; Cunningham et al., 2015; Edwards et al., 2019; Figlewski et al., 2017; Fusco et al., 2014; Goodwill et al., 2016; Ilic et al., 2016; Kim et al., 2010; Lindenberg et al., 2010; Mortensen et al., 2016; Nair et al., 2011; Polanowska, Lesniak, Seniow, & Czlonkowska, 2013; Polanowska, Lesniak, Seniow, Czepiel, et al., 2013; Rabadi & Aston, 2017; Rocha et al., 2016; Viana et al., 2014). Edwards et al. (2019) was also susceptible to reporting bias because some outcome measures reported in the methods section were not discussed in the results.

Table 6

Potential biases of the included articles

	Selection bias	Allocation concealment (selection bias)	Therapist blinding (performance bias)	Wrong sample size bias	Reporting bias
(Allman et al., 2016)	?			x	
(Bolognini et al., 2011)		x		x	
(Cunningham et al., 2015)	x	x	x	x	
(Edwards et al., 2019)	x				x
(Figlewski et al., 2017)	x				
(Fusco, Assenza, et al., 2014)	x	x		x	
(Goodwill, Teo, Morgan, Daly, & Kidgell, 2016)	?			x	
(Hesse et al., 2011)				x	
(Ilic et al., 2016)	x			x	
(Kim et al., 2010)	x			x	
(Lindenberg, Renga, Zhu, Nair, & Schlaug, 2010)	?	x		?	
(Mortensen, Figlewski, & Andersen, 2016)	x	x		x	
(Nair, Renga, Lindenberg, Zhu, & Schlaug, 2011)	?	x		x	
(Polanowska, Lesniak, Seniow, & Czlonkowska, 2013)	x	x	x	x	
(Polanowska, Lesniak, Seniow, Czepiel, & Czlonkowska, 2013)	x			x	
(Rabadi & Aston, 2017)	x			x	
(Rocha et al., 2016)	x			x	
(Spielmann, van de Sandt-Koenderman, Heijenbrok-Kal, & Ribbers, 2018b)				x	
(Triccas et al., 2015)			x	x	
(Viana et al., 2014)	x			x	

4.3 Results data-extraction

4.3.1 Study Characteristics

Of the 20 included studies, three investigated tDCS treatment in post-stroke patients with aphasia and 17 investigated tDCS in patients with upper extremity neuromotor impairments. The mean age of the participants of the included studies ranged between 42.6 (Bolognini et al., 2011) and 67.8 years (Edwards et al., 2019). Of all the included studies, Rabadi and Aston (2017) was the only one that did not include any women. The percentage of women in the other studies ranged from 20% to 66.67%. The study by Hesse et al. (2011) had the largest sample, including 96 participants. Cunningham et al. (2015) had the smallest, including 12 participants. There was one study examining the acute stage of recovery (Rabadi & Aston, 2017), three the subacute stage (Hesse et al., 2011; Polanowska, Lesniak, Seniow, Czepiel, et

al., 2013; Spielmann et al., 2018), 11 the chronic stage (Allman et al., 2016; Cunningham et al., 2015; Edwards et al., 2019; Goodwill et al., 2016; Ilic et al., 2016; Lindenberg et al., 2010; Mortensen et al., 2016; Nair et al., 2011; Rocha et al., 2016; Viana et al., 2014), three examining the acute and subacute stage (Fusco et al., 2014; Kim et al., 2010; Polanowska, Lesniak, Seniow, & Czlonkowska, 2013) and two the subacute and chronic stage (Figlewski et al., 2017; Triccas et al., 2015). Of the included studies, 11 used anodal tDCS, three cathodal tDCS, three used both and three used bihemispheric tDCS. Looking at the intervention parameters, the used intensity ranged between 1 mA and 2 mA and the duration of the real tDCS between ten and 40 minutes. Seven studies applied tDCS immediately before the other therapy (Edwards et al., 2019; Fusco et al., 2014; Ilic et al., 2016; Polanowska, Lesniak, Seniow, & Czlonkowska, 2013; Polanowska, Lesniak, Seniow, Czepiel, et al., 2013; Spielmann et al., 2018), two started the other therapy within one hour after the allocated treatment was given (Rabadi & Aston, 2017; Rocha et al., 2016) and ten studies applied tDCS during the other therapy (Allman et al., 2016; Cunningham et al., 2015; Figlewski et al., 2017; Goodwill et al., 2016; Hesse et al., 2011; Kim et al., 2010; Lindenberg et al., 2010; Mortensen et al., 2016; Nair et al., 2011; Triccas et al., 2015). Bolognini et al. (2011) and Viana et al. (2014) did not mention the moment of application. The majority of the studies used electrodes with an active area of 35 cm^2 (Allman et al., 2016; Bolognini et al., 2011; Cunningham et al., 2015; Edwards et al., 2019; Figlewski et al., 2017; Fusco et al., 2014; Hesse et al., 2011; Mortensen et al., 2016; Polanowska, Lesniak, Seniow, & Czlonkowska, 2013; Polanowska, Lesniak, Seniow, Czepiel, et al., 2013; Rabadi & Aston, 2017; Rocha et al., 2016; Spielmann et al., 2018; Triccas et al., 2015; Viana et al., 2014). Three studies used electrodes of 25 cm^2 (Goodwill et al., 2016; Ilic et al., 2016; Kim et al., 2010), one study 16.3 cm^2 (Lindenberg et al., 2010) and Nair et al. (2011) did not mention the electrode size. The total intervention duration ranged between five days (Mortensen et al., 2016) and 12 weeks (Edwards et al., 2019). More information about the study characteristics can be found in table 7.

Table 7

Study characteristics of the included studies

						Intervention				Outcome	
	Disability	Number of participants	% Women	Mean age (years) ±SD	Recovery stage	Parameters Intensity duration Electrode size	Positioning Active electrode Refference electrode	Total intervention duration (sessions per week)	Other therapy	Outcome measures	Follow up
Aphasia											
(Polanowska, Lesniak, Seniow, & Czlonkowska, 2013)	Aphasia (fluent and non-fluent)	37	35.14	A: 57.6 ± 9.6 S: 62 ± 11.9	Acute Subacute	1 mA A: 10 min, S: 25 s Immediately before 35 cm²	Anode: L. hemisphere posterior IFC (crossing point between T3-Fz and F7-Cz International 10-20 EEG System) Cathode: above R. supraorbital area	3 weeks (5)	SLT 45 min, 5x week	Short Boston Diagnostic Aphasia Examination	3 months
(Polanowska, Lesniak, Seniow, Czepiel, & Czlonkowska, 2013)	Aphasia (non-fluent)	24	41.67	A: 56.1 ± 10.1 S: 61 ± 14.4	Subacute	1 mA A: 10 min, S: 25 s Immediately before 35 cm²	Anode: Broca's area (crossing point between T3-Fz and F7-Cz, International 10-20 EEG System) Cathode: above R. supraorbital region	3 weeks (5)	SLT 45 min, 5x week PT 45 min daily	Computerized oral naming test	3 months
(Spielmann, van de Sandt-Koenderman, Heijenbrok-Kal, & Ribbers, 2018b)	Aphasia (fluent and non-fluent)	58	31	A: 57.9 ± 9.6 S: 59.7 ± 10.3	Subacute	1 mA A: 20 min, S: 30 s Immediately before 35 cm²	Anode: L. inferior frontal gyrus Cathode: R. supraorbital region	2x 2 weeks (5)	SLT 45 min	Prim.: Boston Naming Test (BNT) Sec.: Naming performance on trained and untrained items, Aphasia Severity Rating Scale (ASRS), Amsterdam Nijmegen Everyday Language Test (ANELT), Wong-Baker Faces 5-point Pain Rating Scale	6 months
Upper extremity											
(Allman et al., 2016)	Hemiparesis	26	26.92	A: 59.5 ± 12.1 S: 66.8 ± 10.4	Chronic	1 mA A: 20 min, S: 10 s During 35 cm²	Anode: ipsilesional M1 (5 cm lateral to Cz: C3) Cathode: contralateral supraorbital ridge	9 days	Graded Repititive Arm Supplementary Program 60 min	ARAT, UE-FMA, WMFT, fMRI (voxel-based morphometry (VBM), fractional anisotropy (FA))	3 months
(Bolognini et al., 2011)	Hemiparesis	14	64.29	B: 42.6 S: 50.9 Total: 46.7	Chronic	2 mA B: 40 min, S: 30 s NA 35 cm²	Anode: ipsilesional M1 (C3/C4, International 10-20 EEG System) Cathode: contralesional M1	2 weeks (5)	CIMT Training affected arm 4h, 5x week Restrain of non-paretic hand 90% of hours awake (daily)	Prim.: JTHFT, Handgrip strength, UE-FMA, MAL Transcallosal Inhibition (TI), MEPs	1 month
(Cunningham et al., 2015)	Hemiparesis	12	33.33	A: 63.6 S: 58.8 Total: 61 ± 9	Chronic	1 mA A: 30 min, S: 30-60 s During 35 cm²	Anode: center ± 2.5 cm anterior to the ipsilesional M1 that evoked the most optimal paretic hand movements with TMS Cathode: contralesional supraorbital area	5 weeks (3)	CIMT 30 min 2x day (3x week)	UE-FMA, NHPT, MAL, fMRI (MEPs, cortical map size)	/
(Edwards et al., 2019)	Hemiparesis	82	39	Total: 67.8	Chronic	2 mA A: 20 min S: 30 s ramped up + 30 s ramped down (2x) Immediately before 35 cm²	Anode: centered 5 cm lateral to the vertex Cathode: contralateral supraorbital area	12 weeks (3)	Robot-assisted arm training ± 1h	Prim.: UE-FMA Sec.: WMFT, BI, SIS, MRC, TMS measures (RMT, MEPs)	6 months

						Intervention				Outcome	
	Disability	Number of participants	% Women	Mean age (years) ±SD	Recovery stage	Parameters Intensity duration Electrode size	Positioning Active electrode Refference electrode	Total intervention duration (sessions per week)	Other therapy	Outcome measures	Follow up
Upper extremity											
(Figlewski et al., 2017)	Hemiparesis	44	29.55	A: 60 ± 11 S: 61 ± 10	Subacute Chronic	1.5 mA A: 30 min, S: 30 s During 35 cm²	Anode: ipsilesional M1 (C3 or C4, International 10-20 EEG System) Cathode: contralateral supraorbital region	2 weeks (4-5)	CIMT 6h daily, restrain of nonparetic hand during 90% of hours awake	Prim.: WMFT-Functional Ability Scale (WMFT-FAS) Sec.: WMFT Performance Time (WMFT TIME), Handgrip strength, Lifting Cuff Weights	/
(Fusco, Assenza, et al., 2014)	Hemiparesis	14	42.86	C: 56.4 S: 60 Total: 58.36 ± 14.35	Acute Subacute	1.5 mA (S: 0 mA) C: 10 min, S: 10 min. Imediately before 35 cm²	Cathode: contralesional M1 (C3-C4 according to International 10-20 EEG System) Anode: noncephalic side, above R. shoulder, contralateral to the electric circuit of the heart	2 weeks (5)	Motor Rehabilitation session (upper limb and locomotor training) 45 min 2x day	Canadian Neurological scale (CNS), BI, NHPT, Handgrip strength, UE-FMA Timed Up and Go Test, 6 Minutes Walking Test, 10 Meter Walking Test, Rivermead Mobility Index, Functional Ambulation Classification	1 month + after inpatient rehabilitation
(Goodwill, Teo, Morgan, Daly, & Kidgell, 2016)	Hemiparesis	15	66.67	B: 57.6 S: 56.1 Total: 56.9	Chronic	1.5 mA B: 20 min, S: 5 s During 25 cm²	Anode: ipsilesional M1 (representation ECR) Cathode: contralesional M1 (representation ECR)	3 weeks (3)	Individual supervized Upper Limb Training 40 min	Motor Assement Scale, Handgrip strength, Tardieu scale, Mmax and pre-stimulus RmsEMG, Cortical excitability: AMT, MEPs, Laterality Index, Cortical Silent Period, Short-interval intracortical inhibition	3 weeks
(Hesse et al., 2011)	Hemiparesis	96	38.54	A: 63 ± 10.5 C: 65.4 ± 8.6 S: 65.6 ± 10.3	Subacute	2 mA (A, C) 0 mA (S) 20 min During 35 cm²	A: anode: presumed hand area of the lesioned hemisphere (C3 position according to the 10-20 EEG System) cathode: above the the contralateral orbit (C4) C: cathode: persumed hand area of the nonlesioned hemisphere (C3) anode: above the contralateral orbit (C4) S: like A or C	6 weeks (5)	Robot-assisted Bi-Manu Track 20 min (5x week) Comprehensive rehabilitaion program 45 min indivual PT 5x week 30 min individual OT (4x week) Ergometer training (5x week)	Prim.: UE-FMA, ARAT Sec.: BI, Box and Block Test, MRC, MAS	3 months
(Ilic et al., 2016)	Hemiparesis	26	34.62	A: 58.3 ± 7.7 S: 62 ± 3.9 Total: 60 ± 6.4	Chronic	2 mA A: 20 min, S: 60 s Immediately before 25 cm²	Anode: ipsilesional M1 hand area (C3-C4, International 10-20 EEG System) Cathode: contralesional supraorbital region (Fp1 or Fp2)	2 weeks (5)	OT 45 min	Prim: modified JTHFT Sec: Handgrip strength, UE-FMA	1 month
(Kim et al., 2010)	Hemiparesis	18	38.89	A: 55.3 ± 16.4 C: 53.6 ± 14.9 S: 62.9 ± 9.2	Acute Subacute	2 mA A, C: 20 min, S: 1 min During 25 cm²	A, S: anode: ipsilesional M1 (hot-spot of paretic FDI (first dorsal interossei)) Cathode: supraorbital region C: cathode: contralesional M1 (hot-spot of the FDI) Anode: supraorbital region	2 weeks (5)	OT 30 min	UE-FMA, modified BI	6 months
(Lindenberg, Renga, Zhu, Nair, & Schlaug, 2010)	Hemiparesis	20	25	B: 61.7 ± 14.7 S: 55.8 ± 12.9	Chronic	1.5 mA B: 30 min, S: ramped up and down over 30 s During 16.3 cm²	Anode: ipsilesional M1 (C3 and C4 International 10-20 EEG System) Cathode: contralesional M1 (C3 and C4 Interational 10-20 EEG System)	1 week (5)	PT and OT 60 min	Prim.: UE-FMA Sec.: WMFT, fMRI	1 week

						Intervention				Outcome	
	Disability	Number of participants	% Women	Mean age (years) ±SD	Recovery stage	Parameters Intensity duration Electrode size	Positioning Active electrode Refference electrode	Total intervention duration (sessions per week)	Other therapy	Outcome measures	Follow up
Upper extremity											
(Mortensen, Figlewski, & Andersen, 2016)	Hemiparesis	15	46.67	A: 65,5 S: 59.3 Total: 62.6	Chronic	1.5 mA A: 20 min, S: 30 s During 35 cm²	Anode: ipsilesional M1 (C3 and C4, International 10-20 EEG System) Cathode: contralesional suborbital region	5 days	OT 30 min	Prim.: JTHFT Sec: SIS, Handgrip strength	1 week
(Nair, Renga, Lindenberg, Zhu, & Schlaug, 2011)	Hemiparesis	14	35.71	C: 61 ± 12 S: 56 ± 15 Total: 55.8	Chronic	1 mA C: 30 min, S: ramped up and down During NA	Cathode: contralesional motor region (C3 or C4 of the International 10-20 EEG System) Anode: contralateral supraorbital region	1 week (5)	OT 60 min	Prim: Range of Motion (ROM), UE-FMA Sec.: fMRI	1 week
(Rabadi & Aston, 2017)	Hemiparesis	16	0	C: 62 ± 11 S 63 ± 6 Total: 62 ± 9	Acute	1 mA C: 30 min, S: 30 s Before 35 cm²	Cathode: contralesional M1 hand area (C3/4, International 10-20 EEG System) Anode: contralateral suborbital area	2 weeks (5)	Standard 3h in-patient rehabilitation therapy 1h additional OT	Prim: ARAT Sec.: Functional Independance Measure (FIM), FIM - Activities of Daily Living (FIM-ADL)	3 months
(Rocha et al., 2016)	Hemiparesis	21	28.57	C: 58.5 A: 58.3 S: 58.5	Chronic	1 mA A: 13 min, C: 9 min, S: 30 s Before 35 cm²	A, S: anode: ipsilesional M1 (C3 or C4 accoring to 10-20 EEG System) Cathode: above supraorbital region C: cathode: contralesional M1 Anode: above the supraorbital region	4 weeks (3)	mCIMT Intensive training paretic limb 1h (3x week) Conventional therapy 6h daily	Prim: UE-FMA Sec.: MAL, Handgrip strength	1 month
(Triccas et al., 2015)	Hemiparesis	23	39.13	A: 64.3 S: 62.5 Total: 63.4 ± 12	Subacute Chronic	1 mA A: 20 min, S: faded-in and faded-out over 10 s During 35cm²	Anode: ipsilesional M1 (C3 and C4 of the International 10-20 EEG System) Cathode: contralateral supraorbital region	8 weeks (2-3)	Robot Therapy 1h	Prim.: UE-FMA Sec.: ARAT, MAL, SIS	3 months
(Viana et al., 2014)	Hemiparesis	20	20	A: 56 ± 10.2 S: 55 ± 12.2	Chronic	2 mA A: 13 min, S: 30 s NA 35 cm²	Anode: ipsilesional M1 (C3 or C4, International 10-20 EEG System) Cathode: above contralateral orbit	5 weeks (3)	Virtual Reality Training 1h	Prim: UE-FMA, WMFT Sec: MAS, Handgrip strength, Stroke Specific Quality of Life Scale	/

Note : A, anodal tDCS group; AMT, active motor threshold; ARAT, Action Research Arm Test; B, bihemispheric tDCS group; BI, Barthel Index; C: cathodal tDCS group; CIMT, Constraint-induced movement therapy; ECR, m. extensor carpi radialis; JTHFT, Jebsen-Taylor Hand Function Test; L., left; MAL, Motor Activity Log rating scale; MAS, Modified Aschworth Scale; MEPs, Motor Evoked Potentials; MRC, Medical Research Council motor power score; M1, Primary Motor Cortex; NA, not applicable; OT, occupational therapy; Prim., primary; PT, physical therapy; R., right; S, sham group; Sec., secondary; SIS, Stroke Impact Scale; SLT, Speach and Language Therapy; UE-FMA, Upper extremity Fugl-Meyer Assessment; WMFT, Wolf Motor Function Test; NHPT, Nine-Hole Peg Test

4.3.2 Aphasia

Spielmann et al. (2018) primarily investigated the Boston Naming test (BNT). Within group analysis showed that both groups scored significantly ($p<0.001$) better immediately after intervention and at six months follow-up. There were no significant ($p=0.725$) between group changes at any time.

Polanowska, Lesniak, Seniow, Czepiel, et al. (2013) used a computerized oral naming test which is a modified version of the Boston Naming test (mBNT), containing 40 items of the BNT. For the scoring, a distinction is made between Naming accuracy and Naming time. Within group comparison showed significant (anodal: $r=0.62$, $p=0.001$; sham: $r=0.55$, $p=0.014$) changes for both groups at Naming accuracy, which remained stable at three months follow-up (anodal: $r=0.56$, $p=0.004$; sham: $r=0.63$, $p=0.005$). At the subdomain Naming time, the anodal group was the only one that improved at both assessment times compared to baseline with an effect size of respectively 0.61 ($p=0.002$) and 0.45 ($p=0.02$). Between group comparisons did not show differences at any measuring point.

Polanowska, Lesniak, Seniow, and Czlonkowska (2013) used the short version of the Boston Diagnostic Aphasia Examination (BDAE). It contains BDAE-Naming (BDAE-N), BDAE-Comprehension (BDAE-C) and BDAE-Repetition (BDAE-R). Results for the BDAE-N and BDAE-C were significant for the anodal and sham group at the end of treatment (anodal: BDAE-N $p=0.001$, BDAE-C $p=0.001$; sham BDAE-N $p=0.001$, BDAE-C $p=0.019$) and at three months follow-up (anodal: BDAE-N $p=0.01$, BDAE-C $p=0.001$; sham BDAE-N $p=0.004$, BDAE-C $p=0.001$). Between group differences were not significant. Results of the BDAE-R showed significant improvements for the anodal group at post intervention ($p=0.005$) and follow-up ($p=0.006$). The sham group only improved significantly at follow-up ($p=0.015$). Between group differences were not significant at any time.

Results regarding aphasia can be found in table 8.

Table 8

Aphasia: results of clinical outcome measures

		(Polanowska, Lesniak, Seniow, Czepiel, & Czlonkowska, 2013)	(Polanowska, Lesniak, Seniow, & Czlonkowska, 2013)	(Spielmann, van de Sandt-Koenderman, Heijenbrok-Kal, & Ribbers, 2018b)
ASRS	WG: Post1 - Pre	NA	NA	NA
	WG: Post2 - Pre	NA	NA	NA
	BG: Post1 - Pre	NA	NA	A - S: NS
	BG: Post2 - Pre	NA	NA	A - S: NS
Boston Naming Test	WG: Post1 - Pre	NA	NA	A: * S: *
	WG: Post2 - Pre	NA	NA	A: * S: *
	BG: Post1 - Pre	NA	NA	A - S: NS
	BG: Post2 - Pre	NA	NA	A - S: NS
Short version of BDAE	WG: Post1 - Pre	NA	Naming A: 49.7 ± 18.8 - 37.9 ± 22.8* S: 47.7 ± 21.8 - 40.4 ± 22.3* Comprehension A: 50.7 ± 11.5 - 45.9 ± 12.7* S: 50.1 ± 13 - 46.3 ± 11.7* Repetition A: 10.3 ± 2.9 - 8.2 ± 3.9* S: 8.5 ± 3.7 - 8 ± 3.4	NA
	WG: Post2 - Pre	NA	Naming A: 50.7 ± 23.6 - 37.9 ± 22.8* S: 47.3 ± 22.6 - 40.4 ± 22.3* Comprehension A: 51.2 ± 11.6 - 45.9 ± 12.7* S: 52.9 ± 8.6 - 46.3 ± 11.7* Repetition A: 10.1 ± 8.3 - 8.2 ± 3.9* S: 9.2 ± 4.3 - 8 ± 3.4*	NA
	BG: Post1 - Pre	NA	Naming A - S: NS Comprehension A - S: NS Repetition A - S: NS	NA
	BG: Post2 - Pre	NA	Naming A - S: NS Comprehension A - S: NS Repetition A - S: NS	NA
Computerized Oral Naming Test Accuracy, *Time* (Median ± IQR)	WG: Post1 - Pre	A: 52 ± 42 - 42 ± 43* S: 55 ± 45.3 - 46.5 ± 43.8* *A: 2.2 ± 1.2 - 2.9 ± 1.4** *S: 2.9 ± 1.5 - 2.6 ± 2*	NA	NA
	WG: Post2 - Pre	A: 62 ± 28.5 - 42 ± 43* S: 58.5 ± 36.8 - 46.5 ± 43.8* *A: 2.5 ± 1.3 - 2.9 ± 1.4** *S: 3 ± 1.7 - 2.6 ± 2*	NA	NA
	BG: Post1 - Pre	A - S: NS *A - S: NS*	NA	NA
	BG: Post2 - Pre	A - S: NS *A - S: NS*	NA	NA

Note: A, anodal tDCS group; ASRS, Aphasia Severity Rating Scale; BDAE, Boston Diagnostic Aphasia Examination; BG, between group; IQR, interquartile range; NA, not applicable; NS, not significant; Post1, after intervention; Post2, follow-up; Pre, baseline; S, sham group; WG, within group; *, significant ($p \leq 0.05$)

4.3.3 Upper extremity

See table 9 for details of the results.

4.3.3.1 Action Research Arm Test (ARAT)

Of the 17 included studies that investigated the upper limb function, three studies used the ARAT. Triccas et al. (2018) showed a significant effect of time ($p<0.001$). No group or time x group effect was found to be significant. Rabadi and Aston (2017) showed no between or within group effects. Results at follow-up were not mentioned. Allman et al. (2016) showed significant within group improvement at both post-intervention (sham: $p<0.05$, anodal: $p<0.05$) and at three months follow-up (sham: $p<0.05$, anodal: $p<0.05$) for sham and anodal tDCS. They showed significant between group differences at three months follow-up in favour of the anodal group ($p<0.001$). The anodal and sham tDCS group differed significantly across all measuring points ($p=0.031$).

4.3.3.2 Upper Extremity Fugl-Meyer Assessment (UE-FMA)

This test was used by 13 studies. Allman et al. (2016), Cunningham et al. (2015), Edwards et al. (2019), Hesse et al. (2011), Rocha et al. (2016) Triccas et al. (2015) and Viana et al. (2014) all found significant within group results at post-intervention in the anodal group ($p<0.05$, $p=0.028$, $p<0.0001$, $p<0.001$, $p\leq0.05$, $p<0.001$, $p\leq0.05$). Allman et al. (2016), Edwards et al. (2019), Rocha et al. (2016) and Triccas et al. (2015) all showed significant within group results in the anodal group at follow-up ($p<0.05$, $p<0.0001$, $p\leq0.05$, $p=0.012$). At post-intervention, only Rocha et al. (2016) found a significant difference between the anodal and the sham group ($p\leq0.05$). For the anodal group, no significant between group differences were found by any of the studies (Allman et al., 2016; Cunningham et al., 2015; Edwards et al., 2019; Hesse et al., 2011; Ilic et al., 2016; Triccas et al., 2015; Viana et al., 2014).

The cathodal group showed significant within group differences at post-intervention ($p<0.001$, $p\leq0.05$) (Fusco et al., 2014; Hesse et al., 2011; Rocha et al., 2016) and at follow-up ($p\leq0.05$) (Rocha et al., 2016). Nair et al. (2011) found significant within group differences for both the cathodal ($p<0.05$) and sham group ($p<0.05$) at one week follow-up. Fusco et al. (2014) found a significant improvement in both the cathodal (significant time effect, $p=0.045$) and sham

group (significant time effect, p=0.003) over the course of in-patient rehabilitation. Hesse et al. (2011) also found significant within group differences for the anodal and sham group at post-intervention (p<0.001). Kim et al. (2010) showed better results in the cathodal group compared to the sham group (p<0.05), but no differences were found in the anodal tDCS group at one-week follow-up.

Bolognini et al. (2011) showed a significant time effect (p<0.001) for the bihemispheric group, no post-hoc analysis was performed. For the sham group, no significant time effect was mentioned, while Lindenberg et al. (2010) did find a significant difference at both measuring points (p<0.001, p<0.001). For the tDCS group, significant differences at both measuring points were found (p<0.01, p<0.001). Between group changes at both post-intervention and at one-week follow-up were found significant in favour of the bihemispheric group (p<0.001, p<0.001) by Lindenberg et al. (2010). Bolognini et al. (2011) was the only one showing a significant time x group difference in favour of the tDCS group but did not use post-hoc analysis (p<0.01).

4.3.3.3 Wolf Motor Function Test (WMFT)

The WMFT was investigated by five studies. Allman et al. (2016) and Edwards et al. (2019) both found significant within group differences at post-intervention (p<0.05, p<0.0001) and at follow-up (p<0.05, p<0.0001) in favour of the anodal group. For the sham group, Allman et al. (2016) found a significant within group difference at post intervention (p<0.05) only, while Edwards et al. (2019) found significant differences at post-intervention (p=0.0003) as well as at six months follow-up (p=0.0001). Figlewski et al. (2017) and Viana et al. (2014) found a significant within group change for both the sham (p<0.01, p≤0.05) and the anodal group (p<0.01, p≤0.05) at post-intervention. A significant between group difference in favour of anodal tDCS at three months follow-up (p<0.001) was found by Allman et al. (2016). The sham and real tDCS group differed significantly across all time points (p<0.037) (Allman et al., 2016). Figlewski et al. (2017) found a significant between group difference in favour of anodal tDCS at post-intervention (p<0.001, p=0.03). Lindenberg et al. (2010) showed significant within group differences in both sham (p=0.020, p=0.031) and bihemispheric tDCS (p<0.001, p<0.001), and between group analysis was in favour of bihemispheric tDCS (p=0.005, p-0.007) at both post-intervention and at one-week follow-up.

4.3.3.4. Jebsen-Taylor Hand Function Test (JTHFT)

Significant within group improvements were found at post-intervention ($p<0.001$) and at one-month follow-up ($p<0.001$) for the anodal tDCS group. No results for the sham group were found significant. (Ilic et al., 2016). Mortensen, Figlewski, and Andersen (2016) showed a significant time effect for both the anodal and sham group, but no post-hoc analysis was performed. Significant between group differences in favour of the anodal group at post-intervention ($p<0.001$) and at one-month follow-up ($p<0.001$) were found by Ilic et al. (2016), while Mortensen et al. (2016) did not find any significant between group results.

For the bihemispheric tDCS group, there was a significant within group change at post-intervention ($p<0.01$) and at one-month follow-up ($p<0.01$). There were no significant improvements shown in the sham group. Between group analysis showed a significant difference in favour of the real tDCS at both measuring points ($p<0.01$, $p<0.01$) (Bolognini et al., 2011).

4.3.3.5 Barthel Index (BI)

Fusco et al. (2014) found a significant within group improvement for both the cathodal (significant time effect, $p=0.012$) and sham group (significant time effect $p=0.001$). Hesse et al. (2011) did not mention within group results of significance. Both studies did not find significant between group differences. Kim et al. (2010) did not find a significant improvement between the three groups, anodal, cathodal and sham**,** at six months follow-up, the other results were not mentioned.

4.3.3.6 Handgrip strength

Concerning handgrip strength, Figlewski et al. (2017) and Viana et al. (2014) showed significant within group improvements for both the anodal ($p<0.001$, $p\leq0.05$) and the sham group ($p<0.001$, $p\leq0.05$) at post-intervention. Mortensen et al. (2016) only found a significant time effect for the anodal group ($p<0.05$), but no post-hoc analysis was performed. Improvements of the sham group were not significant at any measuring point. Regarding the between group comparison, Mortensen et al. (2016) showed a significant difference in favour of the anodal group at post-intervention ($p=0.025$), while Figlewski et al. (2017), Ilic et al. (2016) and Viana et al. (2014) did not show any significant results at any point in time.

Fusco et al. (2014) did not find any significant change for the cathodal or sham group, neither within group nor between group.

In the bihemispheric group, there was a significant time effect ($p<0.05$), but no post-hoc analysis was used. The sham group did not show this effect. A significant time x group interaction was found, but no post-hoc analysis was performed (Bolognini et al., 2011). Goodwill et al. (2016) did not show any significant results at both post-intervention and at three weeks follow-up.

Rocha et al. (2016) found a significant within group difference for the sham group at post-intervention ($p\leq0.05$), but this was not maintained after one-month follow-up.

4.3.3.7 Motor Activity Log rating scale (MAL)

The MAL consists of two parts, amount and quality, and was used by four studies. Bolognini et al. (2011) found significant within group differences for the bihemispheric ($p<0.05$) and sham group ($p<0.05$) on the component amount at one-month follow-up ($p<0.05$). For the component quality, there were significant changes for both groups at post-intervention and at one-month follow-up ($p<0.05$). Between group differences were not significant. The study by Cunningham et al. (2015) only mentioned a significant difference in the sham group at post-intervention ($p=0.028$) for the component quality. Rocha et al. (2016) showed significant improvements on the components amount and quality in both the anodal ($p\leq0.05$) and cathodal groups ($p\leq0.05$) at post-intervention. At follow-up, all groups showed significant changes on the component amount ($p\leq0.05$). As for quality, all but the sham group showed significant improvements ($p\leq0.05$) (Rocha et al., 2016). Triccas et al. (2015) found a significant time effect ($p<0.002$) but group or time x group interactions were not significant. No between group differences were mentioned by any of the studies at any point in time (Bolognini et al., 2011; Cunningham et al., 2015; Rocha et al., 2016; Triccas et al., 2015).

4.3.3.8 Modified Ashworth Scale (MAS)

Considering the MAS, Hesse et al. (2011) did not mention at any measuring point if the within results were significant or not. Between group analysis did not reveal significant results for any group at both post-intervention and at three months follow-up. Viana et al. (2014) did not find any significant results.

4.3.3.9 Nine-Hole Peg Test (NHPT)

In the study by Fusco et al. (2014), all participants improved significantly independent of group allocation (significant time effect, p=0.007). No significant between group changes were found. The study by Cunningham et al. (2015) did not show any significant between or within group results at any time.

4.3.3.10 Medical Research Council motor power (MRC)

Hesse et al. (2011) did not mention within group results of significance for the anodal, cathodal and sham groups at both post-intervention and follow-up. The study found no significant between group differences at any measuring point.

4.3.3.11 Motor Assessment Scale

Goodwill et al. (2016) found significant within group changes for both the bihemispheric ($p<0.001$) and sham tDCS group ($p<0.001$) at post-intervention. After three weeks follow-up, there only was a significant improvement in the bihemispheric group ($p<0.001$). Between group comparison only showed a significant difference at follow-up in favour of the bihemispheric group (p=0.002).

4.3.3.12 Functional Impact Measure (FIM)

Results for the FIM were not significant between or within the groups at both post-intervention and at three months follow-up (Rabadi & Aston, 2017).

4.3.3.13 Range of Motion (ROM)

Nair et al. (2011) was the only one to show a significant between group difference at post-intervention ($p<0.04$) and at one-week follow-up ($p<0.04$) in favour of the cathodal group. Within group results were not mentioned.

Table 9

Upper extremity: results of clinical outcome measures

		(Allman et al., 2016)	(Bolognini et al., 2011)	(Cunningham et al., 2015)	(Edwards et al., 2019)	(Figlewski et al., 2017)	(Fusco, Assenza, et al., 2014)	(Goodwill, Teo, Morgan, Daly, & Kidgell, 2016)	(Hesse et al., 2011)	(Ilic et al., 2016)	(Kim et al., 2010)	(Lindenberg, Renga, Zhu, Nair, & Schlaug, 2010)	(Mortensen, Figlewski, & Andersen, 2016)	(Nair, Renga, Lindenberg, Zhu, & Schlaug, 2011)	(Rabadi & Aston, 2017)	(Rocha et al., 2016)	(Triccas et al., 2015)	(Viana et al., 2014)
ARAT	WG: Post1 - Pre	A: 29.91 ± 21.54 - 20.27 ± 17.37* S: 32.54 ± 21.54 - 26.27 ± 20.17*	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	C: 10.1 ± 13.5 S: 1.7 ± 4.4	NA		NA
	WG: Post2 - Pre	A: 30.45 ± 20.92 - 20.27 ± 17.37* S: 31.31 ± 21.84 - 26.27 ± 20.17*	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	G: X^2 = 1.403 TxG: X^2 = 2.293	NA
	BG: Post1 - Pre	A - S: NS	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	C - S: NS	NA	T: *	NA
	BG: Post2 - Pre	A - S: 5.763 CI [1.560 to 9.966]*	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA		NA
UE-FMA	WG: Post1 - Pre	A: 50.63 ± 11.16 - 38.9 ± 15.89* S: 45.53 ± 14.62 - 36.42 ± 17.38*	B: 31.7 - 25.4: T * S: T^{NS} No post-hoc analysis	A: 47.5 ± 12 - 40.67 ± 14* S: 49.33 ± 10 - 46.67 ± 11	A: 32 ± 18.8 - 25.7 ± 16.3* S: 33.4 ± 19.2 - 25.3 ± 16.3*	NA	C: T* S: T* no post-hoc analysis	NA	A: 19.1 ± 14.4 - 7.8 ± 3.8* C: 18.9 ± 10.5 - 7.9 ± 3.4* S: 19.2 ± 15.0 - 8.2 ± 4.4*	NA	NA	B: 43.8 ± 12.3 - 38.2 ± 13.3* S: 41 ± 11.8 - 39.8 ± 11.5*	NA	NA	NA	C: 12.7 ± 5.4* A: 19.4 ± 6.2* S: 7.7 ± 8.3	A: 8.73* S: 7.73*	A: 9.3 ± 5.7* S: 7.5 ± 7.1*
	WG: Post2 - Pre	A: 48.18 ± 14.35 - 38.90 ± 15.89* S: 43.15 ± 16.29 - 36.42 ± 17*	B: 33.3 - 25.4: T * S: T^{NS} No post-hoc analysis	NA	A: 32.3 ± 18.8 - 25.7 ± 16.3* S: 35.1 ± 19.3 - 25.3 ± 16.3*	NA		NA	A: 23.2 ± 18.3 - 7.8 ± 3.8^{NA} C: 23.5 ± 14.5 - 7.9 ± 3.4^{NA} S: 22.5 ± 17.1 - 8.2 ± 4.4^{NA}	NA	NA	B: 20.7% ± 18.9%* S: 3.2% ± 3.2%*	NA	C: 13.9% ± 7.7%* S: 6.4% ± 7.2%*	NA	C: 13.4 ± 3.8* A: 21.4 ± 12* S: 8 ± 13.4	A: 7.18* S: 7.09*	NA
	BG: Post1 - Pre	A - S: NS		A - S: NS	A - S: NS	NA	C - S: NS	NA	NS	A - S: NS	NA	B - S: *	NA	NA	NA	C - S: 5.0 CI [-3.1 to 3.2] A - S: 11.7 CI [3.1 to 20.3]* A - C: 6.7 CI [-13.47 to 0.07]	A - S: NS	A - S: 1.6 CI [-10.9 to 16.5]
	BG: Post2 - Pre	A - S: 2.898 CI [-2.136 to 7.932]	B - S: TxG * No post-hoc analysis	NA	A - S: NS	NA	C - S: NS	NA	NS	A - S: NS	C - S: * A - S: NS A - C: NS	B - S: *	NA	NA	NA	NA	A - S: NS	NA
WMFT (s)	WG: Post1 - Pre	A: 47.18 ± 17.46 - 37.91 ± 20.21* S: 48 ± 23.42 - 39.65 ± 25.39*	NA	NA	A: 68.5 ± 23.2 - 56 ± 47.2* S: 76.1 ± 54 - 60 ± 48.3*	A: 52 ± 10.2 - 43.6 ± 9.7* S: 51.3 ± 9.9 - 45.9 ± 10*	NA	NA	NA	NA	NA	B: 0.74 ± 0.48 - 0.87 ± 0.55* S: 0.79 ± 0.47 - 0.83 ± 0.49*	NA	NA	NA	NA	NA	A: 0.4 ± 0.1* S: 0.3 ± 0.2*
	WG: Post2 - Pre	A: 48.36 ± 18.19 - 37.91 ± 20.21* S: 43.09 ± 23.78 - 39.65 ± 25.39	NA	NA	A: 72.7 ± 54.5 - 56 ± 47.2* S: 51.8 ± 57.8 - 60 ± 48.3*	NA	NA	NA	NA	NA	NA	B: 0.73 ± 0.49 (-19.1% ± 9%)* S: 0.78 ± 0.46 - 0.83 ± 0.49 (-6% ± 10.5%)*	NA	NA	NA	NA	NA	NA	NA
	BG: Post1 - Pre	A - S: NS	NA	NA	A - S: NS	A - S: 2.9 (0.25 to 5.57)*	NA	NA	NA	NA	NA	B - S: *	NA	NA	NA	NA	NA	A - S: 0.1 CI [-1 to 1.2]
	BG: Post2 - Pre	A - S: 6.871 CI [3.411 to 10.331]*	NA	NA	A - S: NS	NA	NA	NA	NA	NA	NA	B - S: *	NA	NA	NA	NA	NA	NA
JTHFT	WG: Post1 - Pre	NA	B: 70s - 102s* S: NS	NA	NA	NA	NA	NA	NA	A: * S: NS	NA	NA	A: 29.3 ± 5.6%: T * S: 23.4 ± 9.3%: T * No post-hoc analysis	NA	NA	NA	NA	NA
	WG: Post2 - Pre	NA	B: 72s - 102s* S: NS	NA	NA	NA	NA	NA	NA	A: * S: NS	NA	NA	A: 30.5 ± 7.1%: T * S: 24.2 ± 12.2%: T * No post-hoc analysis	NA	NA	NA	NA	NA
	BG: Post1 - Pre	NA	B - S: *	NA	NA	NA	NA	NA	NA	A - S: *	NA	NA	A - S: NS	NA	NA	NA	NA	NA
	BG: Post2 - Pre	NA	B - S: *	NA	NA	NA	NA	NA	NA	A - S: *	NA	NA	A - S: NS	NA	NA	NA	NA	NA
BI	WG: Post1 - Pre	NA	NA	NA	NA	NA	C: T*	NA	A: 53.6 ± 14.5 - 34.1 ± 6.4NA C: 59.2 ± 12.4 - 34.2 ± 7.6NA S: 56.3 ± 15.5 - 35.0 ± 7.8NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	WG: Post2 - Pre	NA	NA	NA	NA	NA	S: T* no post-hoc analysis	NA	A: 64.2 ± 19.7 - 34.1 ± 6.4NA C: 71.6 ± 15.7 - 34.2 ± 7.6NA S: 65.5 ± 20.7 - 35.0 ± 7.8NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	BG: Post1 - Pre	NA	NA	NA	NA	NA	C - S: NS	NA	NS	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	BG: Post2 - Pre	NA	NA	NA	NA	NA	C - S: NS	NA	NS	NA	C - S: NS C - A: NS A - S: NS	NA	NA	NA	NA	NA	NA	NA	NA
Handgrip strength	WG: Post1 - Pre	NA	B: 3.2 - 2.1: T * S: T^{NS} No post-hoc-analysis	NA	NA	A: 21.1 ± 10.8 - 18.5 ± 10.7* S: 19.7 ± 9.3 - 17.3 ± 9.3*	C: -1.4 ± 1.9 S: 1 ± 2	B: NS S: NS	NA	NA	NA	NA	A: 12% IQR [3.7 - 23.0]: T * S: -1.3% IQR [-4.4 - 10.6] No post-hoc analysis	NA	NA	C: 1.4 ± 2.7 A: 5.1 ± 9.8 S: 2.5 ± 1.8*	NA	A: 1.2 ± 3.2* S: 2.7 ± 4.1*
	WG: Post2 - Pre	NA	B: 3.1 - 2.1: T * S: T^{NS} No post-hoc analysis	NA	NA	NA	C: NS S: NS	B: NS S: NS	NA	NA	NA	NA	A: 23% IQR [5.0 - 35.2]: T * S: 12.2% IQR [4.8 - 18.1] No post-hoc analysis	NA	NA	C: 2.3 ± 2 A: 7.6 ± 9 S: 1.6 ± 4.6	NA	NA
	BG: Post1 - Pre	NA	TxG*: no post-hoc analysis	NA	NA	A - S: NS	C - S: NS	B - S: NS	NA	A - S: NS	NA	NA	A - S: *	NA	NA	C - S: -1.1 CI [-3.8 to 1.6] A - S: 2.6 CI [-5.7 to 10.8] A - C: 3.7 CI [-12.07 to 4.67]	NA	A - S: -1.5 CI [-6 to 7.7]
	BG: Post2 - Pre	NA	TxG*: no post-hoc analysis	NA	NA	NA	C - S: NS	B - S: NS	NA	A - S: NS	NA	NA	A - S: NS	NA	NA	NA	NA	NA

		(Allman et al., 2016)	(Bolognini et al., 2011)	(Cunningham et al., 2015)	(Edwards et al., 2019)	(Figlewski et al., 2017)	(Fusco, Assenza, et al., 2014)	(Goodwill, Teo, Morgan, Daly, & Kidgell, 2016)	(Hesse et al., 2011)	(Ilic et al., 2016)	(Kim et al., 2010)	(Lindenberg, Renga, Zhu, Nair, & Schlaug, 2010)	(Mortensen, Figlewski, & Andersen, 2016)	(Nair, Renga, Lindenberg, Zhu, & Schlaug, 2011)	(Rabadi & Aston, 2017)	(Rocha et al., 2016)	(Triccas et al., 2015)	(Viana et al., 2014)
MAL Amount/ *Quality*	WG: Post1 - Pre	NA	B: NS S: NS *B: ** *S: **	A: 1.9 ± 1.3 - 1.3 ± 1 S: 2.4 ± 1.1 - 1.4 ± 0.85 *A: 2.1 ± 1.4 - 1.4 ± 0.9* *S: 2.4 ± 0.8 - 1.5 ± 0.58**	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	C: 1.11 ± 0.8* A: 0.97 ± 0.6* S: 0.76 ± 0.8 *C: 1.03 ± 0.7** *A: 0.92 ± 0.5** *S: 0.56 ± 1.1*		NA
	WG: Post2 - Pre	NA	B: * S: * *B: ** *S: **	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	C: 1.5 ± 1* A: 1.3 ± 0.8* S: 1 ± 0.8* *C: 1.2 ± 0.6** *A: 1.4 ± 0.5** *S: 0.6.± 0.8*	G: F = 0.228 TxG: NS	NA
	BG: Post1 - Pre	NA	B - S: NS	A - S: NS *A - S: NS*	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	C - S: 0.34 CI [-0.6 to 1.3] A - S: 0.2 CI [-0.6 to 1.1] A - C: 0.14 CI [-0.68 to 0.96] *C - S: 0.49 CI [-0.6 to 1.6]* *A - S: 0.37 CI [-0.7 to 1.4]* *A - C: 0.11 CI [-0..31 to 0.53]*	T: F = 8.537*	NA
	BG: Post2 - Pre	NA	B - S: NS	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA		NA
MAS	WG: Post1 - Pre	NA	NA	NA	NA	NA	NA	NA	A: 3.3 ± 3.6 - 1.6 ± 2.9* C: 3.5 ± 4.9 - 1.0 ± 1.8* S: 3.5 ± 4.0 - 1.4 ± 2.7*	NA	NA	NA	NA	NA	NA	NA	NA	A: 0.4 ± 1.0 S: 0
	WG: Post2 - Pre	NA	NA	NA	NA	NA	NA	NA	A: 3.6 ± 6.9 - 1.6 ± 2.9* C: 3.5 ± 5.0 - 1.0 ± 1.8* S: 3.8 ± 5.5 - 1.4 ± 2.7*	NA	NA	NA	NA	NA	NA	NA	NA	NA
	BG: Post1 - Pre	NA	NA	NA	NA	NA	NA	NA	NS	NA	NA	NA	NA	NA	NA	NA	NA	A - S: 0.4 CI [-0.9 to 0.4]
	BG: Post2 - Pre	NA		NA	NA	NA	NA	NA	NS	NA	NA	NA	NA	NA	NA	NA	NA	NA
NHPT	WG: Post1 - Pre	NA	NA	A: 7.5 ± 3.7 - 3.7 ± 4.4 S: 4.2 ± 4.4 - 2.3 ± 4.5	NA	NA	C: T* S: T*	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	WG: Post2 - Pre	NA	NA	NA	NA	NA	no post-hoc analysis	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	BG: Post1 - Pre	NA	NA	A - S: NS	NA	NA	C - S: NS	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	BG: Post2 - Pre	NA	NA	NA	NA	NA	C - S: NS	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
MRC	WG: Post1 - Pre	NA	NA	NA	NA	NA	NA	NA	A: 11.9 ± 12.9 - 3.5 ± 3.6* C: 13.7 ± 10.4 - 2.9 ± 3.4* S: 12.8 ± 12.1 - 3.4 ± 3.2*	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	WG: Post2 - Pre	NA	NA	NA	NA	NA	NA	NA	A: 11.7 ± 14.4 - 3.5 ± 3.6* C: 13.5 ± 10.3 - 2.9 ± 3.4* S: 13.5 ± 14.3 - 3.4 ± 3.2*	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	BG: Post1 - Pre	NA	NA	NA	NA	NA	NA	NA	NS	NA	NA	NA	NA	NA	NA	NA	NA	NA
	BG: Post2 - Pre	NA	NA	NA	NA	NA	NA	NA	NS	NA	NA	NA	NA	NA	NA	NA	NA	NA
Motor Assessment Scale	WG: Post1 - Pre	NA	NA	NA	NA	NA	NA	B: 10 ± 1.4 - 6 ± 1.3 (62%)* S: 9 ± 2.3 - 6 ± 1.9 (43%)*	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	WG: Post2 - Pre	NA	NA	NA	NA	NA	NA	B: 10 ± 1.5 - 6 ± 1.3 (64%)* S: 8 ± 2.2 - 6 ± 1.9 (21%)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	BG: Post1 - Pre	NA	NA	NA	NA	NA	NA	B - S: 62% - 43%	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	BG: Post2 - Pre	NA	NA	NA	NA	NA	NA	B - S: 64% - 21%*	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

		(Allman et al., 2016)	(Bolognini et al., 2011)	(Cunningham et al., 2015)	(Edwards et al., 2019)	(Figlewski et al., 2017)	(Fusco, Assenza, et al., 2014)	(Goodwill, Teo, Morgan, Daly, & Kidgell, 2016)	(Hesse et al., 2011)	(Ilic et al., 2016)	(Kim et al., 2010)	(Lindenberg, Renga, Zhu, Nair, & Schlaug, 2010)	(Mortensen, Figlewski, & Andersen, 2016)	(Nair, Renga, Lindenberg, Zhu, & Schlaug, 2011)	(Rabadi & Aston, 2017)	(Rocha et al., 2016)	(Triccas et al., 2015)	(Viana et al., 2014)
FIM	WG: Post1 - Pre	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	C: 22.4 ± 15.7 S: 25.3 ± 5.3	NA	NA	NA
	WG: Post2 - Pre	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	C: 31.4 ± 18.1 S: 42.7 ± 14.9	NA	NA	NA
	BG: Post1 - Pre	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	C - S: NS	NA	NA	NA
	BG: Post2 - Pre	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	C - S: NS	NA	NA	NA
ROM	WG: Post1 - Pre	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	C: 19.2% ± 11.3% (NA) S: 3.6% ± 1.7% (NA)	NA	NA	NA	NA
	WG: Post2 - Pre	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	C: 17.5% ± 12.8% (NA) S: 4.2% ± 3.1% (NA)	NA	NA	NA	NA
	BG: Post1 - Pre	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	C - S: *	NA	NA	NA	NA
	BG: Post2 - Pre	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	C - S: *	NA	NA	NA	NA

Note: A, anodal tDCS group; ARAT, Action Research Arm Test; B, bihemispheric tDCS group; BG, between group; BI, Barthel Index; C, cathodal tDCS group; FIM, Functional Independance Measure; G, effect of group; IQR, interquartile range; JTHFT, Jebsen-Taylor Hand Function Test; MAL, Motor Activity Log rating scale; MAS, Modified Aschworth Scale; MRC, Medical Research Council motor power score; NA, not applicable; NHPT, Nine-Hole Peg Test ; NS, not significant; Post1, after intervention; Post2, follow-up; Pre, baseline; S, sham group; T, effect of time; TxG, time x group interaction; UE-FMA, upper extremity Fugl-Meyer Assessment; WG, within group; WMFT, Wolf Motor Function Test; *, significant ($p \leq 0.05$)

4.3.4 Neurophysiologic measures

Results are listed in table 10.

4.3.4.1 Voxel-based morphometry (VBM) and fractional anisotropy (FA)

VBM, used for measuring grey matter volume, and FA, measuring asymmetry of the corticospinal tract were investigated by Allman et al. (2016). Between group analysis revealed a significantly greater increase of grey matter in the anodal group compared to the sham group at both post-intervention ($p<0.05$) and at three months follow-up ($p<0.05$). No correlations with behavioural measures were found significant. For the FA, a positive correlation between the change in UE-FMA and baseline FA was found ($p=0.015$). Other correlations and within group results were not significant.

4.3.4.2 fMRI activity

There was a significant between group difference in favour of the anodal tDCS group compared with the sham group at both post-intervention ($p<0.05$) and at one-month follow-up ($p<0.05$). Correlations with behavioural measures were not significant (Allman et al., 2016). Lindenberg et al. (2010) found significant increases in fMRI activity in the bihemispheric tDCS group for the ipsilesional primary motor and premotor cortex when performing wrist and elbow movements compared to resting state ($p<0.05$). Contralesional inferior frontal gyrus only improved significantly between baseline and post-intervention in the bihemispheric group when performing wrist movements compared to rest ($p<0.05$). Results in the sham group were not significant.

4.3.4.3 Corticomotor map size

Cunningham et al. (2015) was the only one that found a significant decrease in the sham group of the ipsilesional hemisphere at post-intervention ($p=0.046$). No significant changes of map size were found for the contralateral hemisphere. A significant positive correlation between changes in UE-FMA and contralesional motor map size were found ($r=0.638$, $p=0.046$). The correlation between baseline UE-FMA and changes in contralesional motor map size was not found to be significant.

4.3.4.4 Active Motor Threshold (AMT)

Goodwill et al. (2016) investigated the AMT but did not find any significant between group results at either post-intervention or at three weeks follow-up.

4.3.4.5 Laterality Index (LI)

Goodwill et al. (2016) showed a significant decrease of LI in the bihemispheric tDCS group, at both post-intervention ($p<0.001$) and after three weeks follow-up ($p=0.03$), but not in the sham group. Lindenberg et al. (2010) showed a significant positive correlation between the change of LI and the change of WMFT in the bihemispheric tDCS group ($r=0.72$, $p=0.029$). No significant differences on the WMFT were found in the sham group and no correlations were found between LI and the UE-FMA in any group.

4.3.4.6 Motor Evoked Potentials (MEPs)

Three studies investigated MEPs. For MEP amplitude Bolognini et al. (2011) found a significant within group increase of amplitude in the ipsilesional hemisphere for the bihemispheric group ($p<0.05$) and a significant decrease in the contralesional hemisphere for both the bihemispheric and sham group at post-intervention ($p<0.05$). Goodwill et al. (2016) showed a significant increase in amplitude in the bihemispheric group for the paretic upper extremity at both post-intervention ($p<0.001$) and at three weeks follow-up ($p<0.001$). Within group analysis of the paretic upper extremity did not yield significant results in the sham group, nor were there significant results for the non-paretic limb in either group. Edwards et al. (2019) did not find any significant within group changes. None of the studies showed significant between group results (Bolognini et al., 2011; Edwards et al., 2019; Goodwill et al., 2016). At post-intervention, a significantly higher proportion of patients with a MEP higher or equal to 0.05 mV achieved five points or more on the UE-FMA compared with patients with a MEP lower than 0.05 mV (=0.018). This outcome was not maintained at six months follow-up (Edwards et al., 2019). Bolognini et al. (2011) showed a significant positive correlation between changes in MEPs amplitude from the ipsilesional hemisphere and UE-FMA scores ($r=0.67$, $p<0.01$).

4.3.4.7 Resting Motor Threshold (RMT)

Cunningham et al. (2015) did not find any significant results. In contrast, Edwards et al. (2019) found that RMT in the ipsilesional hemisphere decreased significantly in the anodal group at post-intervention ($p=0.029$), which was maintained at six months follow-up ($p=0.029$). Changes of RMT in the contralesional hemisphere were not significant in either group, nor were there significant between group results at any measuring point (Edwards et al., 2019).

4.3.4.8 Transcallosal Inhibition (TI)

At post-intervention, TI of the ipsilesional cortex by the contralesional motor cortex was reduced significantly in the bihemispheric tDCS group ($p<0.04$) while results in the sham group were not significant. TI of the ipsilesional on the contralesional motor cortex did not change in any group and none of the between group results were significant. A significant negative correlation was found between change of TI by contralesional to ipsilesional motor cortex and change of UE-FMA ($r=-0.81$, $p<0.01$) and JTHFT ($r=-0.55$, $p<0.02$) (Bolognini et al., 2011).

4.3.4.9 Ipsilateral Silent Period (ISP)

Results considering the ISP investigated by Cunningham et al. (2015), showed a significant increase at post-intervention in the anodal ($p=0.046$), but not in the sham group. The study also investigated interhemispheric inhibition. Anodal tDCS significantly increased the ability of the ipsilesional hemisphere to counter inhibition by the contralesional hemisphere at post-intervention ($p<0.05$). Other results were not significant.

4.3.4.10 Cortical Silent Period (CSP) and Short-Interval Intracortical Inhibition (SICI)

For the CSP of the non-paretic upper extremity, a significant increase of 33% was found in the bihemispheric group at post-intervention ($p=0.01$) and was maintained at three weeks follow-up ($p=0.04$). The sham tDCS did not yield significant outcomes. Between group analysis only showed a significant difference in favour of the real tDCS group at post-intervention ($p=0.04$). Results for SICI only showed a significant increase in the bihemispheric group for the non-paretic upper extremity at three weeks follow-up ($p<0.05$). None of the other, paretic and non-paretic, within group results were significant. Between group analysis showed a significant increase, in the non-paretic upper extremity, of 27% in the bihemispheric compared

to the sham group at six weeks follow-up (p=0.04). Other between group comparisons were not significant (Goodwill, Teo, Morgan, Daly, & Kidgell, 2016).

Table 10

Results of neurophysiologic outcome measures

	(Allman et al., 2016)	(Bolognini et al., 2011)	(Cunningham et al., 2015)	(Edwards et al., 2019)	(Goodwill, Teo, Morgan, Daly, & Kidgell, 2016)	(Lindenberg, Renga, Zhu, Nair, & Schlaug, 2010)
VBM	BG Post1 - Pre A - S: * BG Post2 - Pre A - S: *	NA	NA	NA	NA	NA
Correlation with clinical scores	NS	NA	NA	NA	NA	NA
FA asymmetrie of corticospinal tract	WG Post1 - Pre, Post2 - Pre A: NS S: NS	NA	NA	NA	NA	NA
Correlation with clinical scores	+ Corr. △UE-FMA/ baseline FA: *	NA	NA	NA	NA	NA
fMRI activity	BG Post1 - Pre, Post2 - Pre A - S: *	NA	NA	NA	NA	WG Post1 - Pre B: IL primary motor/ premotor cortex (wrist, elbow vs. rest) ↑ * B: CL IFG (wrist vs. rest) ↑ * S: IL primary motor/ premotor cortex: NS S: CL IFG: NS
Correlation with clinical scores	NS	NA	NA	NA	NA	NA
Corticomotor Map Size	NA	NA	CL HS WG Post1 - Pre A: NS S: NS BG Post1 - Pre A - S: NS IL HS WG Post1 - Pre A: NS S: ↓ *	NA	NA	NA
Correlation with clinical scores	NA	NA	+ Corr. △UE-FMA/ △CL motor map size: * Corr. Baseline UE-FMA/ △CL motor map size: NS	NA	NA	NA
AMT	NA	NA	NA	NA	BG Post1 - Pre, Post2 - Pre A - S: NS	NA
LI	NA	NA	NA	NA	WG Post1 - Pre, Post2 - Pre B: ↓ * S: NS	NA
Correlation with clinical scores	NA	NA	NA	NA	NA	B: + Corr. △ LI/ △WMFT: * S: Corr. △ LI/ △WMFT: NS B: Corr. △ LI/ △UE-FMA: NS S: Corr. △ LI/ △UE-FMA: NS
MEPs Amplitude/ *presence*	NA	WG Post1 - Pre IL HS B: ↑ * S: NS CL HS B: ↓ * S: ↓ * BG Post1 - Pre B - S: NS	NA	WG IL HS A: NS S: NS WG CL HS A: NS S: NS	WG Post1 - Pre, Post2 - Pre Paretic UE: B: ↑ * S: NS Non-paretic UE: B: NS S: NS BG Post1-Pre, Post2-Pre Paretic and non-paretic B - S: NS	NA
Correlation with clinical scores	NA	IL HS + Corr. △MEP amplitude/ △UE-FMA: *	NA	*Post1:* *Prop. UE-FMA >= 5 pts: MEP + > MEP - : ** *Post2:* *Prop. UE-FMA >= 5 pts: MEP + > MEP - : NS*	NA	NA
RMT	NA	NA	WG Post1 - Pre A: NS S: NS	WG Post1 - Pre, Post2 - Pre A: IL HS ↓ * A: CL HS: NS S: IL, CL HS: NS BG Post1 - Pre, Post2 - Pre A - S: NS	NA	NA

	(Allman et al., 2016)	(Bolognini et al., 2011)	(Cunningham et al., 2015)	(Edwards et al., 2019)	(Goodwill, Teo, Morgan, Daly, & Kidgell, 2016)	(Lindenberg, Renga, Zhu, Nair, & Schlaug, 2010)
TI	NA	WG Post1 - Pre CL on IL motor cortex B: ↓ * S: NS IL on CL motor cortex B: NS S: NS BG Post1 - Pre B - S: NS	NA	NA	NA	NA
Correlation with clinical scores	NA	- Corr. △ CL to IL TI/ △UE-FMA: * - Corr. △ CL to IL TI/ △JTHFT: *	NA	NA	NA	NA
ISP	NA	NA	WG Post1 - Pre A: ↑ * S: NS	NA	NA	NA
CSP	NA	NA	NA	NA	Non-paretic UE WG Post1 - Pre B: ↑ * S: NS BG Post1 - Pre B - S: * WG Post2 - Pre B: ↑ * S: NS BG Post2 - Pre B - S: NS	NA
SICI	NA	NA	NA	NA	WG Post1 - Pre Paretic: B, S: NS Non-paretic: B,S: NS WG Post2 - Pre Paretic: B, S: NS Non-paretic: B: ↑ *, S: NS BG Post1 - Pre Paretic: B - S: NS Non-paretic: B - S: NS BG Post2 - Pre Paretic: B - S: NS Non-paretic: B - S: *	NA
Interhemispheric inhibition	NA	NA	WG: Post1 - Pre A: IL HS counters inhibition by CL HS: * A: by CL HS: NS A: by IL HS: NS S: IL HS counters inhibition by CL HS: NS S: by CL HS: NS S: by IL HS: NS	NA	NA	NA

Note: A, anodal tDCS group; AMT, active motor threshold; B, bihemispheric tDCS group; BG, between group; CL, contralesional; Corr., correlation; CSP, cortical silent period; FA, fractional anisotropy; HS, hemisphere; IFG, Inferior Frontal Gyrus; IL, ipsilesional; ISP, ipsilateral silent period; JTHFT, Jebsen-Taylor Hand Function Test; LI, laterality Index; MEPs, motor evoked potentials; NA, not applicable; NS, not significant; Post 1, after intervention; Post 2, follow-up; Pre, baseline; prop., proportion; RMT, resting motor threshold; S, sham group; SICI, short-interval intracortical inhibition; TI, transcallosal inhibition; UE, upper extremity; UE-FMA, Upper Extremity Fugl-Meyer Assessment; VBM, voxel-based morphometry; WG, within group; WMFT, Wolf Motor Function Test; *, significant ($p \leq 0.05$)

5 Discussion

5.1 Reflections quality of the studies

In this systematic review, the adjuvant effect of transcranial direct current stimulation (tDCS) on the rehabilitation of stroke was investigated.

A major remark on the quality of the included studies is the number of participants that were included. Most sample sizes were too small to draw a reliable conclusion from, which makes these studies susceptible to wrong sample size bias (Allman et al., 2016; Bolognini et al., 2011; Cunningham et al., 2015; Fusco et al., 2014; Goodwill, Teo, Morgan, Daly, & Kidgell, 2016; Hesse et al., 2011; Ilic et al., 2016; Kim et al., 2010; Lindenberg, Renga, Zhu, Nair, & Schlaug, 2010; Mortensen, Figlewski, & Andersen, 2016; Nair, Renga, Lindenberg, Zhu, & Schlaug, 2011; Polanowska, Lesniak, Seniow, & Czlonkowska, 2013; Polanowska, Lesniak, Seniow, Czepiel, & Czlonkowska, 2013; Rabadi & Aston, 2017; Rocha et al., 2016; Spielmann, van de Sandt-Koenderman, Heijenbrok-Kal, & Ribbers, 2018; Triccas et al., 2015; Viana et al., 2014). Furthermore, the included studies turned out to be very heterogeneous. Differences were seen in total intervention duration and in recovery stage, ranging from acute to chronic. Moreover, a large variety of outcome measures was used, what makes it difficult to compare the results of the different studies to one another. This all makes it harder to draw a conclusion about the adjuvant effect of tDCS.

At first sight, all the included studies were of good quality, however many articles did not mention or did not use intention to treat analysis (Allman et al., 2016; Bolognini et al., 2011; Cunningham et al., 2015; Edwards et al., 2019; Figlewski et al., 2017; Fusco et al., 2014; Goodwill et al., 2016; Ilic et al., 2016; Kim et al., 2010; Lindenberg et al., 2010; Nair et al., 2011; Polanowska, Lesniak, Seniow, & Czlonkowska, 2013; Polanowska, Lesniak, Seniow, Czepiel, et al., 2013; Triccas et al., 2015; Viana et al., 2014). This makes it impossible to know whether participants were assessed in the groups they were allocated to. Four studies could not obtain results from a sufficient amount of participants to draw reliable conclusions (Fusco et al., 2014; Nair et al., 2011; Rabadi & Aston, 2017; Rocha et al., 2016).

In the studies of Lindenberg et al. (2010), Polanowska, Lesniak, Seniow, and Czlonkowska (2013) and Rabadi and Aston (2017), the assessors were not blinded to group allocation, and three studies did not mention if the therapists were blinded to group allocation (Cunningham

et al., 2015; Polanowska, Lesniak, Seniow, & Czlonkowska, 2013; Triccas et al., 2015). This could possibly influence the behavior of the therapists to the participants allocated in the intervention group, suggesting performance bias. This, as well as the risk of other potential biases, must be taken into account.

Data regarding the efficacy of tDCS were mostly obtained from studies that were conducted in a single center (Allman et al., 2016; Cunningham et al., 2015; Edwards et al., 2019; Figlewski et al., 2017; Fusco et al., 2014; Goodwill et al., 2016; Ilic et al., 2016; Kim et al., 2010; Lindenberg et al., 2010; Mortensen et al., 2016; Nair et al., 2011; Polanowska, Lesniak, Seniow, & Czlonkowska, 2013; Polanowska, Lesniak, Seniow, Czepiel, et al., 2013; Rabadi & Aston, 2017; Rocha et al., 2016; Viana et al., 2014). This implies that only patients who were able to go to or those who were treated at the specific clinics could participate in their research. This decreases the external validity of the results, making them less generalisable. A possible reporting bias is present in Edwards et al. (2019) because they did not report all results they set out to investigate. Furthermore, multiple studies did not perform post-hoc analysis of some key outcomes (Bolognini et al., 2011; Fusco et al., 2014; Mortensen et al., 2016). This makes relevant data difficult to interpret when the investigated independent variables have more than two levels. It also makes it impossible to determine whether results are clinically relevant, since an effect size cannot be determined. Furthermore, there were seven studies which did not mention if the allocation was concealed (Bolognini et al., 2011; Cunningham et al., 2015; Fusco et al., 2014; Lindenberg et al., 2010; Mortensen et al., 2016; Nair et al., 2011; Polanowska, Lesniak, Seniow, & Czlonkowska, 2013). Due to this, it is uncertain if the method of allocation was kept secret, causing a chance of selection bias.

5.2 Reflections on findings

Looking at the results of the studies examining aphasia, no between group differences were found significant (Polanowska, Lesniak, Seniow, & Czlonkowska, 2013; Polanowska, Lesniak, Seniow, Czepiel, et al., 2013; Spielmann et al., 2018). This can be due to interference of spontaneous recovery, a mechanism which is present in the subacute stage of recovery, as we see that both the sham and real tDCS group improved after intervention which was preserved during follow-up. These findings are comparable to those of a recent review, which reported no significant differences (Biou et al., 2019). However, they did find evidence that tDCS is an effective adjuvant treatment to enhance rehabilitation in chronic post-stroke patients. It is

hypothesised that this can be attributed to the plateau patients reach in the chronic stage (which is a relatively stable stage)(Spielmann et al., 2018) since the greatest improvement is seen during the first six months (Nicholas, Helm-Estabrooks, Ward-Lonergan, & Morgan, 1993). Despite similar findings regarding chronic patients, Elsner et al. (2015) found no different effect of tDCS between the acute, subacute and chronic stage on the change in naming accuracy. One of the included studies in this review found that cathodal tDCS resulted in greater improvements than anodal and sham tDCS after stimulation of Wernicke's area in patients with fluent aphasia (You, Kim, Chun, Jung, & Park, 2011). However, cathodal tDCS did not show a significant effect when it is applied over Broca's area in patients with non-fluent aphasia (Monti et al., 2008), which corresponds to our findings. Shah-Basak, Wurzman, Purcell, Gervits, and Hamilton (2016) compared tDCS and rTMS and found significant effects in chronic and subacute patients for rTMS. This in contrast to tDCS, which was only significant in a chronic population. Significant effects were found for fluent as well as for non-fluent aphasia (Rubi-Fessen et al., 2015), indicating that, although TMS is more expensive and less flexible, it might be a better adjunct to treatment of patients in the subacute stage.

We can conclude that interventions in the subacute stage of aphasia have promising effects, but the additional tDCS does not ameliorate these effects. Investigating responses to therapy might be more interesting in the chronic stage, since it is hard to differentiate spontaneous recovery and responses to treatment (Crinion & Leff, 2007).

Cathodal tDCS resulted in better improvements in ROM in a chronic population with moderate to severe impairments, an effect which was maintained at one-week follow-up (Nair et al., 2011). This finding is not in line with another study that investigated the effects of tDCS on ROM in a similar population, since they found no difference at all (Menezes et al., 2018). This might be because anodal tDCS was applied, while Nair et al. (2011) used cathodal tDCS.

When it comes to finger dexterity, anodal and cathodal tDCS did not have any effect, regardless of the stage post-stroke (Cunningham et al., 2015; Fusco et al., 2014). This finding is in line with Potter-Baker et al. (2018) who reported no notable improvements on the NHPT.

There was only one study that reported anodal tDCS increased gains in handgrip strength in the chronic stage (Mortensen et al., 2016), and none which reported any result following cathodal or bihemispheric tDCS (Bolognini et al., 2011; Fusco et al., 2014; Goodwill et al., 2016; Rocha et al., 2016). A previous study reported no effect on handgrip strength, but did see an

increase in muscle strength during shoulder abduction in the sham, anodal and cathodal group, with significantly more improvement in the combined anodal and cathodal group (Khedr et al., 2013). This is in controversy with our findings, where no significant results at any measuring point were found for either anodal or cathodal tDCS in the subacute stage (Hesse et al., 2011). Concerning muscle tone, no improvements were reported by any of the studies for anodal and cathodal tDCS in the subacute to chronic group (Hesse et al., 2011; Viana et al., 2014). This is in contrast with Wu et al. (2013), who found a significant decrease in muscle tone after application of cathodal tDCS in a subacute to chronic population. At follow-up, muscle tone decreased even more, however not significant.

Motor function, assessed by the Motor Assessment Scale, improved equally in the bihemispheric and sham group at post-intervention for patients in the chronic stage, but there was only a significant difference at three weeks follow-up in the bihemispheric group (Goodwill et al., 2016). This indicates tDCS might be effective, but only in the long term when it is applied during a longer period.

Controversial results were found regarding the Action Research Arm Test (ARAT). One study with acute stroke survivors reported no effect in either group (Rabadi & Aston, 2017), while another study with chronic patients showed improvements in both groups, with an additional effect in the a-tDCS group (Allman et al., 2016). This might be due to small sample sizes of both studies. Comparing the subacute and the chronic population, differences were found with a significant improvement post-intervention and at follow-up for the subacute group, but not for the chronic group (Triccas et al., 2018). This shows that the influence of recovery stage is unclear, and that more research is needed to further investigate it. In a previous study with stroke survivors with severe chronic hemiparesis, the effects of cathodal, anodal and bihemispheric tDCS were compared to each other and sham stimulation, whereby no additional improvements as a result of the adjuvant tDCS treatment were seen (Chelette, Carrico, Nichols, Salyers, & Sawaki, 2014).

Half of the studies investigating the Wolf Motor Function Test (WMFT) found evidence in favour of anodal tDCS at one week and at three months follow-up in both the subacute and chronic stage (Allman et al., 2016; Figlewski et al., 2017), indicating anodal tDCS might have an influence on motor function. A similar finding was found for bihemispheric tDCS, where the improvement of motor function was significantly better in the real tDCS group (Lindenberg et

al., 2010). Concerning hand function, some controversy exists. One study reported no additional effect of anodal tDCS in the chronic stage (Mortensen et al., 2016), while Bolognini et al. (2011) and Ilic et al. (2016) found an improvement of hand function in chronic patients that was maintained during follow-up for anodal and bihemispheric tDCS.

A large amount of studies investigated motor-recovery post-stroke using the Upper Extremity Fugl-Meyer Assessment (UE-FMA). However, only few found differences in favour of tDCS for patients with either acute, subacute or chronic stroke. For anodal tDCS, there was only one study that reported better improvements (Rocha et al., 2016). The same finding was seen in cathodal tDCS at six months follow-up (Kim et al., 2010) and in bihemispheric tDCS at post-intervention and at one- week follow-up (Lindenberg et al., 2010). Other data reported improvements in all groups - anodal, cathodal and sham tDCS - showing tDCS has no supplementary effect (Allman et al., 2016; Bolognini et al., 2011; Cunningham et al., 2015; Edwards et al., 2019; Fusco et al., 2014; Hesse et al., 2011; Nair et al., 2011; Rocha et al., 2016; Triccas et al., 2015; Viana et al., 2014).

Regarding functional independence, none of the studies reported a greater improvement caused by cathodal tDCS and most of them did not find any significant improvements at all, regardless of which group the participants were in (Fusco et al., 2014; Hesse et al., 2011; Kim et al., 2010; Rabadi & Aston, 2017). No studies were conducted in the chronic stage post-stroke. This is in contrast with a previous study, which found a larger improvement in functional independence in the anodal group in subacute stroke (Andrade et al., 2017). These findings are rising the question whether anodal tDCS might be superior over cathodal tDCS regarding functional independence.

Lastly, none of the studies reported that anodal, cathodal or bihemispheric tDCS had a greater effect on both components of the MAL at post-intervention or at follow-up (Bolognini et al., 2011; Cunningham et al., 2015; Rocha et al., 2016; Triccas et al., 2015).

In general, most patients had improvements in function, but there was no difference between sham and real tDCS. Consequently, the improvements were more likely to be a result of the administered therapy, instead of the supplementary tDCS treatment. Another remark is the lack of research about tDCS in the acute stage following stroke, with only three of the 20 studies investigating this.

Concerning the neurophysiological measurements, Allman et al. (2016) showed a significant increase of grey matter in the anodal group at post-intervention and at three months follow-up, yet there were no correlations with behavioural measures. However, a positive correlation was seen between the change in UE-FMA and baseline FA: worse clinical scores on the UE-FMA at baseline were associated with greater fractional anisotropy, which measures the asymmetry of the corticospinal tract microstructure (Allman et al., 2016). This could indicate a higher potential for improvement on the UE-FMA for patients with more asymmetry at baseline. Furthermore, there was a significant positive correlation between changes in UE-FMA and contralesional motor map size (Cunningham et al., 2015), indicating increased functional ability goes together with increasing corticomotor map sizes. Another finding is that less inhibition of the ipsilesional motor cortex following bihemispheric tDCS corresponds with better functional performance, as measured by the UE-FMA and JTHFT (Bolognini et al., 2011).

fMRI activity was higher in the anodal and bihemispheric tDCS group, indicating an increased activation of the ipsilesional motor cortical areas. This increase was associated with clinical improvements (Allman et al., 2016; Lindenberg et al., 2010). Moreover, a significant increase of the ISP was seen at post-intervention in the anodal group, as well as an increase in the ability of the ipsilesional hemisphere to counter inhibition by the contralesional hemisphere (Cunningham et al., 2015).

As indicated by the Laterality Index (LI), hemispheric dominance significantly decreased in the bihemispheric group, which results in a better hemispheric balance (Goodwill et al., 2016). Secondly, an increase in LI went together with an increased score on the WMFT (Lindenberg et al., 2010). Bihemispheric tDCS was also responsible for a greater increase of the Cortical Silent Period (CSP) and the Short-Interval Intracortical Inhibition (SICI) in the non-paretic upper extremity, and this inhibition may contribute to the greater retention in motor function (Goodwill et al., 2016).

Regarding all the other neurophysiological measurements, no significant results were seen showing anodal or bihemispheric tDCS has an adjuvant effect (Bolognini et al., 2011; Cunningham et al., 2015; Edwards et al., 2019; Goodwill et al., 2016). All studies were conducted in a chronic stroke population, and none of them used cathodal tDCS as an additional therapy.

5.3 Strengths and limitations of the review

There were some limitations in this review. First of all, only two databases were searched and due to the limited time frame in which this review was conducted, it is possible that some relevant articles were missed.

Strengths of this review include the following. Most of the included studies were published recently, which makes the use of outdated material less likely. Furthermore, to increase reliability, only randomized controlled trials and studies that scored four or less on the PEDro Checklist were excluded. By defining the beginning and end of each recovery stage, a greater uniformity was achieved. This resulted in a better analysis because at first, these different studies used different definitions for each recovery stage.

5.4 Recommendations for future research

A large heterogeneity of outcome measures is present between the included studies. Further research is advised that sets out to determine the most valid and user-friendly assessment tool for the different domains (upper limb motor skills, aphasia, …). This could greatly homogenise future research. If a valid statement on the usefulness of tDCS was to be made, larger studies of better quality with a longer follow-up period are required.

Compared to chronic aphasia, there is only limited research regarding aphasia in the subacute stage, with only a few showing significant effects. This demonstrates the need for more and larger studies.

6 Conclusion

Current evidence indicates a promising added value of tDCS for the rehabilitation of the upper limb function. Looking at aphasia, tDCS did not provide an additional effect over conventional treatment alone. Furthermore, no superiority was found between the different forms of tDCS. However, because most studies were small and of average quality, all results should be interpreted with caution. More and stronger research investigating the effect of tDCS in stroke survivors is needed to draw reliable conclusions.

7 References

7.1 Included articles

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Part 2: The Research Protocol

The adjuvant effect of tDCS on the rehabilitation of the upper limb and aphasia following stroke: Protocol and Rationale.

Van den Eede N. and Van der Veken E.

1 Introduction

Stroke is one of the leading causes of adult-onset disability (Dobkin, 2004), only 25% of the stroke survivors return to their previous level of physical functioning and everyday participation (Dobkin, 2005). Most of the recovery occurs within the first two to three months, at this point we also see in the conventional rehabilitation a transition from cure to care. Beyond this point, in the chronic stage, stroke survivors benefit less from conventional rehabilitation treatment techniques (Ilic et al., 2016). Recent research gives room to a more positive view that puts the emphasis on reorganization, compensation and neuroplasticity. Transcranial direct current stimulation (tDCS) can facilitate these mechanisms.

Transcranial direct current stimulation is a non-invasive brain stimulation technique that delivers low-intensity, direct current to cortical areas and its purpose is to facilitate or inhibit spontaneous neuronal activity (Brunoni et al., 2012). The current intensity is usually ranging from 0.5 to 2 mA (Tortella et al., 2015). Because no serious adverse events have been reported, it is a popular application in rehabilitative programs (Russo, Souza Carneiro, Bolognini, & Fregni, 2017).

After a focal lesion, the balance of interhemispheric communication is disrupted and the output from the lesioned hemisphere is reduced. Based on this hypothesis, contralesional and ipsilesional plastic changes may be induced by cortical stimulation after stroke, which could lead to a shift of this imbalance (Marquez, van Vliet, McElduff, Lagopoulos, & Parsons, 2015). To promote adaptive neuroplasticity, the activity of the perilesional region is stimulated, whereas the activity of the homologous area of the contralesional hemisphere is inhibited (Lefaucheur et al., 2017). Anodal tDCS causes neuronal hypopolarisation, which leads to increased excitability of the underlying cortex (Nitsche & Paulus, 2000). These changes in cortical excitability are often measured and evaluated by TMS.

Following stroke, patients encounter many impairments which affect various aspects of their activities of daily living. A common deficit after stroke is impairment of the upper extremity. Many rehabilitation techniques have been described, yet 30% to 66% of stroke survivors do not restore the function of the affected arm (van der Lee et al., 1999) and 15% to 30% of the survivors experience a permanent disability (Rosamond et al., 2008). Therefore a more effective therapy that results in better outcomes for stroke survivors and a lower cost of therapy and care is needed (Blank, French, Pehlivan, & O'Malley, 2014). Marquez et al. (2015) stated that patients who are in the chronic phase with mild-to-moderate motor impairments presumably benefit most from tDCS-treatment, and motor improvements last longer when tDCS is applied in combination with training (Hummel et al., 2008). Another important factor is timing. As shown in Stagg et al. (2011), timing of stimulation concerning motor learning has an influence on learning speed, whereby faster learning was seen when anodal tDCS is applied during motor learning. These findings demonstrate that there is promising evidence, yet little is known about the long-term effects of the adjuvant value of tDCS. In a previous unpublished review, more than half of the included studies had either no follow-up, or a follow-up of a month or less (Van den Eede, Van der Veken & Meesen, 2019, Unpublished thesis). Therefore, further research is needed to explore the potential concerning long-term recovery.

2 Purpose

2.1 Research questions

The following research question is formulated: “What are the long-term effects of anodal tDCS as an adjuvant treatment on the rehabilitation of the upper extremity following stroke?”

2.2 Hypothesis

Transcranial direct current stimulation is expected to have a significant effect on the improvement of the upper limb function in the long term when it is an adjunct to conventional therapy.

3 Methods

3.1 Design

A longitudinal randomized controlled trial over a period of two months with an additional follow-up of three months is proposed. Participants will be randomly divided in one of two groups: an experimental or a control group. All evaluations will be prior at baseline and after one and two months, whereby clinical outcomes are collected. Additional measurements will be done at one, two and three months-follow-up.

3.2 Participants

Participants will be patients in the chronic stage of stroke who already completed their stroke rehabilitation and reached a plateau concerning recovery of function. This to avoid the mechanism of spontaneous recovery in the acute and subacute phase, which can be a confounder.

Patients in the experimental group will receive conventional therapy, combined with an additional treatment of anodal tDCS. Patients in the control group will receive conventional therapy as well, but in combination with sham tDCS. Baseline characteristics will not be significantly different.

3.2.1 Inclusion criteria

Patients will be included if they meet the following inclusion criteria: adults aged 18 years or older who had a first-ever stroke, confirmed with brain imaging, time since stroke onset of at least 6 months and having reached a plateau in recovery, UE-FMA score between 31 and 52 and having provided informed written consent.

3.2.2 Exclusion criteria

Patients will be excluded if they have any of the following: severe mental health condition or cognitive impairment (MMSE < 18), taking medications that could affect brain activity (e.g. anti-epileptic drugs), dysphagia that limits communication, contraindications to tDCS and other major neurological or neuromuscular/orthopaedic problems that could interfere with the interpretation of the results.

3.2.3 Recruitment

Participants will be recruited from the Rehabilitation and MS-Centre Overpelt. Once potential patients have been identified, more information will be provided by the main researcher. After signing informed consent, patients will be included.

3.3 Medical ethics

The application is submitted. All participants will sign an informed written consent.

3.4 Intervention

It will be a two-month training intervention, performed three times a week. Anodal tDCS will be applied during conventional therapy, while the sham group will only receive 20 seconds of anodal tDCS, before the stimulation is switched off. Since it is hard to predict the specific needs of the participants, conventional therapy is not yet defined, but it is likely to be a combination of neuro developmental treatment techniques (NDT), task-oriented training and calisthenics. Each session will last about 45 minutes.

Direct currents will be transferred via a pair of saline-soaked surface sponge electrodes (35 cm^2) and delivered by a battery-driven constant current stimulator with a maximum output of 2mA. The anodal electrode will be fixed over the primary motor cortex (M1, C3-C4, International 10-20 EEG System) of the lesioned hemisphere and the cathodal electrode above the contralateral orbit.

3.5 Outcome measures

3.5.1 Primary outcome measures

The primary outcome measure will be any observed change in results of the Upper Extremity Fugl-Meyer Assessment (UE-FMA) and the Action Research Arm Test (ARAT).

The UE-FMA (appendix A) evaluates and measures recovery and consists of three subtests: motor function (24 items, score 0 to 66, sections A: shoulder, elbow, forearm; B: wrist; C: hand and D: coordination/speed), sensation (6 items, score 0 to 12) and passive joint motion and joint pain (12 items, score 0 to 48). A 3-point ordinal scale (0, 1 or 2) is used to score each item. Total score reaches from 0 to 126, with a higher score indicating a better arm-hand

capacity. A very high inter-rater reliability (ICC ranging from 0.971 to 0.997, ρ between 0.969 and 0.995) is reported, as well as a very high test-retest reliability (ICC ranging from 0.936 to 0.973, ρ between 0.883 and 0.961), with the exception sensation (ICC=0.806, ρ =0.672), which was less reliable (Platz et al., 2005). Kim et al. (2012) shows a good concurrent validity with other outcome measures such as the Jebsen-Taylor Hand Function Test, the Motor Assessment Scale and the Berg Balance Scale.

The ARAT assesses upper extremity performance using objects varying in shape, weight and size. It comprises four subtests: grasp (6 items), grip (4 items), pinch (6 items) and gross movement (3 items). Each item is scored on a 4-point ordinal scale ranging from 0 to 3, and a total of 57 points can be obtained whereby a higher score equals a better upper extremity performance. The ARAT has a very high inter-rater reliability (ICC ranging from 0.964 to 0.999, ρ between 0.958 and 0.999) and a very high test-retest reliability (ICC ranging from 0.894 to 0.976, ρ between 0.897 and 0.976) for all four subtests (Platz et al., 2005). Predictive validity was found to be moderate to excellent between the ARAT and the functional ability scale of the Wolf Motor Function Test (WMFT-FAS, ρ =0.76), the performance time of the Wolf Motor Function Test (WMFT-TIME, ρ =-0.66) and the Stroke Impact Scale hand function (ρ =0.58) (Chen, Lin, Wu, & Chen, 2012).

3.5.2 Secondary outcome measures

After each session, participants are asked to rate their Quality of Life, using the EuroQoL-5D-3L (appendix B). This questionnaire consists of five domains: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The result is a 5-digit number that defines a person's health status, with scores ranging from 11111 (no problem at all) to 33333 (extreme problems in all five dimensions). The first number indicates problems in mobility, the second in self-care, the third in usual activities, the fourth in pain/discomfort and the fifth in anxiety/depression. Hunger, Sabariego, Stollenwerk, Cieza, and Leidl (2012) found excellent test-retest reliability (ICC=0.81).

3.6 Data-analysis

For each test, repeated-measures analyses of variance (ANOVA) will be performed, with a within-subjects factor Time (baseline, one and two months and one, two and three- months follow-up) and a between-subjects factor Group (anodal and sham tDCS). The Bonferroni correction will be used for post-hoc analysis. Correlation between baseline scores and percentage improvements in UE-FMA and ARAT will be tested using the Pearson's correlation test. Statistical significance will be shown by a p-value <0.05.

4 Time planning

The intervention will start in the autumn of 2019 and will be executed over a period of three months. Data will be collected and analysed during and after the intervention.

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6 Appendices

Appendix A: score form UE-FMA

FUGL-MEYER ASSESSMENT ID:
UPPER EXTREMITY (FMA-UE) Date:

Assessment of sensorimotor function Examiner:

Fugl-Meyer AR, Jaasko L, Leyman I, Olsson S, Steglind S: The post-stroke hemiplegic patient. A method for evaluation of physical performance. Scand J Rehabil Med 1975, 7:13-31.

A. UPPER EXTREMITY, sitting position					
I. Reflex activity			**none**	**can be elicited**	
Flexors: biceps and finger flexors			0	2	
Extensors: triceps			0	2	
Subtotal I (max 4)					
II. Volitional movement within synergies, without gravitational help			**none**	**partial**	**full**
Flexor synergy: Hand from contralateral knee to ipsilateral ear. From extensor synergy (shoulder adduction/ internal rotation, elbow extension, forearm pronation) to flexor synergy (shoulder abduction/ external rotation, elbow flexion, forearm supination). **Extensor synergy**: Hand from ipsilateral ear to the contralateral knee	Shoulder	retraction	0	1	2
		elevation	0	1	2
		abduction (90°)	0	1	2
		external rotation	0	1	2
	Elbow	flexion	0	1	2
	Forearm	supination	0	1	2
	Shoulder	adduction/internal rotation	0	1	2
	Elbow	extension	0	1	2
	Forearm	pronation	0	1	2
Subtotal II (max 18)					
III. Volitional movement mixing synergies, without compensation			**none**	**partial**	**full**
Hand to lumbar spine	cannot be performed, hand in front of SIAS hand behind of SIAS (without compensation) hand to lumbar spine (without compensation)		0	1	2
Shoulder flexion 0°-90° elbow at 0° pronation-supination 0°	immediate abduction or elbow flexion abduction or elbow flexion during movement complete flexion 90°, maintains 0° in elbow		0	1	2
Pronation-supination elbow at 90° shoulder at 0°	no pronation/supination, starting position impossible limited pronation/supination, maintains position complete pronation/supination, maintains position		0	1	2
Subtotal III (max 6)					
IV. Volitional movement with little or no synergy			**none**	**partial**	**full**
Shoulder abduction 0 - 90° elbow at 0° forearm pronated	immediate supination or elbow flexion supination or elbow flexion during movement abduction 90°, maintains extension and pronation		0	1	2
Shoulder flexion 90°- 180° elbow at 0° pronation-supination 0°	immediate abduction or elbow flexion abduction or elbow flexion during movement complete flexion, maintains 0° in elbow		0	1	2
Pronation/supination elbow at 0° shoulder at 30°-90° flexion	no pronation/supination, starting position impossible limited pronation/supination, maintains extension full pronation/supination, maintains elbow extension		0	1	2
Subtotal IV (max 6)					
V. Normal reflex activity evaluated only if full score of 6 points achieved on part IV					
biceps, triceps, finger flexors	0 points on part IV or 2 of 3 reflexes markedly hyperactive 1 reflex markedly hyperactive or at least 2 reflexes lively maximum of 1 reflex lively, none hyperactive		0	1	2
Subtotal V (max 2)					
Total A (max 36)					

B. WRIST support may be provided at the elbow to take or hold the position, no support at wrist, check the passive range of motion prior testing		none	partial	full
Stability at 15° dorsiflexion elbow at 90°, forearm pronated shoulder at 0°	less than 15° active dorsiflexion dorsiflexion 15°, no resistance is taken maintains position against resistance	0	1	2
Repeated dorsiflexion / volar flexion elbow at 90°, forearm pronated shoulder at 0°, slight finger flexion	cannot perform volitionally limited active range of motion full active range of motion, smoothly	0	1	2
Stability at 15° dorsiflexion elbow at 0°, forearm pronated slight shoulder flexion/abduction	less than 15° active dorsiflexion dorsiflexion 15°, no resistance is taken maintains position against resistance	0	1	2
Repeated dorsiflexion / volar flexion elbow at 0°, forearm pronated slight shoulder flexion/abduction	cannot perform volitionally limited active range of motion full active range of motion, smoothly	0	1	2
Circumduction	cannot perform volitionally jerky movement or incomplete complete and smooth circumduction	0	1	2
	Total B (max 10)			

C. HAND support may be provided at the elbow to keep 90° flexion, no support at the wrist, compare with unaffected hand, the objects are interposed, active grasp		none	partial	full
Mass flexion from full active or passive extension		0	1	2
Mass extension from full active or passive flexion		0	1	2
GRASP				
A – flexion in PIP and DIP (digits II-V) **extension in MCP II-V**	cannot be performed can hold position but weak maintains position against resistance	0	1	2
B – thumb adduction 1-st CMC, MCP, IP at 0°, scrap of paper between thumb and 2-nd MCP joint	cannot be performed can hold paper but not against tug can hold paper against a tug	0	1	2
C - opposition pulpa of the thumb against the pulpa of 2-nd finger, pencil, tug upward	cannot be performed can hold pencil but not against tug can hold pencil against a tug	0	1	2
D – cylinder grip cylinder shaped object (small can) tug upward, opposition in digits I and II	cannot be performed can hold cylinder but not against tug can hold cylinder against a tug	0	1	2
E – spherical grip fingers in abduction/flexion, thumb opposed, tennis ball	cannot be performed can hold ball but not against tug can hold ball against a tug	0	1	2
	Total C (max 14)			

D. COORDINATION/SPEED after one trial with both arms, blind-folded, tip of the index finger from knee to nose, 5 times as fast as possible		**marked**	**slight**	**none**
Tremor		0	1	2
Dysmetria	pronounced or unsystematic slight and systematic no dysmetria	0	1	2
		> 5s	**2 - 5s**	**< 1s**
Time	more than 5 seconds slower than unaffected side 2-5 seconds slower than unaffected side maximum difference of1 second between sides	0	1	2
		Total D (max 6)		
		TOTAL A-D (max 66)		

H. SENSATION, upper extremity blind-folded, compared with unaffected side		**anesthesia**	**hypoesthesia dysesthesia**	**normal**
Light touch	upper arm, forearm	0	1	2
	palmar surface of the hand	0	1	2
		absence less than 3/4 correct	**3/4 correct considerable difference**	**correct 100% little or no difference**
Position small alterations in the position	shoulder	0	1	2
	elbow	0	1	2
	wrist	0	1	2
	thumb (IP-joint)	0	1	2
			Total H (max12)	

J. PASSIVE JOINT MOTION, upper extremity				**J. JOINT PAIN** during passive motion, upper extremity		
Sitting position, compare with unaffected side	only few degrees (less than 10° in shoulder)	decreased	normal	pronounced constant pain during or at the end of movement	some pain	no pain
Shoulder						
Flexion (0° - 180°)	0	1	2	0	1	2
Abduction (0°-90°)	0	1	2	0	1	2
External rotation	0	1	2	0	1	2
Internal rotation	0	1	2	0	1	2
Elbow						
Flexion	0	1	2	0	1	2
Extension	0	1	2	0	1	2
Forearm						
Pronation	0	1	2	0	1	2
Supination	0	1	2	0	1	2
Wrist						
Flexion	0	1	2	0	1	2
Extension	0	1	2	0	1	2
Fingers						
Flexion	0	1	2	0	1	2
Extension	0	1	2	0	1	2
Total (max 24)				**Total** (max 24)		

A. UPPER EXTREMITY	/36
B. WRIST	/10
C. HAND	/14
D. COORDINATION / SPEED	/ 6
TOTAL A-D (motor function)	/66

H. SENSATION	/12
J. PASSIVE JOINT MOTION	/24
J. JOINT PAIN	/24

Appendix B: Example of a filled in EuroQoL-5D-3L

By placing a check-mark in one box in each group below, please indicate which statements best describe your own state of health today.

Levels of perceived problems are coded as follows

Mobility

I have no problems in walking about	☑	1 ☑	
I have some problems in walking about	☐	2 ☐	Level = 1
I am confined to bed	☐	3 ☐	

Self-Care

I have no problems with self-care	☑	1 ☑	
I have some problems washing or dressing myself	☐	2 ☐	Level = 1
I am unable to wash or dress myself	☐	3 ☐	

Usual Activities *(e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities	☑	1 ☑	
I have some problems with performing my usual activities	☐	2 ☐	Level = 1
I am unable to perform my usual activities	☐	3 ☐	

Pain / Discomfort

I have no pain or discomfort	☐	1 ☐	
I have moderate pain or discomfort	☑	2 ☑	Level = 2
I have extreme pain or discomfort	☐	3 ☐	

Anxiety / Depression

I am not anxious or depressed	☐	1 ☐	
I am moderately anxious or depressed	☐	2 ☐	Level = 3
I am extremely anxious or depressed	☑	3 ☑	

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UHASSELT
KNOWLEDGE IN ACTION

VOORTGANGSFORMULIER WETENSCHAPPELIJKE STAGE DEEL 1

DATUM	INHOUD OVERLEG	HANDTEKENINGEN
14/11	Inleiding onderwerp + afspraken	Promotor: Copromotor/begeleider: Student(e): Student(e):
10/12	contactmoment 1 - onderzoeksvraag - kwaliteitsbeoordeling	Promotor: Copromotor/begeleider: Student(e): Student(e):
20/03	goedkeuring exclusiecriteria	Promotor: Copromotor/begeleider: Student(e): Student(e):
6/05	bespreken aanpassing zoekstrategie vragen: data extractie	Promotor: Copromotor/begeleider: Student(e): Student(e):
14/05	bespreken inleiding 1e draft vragen resultaten, protocol	Promotor: Copromotor/begeleider: Student(e): Student(e):
21/05	overlopen neurofysiologische uitkomstmaten	Promotor: Copromotor/begeleider: Student(e): Student(e):
27/05	oefenmoment: verdediging MP	Promotor: Copromotor/begeleider: Student(e): Student(e):
		Promotor: Copromotor/begeleider: Student(e): Student(e):
		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):