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REVIEW

Rehabilitation interventions of unilateral spatial neglect based on the functional outcome measure: A systematic review and meta-analysis

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ABSTRACT

This review aimed to examine the bottom-up and top-down rehabilitation intervention effectiveness based on the functional outcome measure as immediate effect and long-term effect for unilateral spatial neglect conditions. The RCT studies were collected by searching in three databases J-Stage, PubMed, and PEDro from 2008 through 2018. The studies which used the following instruments: BI, CBS, FMA, and FIM, as the functional outcome with the PEDro score of six and above, were eligible for inclusion. A total of 492 participants in 13 studies included from 291 studies initially identified. The meta-analysis for overall ES revealed that BI and CBS had a significant mean of SMD = 0.65 (95% CI, 0.23–1.07; $p = 0.003$; $I^2 = 65\%$), and SMD = −0.23 (95% CI, −0.45 to −0.01; $p = 0.04$; $I^2 = 35\%$) respectively, while FMA and FIM had an insignificant mean of SMD = 0.14 (95% CI, −0.08–0.37; $p = 0.22$; $I^2 = 0\%$), and SMD = −0.22 (95% CI, −0.69–0.25; $p = 0.37$; $I^2 = 0\%$) respectively. Based on the results, although indicated the heterogeneity representation across studies, it showed that the top-down intervention approach of high-frequency rTMS was more effective in enhancing the functional abilities and ADL of unilateral spatial neglect patients on the immediate effects but not necessarily in the long-term effects.

Abbreviations: ADL: Activity Daily Living; BI: Barthel Index; CBS: Catherine Bergego Scale; CI: Confidence Interval; CIT: Constraint-Induced Therapy; CR*P*: Conventional Rehabilitation Program; E*P*: Eye Patching; FAABT: Functional and/or ADL Assessment Based Test; FIM: Functional Independence Measure; FMA: Fugl-Meyer Assessment; FNI: Functional Neglect Index; HEPOKS: Hemi-field Eye Patching and Repetitive Optokinetic Stimulation; KAT: Kinesthetic Ability Training; K-MBI: Korean-Modified Barthel Index; LA: Limb Activation; MT: Mirror Therapy; NABT: Neglect Assessment Based Test; NIBS: Non-Invasive Brain Stimulation; OKS: Optokinetic Stimulation; PA: Prism

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Adaptation; PEDro: Physiotherapy Evidence Database; RCT: Randomized Controlled Trial; rTMS: repetitive Transcranial Magnetic Stimulation; SABT: Scale Assessment Based Test; SC: Sensory Cueing; SEM: Standard Error of the Mean; SEMT: Saccadic Eye Movement Training; SMD: Standardized Mean Difference; SPT: Smooth Pursuit Eye Movement Training; TBS: Theta-Burst stimulation; TSA: Task-Specific Activities; UBNI: Unawareness and Behavioral Neglect Index; USN: Unilateral Spatial Neglect; VSE: Visual Scanning Exercises; VST: Visual Scanning Training

Introduction

Unilateral spatial neglect (USN) following a stroke is a highly prevalent deficit problem, negatively affecting rehabilitation outcome and recovery after stroke, as well as increasing the risk of falls, long-term care placement, and difficulties with activities of daily living (ADL) (Gillen et al., 2005; Gustavo et al., 2013; Jehkonen et al., 2006; Lisa et al., 2013). Thirty to fifty percent of stroke survivors are affected by spatial neglect, to optimize rehabilitation outcomes, specific and systematic spatial rehabilitation is needed (Chen et al., 2015; Luaute et al., 2006). Currently, the investigation of standard USN assessment to determine which is sensitive to detect mild deficits and encompasses the heterogeneity of this disorder is still under development (Menon-nair et al., 2007). Furthermore, there is a limited number of high-quality studies that establish the effectiveness of conventional USN treatments in improving functional outcomes and reducing disability (Bowen et al., 2013; Ogourtsova et al., 2017).

Spatial neglect is a sign of damage to the right hemisphere and typically characterized by a failure to respond to stimuli administered towards the body opposite to the lesion (Bowen et al., 2013; Kerkhoff & Schenk, 2012; Lisa et al., 2013; Ting et al., 2011). While neglect most commonly occurs after right-hemisphere lesions, severity is similar between a left-brain injury such as right-brain injury in acute (Lisa et al., 2013; Suchan et al., 2012). However, generally reported that left-sided USN is more severe than right-sided USN (Ten Brink et al., 2017a). Identifying the types of region-specific neglect is required when diagnosing neglect using adequately sensitive measures to adjust the relevant rehabilitation programme (Nijboer et al., 2014a; Pitteri et al., 2018).

Research on evaluation and intervention of USN conditions are still being developed. Several rehabilitation methods have been advanced to improve spatial neglect which can be classified into the bottom-up and top-down approach of interventions (Azouvi et al., 2017; Luaute et al., 2006; Maxton et al., 2013). The top-down approach emphasizes training the person to voluntarily compensate for their neglect, which requires awareness and a high level of active participation by the patient (Adair & Barrett, 2008; Bowen et al., 2013). In contrast, bottom-up approaches are based on the manipulation of a patient's sensory environment and so require less awareness of behavioural bias (Bowen et al., 2013; Conti & Arnone, 2016; Varalta et al., 2019). In literature, the bottom-up approaches have more frequently been proposed and developed, such as the prism adaptation (PA) procedure, which is one of the most widely studied and used (Gammeri et al., 2020; Jacquin-Courtois et al., 2013; Redding & Wallace, 2006; Rode et al., 2006). However, the top-down approach seems more potential and promising, such as the repetitive transcranial magnetic stimulation (rTMS), with all its limitations of implementation and still less evidence (Dionísio et al., 2018; Du et al., 2016; Lefaucheur et al., 2014; Sebastianelli et al., 2017).

Several studies identified various effective treatments for the alleviation of the symptoms of unilateral neglect with different behavioural assessments and functional outcome instruments that have been used widely as parameters for therapeutic achievement (Azouvi, 2017; Azouvi et al., 2003; Chen et al., 2012; Conti & Arnone, 2016; Leonardo et al., 2019; Nijboer et al., 2014b; Pierce & Buxbaum, 2002; Stein et al., 2016). The mechanisms underlying beneficial effects of the bottom-up and top-down interventions in USN are still being investigated (Corbetta et al., 2005; Hillis, 2006; Jacquin-Courtois, 2015; Karnath, 2015; Machner et al., 2012). However, the level of evidence is still low, as shown in recent meta-analyses with small sample size, methodological bias, and contradictory results (Azouvi et al., 2017; Champod et al., 2018; Lisa et al., 2013; Liu et al., 2019; Salazar et al., 2018; Yang et al., 2013).

There are few studies found on USN related to functional outcome in balance functions (Geurts et al., 2005; Hugues et al., 2019). Whereas, one of the most imperative factors that determine independence in basic ADL is balance functions (Nijboer et al., 2014b). Studies confirmed the negative effect of neglect on functional outcomes in a large sample and showed the importance of evaluating and training according to neglect subtype to improve functional independence (Matano et al., 2015; Nijboer et al., 2013; Spaccavento et al., 2017). Moreover, there is a gap in neglect research and its long-term effects on ADL (Kerkhoff & Schenk, 2012; Veldema et al., 2019). Therefore, further investigations are needed to examine the role of awareness in functional outcome by subtypes of neglect. Other aspects that could evaluate include the efficacy of neuropsychological treatment of neglect and its relation with the functional outcome (Spaccavento et al., 2017).

This systematic review used the components of Participants, Interventions, Comparisons, Outcomes (PICO) to define a specific research question. Participants: Stroke patient of right brain damage that commonly called unilateral spatial neglect. Interventions: Any rehabilitation approach included bottom-up and top-down interventions. Comparisons: No stimulation or sham adaptation or sham stimulation or conventional treatment. Outcomes: Functional outcome and ADL as an immediate and or long-term effect. Accordingly, the

PICO question is: "Which rehabilitation intervention more effective than conventional treatment in improving functional outcome and ADL as an immediate and or long-term effect for unilateral spatial neglect patients?". Thus, we aimed to determine which interventions in RCT studies have the most effective treatment concerning the functional outcome and ADL as immediate effect and long-term effect by comparing the bottom-up and top-down rehabilitation intervention to clarify whether there are efficient, effective, and practical interventions for the recovery from neglect.

Method

Database sources

The PRISMA guidelines were used in the review design and reporting of the current review and meta-analysis (Moher et al., 2009). This review consulted three databases J-Stage, PubMed, and PEDro, according to PICO statement, the following keyword "neglect" and "unilateral spatial neglect" is used. The date of publication was limited from January 2008 to December 2018 to converge the advancement of research in the past ten years. Only clinical trials with human subjects published in English are searched. The electronic search database step and flow are illustrated in PRISMA flow diagram (Figure 1).

Selection criteria

Based on PICO components, this review only considered RCT studies for an adult stroke patient with USN. Age, duration from the onset, type of stroke, and location were not specified. Only studies that examined the outcomes based on functional or activity assessments such as Barthel Index (BI), Catherine Bergego Scale (CBS), Fugl-Meyer Assessment (FMA), and Functional Independence Measure (FIM) were included. Both bottom-up and top-down interventions aimed to improve the functional abilities and activities of the persons with USN were included in this study.

This review excluded the studies with the following criteria: (1) single research or one group study, (2) study protocol or ongoing trial status, (3) total sample size < 20, and (4) articles that does not meet the quality assessment criteria of PEDro score of six and above (Paci et al., 2010).

Quality assessment

Quality assessment of the included RCT studies was conducted according to the PEDro scale to examine the quality of the studies and risk of bias. The PEDro scale is a valid measure of the methodological quality of clinical trials and can be used to quantity risk of bias (Morton, 2009; Moseley et al., 2019b). The use of PEDro is quite widely recognized in various RCT studies and reviews,

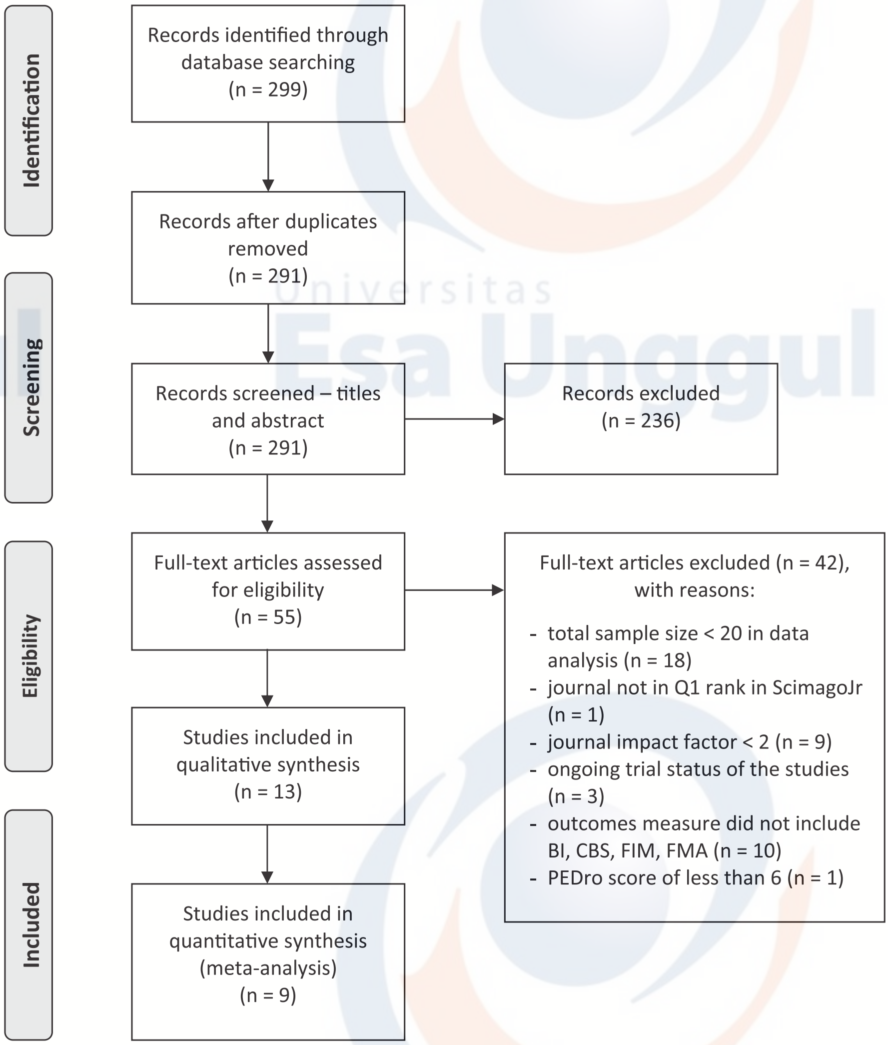

Figure 1. Overview of the search and selection process based on PRISMA flow diagram (Moher et al., 2009).

especially in the physiotherapy area (Moseley et al., 2019a; Takasaki et al., 2016). We adopt a PEDro score that has been displayed on the PEDro website database, but tries to reconfirm each item of assessment. There are 11 rating items on the PEDro score (Moseley et al., 2002). A rating scale of 6 as "fair" and range of 7–8 as "good" and scale of 9 as "excellent" (Maher et al., 2003; Morton, 2009). Eligibility criteria are unused as a component in the total. Each study can obtain a maximum cumulative measurement of 10. The PEDro scores of each article are listed in Table 2. Journal database quality parameters from the studies obtained were determined by including studies from journals in quartile 1 (Q1) ranking on ScimagoJr (www.scimagojr.com) and a journal impact factor of greater than two.

Data extraction and analysis

The titles and abstracts are screened repeatedly checked by the primary investigator (first author) carefully to sort out the study according to the criteria based on the purpose of the review. After identifying studies that satisfied the criteria, full-text articles were retrieved and examined in detail to identify the study characteristics and the research quantitative data classification, necessary for the extraction of outcome data measurement results. This review collected the number of groups and subjects, methods and types of interventions, time since stroke, laterality of lesion, length of intervention, outcome measures, and final results of the studies. The sequence of these review methods was established prior to the conduct.

Cohen's d was calculated on each treatment effect size (ES) and compared among different interventions of these studies relating to the four functional outcome measures. Forest plot graphs were compiled for meta-analysis using the review manager (RevMan) software version 5.3 (Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2014) and were visualized in Figures 2–4. This review computed the random-effect model, 95% confidence interval (CI), presented the standardized mean difference (SMD) as the ES and including measures of consistency (I^2). The pooled intervention effect size of a similar treatment was also shown in Tables 3 and 4 to compare the effectiveness in each outcome measure and categorized as the immediate effect and long-term effect. The efficacy between the bottom-up intervention and top-down intervention are shown in Table 5 to present the effect estimate with the SMD statistical method of the pooled intervention categorized as the immediate and long-term effect.

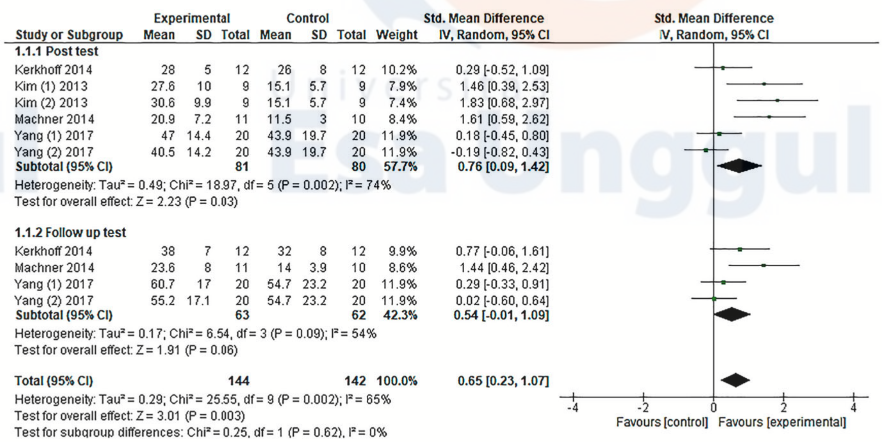

Figure 2. Forest plot of intervention and control group comparison, outcome: Barthel Index (post-test/immediate effects and follow-up test/long-term effects).

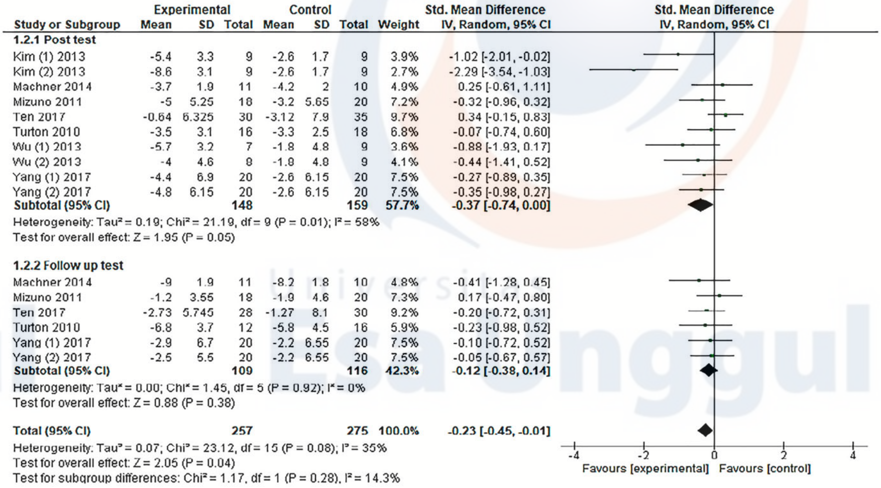

Figure 3. Forest plot of intervention and control group comparison, outcome: Catherine Bergego Scale (post-test/immediate effects and follow-up test/long-term effects).

Results

The search overview and selection process based on PRISMA flow diagram illustrated in Figure 1. The search strategies by filtering criteria applied in January 2019 period in three mentioned databases and limited by publication date from 2008/01/01 to 2018/12/31. The studies that founded in overlap (8 of 299 collected articles) were excluded before the selection process so that this review did not perform study selection and data extraction in duplicate. The 236 articles which are not fit the criteria were excluded based on the title and abstract selection process. The 42 articles also excluded after selected based on the journal and article body, the list and its reasons are showed in Table 3

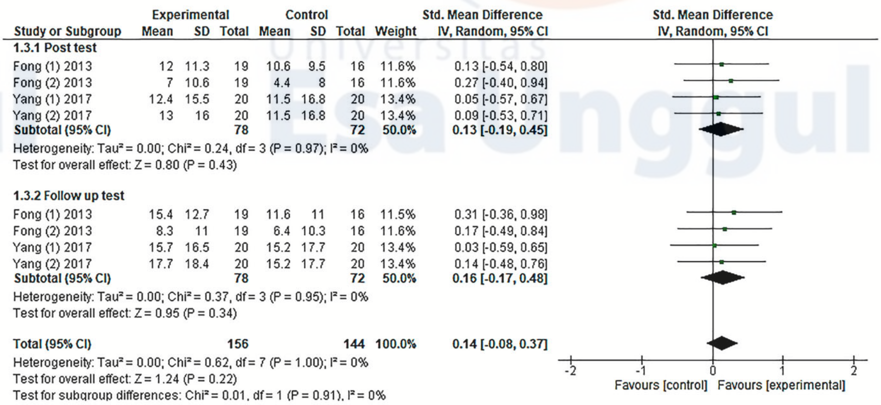

Figure 4. Forest plot of intervention and control group comparison, outcome: Fugl-Meyer Assessment test (post-test/immediate effects and follow-up test/long-term effects).

(see Supplemental data). The list of the included studies as much as 13 articles and their characteristics are showed in Table 1.

The overall feature of the studies

The studies descriptions and characteristics

The studies characteristics are summarized in Table 1. Twelve of the thirteen included studies are RCT have a control group. The total number of subjects was 492. The number of studies by database source of the journal were Pubmed/Medline eight (61.5%), both PEDro and Pubmed/Medline five (38.5%), and no study from J-Stage and PEDro only. The number of studies by impact factor of the journal was ten studies (76.9%) in two to six score, two studies (15.2%) in six to ten score, one study (7.7%) in ten to fourteen score. The lengths of interventions average conducted for approximately two to three weeks. The shortest and most intensive experiment period was every day for seven days is an intervention of the combination of hemifield eye patching and repetitive optokinetic stimulation (HEPOKS) and usual stroke care by Machner et al. (2014). In contrast, five interventions lasted up to four weeks.

The participant characteristics of the studies

The participant characteristics are summarized in Table 1. The subjects number of 332 (67.48%) from nine included studies (Fong et al., 2013; Kerkhoff et al., 2014; Kim et al., 2013; Machner et al., 2014; Mizuno et al., 2011; Ten Brink et al., 2017b; Turton et al., 2010; Wu et al., 2013; Yang et al., 2017) were involved in the quantitative review. The subjects number of 160 (32.52%) from four included studies (Cazzoli et al., 2012; Kutlay et al., 2018; Pandian et al., 2014; Van Wyk et al., 2014) were elaborated in the qualitative review. The highest number of participants was $n = 69$ in the study of PA by Ten Brink et al. (2017b), while the smallest amount of participants was $n = 21$ in the study of combined HEPOKS and usual stroke care by Machner et al. (2014). The most acute time since the onset was 48 h in the study by Pandian et al. (2014). The longest time since the onset was around 13 months in the study by Wu et al. (2013). Ten studies involved participants with right-sided brain lesions, while three studies included participants with left-side brain lesions.

Quality assessment

The quality assessment results using the PEDro scale can be seen in Table 2. The number of studies by PEDro score was one study (7.7%) has score six (fair), four studies (30.8%) have score seven (good), and six studies (46.2%) have score eight (good), and two studies (15.4%) have score nine (excellent) criteria. Based on the assessment results on each PEDro item, all included studies (100%) known to have a random allocation, groups similar at baseline, and

Table 1. The overview of the participant and studies characteristics of the included studies in the review.

No	Study Journal IF Pedro score	Group Sample size (n)	Method/ Intervention	Top-Down/ Bottom-Up	Time Since Stroke	Side of the brain damage or lesions	Length of study	Outcome Measure	Test Category	Result P/N	Result Data Format
1.	Turton et al. (2010), 2.667 8	Con: n1 = 18	ST, Flat plain glasses	Bottom-Up	47 ± 39 days	Right hemisphere Hemianopia = 4	Once a day, each weekday for two weeks	Primary: CBS Secondary: BIT MI	FAABT NABT FAABT	*P*	
		Exp: n2 = 16	PA	Bottom-Up	45 ± 23 days	Right hemisphere Hemianopia = 3					
		Total = 34									
2.	Mizuno et al. (2011) 3.757 9	Exp: n1 = 20	PA	Bottom-Up	64.4 ± 20.9 days	Right-brain damage Hemianopia (+) = 3 Hemianopia (–) = 17	Twice daily (about 20 min each session), five days per week, for two weeks, a total of 20 sessions	BIT CBS FIM SIAS	NABT FAABT FAABT SABT	*P*	FIM data displayed in the form of images
		Con: n2 = 18	Neutral plastic glasses	Bottom-Up	67.1 ± 18.4 days	Right-brain damage Hemianopia (+) = 3 Hemianopia (–) = 15					
		Total = 38									
3.	Cazzoli et al. (2012) 11.814 7	Exp 1: n1 = NR	*Continuous* TBS, then sham	Top-Down	Mean = 26.63 days SEM = 4.44 days	Right hemisphere	3 – 4 weeks	CBS Vienna test Paper-pencil assessment	FAABT NABT NABT	*P*	CBS data displayed in the form of images and SEM
		Exp 2: n2 = NR	Sham, then *continuous* TBS	Top-Down							
		Con: n3 = NR Total = 24	No stimulation	Unspecific							

(*Continued*)

Table 1. Continued.

No	Study Journal IF Pedro score	Group Sample size (n)	Method/ Intervention	Top-Down/ Bottom-Up	Time Since Stroke	Side of the brain damage or lesions	Length of study	Outcome Measure	Test Category	Result *P/N*	Result Data Format
4.	Wu et al. (2013) 3.325 8	Exp 1: n1 = 7	CIT + EP	Bottom-Up	13.0 ± 13.9 months	Handedness right = 7 Handedness left = 0	2 h/day, five days/week, for three weeks	Primary: CBS Secondary: Eye movement analysis Trunk–arm kinematic analysis	FAABT NABT FAABT	*P*/N	Follow up data is not available
		Exp 2: n2 = 8	CIT	Bottom-Up	10.1 ± 10.4 months	Handedness right = 7 Handedness left = 1					
		Con: n3 = 9	CT	Bottom-Up	13.7 ± 14.1 months	Handedness right = 9 Handedness left = 0					
		Total = 24									
5.	Kim et al. (2013) 2.697 7	Exp 1: n1 = 9	Low-frequency rTMS	Top-Down	14.2 ± 4.7 days	Cortical lesions = 8 (88.9%) Right-side lesions = 9 (100%)	Five times per week, for two weeks, and a total of 10 sessions	MFVPT LBT SCT CBS K-MBI	UT NABT NABT FAABT FAABT	*P*	Means ± SD data displayed as a form of change or difference, Follow up data is not available
		Exp 2: n2 = 9	High-frequency rTMS	Top-Down	14.3 ± 3.6 days	Cortical lesions = 7 (77.8%) Right-side lesions = 9 (100%)					
		Con: n3 = 9	SS	Top-Down	16.4 ± 8.5 days	Cortical lesions = 8 (88.9%) Right-side lesions = 9 (100%)					
		Total = 27									

6.	Fong et al. (2013) 2.738 8	Exp: n1 = 19 Con: n2 = 16 Total = 35	Contralesional SC + LA S/CR	Bottom-Up Bottom-Up	24.3 ± 18.5 days 22.3 ± 12.0 days	Subacute left hemiplegic	3 h a day, five days per week, for three weeks	BIT cancellation tasks BIT drawing tasks FIM FTHUE FMA – UL FMA – Hand	NABT NABT FAABT FAABT FAABT FAABT	N	
7.	Van Wyk et al. (2014) 3.757 8	Exp: n1 = 12 Con: n2 = 12 Total = 24	SEMT + VSE + TSA TSA	Bottom-Up Bottom-Up	1 and 3 weeks	NR, ischemic or hemorrhagic cerebral vascular	Four weeks	KDT SCT BI	UT NABT FAABT	*P*	Data showed in median, interquartile and figure
8.	Kerkhoff et al. (2014) 3.757 7	Exp 1: n1 = 12 Exp 2: n2 = 12 Total = 24	VST SPT	Bottom-Up Bottom-Up	37 ± 5 days 30 ± 4 days	Right hemisphere	VST: 27 ± 3 days SPT: 33 ± 2 days	Primary: FNI Secondary: UBNI HI BI Rehabilitation phase	NABT FAABT UT FAABT UT	*P*/N	
9.	Pandian et al. (2014) 8.689 8	Exp: n1 = 27 Con: n2 = 21 Total = 48	MT + LA SMT + LA	Bottom-Up Bottom-Up	48 h	Right hemisphere = 21 (78%) Left hemisphere = 6 (22%) Right hemisphere = 16 (76%) Left hemisphere = 5 (24%)	1–2 h a day, five days in a week, and for four weeks	Primary: SCT LBT PIT Secondary: FIM mRS	NABT NABT NABT FAABT SABT	*P*	Mean, and SD data are not available

(*Continued*)

Table 1. Continued.

No	Study Journal IF Pedro score	Group Sample size (n)	Method/ Intervention	Top-Down/ Bottom-Up	Time Since Stroke	Side of the brain damage or lesions	Length of study	Outcome Measure	Test Category	Result P/N	Result Data Format
10.	Machner et al. (2014) 6.0466	Exp: n1 = 11	Combined of HEP + OKS + usual stroke care	Bottom-Up	3 ± 1 days	Right hemisphere	all-day for seven days	Primary: NTB CBS Secondary: BI mRS NIHSS	NABT FAABT FAABT SABT SABT	*P*/N	Means ± SD data displayed as a form of change or difference
		Con: n2 = 10	Usual stroke care	Bottom-Up	5 ± 1 days						
		Total = 21									
11.	Yang et al. (2017) 2.738 9	Con: n1 = 20	Not Combined: CR	Bottom-Up	42.5 ± 30.6 days	Frontal lobe = 14 (70%) Temporal lobe = 17 (85%) Parietal lobe = 14 (70%) Occipital lobe = 6 (30%) Insular lobe = 10 (50%) Basal ganglia = 11 (55%) Thalamus = 3 (15%)	The 2-week conventional rehabilitation treatment consisted of 30 sessions of 45 min each, two sessions for physiotherapy sessions, and one occupational therapy session daily, for five days per week	Primary: BIT BIT – Cancellation tasks BIT – Drawing tasks CBS Secondary: FMA ARAT MBI	NABT NABT NABT FAABT FAABT FAABT FAABT	*P*/N	
		Exp 1: n2 = 20	Combined: rTMS + SC	Top-Down Bottom-Up	36.6 ± 33.2 days	Frontal lobe = 11 (55%) Temporal lobe = 12 (60%) Parietal lobe = 9 (45%) Occipital lobe = 2 (10%) Insular lobe = 4 (20%)					

					Basal ganglia = 13 (65%) Thalamus = 1 (5%)				
	Exp 2: n3 = 20	rTMS	Top-Down	37.5 ± 26 days	Frontal lobe = 13 (65%) Temporal lobe = 15 (75%) Parietal lobe = 13 (65%) Occipital lobe = 3 (15%) Insular lobe = 8 (40%) Basal ganglia = 13 (65%) Thalamus = 3 (15%)				
	Total = 60								
12. Ten Brink et al. (2017b) 3.757 8	Exp: n1 = 34	PA	Bottom-Up	41.50 days	Lesion side, Left = 21% Right = 77% Bilateral = 3% Neglect side, left = 82%	The treatment was performed once a day, each working day, for two weeks in addition to usual care	Primary: CBS Secondary: MAC Static paper-and-pencil task	FAABT UT NABT	N
	Con: n2 = 35	SA	Bottom-Up	37.00 days	Lesion side, Left = 21% Right = 73% Bilateral = 6% Neglect side, left = 77%				
	Total = 69								

(*Continued*)

Table 1. Continued.

No	Study Journal IF Pedro score	Group Sample size (n)	Method/ Intervention	Top-Down/ Bottom-Up	Time Since Stroke	Side of the brain damage or lesions	Length of study	Outcome Measure	Test Category	Result *P*/N	Result Data Format
13.	Kutlay et al. (2018) 2.183 7	Con: n1 = 28	CRP	Bottom-Up	Three months	Right hemiplegia = 3 (10.7%) Left hemiplegia = 25 (89.3%)	Duration: 4 weeks, five days a week, 2–3 h/day	BIT FIM	NABT FAABT	*P*	Data showed in median and interquartile
		Exp: n2 = 25	KAT + CRP	Bottom-Up	4 months	Right hemiplegia = 1 (4%) Left hemiplegia = 24 (96%)					
		Total = 64									

Abbreviations: ARAT = Action Research Arm Test; BI = Barthel Index; BIT = Behavioural Inattention Test; CBS = Catherine Bergego Scale; CIT = Constraint-Induced Therapy; Con = Control; CR = Conventional Rehabilitation; CR*P* = Conventional Rehabilitation Program; CT = Conventional Treatment; E*P* = Eye Patching; Ex*p* = Experiment; FAABT = Functional and/or ADL Assessment Based Test; FIM = Functional Independence Measure; FMA = Fugl-Meyer Assessment; FNI = Functional Neglect Index; FTHUE = Functional Test for the Hemiplegic Upper Extremity; HE*P* = Hemi-field Eye Patching; HI = Help Index; KAT = Kinesthetic Ability Training; KDT = King-Devick Test; K-MBI = Korean-Modified Barthel Index; LA = Limb Activation; LBT = Line Bisection Test; MAC = Mobility Assessment Course; MBI = Modified Barthel index; MFVPT = Motor-Free Visual Perception Test; MI = Motricity Index; mRS = modified Rankin Scale; MT = Mirror Therapy; N = Negative; NABT = Neglect Assessment Based Test; NIHSS = National Institutes of Health Stroke Scale; NR = Not Reported; NTB = Neuropsychological Test Battery; OKS = Optokinetic Stimulation; *P* = Positive; *P*/N = Positive/Negative; PA = Prism Adaptation; PIT = Picture Identification Task; rTMS = repetitive Transcranial Magnetic Stimulation; S/CR = Sham or Conventional rehabilitation; SA = Sham Adaptation; SABT = Scale Assessment Based Test; SC = Sensory Cueing; SCT = Star Cancellation Test; SD = Standard Deviation; SEM = Standard Error of Mean; SEMT = Saccadic Eye Movement Training; SIAS = Stroke Impairment Assessment Set; SMT = Sham Mirror Therapy; SPT = Smooth Pursuit Eye Movement Training; SS = Sham Stimulation; ST = Sham Treatment; TBS = Theta-Burst stimulation; TSA = Task Specific Activities; UBNI = Unawareness and Behavioral Neglect Index; UL = Upper Limb; UT = Unspecific Test; VSE = Visual Scanning Exercises; VST = Visual Scanning Training.

Table 2. PEDro scores of included studies.

		1	2	3	4	5	6	7	8	9	10	11		
No	Study	Eligibility Criteria	Random Allocation	Concealed Allocation	Groups Similar at Baseline	Participant Blinding	Therapist Blinding	Assessor Blinding	<15% Dropouts	Intention to-Treat Analysis	Between Group Difference Reported	Point Estimate and Variability Reported	Score Total (0–10)	Quality
1	Turton et al. (2010)	Yes	1	1	1	1	0	1	1	0	1	1	8	Good
2	Mizuno et al. (2011)	Yes	1	1	1	1	1	1	1	0	1	1	9	Excellent
3	Cazzoli et al. (2012)	Yes	1	1	1	1	1	1	0	0	1	0	7	Good
4	Wu et al. (2013)	Yes	1	1	1	1	1	1	1	0	1	0	8	Good
5	Kim et al. (2013)	Yes	1	0	1	1	1	0	1	0	1	1	7	Good
6	Fong et al. (2013)	Yes	1	1	1	1	0	1	1	1	1	0	8	Good
7	Van Wyk et al. (2014)	Yes	1	1	1	1	0	1	1	0	1	1	8	Good
8	Kerkhoff et al. (2014)	Yes	1	1	1	0	1	1	1	0	1	0	7	Good
9	Pandian et al. (2014)	Yes	1	0	1	1	1	1	1	0	1	1	8	Good
10	Machner et al. (2014)	Yes	1	1	1	0	0	0	1	0	1	1	6	Fair
11	Yang et al. (2017)	Yes	1	1	1	1	0	1	1	1	1	1	9	Excellent
12	Ten Brink et al. (2017b)	Yes	1	0	1	1	1	0	1	1	1	1	8	Good
13	Kutlay et al. (2018)	Yes	1	1	1	1	0	1	0	0	1	1	7	Good

between-group difference reported. Only three studies had the intention to treat analysis, two studies have > 15% dropouts, and one study had participant blinding, therapist blinding, and assessor blinding (Table 2).

The bottom-up and top-down intervention overview of the studies

The proportion group number of intervention methods of the included studies to resolve the USN conditions indicated that the bottom-up intervention approach was more commonly implemented (73.3%) in twenty-two groups than the top-down intervention approach (20%) in six groups, one group of the bottom-up and top-down combination intervention approach (3.3%) by Yang et al. (2017), and one group of the unspecific (no stimulation) intervention (3.3%) as control by Cazzoli et al. (2012) (Table 1). The PA was the most frequently used bottom-up intervention approach, which was implemented in three studies by Turton et al. (2010), Mizuno et al. (2011), and Ten Brink et al. (2017). All three studies used CBS as a post-test and follow-up test. The rTMS was the most commonly used top-down intervention approach, which was implemented by Kim et al. (2013) that uses BI and CBS as a post-test only and Yang et al. (2017) that use BI, CBS, and FMA as post-test and follow-up test (Tables 3–5).

The functional outcome measure overview of the studies

This review was focused on four types of functional measurement outcomes of BI, CBS, FMA, and FIM in quantitative analysis. The meta-analysis with SMD and

Table 3. The immediate (post-test) effect size of each intervention.

Outcomes	Study	Intervention	Effect size
BI	Kim et al. (2013) (2)	High-frequency rTMS	1.83 (0.68, 2.97)
	Machner et al. (2014)	Combined of HEP + OKS + usual stroke care	1.61 (0.59, 2.62)
	Kim et al. (2013) (1)	Low-frequency rTMS	1.46 (0.39, 2.53)
	Kerkhoff et al. (2014) (1)	SPT	0.29 (−0.52, 1.09)
	Yang et al. (2017) (1)	rTMS + SC	0.18 (−0.45, 0.80)
	Yang et al. (2017) (2)	rTMS	−0.19 (−0.82, 0.43)
	Kerkhoff et al. (2014) (2)	VST	−0.29 (−1.09, 0.52)
CBS	Kim et al. (2013) (2)	High-frequency rTMS	−2.29 (−3.54, −1.03)
	Kim et al. (2013) (1)	Low-frequency rTMS	−1.02 (−2.01, −0.02)
	Wu et al. (2013) (1)	Combined CIT + EP	−0.88 (−1.93, 0.17)
	Wu et al. (2013) (2)	CIT	−0.44 (−1.41, 0.52)
	Yang et al. (2017) (2)	rTMS	−0.35 (−0.98, 0.27)
	Yang et al. (2017) (1)	rTMS + SC	−0.27 (−0.89, 0.35)
	Mizuno et al. (2011)	PA	0.03 (−0.37, 0.43)
	Ten Brink et al. (2017)	PA	(pooled)
	Turton et al. (2010)	PA	(pooled)
	Machner et al. (2014)	Combined of HEP + OKS + usual stroke care	0.25 (−0.61, 1.11)
FMA	Fong et al. (2013) (2), hand	Contralesional SC + LA	0.27 (−0.40, 0.94)
	Fong et al. (2013) (1), UL	Contralesional SC + LA	0.13 (−0.54, 0.80)
	Yang et al. (2017) (2)	rTMS	0.09 (−0.53, 0.71)
	Yang et al. (2017) (1)	rTMS + SC	0.05 (−0.57, 0.67)
FIM	Fong et al. (2013) (1)	Contralesional SC + LA	−0.32 (−0.99, 0.35)

Table 4. The long-term (follow up-test) effect size of each intervention.

Outcomes	Study	Intervention	Effect size
BI	Machner et al. (2014)	Combined of HEP + OKS + usual stroke care	1.44 (0.46, 2.42)
	Kerkhoff et al. (2014) (1)	SPT	0.77 (−0.06, 1.61)
	Yang et al. (2017) (1)	rTMS + SC	0.29 (−0.33, 0.91)
	Yang et al. (2017) (2)	rTMS	0.02 (−0.60, 0.64)
	Kerkhoff et al. (2014) (2)	VST	−0.77 (−1.61, 0.06)
CBS	Machner et al. (2014)	Combined of HEP + OKS + usual stroke care	−0.41 (−1.28, 0.45)
	Mizuno et al. (2011)	PA	−0.10 (−0.45, 0.26)
	Ten Brink et al. (2017)	PA	(pooled)
	Turton et al. (2010)	PA	(pooled)
	Yang et al. (2017) (1)	rTMS + SC	−0.10 (−0.72, 0.52)
	Yang et al. (2017) (2)	rTMS	−0.05 (−0.67, 0.57)
FMA	Fong et al. (2013) (1), UL	Contralesional SC + LA	0.31 (−0.36, 0.98)
	Fong et al. (2013) (2), hand	Contralesional SC + LA	0.17 (−0.49, 0.84)
	Yang et al. (2017) (2)	rTMS	0.14 (−0.48, 0.76)
	Yang et al. (2017) (1)	rTMS + SC	0.03 (−0.59, 0.65)
FIM	Fong et al. (2013) (1)	Contralesional SC + LA	−0.12 (−0.78, 0.55)

95% CI using random-effects models calculations were applied to compare the effect of the interventions based on BI, CBS, FMA, and FIM as the functional outcome measures and ADL, the results displayed in the forest plot (Figures 2–4).

The effect of rehabilitation interventions on restoring functional ability and ADL

The Barthel Index

The BI tests were used in studies by Van Wyk et al. (2014), Kerkhoff et al. (2014), and Machner et al. (2014). Korean-Modified Barthel Index (K-MBI) was used in the study by Kim et al. (2013). Modified Barthel Index (MBI) used in the study by Yang et al. (2017). However, the data result in the study by Van Wyk et al. (2014) was excluded in meta-analysis in that data was displayed differently in median, interquartile, and figure. The BI forest plot of the interventions and control group comparison covered in four studies were described in Figure 2.

Table 5. The bottom-up and top-down pooled intervention on neglect rehabilitation.

Outcome or subgroup	Studies	Participants	Statistical method	Effect estimate
Bottom-up: PA				
CBS	3	261	SMD (IV, random, 95% CI)	−0.02 (−0.26, 0.23)
Immediate effects	3	137	SMD (IV, random, 95% CI)	0.03 (−0.37, 0.43)
Long-term effects	3	124	SMD (IV, random, 95% CI)	−0.10 (−0.45, 0.26)
Top-down: rTMS				
CBS	2	196	SMD (IV, random, 95% CI)	−0.50 (−0.97, −0.02)
Immediate effects	2	116	SMD (IV, random, 95% CI)	−0.82 (−1.55, −0.10)
Long-term effects	1	80	SMD (IV, random, 95% CI)	−0.08 (−0.51, 0.36)
BI	2	196	SMD (IV, random, 95% CI)	0.45 (−0.07, 0.96)
Immediate effects	2	116	SMD (IV, random, 95% CI)	0.70 (−0.17, 1.58)
Long-term effects	1	80	SMD (IV, random, 95% CI)	0.16 (−0.28, 0.60)
FMA	1	160	SMD (IV, random, 95% CI)	0.08 (−0.23, 0.39)
Immediate effects	1	80	SMD (IV, random, 95% CI)	0.07 (−0.37, 0.51)
Long-term effects	1	80	SMD (IV, random, 95% CI)	0.08 (−0.36, 0.52)

The meta-analysis was showed a significant mean ES in immediate effect of SMD = 0.76 (95% CI, 0.09–1.42; $p = 0.03$) on six trials which indicated that there was represent substantial heterogeneity ($p = 0.002$; $I^2 = 74\%$) across the studies, an insignificant mean ES in long-term effects of SMD = 0.54 (95% CI, −0.01–1.09; $p = 0.06$) on four trials which indicated that there was represent moderate to substantial heterogeneity ($p = 0.09$; $I^2 = 54\%$) across the studies, and a significant mean ES for overall effect of SMD = 0.65 (95% CI, 0.23–1.07; $p = 0.003$) in total which indicated that there was represent substantial heterogeneity ($p = 0.002$; $I^2 = 65\%$) across the overall trials of studies.

The Catherine Bergego Scale

The CBS were used in the studies by Turton et al. (2010), Mizuno et al. (2011), Cazzoli et al. (2012), Wu et al. (2013), Kim et al. (2013), Machner et al. (2014), Yang et al. (2017), and Ten Brink et al. (2017b). However, the data result in the study by Cazzoli et al. (2012) was excluded in meta-analysis in that data was displayed differently in the form of image and standard error of the mean (SEM). The CBS forest plot of the interventions and control group comparison covered in seven studies were described in Figure 3. Contrarily, the negative mean value of the CBS difference indicated an increase in the measurement score. The meta-analysis was showed a significant mean ES in immediate effect of SMD = −0.37 (95% CI, −0.74–0.00; $p = 0.05$) on ten trials which indicated that there was represent moderate to substantial heterogeneity ($p = 0.01$; $I^2 = 58\%$) across the studies, an insignificant mean ES in long-term effects of SMD = −0.12 (95% CI, −0.38–0.14; $p = 0.38$) on six trials which indicated that there was represent homogeneity ($p = 0.92$; $I^2 = 0\%$) across the studies, and a significant mean ES for overall effect of SMD = −0.23 (95% CI, −0.45 to −0.01; $p = 0.04$) in total which indicated that there was might not be important to represent moderate heterogeneity ($p = 0.08$; $I^2 = 35\%$) across the overall trials of studies.

The Fugl-Meyer Assessment

The FMA test was used in two articles (Yang et al., 2017; Fong et al., 2013). The FMA forest plot of the interventions and control group comparison covered in two studies described in Figure 4. The meta-analysis was showed an insignificant mean ES in immediate effect of SMD = 0.13 (95% CI, −0.19–0.45; $p = 0.43$) on four trials which indicated that there was represent homogeneity ($p = 0.97$; $I^2 = 0\%$) across the studies. Likewise, there was an insignificant mean ES in long-term effects of SMD = 0.16 (95% CI, −0.17–0.48; $p = 0.34$) on four trials which indicated that there was represent homogeneity ($p = 0.95$; $I^2 = 0\%$) across the studies. An insignificant mean ES for overall effect of SMD = 0.14 (95% CI, −0.08–0.37; $p = 0.22$) in total which indicated that there was represent homogeneity ($p = 1.00$; $I^2 = 0\%$) across the overall trials of studies.

The Functional Independence Measure

The FIM tests were used in four studies (Fong et al., 2013; Kutlay et al., 2018; Mizuno et al., 2011; Pandian et al., 2014). However, only the study by Fong et al. (2013) suitably included in the meta-analysis. The FIM forest plot of the intervention and control group comparison covered only in one study. With heterogeneity representation that was not applicable in post-test and follow-up test, the meta-analysis was showed an insignificant mean ES in immediate effect of SMD = −0.32 (95% CI, −.99–0.35; $p = 0.35$) on one trial, an insignificant mean ES in long-term effects of SMD = −0.12 (95% CI, −0.78–0.55; $p = 0.73$) on one trial, and an insignificant mean ES for overall effect of SMD = −0.22 (95% CI, −0.69–0.25; $p = 0.37$) in total which indicated that there was represent homogeneity ($p = 0.67$; $I^2 = 0\%$) across two tests of trial.

The pooled effect size of each intervention

The immediate effect

The ES of each intervention on the immediate outcome was presented in Table 3. The top-down intervention of high-frequency rTMS by Kim et al. (2013) appeared to be the most effective approach based on BI and CBS post-test results, while the FMA and FIM showed insignificant ES test results.

The long-term effect

The ES of each intervention on each long-term outcome was presented in Table 4. The bottom-up intervention of combined HEPOKS and usual stroke care by Machner et al. (2014) appeared to be the most effective approach based on BI post-test results only. While the CBS, FMA, and FIM showed insignificant ES test results.

The bottom-up and top-down pooled intervention on neglect rehabilitation

The pooled ES of the bottom-up intervention of PA and top-down intervention of rTMS was presented in Table 5. The overall results demonstrated that the effect estimate of the top-down approach of rTMS seems to be more effective immediately in improving the functional abilities and daily activities of USN patients based on CBS. While the rTMS based on BI and FMA to be insignificant as same as the PA approach on the effect estimate results of CBS appears to be insignificant.

Discussion

This review intended to find out the most effective intervention in alleviating neglect conditions related to the improved functional abilities of the USN. Two studies concluded the positive results of PA interventions based on CBS were described on trials in the right hemisphere stroke (Turton et al., 2010) and in subacute right brain damage (Mizuno et al., 2011), which some of the subjects were hemianopia. The studies proved that ADL improves significantly in patients with subacute stroke by PA therapy. However, a study by Ten Brink et al. (2017) deduced conversely reported in the subacute stroke, in some conditions of the subjects were left and bilateral neglect, which was comparable for situations of varying complexity. These results in line with several studies that demonstrate the effectiveness difference of PA due to the procedural differences, although the PA had established clinically and had an impact on the possibility of recovery of neglect by inducing plasticity in sensorimotor and spatial representations (Abbruzzese et al., 2019; Làdavas et al., 2011; Redding & Wallace, 2006; Rode et al., 2006). However, an in-depth understanding of physiological mechanisms and corresponding neural substrates remains unavailable (Prablanc et al., 2020). Therefore, the possible impact of cognitive mechanisms and neural circuits on the effects of PA is still being developed (Anelli & Frassinetti, 2019).

In this review, the application of the top-down intervention approach founded in three studies (Cazzoli et al., 2012; Kim et al., 2013; Yang et al., 2017). The study of rTMS by Kim et al. (2013) concluded positive results of the high-frequency and low-frequency of rTMS interventions in acute USN on the immediate effect of BI and CBS. It was suggested that not only low-frequency rTMS but also high-frequency rTMS could be a promising non-invasive method for the therapy of visuospatial neglect in patients with acute stroke. In contrast, another study by Yang et al. (2017) concluded negative results of the combined rTMS with SC and rTMS interventions or conventional rehabilitation programmes (CRP) alone in sub-acute USN on both immediate effect and long-term effects of BI, CBS, and FMA. This result confirms that the arm function improvement was not associated with enhanced independence in ADL (Yang et al., 2017). Whereas, the study of TBS by Cazzoli et al. (2012) concluded positive results of CBS in patients suffered a first ischemic or hemorrhagic lesion to the right hemisphere and explained that negative severity was significantly reduced by the application of continuous TBS but not of sham stimulation. This result lends support to potential effective strategy in accelerating recovery from visuospatial neglect in subacute stroke patients (Koch et al., 2012). However, the evidence level is still limited in the systematic review (Lefaucheur et al., 2014; Cotoi et al., 2019).

According to the results, indeed, non-invasive brain stimulation (NIBS) can improve motor recovery by ameliorating use-dependent plasticity impairment after stroke and offering an immense potential to provide further insight into brain connectivity (Hillis, 2006; Sebastianelli et al., 2017; Takeuchi & Izumi, 2013; Westlake & Nagarajan, 2011). NIBS has the potential to facilitate recovery of hemispatial neglect after stroke but not enough data to claim its routine use (Jacquin-Courtois, 2015; Veldema et al., 2019). Although the efficacy of rTMS has promising results in the remediation of post-stroke USN, but remains controversial, used mainly in terms of the best stimulation parameters (Fan et al., 2018; Fisicaro et al., 2019), and have to further assess the effects in multi-centre clinical trials (Sebastianelli et al., 2017; Klomjai et al., 2015). The studies with rTMS after stroke reported no adverse effects (Johansson, 2011; Dionísio et al., 2018). Furthermore, the rTMS stimulation considered to affect brain excitability and play a role in its plasticity and reliable to improve cognitive abilities and behavioural performance in the context of rehabilitation although it is still continuously influenced by the variable of natural recovery mechanism in the treatment process (Blesneag et al., 2015; Corbetta et al., 2005; Du et al., 2016; Miniussi & Rossini, 2011; Vallar & Bolognini, 2011). While in the early post-stroke period, spontaneous recovery is common (Dąbrowski et al., 2019). In general, the strength of the paretic upper limb, age, gender, and the ability to perform basic ADL are significant predictor variables to influence the independence level in complex ADL of the stroke patients in the long-term recovery (Cioncoloni et al., 2013). However, better characterization of brain changes is still necessary to understand the potential impact on the functional anatomy and synaptic network plasticity induced by rTMS to optimize therapeutic rTMS protocols and to assess their safety (Lefaucheur et al., 2014; Guggisberg et al., 2019).

Two other studies had negative results on CBS (Machner et al., 2014; Wu et al., 2013). The early intervention of combined HEPOKS and usual stroke care in the acute right hemisphere stroke was concluded no additive effect on CBS measurements even though BI showed a positive result in immediate effect and long-term effect. This outcome might be due to spontaneous recovery and the usual stroke care, which more dominant effect (Machner et al., 2014). Furthermore, a study of CIT and EP combination by Wu et al. (2013) on right-side cerebral stroke concluded that CIT + EP and CIT interventions were more effective in daily functional performance than the conventional treatment in patients with neglect syndrome. Although CBS value showed negative results on the immediate effect, CIT might improve eye movement and limb initiation, whereas CIT + EP might facilitate anticipatory control and trunk control (Wu et al., 2013). These results tend to refute that EP might improve visual attention and had the usefulness in clinical practice with different tests (Smania et al., 2013; Sugimoto & Fujino, 2017).

Another study shows a negative result on BI in the immediate effect and long-term effect (Kerkhoff et al., 2014). The study concluded that SPT was better than VST in reducing functional neglect and unawareness in post-acute stroke at one month with left neglect. The significant results based on functional neglect index (FNI) and unawareness and behavioural neglect index (UBNI) functional measurements. Bedside neglect treatment using SPT is practical and feasible early after stroke (Kerkhoff et al., 2014). Moreover, another study indicates a negative result on FMA-hand, FMA-UL, and FIM in immediate effect and a long-term effect (Fong et al., 2013). The study of the combination of contralesional SC and LA in subacute left hemiplegic stroke concluded an insignificant result. The results did not confirm that SC and LA treatment is effective when compared with those receiving placebo to reduce unilateral neglect, but it might be useful for promoting hemiplegic arm performance in stroke patients (Fong et al., 2013).

The other two studies were using the FIM, but the FIM result not recorded in the meta-analysis of this review. A study of the combination of MT and LA by Pandian et al. (2014) in stroke patients with thalamic and parietal lobe lesions concluded that MT is a simple treatment that improves unilateral neglect. Based on the FIM, the patients in the treatment group were more likely to be independent during follow-up (Pandian et al., 2014). Subsequently, a study of the combination of KAT and CRP by Kutlay et al. (2018) in stroke patients with left and right hemiplegia concluded that KAT provides an efficient intervention and clinically meaningful improvement in stroke patients with unilateral spatial neglect (Kutlay et al., 2018). Another study was using the BI, but the BI result not recorded in the meta-analysis of this review. The study of the combination of SEMT, VSE, and TSA by Van Wyk et al. (2014) in ischemic or hemorrhagic cerebral vascular concluded a significant effect on improved USN and visual perceptual processing. The improvement of visual perceptual processing translates to significantly better visual function and the ability to perform ADL following the stroke (Van Wyk et al., 2014).

Clinical implications

Clinically, the rTMS and PA as the most effective approach based on this result need to consider concerning the relevance of the method, the purpose of the intervention, the patient's condition, and the availability of therapeutic devices. Our results provide compelling evidence that both intervention approaches are suitable to apply continuously to solve the neglect functional impact and ADL. However, further investigation still required to examine the appropriateness of the treatment approaches with the individual problems suffered by USN patients specifically.

Study limitations

The strength of this review it was selective to collect studies of high quality according to the PEDro standards and from the first quartile journal with the high impact factor. Although, the PEDro and Cochrane approach leads to different sets and criteria of adequate quality estimates in construct validity (Albanese et al., 2020; Armijo-Olivo et al., 2015), however, there was a moderate agreement of both, so either instrument can still be selected for use (Moseley et al., 2019b). This review also covered both types of bottom-up and top-down intervention approach by involving four functional outcomes in the analysis. However, this review has limitations in that it searches merely from three sources of the journal database, and it was unspecific in limiting the subject categories and not describing each intervention in detail. This review also rules out a third party as a reviewer and not calculated the sensitivity of each trial. Ensuing to the existence of the heterogeneity representation across studies caused difficulties in concluding accordingly. Hence, those limitations are essentials to be a concern as a suggestion enhancement toward future trial research design.

Conclusions

The variety of interventions with the substantial distinctions of the trial protocol implementation and subject characteristics seems to lead difficulties in drawing any conclusion concerning the effectiveness feature of the collected experiments. However, referring to the presented meta-analysis result, it appeared to prove that the top-down interventions of high-frequency rTMS, along with its combination was more enhance the functional abilities and ADL of USN patients on the immediate effects but not necessarily on the long-term effects. The future research recommended to provide more attention concerning functional outcome measurement and long-term ADL and correlating the improvement status of neglect conditions in line with the enhancement of ADL status. Further RCTs research is also needed for each type of intervention modification and its combination with a higher number of subjects and leads to long-term functional improvement efforts.

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