Systematic Review

Evaluation of the impact of bottom-up and top-down approaches on daily activities in people with neglet – a systematic review

Avaliação do impacto das abordagens *bottom-up* e *top-down* nas atividades da vida diária em pessoas com *neglect* – revisão sistemática

Marlene Neves Rosa[1]
Andreia Amorim[2]
Marisa Bartolo[3]
Ana Rita Martins[4]
Catarina Oliveira[5]
Cândida G. Silva[6]

[1]Corrresponding author. Escola Superior de Saúde, Instituto Politécnico de Leiria (Leiria); ciTechCare - Center for Innovative Care and Health Technology (Leiria). Portugal. marlene.rosa@ipleiria.pt
[2-5]Escola Superior de Saúde, Instituto Politécnico de Leiria (Leiria). Portugal. 5160252@my.ipleiria.pt, 5160223@my.ipleiria.pt, 5160222@my.ipleiria.pt, 5160239@my.ipleiria.pt
[6]Centro de Química de Coimbra, Universidade de Coimbra (Coimbra); Escola Superior de Saúde, Instituto Politécnico de Leiria (Leiria). Portugal. candida.silva@ipleiria.pt

ABSTRACT | BACKGROUND: Currently there is no consensus on which are the characteristics of rehabilitation approaches (bottom-up or top-down) most effective in the rehabilitation of ADLs in people with Neglet Syndrome (NS). AIM: To characterize the approaches (bottom-up or top-down) with more impact on ADLs in adults and elderly with NS. **METHODS:** This systematic review was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) recommendation. A bibliographic search was carried out in PubMed, Web of Science, PEDro and Cochrane databases. Experimental studies were considered in which at least one technique of the bottom-up and top-down approaches was used. The Joanna Briggs Institute Critical Appraisal Checklist for RCTs tool was used to assess the methodological quality of the studies. The following combination of keywords was used: Negligence Syndrome OR Unilateral Syndrome OR Negligence (...) AND Activities OF Daily OR Daily Life (...) AND Treatment OR Intervention OR Technique (...). **RESULTS:** 16 studies were included, which 9 include techniques from the bottom-up approach, 6 include techniques from the top-down approach and 1 article includes two techniques, each belonging to each approach. The techniques of the bottom-up approach that increased independence in the ADLs were Visuomotor Feedback Training, Smooth Pursuit Eye Movement Training and the combination of Eye Patching with Constraint-induced Therapy. In the top-down approach, the techniques with the same results were Visual Scanning, Mental Practice, Continuous Theta Burst Stimulation and Transcranial Direct Current Stimulation. **CONCLUSION:** Both bottom-up and top-down approaches increase independence in ADLs. Each approach contains techniques with a significant positive impact on ADLs such as Visuomotor Feedback Training and Continuous Theta Burst Stimulation. The present work also allowed a critical analysis to the classification of the approaches in bottom-up and top-down, since they are not different to the category of rehabilitation mechanisms.

KEYWORDS: Self-Neglect. Perceptual Disorders. Activities of daily living. Rehabilitation.

RESUMO | INTRODUÇÃO: Atualmente não existe um consenso entre quais as caraterísticas das abordagens (*bottom-up* ou *top-down*) mais eficazes na reabilitação das Atividades da Vida Diária (AVDs) em pessoas com Síndrome de Neglect (SN). **OBJETIVO:** Caracterizar as abordagens (*bottom-up* ou *top-down*) e o seu impacto nas AVDs em adultos e idosos com SN. **MÉTODOS:** Esta revisão sistemática foi realizada de acordo com a recomendação PRISMA - *Preferred Reporting Items for Systematic Reviews and Meta-Analyses*. A pesquisa bibliográfica foi realizada nas bases de dados *PubMed*, *Web of Science*, *PEDro* e *Cochrane*. Foram considerados estudos experimentais em que pelo menos uma técnica das abordagens bottom-up e top-down fosse utilizada. A ferramenta *Joanna Briggs Institute Critical Appraisal Checklist for RCTs* foi utilizada para avaliar a qualidade metodológica dos estudos. Foi usada a seguinte combinação de palavras chave: *Neglect Syndrome OR Unilateral Syndrome OR Neglect* (...) *AND Activities of Daily Living OR Daily* (...) *AND Treatment OR Intervention OR Technique* (...). **RESULTADOS:** Foram incluídos 16 estudos, dos quais 9 incluem técnicas de abordagem *bottom-up*, 6 incluem técnicas de abordagem *top-down* e 1 artigo inclui técnicas das duas abordagens. As técnicas da abordagem *bottom-up* que aumentaram a independência nas AVDs foram *Visuomotor Feedback Training*, *Smooth Pursuit Eye Movement Training* e a combinação de *Eye Patching* com *Constraint-induced Therapy*. Na abordagem *top-down* as técnicas com os mesmos resultados foram *Visual Scanning*, *Mental Practice*, *Continuous Theta Burst Stimulation* e *Transcranial Direct Current Stimulation*. **CONCLUSÃO:** As abordagens *bottom-up* e *top-down* aumentam a independência nas AVDs e cada uma contém técnicas com significativo impacto positivo, como *Visuomotor Feedback Training* e *Continuous Theta Burst Stimulation*. O presente trabalho permitiu uma análise crítica à classificação das abordagens em *bottom-up* e *top-down*, uma vez que não são sensíveis à distinção dos mecanismos de reabilitação envolvidos.

PALAVRAS-CHAVE: Autonegligência. Transtornos de Perceção. Atividades quotidianas. Reabilitação.

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Introduction

Neglect Syndrome (SN) is a disabling characteristic that comes from an imbalance in interhemispheric excitability[1] caused mainly from stroke. It occurs in approximately 50% of its survivors and is more severe and prevalent in the right hemisphere, with an incidence of 13% to 82%[2]. Considering the SN symptoms, 20% to 80% of them appear in the acute phase and persist in 75% of individuals in the chronic phase[3,4]. Although this condition is heterogeneous, most individuals do not respond to stimuli located in the contralesional space, compromising the Activities of Daily Living (ADLs) performance[4,5].

The rehabilitation of SN might induce individuals to explore their neglected space, trough different approaches that can be divided into two classifications: bottom-up or top-down[2]. The bottom-up approach is based on the manipulation of the sensory environment, using external stimulation to increase the activation of the injured hemisphere and the neglected side of the body[6]. As an example, this approach includes the Prism Adaptation, Constraint-induced Therapy and Eye Patching technique.

In turn, the top-down approach uses previously acquired learning to influence perception, requiring high levels of patient's attention and collaboration and requiring some degree of awareness of their neglect[6–8]. As an example, this approach includes Visual Scanning, Mental Practice and Continuous Theta Burst Stimulation techniques.

Regarding the existing literature on SN, there is a systematic review that included studies published from 2006 to 2016 with the objective of determining the effectiveness of activity-based interventions and non-activity-based interventions in improving the functional performance of ADLs and reducing neglect[3]. As it did not identify which interventions had a positive impact on the functional performance of the ADLs, this systematic review only concluded which intervention group had the best results and that the majority of the included studies did not emphasize the involvement of the ADLs[3]. In addition, there is also a literature review that aimed to provide an overview of the evidence on the effectiveness of rehabilitation procedures for NS, studying the impact of bottom-up and top-down approaches[7]. However, the results did not explore whether the results obtained transfer to an increase in autonomy for ADLs[7].

About the NS rehabilitation, a systematic review was previously conducted in order to determine the effectiveness of interventions based on the training of functional activities versus unspecific training (eg, electrostimulation) in improving the functional performance of ADLs and in reducing NS symptoms[6]. This review concluded that techniques such as TENS, somatosensory stimulation or mirror therapy are effective in reducing NS symptoms. However, most of the included studies did not consider its effect on the ADLs independence[6]. Another related systematic review, conducted in 2017, described the effectiveness of the bottom-up and top-down approaches in rehabilitation for NS[7]. This paper demonstrated the same methodological limitation, as it did not explore the transfer of the results in NS to the autonomy in performing ADLs[7].

Considering the gaps in these previous systematic reviews, revisiting and characterizing the literature on the effectiveness of bottom-up and top-down approaches in ADLs[4] is crucial to improve the clinical decision process in SN rehabilitation. Thus, the present study aims to characterize the approaches (bottom-up or top-down) with the greatest impact on ADLs in adults and the elderly with NS.

Methods

This systematic review was carried out in accordance with the PRISMA recommendation – Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PROSPERO record CRD42020201670)[10].

Inclusion and exclusion criteria

Randomized controlled studies (RCTs) were included if (1) interventions included bottom-up or top-down techniques; (2) participants were adults (aged 18+ years) with Neglect Syndrome (NS); (3) limitations in ADLs were assessed with specific instruments and the scores before and after the intervention were provided; (4) studies published up to April 2020; (5) available in full text and (6) written in English, Portuguese or Spanish. RCTs were excluded if (1) were published in languages other than English, Portuguese or Spanish; (2) included pharmacological interventions; (3) no differentiation of participants with and without SN; (4) included techniques classified as a mixed approach (bottom-up and top-down); (5) no full text was available; and (6) unfinished studies.

Search Strategy

The bibliographic search was performed in PubMed, Web of Science, PEDro and Cochrane, using the following search strategy: (Neglect Syndrome OR Unilateral Syndrome OR Neglect OR Hemineglect OR Spatial Neglect) AND (Activities of Daily Living OR Daily Routine OR Daily Living) AND (Treatment OR Intervention OR Technique OR Rehabilitation OR Program).

Study selection and data extraction

In a first stage, the studies were screened based on the title and abstract; in the second stage, the full text of the studies was read. These two stages were performed by two independent evaluators and Cohen's Kappa coefficient was calculated to assess the agreement between. Disagreements were resolved by consensus. The values obtained were interpreted according to the following criteria: [0; 0.2] weak agreement, [0.21; 0.4] reasonable agreement, [0.41; 0.6] moderate agreement, [0.61; 0.8] strong agreement, [0.81; 1] almost perfect agreement. These calculations were performed using the IBM SPSS version 26 program.

The data were extracted into a table with the following itens: citation (last name of the first author and year), characteristics of the intervention group (IG) and control group (CG) (number of participants, age, stage of SN), parameters of the rehabilitation programs applied to the IG and CG (technique, number of daily sessions, number of weekly sessions and number of weeks), instruments used to assess limitations in the ADLs with indication of the score before and after the intervention in the IG and GC, main conclusions.

Risk of bias

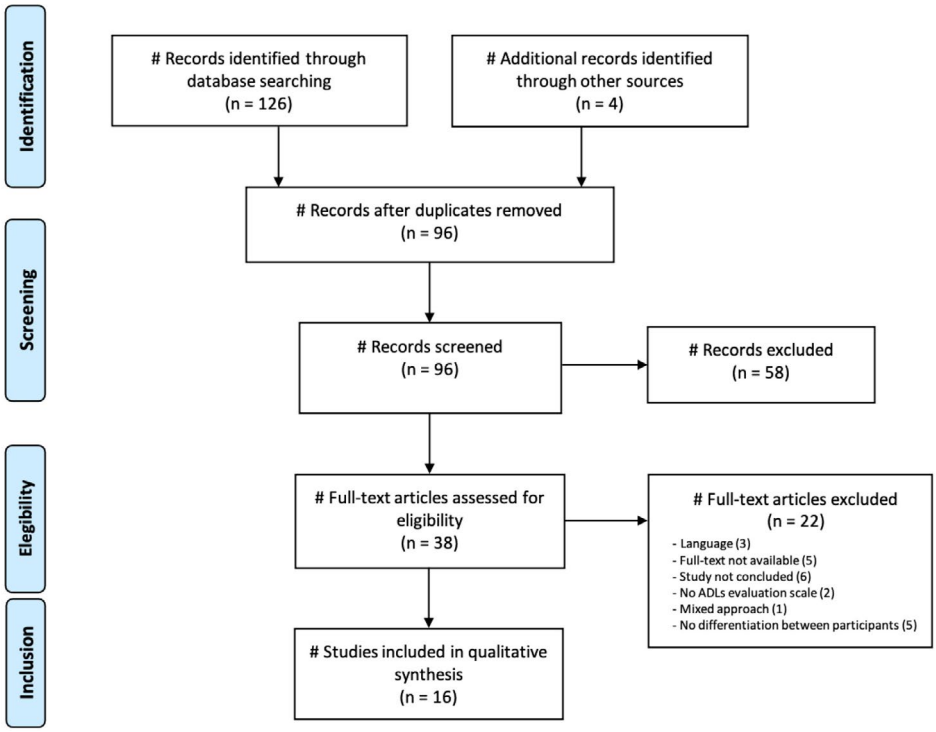
Risk of bias in the selected studies was assessed by two independent researchers using the Joanna Briggs Institute Critical Appraisal Checklist for RCTs[11]. This consists of 13 questions and allows the assessment and determination of the possibility of bias in the design of studies (Questions 1 to 8) and in data analysis (Questions 9-13). Questions can be answered with the values Yes, No, Unclear or Not Applicable. Ranges of values for methodological quality defined were: very poor (0-2), poor (3-5), moderate (6-8), high (9-11) and excellent (12-13)[11].

Results

Study selection

From the literature search, 126 articles were retrieved. After removal of duplicates, 96 articles were left, of which 58 were excluded (based on reading the title and summary) because they did not address NS and / or did not mention the influence of rehabilitation on ADLs. Of the remaining 38 articles, and after reading the full text, another 22 were excluded according to the defined exclusion criteria, resulting in a total of 16 studies for qualitative synthesis (Figure 1). Studies were excluded because (1) the article was not written in English, Portuguese or Spanish (n = 3), (2) the full text was not available (n = 5), (3) the study was not completed (n = 6), (4) an instrument was not applied to assess limitations in ADLs (n = 2), (5) the intervention had a mixed approach (top-down and bottom- up) (n=1), and (6) the participants were not differentiated (n = 5). The kappa values obtained were 0.68 in the selection of studies based on the title and summary (strong agreement) and 0.95 in the selection of studies taking into account the reading of the full text (almost perfect agreement)[12].

Figure 1. Flow chart describing of the protocol of the studies' identification, selection, eligibility and inclusion



Studies with bottom-up interventions

Of the 16 studies included, 9 studies applied interventions with bottom-up techniques (Chart 1.). These studies included a total of 346 participants: 194 belong to the intervention group and 152 to the control group. Two studies[13,14] included two intervention groups. Most studies showed an average age between 56.1 and 74.21 years in the intervention group and between 61.33 to 73.8 years in the control group. As for the SN stage, 2 studies[15,16] intervened in the acute phase, 6 studies[13,17-21] in the subacute phase, one study[22] in the chronic phase, and one study[14] did not report the phase of intervention.

Five different instruments were used to assess the participants' limitations in ADLs before and after the intervention: Catherine Bergego Scale (CBS) [5 studies[14,15,18-20]], Barthel Index (BI) [3 studies[15,16,21]], Functional Independence Measure (FIM) [3 studies[13,17,19]], Score of Independence Index for Neurological and Geriatric Rehabilitation (SINGER) [1 study[21]] and Stroke Impact Scale (SIS) [1 study[22]]. In addition, 4 studies[13,17-19] applied the Behavioral Inattention Test (BIT) to assess the severity of NS.

The bottom-up techniques used were Prism Adaptation [3 studies[18-20]], Eye Patching [4 studies[13-15,17]], robotics [1 study[21]], Visuomotor Feedback Training [1 study (22)] and Smooth Pursuit Eye Movement Training [1 study[16]].

Studies using the Prism Adaptation technique in the intervention group[18-20] compared it with placebo (control group). Only Mizuno et al. (2011)[19] concluded that the intervention group obtained more significant results than the control group in the independence in ADLs (CBS Pre-intervention score: IG = 9.8 ± 6.8; CG = 9.6 ± 6.2 / CBS Post-intervention score: IG = 4.8 ± 3.7; CG = 6.4 ± 5.1) (Chart 1). Additionally, Turton et al. (2010)[18] concluded that the same technique showed more significant results in reducing the symptoms of subacute SN when compared to placebo (Pre-intervention BIT-C Scores: IG = 88 ± 71; CG = 109 ± 70 / Post- intervention: IG = positive variation of 14.8 ± 18.8; CG = positive variation of 9.7 ± 15.9) (Chart 1).

In studies included, the Eye Patching technique was always applied in combination with other techniques. In Tsang et al. (2009)[17], the combination of Eye Patching with Conventional Occupational Therapy

(IG) was compared with Conventional Therapy. Fong et al. (2007)[13] combined Eye Patching and Voluntary Trunk Rotation Training (IG1) and compared it with Voluntary Trunk Rotation Training (IG2) and with Conventional Occupational Therapy (CG). Wu et al. (2013)[14] associated Eye Patching and Constraint-Induced Therapy (IG1), which was compared with the application of Constraint-Induced Therapy only (IG2) and with Occupational Therapy (CG). Machner et al. (2014)[15] associated the Eye Patching and Optokinetic Stimulation (IG) techniques and compared them with a non-specific treatment for NS (CG). Only Wu et al. (2013)[14] inferred that the Eye Patching technique associated with Constraint-Induced Therapy (IG1) resulted in significant improvements in independence in ADLs when compared to Constraint-Induced Therapy alone (IG2) or Conventional Occupational Therapy (CG) (CBS Pre-intervention scores: IG1 = 16.1 ± 3.2; IG2 = 13.9 ± 4.8; GC = 18.1 ± 5.1 / Post-intervention: IG1 = 10.4 ± 3.2; IG2 = 9.9 ± 4.4; CG = 16.3 ± 4.5) (Chart 1).

For the robotic intervention, Karner et al. (2019)[21] compared the use of the PARO (IG) robot, which stimulates a relationship with participants through touch, with the reading of a book (CG) and concluded that the application of the robot did not lead to significant results in participants' independence in the ADLs (SINGER Pre-intervention scores: IG = 7.95 ± 4.63; CG = 8.22 ± 4.49 / Post-intervention scores: IG = 12.48 ± 5.44; CG = 11.11 ± 5.41) (Chart 1).

Rossit et al. (2019) (22) concluded that the Visuomotor Feedback Training (GI) technique is an effective rehabilitation method and can be performed in cases of chronic NS, in addition to showing improvements in ADLs when compared to the intervention of the control group (CG) (SIS Pre-intervention scores: IG = 48.1 ± 9.9; CG = 46.0 ± 8.7 / Post-intervention scores: IG = 50.1 ± 9.5; CG = 56.7 ± 7.0) (Chart 1).

For the Smooth Pursuit Eye Movement Training technique (IG1), Kerkhoff et al. (2014)[16] compared its application with the Visual Scanning technique (IG2; top-down approach) and concluded that the first (IG1) revealed more significant improvements in reducing the symptoms of acute NS than Visual Scanning (IG2), despite both increase independence in ADLs (BI Pre-intervention scores: IG1 = 11 ± 4; IG2 = 15 ± 5 / Post-intervention scores: IG1 = 28 ± 5; IG2 = 26 ± 8) (Chart 1).

In terms of intervention dose, it varied from 1 to 2 daily sessions, 2 to 7 days a week over 1 to 6 weeks. The follow-up in 5 studies[14,17,18,20,21] was incomplete: in 2 studies[14,17] the follow-up was not carried out and in 3 studies[18,20,21] the reason for the dropout of some participants was not specified.

Chart 1. Description of the characteristics and main conclusions of the studies with bottom-up interventions (n = 9) (to be continued)

Study	Characteristics of the intervention group (IG)	Intervention (no. of daily session x no. of week sessions x no. of weeks)	Characteristics of the control group (CG)	Control Group intervention	Scales	Results (mean ± std. deviation)	Conclusions
Turton et al. (2010)	N = 16 (F: 50%; M: 50%) Age: 72 ± 14 Stage: subacute	PA 1 x 5 x 2	N = 18 (F: 39%; M: 61%) Age: 72 ± 14 Stage: subacute	Neutral glasses 1 x 5 x 2	CBS BIT-C	CBS Pre-intervention: PA: 12 ± 5 Control: 11 ± 4 CBS Post-intervention: PA: Positive variation of 3.5 ± 3.1 Control: Positive variation of 3.3 ± 2.5 CBS Follow-up: PA: Positive variation of 6.8 ± 3.7 Control: Positive variation of 5.8 ± 4.5 BIT-C Pre-intervention: PA: 88 ± 71 Control: 109 ±70 BIT-C Post-intervention: PA: Positive variation of 14.8 ±18.8 Control: Positive variation of 9.7 ± 15.9 BIT-C Follow-up: PA: Positive variation of 24.5 ± 15.7 Control: Positive variation of 21.8 ± 22.2	- PA showed more positive results in what concerns independence in ADLs. - The two groups presented improvements, so it was not possible to conclude which was the best intervention.

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Chart 1. Description of the characteristics and main conclusions of the studies with bottom-up interventions (n = 9) (continuation)

Study	Characteristics of the intervention group (IG)	Intervention (no. of daily session x no. of week sessions x no. of weeks)	Characteristics of the control group (CG)	Control Group intervention	Scales	Results (mean ± std. deviation)	Conclusions
Ten Brink et al., 2017	N = 35 (F: 26%; M: 74%) Age: 59.31(14.45) (Median(IQR)) Stage: subacute	PA 1 x 5 x 2	N = 35 (F:31%; M: 69%) Age: 61.48(13.37) (Median(IQR)) Stage: subacute	SA 1 x 5 x 2	CBS	Pre-intervention: PA: 12.83 ± 6.62 SA: 15.43 ±7.54 Post-intervention: PA: 11.74 ± 6.46 SA: 11.97 ± 8.34 Follow-up: PA: 9.46 ± 5.46 SA: 11.04 ± 7.94	- No differences were found between the CBS scores in the two groups.
Mizuno et al., 2011	N = 18 (F: 33%; M: 67%) Age: 66 ± 11.5 Stage: subacute	PA 2 x 5 x 2	N = 20 (F: 25%; M: 75%) Age: 66.6 ± 7.7 Stage: subacute	Neutral glasses 2 x 5 x 2	CBS FIM BIT-C	CBS Pre-intervention: PA: 9.8 ± 6.8 Control: 9.6 ± 6.2 CBS Post-intervention: PA: 4.8 ± 3.7 Control: 6.4 ± 5.1 CBS Follow-up: PA: 3.6 ± 3.4 Control: 4.5 ± 4.1 BIT-C Pre-intervention: PA: 113.3 ± 24.8 Control: 102.1 ± 42.2 BIT-C Post-intervention: PA: 19.7 ± 17.1 Control: 17.8 ± 24.9 BIT-C Follow-up: PA: 133 ± 10.1 Control: 119.8 ± 26.9 *FIM data presented only in plots.*	- PA produced a significant increase in the FIM scores ($p < 0.05$) after the conclusion of the medical release of the participants. - The intervention group achieved higher goals in the ADLs than the control group. - CBS showed an improvement in independence in the ADLs in the intervention group. - PA can significantly increase independence in ADLs in individuals with subacute NS.

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Chart 1. Description of the characteristics and main conclusions of the studies with bottom-up interventions (n = 9) (continuation)

Study	Characteristics of the intervention group (IG)	Intervention (no. of daily session x no. of week sessions x no. of weeks)	Characteristics of the control group (CG)	Control Group intervention	Scales	Results (mean ± std. deviation)	Conclusions
Tsang et al., 2009	N = 17 (F: 29%; M: 71%) Age: 70.47 ±9.30 Stage: subacute	*Half field EP* associated with conventional occupational therapy 4 weeks	N = 17 (F: 47%; M: 53%) Age: 71.82 ± 5.26 Stage: subacute	Conventional treatment 4 weeks	FIM BIT	FIM Pre-intervention: EP: 56.24 ± 15.72 Control: 46.94 ±16.15 FIM Post-intervention: EP: 16.00 ± 14.24 Control: 12.41 ±14.21 BIT Pre-intervention: EP: 34.84 ± 25.99: Control: 43.94 ± 34.56 BIT Post-intervention: EP: 25.06 ± 30.81 Control: 8.29 ± 10.35	- FIM scores showed that conventional treatment with Half field EP was effective in reducing neglect, but failed to show an improvement in independence in ADLs.
Fong et al., 2007	**IG1** N = 20 (F: 35%; M: 65%) Age: 69.9 ± 9.8 **IG2** N = 19 (F: 42%; M: 58%) Age: 69.9 ± 11 Stage: subacute (8 weeks after stroke)	IG1: VTR+EP + Occupational Therapy IG2: VTR + Occupational Therapy 1 x 5 x 6	N = 15 (F: 33%; M: 67%) Age: 73.8 ± 9.9 Stage: subacute (8 weeks after stroke)	Occupational Therapy 1 x 5 x 6	FIM BIT-C	FIM Pre-intervention: IG1: 27.9 ±14.1 IG2: 31,8 ± 12.1 Control: 26.5 ± 11.0 FIM Post-intervention: IG1: 44.3 ± 18.7 IG2: 50.2 ± 19.4 Control: 37.1 ± 16.4 FIM Follow-up: IG1: 51.5 ± 21.7 IG2: 52.9 ± 19.5 Control: 40.7 ± 20.9 BIT-C Pre-intervention: IG1: 58.8 ±36 IG2: 73.6 ± 33.7 Control: 60.4 ± 39.6 BIT-C Post-intervention: IG1: 87.1 ± 40.2 IG2: 100.9 ± 38.1 Control: 78.6 ± 49.2 BIT-C Follow-up: IG1: 101.3 ± 45.3 IG2: 100.9 ± 36.6 Control: 88.8 ± 54.8	- No significant differences were found between the 3 groups in NS symptoms, as evidenced by the BIT-C scores (p = 0.301), and in the independence of the ADLs, as observed in the FIM scores (p = 0.131). - Results do not support the use of the evaluated techniques to improve functional performance in individuals with subacute stroke.

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Chart 1. Description of the characteristics and main conclusions of the studies with bottom-up interventions (n = 9) (continuation)

Study	Characteristics of the intervention group (IG)	Intervention (no. of daily session x no. of week sessions x no. of weeks)	Characteristics of the control group (CG)	Control Group intervention	Scales	Results (mean ± std. deviation)	Conclusions
Wu et al., 2013	**IG1** N = 7 (F:28.6%;M:71.4%) Age: 56.1 ± 14.5 **IG2** N = 8 (37.5% F e 62.5% M) Age: 65.5 ± 9.8 Stage: Not available	IG1: CIT+EP IG2: CIT 1 x 5 x 3	N = 9 (F:22.2%;M:77.8%) Age: 61.33 ± 11.2 Stage: Not available	Occupational Therapy 1 x 5 x 3	CBS	Pre-intervention: IG1: 16.1 ± 3.2 IG2: 13.9 ± 4.8 Control: 18.1 ± 5.1 Post-intervention: IG1: 10.4 ± 3.2 IG2: 9.9 ± 4.4 Control: 16.3 ± 4.5	- Both interventions (IG1, IG2) improved independence in ADLs. - Most evident improvement with the combination CIT + EP (IG1).
Machner et al., 2014	N = 11 (F: 27%; M: 73%) Age: 69 ± 3 Stage: Acute (less than 14 days after stroke)	*Hemifield EP + OKS* 1 x 7 x 1	N = 10 (F: 40%; M: 60%) Age: 69 ± 3 Stage: acute (less than 14 days after stroke)	Treatment not specific to Neglect Syndrome 1 x 7 x 1	CBS BI	CBS Pre-intervention: EP+OS: 17 ± 3 Control: 18 ± 3 BI Pre-intervention EP+OS: 25 ± 10 Control: 36 ± 12 *Post- intervention and follow-up results are only presented in plots.*	- The two groups improved in the measures evaluated, but there was no significant difference (p <0.01 for each group). - An intervention with EP + OKS techniques in cases of acute NS has no additive effects on the remission of the disorder.
Karner et al., 2019	N = 21 (F: 37%; M: 63%) Age: 74.21 ± 6.53 Stage: subacute (average time after stroke: 51.9 days)	*Robot* with the appearance of a seal ((PARO). The robot was placed in the neglected side of the participant so that he/she could see it and hold it. When the participant's attention was fixed on PARO, it moved to the neglected side. 1 x 3 x 2	N = 18 (F:66.7%;M:33.3%) Age: 73.34 ± 8.13 Stage: subacute (average time after stroke: 51.9 days)	Participants were delivered with a book to read out loud. 1 x 3 x 2	BI SINGER (*self-care*)	BI Pre-intervention: PARO: 23.75 ± 14.84 Control: 20.28 ±14.99 SINGER Pre-intervention: PARO: 7.95 ± 4.63 Control: 8.22 ± 4.49 SINGER Post-intervention: PARO: 12.48 ± 5.84 Control: 11.11 ± 5.41 SINGER Follow-up: PARO: 13.48± 5.89 Control: 13.33 ± 5.83	- The intervention PARO did not demonstrate significant results in independence in the ADLs (p <0.01 between pre- and post-intervention). - The intervention the PARO robot revealed significantly greater improvements than those of the control group in the cognitive component.

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Chart 1. Description of the characteristics and main conclusions of the studies with bottom-up interventions (n = 9) (conclusion)

Study	Characteristics of the intervention group (IG)	Intervention (no. of daily session x no. of week sessions x no. of weeks)	Characteristics of the control group (CG)	Control Group intervention	Scales	Results (mean ± std. deviation)	Conclusions
Rossit et al., 2019	N = 10 (F: 70%; M: 30%) Age: 65.6 ± 2.8 Stage: chronic	VFT given by a rod. The participant had to reach, grab and lift it from the center with the unaffected hand to balance it. The intervention was carried out first with the investigator (2 daily sessions in 2 days) and then independently (2 x 5 x 2)	N = 10 (F: 20%; M: 80%) Age: 64.9 ± 2.5 Stage: chronic	The participant had to reach, grasp and lift a rod by its tip with the not neglected hand, and then return it to the starting position. The intervention was carried out first with the investigator (2 daily sessions in 2 days) and then independently (2 x 5 x 2)	SIS	Pre-intervention: VFT: 48.1 ± 9.9 Control: 46.0 ± 8.7 Post-intervention: VFT: 50.1 ± 9.5 Control: 56.7 ± 7.0 Follow-up: VFT: 58.9 ± 9.3 Control: 46.5 ± 8.7	- VFT has proven to be a viable and effective rehabilitation method for individuals with NS. - In terms of increasing independence in ADLs, the results were only beneficial between post-intervention and follow-up (IG: p = 0.01; CG: p = 0.14).
Kerkhoff et al., 2014	**IG1** (*bottom-up*) N = 12 (F:33.4%;M:66.6%) Age: 64 ± 3 **IG2** (*top- down*) N = 12 (F:41.7%;M:58.3%) Age: 64 ± 3 Stage: acute	IG1: SPT Participants performed smooth eye movements. IG2: VS Participants performed saccadic eye movements. 1 x 5 x 4	--------	--------	BI	Pre-intervention: SPT:11 ± 4 VST: 15 ± 5 Post-intervention: SPT: 28 ± 5 VST: 26 ± 8 Follow-up: SPT: 38 ± 7 VST: 32 ± 8	- After the two treatments, the BI scores improved without a differential statistical effect (SPT: p = 0.020; VS: p = 0.046 between the pre-intervention and the follow-up). - In SPT there was an improvement of 154% during treatment and 35.7% after treatment and in VS the improvement was 73% during and 23% after treatment. - SPT reduced functional neglect more than VS.

(ADL – Activity of Daily Life; BI – Barthel Index; BIT – Behavioural Inattention Test; CBS – Catherine Bergego Scale; CIT – Constraint-Induced Therapy; EP – Eye Patching; F – Female; FIM – Functional Independence Measure; CG – Control Group; IG – Intervention Group; M – Male; N – Number of participants; OKS – Optokinetic Stimulation; PA – Prism Adaptation; SA – Sham Adaptation; SINGER – Scores of Independence Index for Neurological and Geriatric Rehabilitation; SIS – Stroke Impact Scale; NS – Neglect Syndrome; VFT – Visuomotor Feedback Training; VTR – Voluntary Trunk Rotation)

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Studies with top-down interventions

Interventions with top-down techniques were described in 7 studies (Chart 2). A total of 207 participants participated in these studies: 126 belonged to the intervention group and 57 to the control group. In one of the studies[23], 24 participants were involved but the number of participants in each group was not indicated. In most studies, participants' average age ranged from 54.6 to 74.3 years in the intervention group, and from 58.7 to 70.6 years in the control group. As for the NS stage, 2 studies[16,24] intervened in the acute phase, 4 studies[1,23,25,26] in the subacute phase and 1 study[27] in the three phases.

Four different instruments were used to assess the limitations of participants in ADLs before and after the intervention: CBS [4 studies[1,23,25,26]], BI [3 studies[16,24,25]] and FIM [2 studies[26,27]]. Only 2 studies[1,27] used the BIT to assess the severity of NS.

The top-down techniques used were Visual Scanning [3 studies[16,24,27]], Mental Practice [1 study[25]], Continuous Theta Burst Stimulation [2 studies[23,26]], Transcranial Direct Current Stimulation [1 study[25]], and Repetitive Transcranial Magnetic Stimulation [1 study[1]].

Van Wyk et al. (2014)[24] compared the Visual Scanning technique associated with Saccadic Eye Movement Training integrated with task specific activities (IG) with a task specific activity training only (CG) and concluded that the combination of techniques revealed a significant effect on increased independence in ADLs. Ferreira et al. (2011)[27] found that the Visual Scanning technique (IG1) obtained more significant results than the Mental Practice technique (IG2) since it improved the symptoms of subacute, acute and chronic NS and increased independence in ADLs (FIM scores [median, min/max] Pre-intervention: IG1 = 81, 41/117; IG2 = 76, 62/120; Post-intervention: IG1 = 84, 60/121; IG2 = 79, 69/125). Kerkhoff et al. (2014)[16], as previously mentioned, concluded that the Smooth Pursuit Eye Movement Training technique revealed more significant improvements in reducing the symptoms of acute NS than Visual Scanning (Chart 2).

Nyffeler et al. (2019)[26] compared two methods of the Continuous Theta Burst Stimulation technique with placebo and concluded that these two methods reduced the severity of subacute NS and had a positive impact on ADLs. In turn, Cazzoli et al. (2012)[23] compared three groups: application of the Continuous Theta Burst Stimulation technique followed by placebo (IG1), placebo followed by Continuous Theta Burst Stimulation (IG2) and placebo (GC). This study concluded that the Continuous Theta Burst Stimulation technique produced a substantial improvement in subacute NS and independence in ADLs (Chart 2).

For the Transcranial Direct Current Stimulation technique, Yi et al. (2016)[25] made a comparison between this technique in anodal form (IG1), the same technique in cathodal form (IGI) and placebo (CG), concluding that the first two techniques combined with Occupational Therapy and Physiotherapy showed improvements in symptoms of subacute SN. However, these improvements did not affect the ADLs (CBS Pre-intervention scores: IG1 = 17 ± 10.6; IG2 = 16.2 ± 6.4; CG = 16.0 ± 9.7 / CBS Post-intervention scores: IG1 = 8.4 ± 9; IG2 = 10 ± 6.2; CG = 12.3 ± 10.8) (Chart 2).

Finally, for the Repetitive Transcranial Magnetic Stimulation technique, Yang et al. (2017)[1] associated it with the Sensory Cueing technique (IG1) and compared this combination with Repetitive Transcranial Magnetic Stimulation only (IG2) and with Conventional Therapy (CG). From the results obtained, the authorS inferred that the combination of the Repetitive Transcranial Magnetic Stimulation and Sensory Cueing techniques is more effective than the isolated technique in reducing the symptoms of subacute NS (BIT Pre-intervention scores: IG1 = 59.0 ± 35.3; IG2 = 56.0 ± 32.2; CG = 58.4 ± 31.0 / BIT Post-intervention scores: IG1 = 99.6 ± 33.0; IG2 = 88.2 ± 28.7; CG = 72.7 ± 33.1). However, there was no significant result in increasing independence in ADLs (CBS Pre-intervention score: IG1 = 18.5 ± 6.8; IG2 = 21.2 ± 6.5; CG = 20.5 ± 5.8 / Post-intervention score: IG1 = 14.1 ± 7.0; IG2 = 16.4 ± 5.8; CG = 17.9 ± 6.5) (Chart 2).

Regarding the intervention dose, the studies carried out 1 daily session, 2 to 5 times a week for 1 to 4 weeks. Follow-up was not clearly performed in 2 studies[24,26], since one[26] did not specify the reasons for the dropout of some participants and the other[24] did not conducted a detailed analysis of the results.

Chart 2. Description of the characteristics and main conclusions of the studies with top-down interventions (n=7) (to be continued)

Study	Characteristics of the intervention group (IG)	Intervention (no. of daily session x no. of week sessions x no. of weeks)	Characteristics of the control group (CG)	Control Group intervention	Scales	Results (mean ± std. deviation)	Conclusions
Ferreira et al., 2011	**IG1:** N = 5 (F: 60%; M: 40%) Age: 72 (média) **IG2:** N = 5 (F: 40%; M: 60%) Age: 62.4 (mean) Stage: subacute, acute and chronic	IG1: VS IG2: MP Each of the 4 tasks (15 minutes each) 1 x 5 x 2	N = 5 (F: 60%;M: 40%) Age: 64.2 (mean) Stage: subacute, acute and chronic	Without treatment for the condition 1 x 5 x 2	FIM BIT	FIM Pre-intervention: IG1: 81; 41/117 IG2: 76; 62/120 Control: 63; 56/100 FIM Post-intervention: IG1: 84; 60/121 IG2: 79; 69/125 Control: 65; 55/103 FIM Follow-up: IG1: 88; 58/125 IG2: 87; 65/126 BIT Pre-intervention: IG1: 102; 38/122 IG2: 91; 36/112 Control: 81; 37/110 BIT Post-intervention: IG1: 126; 100/136 IG2: 97; 85/139 Control: 82; 40/112 BIT Follow-up: IG1: 125; 85/131 IG2: 85; 44/134 *Results presented as median; min/max.*	- VS technique obtained more significant results when compared to the MP technique in improving the symptoms of NS and in increasing the independence of the ADLs (p = 0.35 among the 3 groups in the FIM self-care category).

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Chart 2. Description of the characteristics and main conclusions of the studies with top-down interventions (n=7) (continuation)

Study	Characteristics of the intervention group (IG)	Intervention (no. of daily session x no. of week sessions x no. of weeks)	Characteristics of the control group (CG)	Control Group intervention	Scales	Results (mean ± std. deviation)	Conclusions
Van Wyk et al., 2014	N = 12 (sex distribution not available) Age: Min:19;Max 74 Stage: acute	VS (*top down*) with *Saccadic Eye Movement Training* (*bottom-up*) and activity specific tasks 1 x 5 x 4	N = 12 (sex distribution not available) Age: Min:19;Max: 74 Stage: acute	Activity specific tasks 1 x 5 x 4	BI	*Data available only in plots.*	- Improvement of symptoms of NS and perceptual processing in the intervention group. - These results were associated with a significant improvement in oculomotor function, saccadic eye movements and a greater increase in independence in ADLs (p = 0.004 between IG and CG after the intervention).
Kerkhoff et al., 2014	**IG1** (*bottom-up*) N = 12 (F:33.4%;M:66.6%) Age: 64 ± 3 **IG2** (*top- down*) N = 12 (F:41.7%;M:58.3%) Age: 64 ± 3 Stage: acute	IG1: SPT Participants performed smooth eye movements. IG2: VS Participants performed saccadic eye movements. 1 x 5 x 4	--------	--------	BI	<u>Pre-intervention:</u> SPT:11 ± 4 VST: 15 ± 5 <u>Post-intervention:</u> SPT: 28 ± 5 VST: 26 ± 8 <u>Follow-up:</u> SPT: 38 ± 7 VST: 32 ± 8	- After the two treatments, the BI scores improved without a differential statistical effect (SPT: p = 0.020; VS: p = 0.046 between the pre-intervention and the follow-up). - In SPT there was an improvement of 154% during treatment and 35.7% after treatment and in VS the improvement was 73% during and 23% after treatment. - SPT reduced functional neglect more than VS.

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Chart 2. Description of the characteristics and main conclusions of the studies with top-down interventions (n=7) (continuation)

Study	Characteristics of the intervention group (IG)	Intervention (no. of daily session x no. of week sessions x no. of weeks)	Characteristics of the control group (CG)	Control Group intervention	Scales	Results (mean ± std. deviation)	Conclusions
Nyffeler et al., 2019	**Grupo 8cTBS**: N = 10 (F:50%; M: 50%) Age: 67.8 ± 10.13 **Grupo 16cTBS**: N = 10 (F: 40%; M: 60%) Age: 74.3 ± 10.23 Stage: subacute	cTBS, with one group doing 8 trains (8cTBS) and another group doing 16 (16cTBS) in the left posterior parietal cortex. - 8cTBS: 4 continuous trains for 2 days. - 16cTBS: 4 continuous trains for 4 days. - Each train lasted 44seg and 801 pulses with 267 discharges, each with 3 pulses of 30Hz	N = 10 (F:30%; M: 70%) Age: 70.60± 11.44 Stage: subacute	Placebo with the same conditions as the group that made 8 trains in total (the participants in this group did not have NS)	CBS FIM	<u>CBS Pre-intervention:</u> 8cTBS: 16.10 ± 6,79 16cTBS: 18.3 ± 7.39 Control: 17.50 ± 4.99 <u>FIM Pre-intervention:</u> 8cTBS: 47.20 ± 19.11 16cTBS: 48.70 ± 19.11 Control: 41.30 ± 16.80 - *Post-intervention data available only in plots.*	- Scores of the two scales revealed significant improvements in the two groups that performed cTBS in relation to the control group. - FIM revealed a more significant improvement in the group that performed a total of 16 trains (8cTBS: p = 0.04; 16cTBS: p = 0.02 between pre- and post-intervention). - The technique used significantly improves and accelerates the recovery of NS, as well as the overall functional result.

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Chart 2. Description of the characteristics and main conclusions of the studies with top-down interventions (n=7) (continuation)

Study	Characteristics of the intervention group (IG)	Intervention (no. of daily session x no. of week sessions x no. of weeks)	Characteristics of the control group (CG)	Control Group intervention	Scales	Results (mean ± std. deviation)	Conclusions
Cazzoli et al., 2012	N* = 24 (F: 29.2%;M: 70.8%) Age: 58 (2.25) Mean (SEM) Stage: subacute **Total of the 2 groups*	First cTBS and then placebo or vice versa in the left posterior parietal cortex 4 continuous trains for 2 days. Each train lasted 44 sec and had 801 pulses with 267 discharges, each with 3 pulses of 30Hz Groups also had Occupational Therapy, Neuropsychology and Physiotherapy	See IG characteristics	Placebo did not receive any type of electrostimulation Groups also had Occupational Therapy, Neuropsychology and Physiotherapy	CBS	*Data available only in plots.*	- The application of the cTBS technique produced a significant improvement in SN and independence in ADLs that persisted for at least three weeks, and this improvement was reflected by the reduced CBS scores (cTBS: p <0.001; GC: p = 0.128 between the pre- and post-intervention).
Yi et al., 2016	**tDCS anodal**: N = 10 (F: 30%; M: 70%) Age: 63 ± 8.5 **tDCS catodal**: N = 10 (F: 20%; M: 80%) Age: 61.6 ± 12.2 Stage: subacute	anodal tDCS in the right parietal cortex or cathodal tDCS in the left parietal cortex (direct current of 2mA for 30 minutes), both during conventional Occupational Therapy 1 x 5 x 3 All participants received conventional physical therapy over 3 weeks.	N = 10 (F: 40%; M: 60%) Age: 61.7 ± 9.5 Stage: subacute	Placebo with the same protocol as the anodal tDCS group 1 x 5 x 3	CBS BI	<u>CBS Pre-intervention:</u> tDCS anodal: 17±10.6 tDCS catodal: 16.2±6.4 Control: 16.0±9.7 <u>CBS Post-intervention:</u> tDCS anodal: 8.4 ± 9 tDCS catodal: 10 ± 6.2 Control: 12.3 ± 10.8 <u>BI Pre-intervention:</u> tDCS anodal: 19.1±11.8 tDCS catodal: 22.5±12.2 Control: 22.1±15.8 <u>BI Post-intervention:</u> tDCS anodal: 42.1±21.3 tDCS catodal: 46±20.5 Control: 36.8 ± 13.3	- Improvement in CBS scores between pre- and post-intervention, but this improvement was not significantly different between the three groups, although there was a positive trend in CBS scores in the intervention group. - tDCS can be a successful adjunctive therapeutic modality in the rehabilitation of NS, however it may not have repercussions on ADLs.

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Chart 2. Description of the characteristics and main conclusions of the studies with top-down interventions (n=7) (conclusion)

Study	Characteristics of the intervention group (IG)	Intervention (no. of daily session x no. of week sessions x no. of weeks)	Characteristics of the control group (CG)	Control Group intervention	Scales	Results (mean ± std. deviation)	Conclusions
Yang et al., 2017	**Group rTMS (*top-down*) + SC (*bottom-up*)**: N = 20 (F: 30%; M: 70%) Age: 54.6 ± 11.8 **Group rTMS:** N = 20 (F: 40% F; M: 60%) Age: 60.7 ± 12.2 Stage: subacute	rTMS + SC or just rTMS in the contralesional hemisphere. The two groups also underwent conventional rehabilitation (2 sessions of Physiotherapy and 1 of Occupational Therapy) Protocol of the rTMS technique: 900 low frequency pulses (1HZ) SC technique protocol: use of a device that emitted a 196 H vibratory stimulus every 5 minutes 1 x 5 x 2	N = 20 (F: 15%; M: 85%) Age: 58.7 ± 12.7 Stage: subacute	Conventional rehabilitation (2 sessions of Physiotherapy and 1 of Occupational Therapy) 1 x 5 x 2	CBS BIT-C	<u>CBS Pre-intervention:</u> rTMS+SC: 18.5 ± 6.8 rTMS: 21.2 ± 6.5 Control: 20.5 ± 5.8 <u>CBS Post-intervention:</u> rTMS+SC: 14.1 ± 7.0 rTMS: 16.4 ± 5.8 Control: 17.9 ± 6.5 <u>CBS Follow-up:</u> rTMS+SC: 11.2 ± 6.4 rTMS: 13.9 ± 5.2 Control: 15.7 ± 6.6 <u>BIT-C Pre-intervention:</u> rTMS+SC: 59.0 ± 35.3 rTMS: 56.0 ± 32.2 Control: 58.4 ± 31.0 <u>BIT-C Post-intervention:</u> rTMS+SC: 99.6 ± 33.0 rTMS: 88.2 ± 28.7 Control: 72.7 ± 33.1 <u>BIT-C Follow-up:</u> rTMS+SC: 108.8 ± 27.1 rTMS: 99 ± 26.5 Control: 76.7 ± 33.2	- BIT-C scores for combining the rTMS + SC techniques suggest it is more effective than just the rTMS technique for improving SN. - There was no significant result at the functional level as observed by the CBS scores (p <0.01 between pre and post-intervention). - The use of rTMS + SC techniques was not more effective than conventional rehabilitation to improve ADLs and arm functions in individuals with stroke in the right hemisphere.

(ADL – Activity of Daily Life; BI – Barthel Index; BIT – Behavioural Inattention Test; CBS – Catherine Bergego Scale; cTBS – Continuous Transcranial Theta Burst Stimulation; F – Female; FIM – Functional Independence Measure; CG – Control Group; IG – Intervention Group; M –Male; MP – Mental Practice; N – Number of participants; rTMS – Repetitive Transcranial Magnetic Stimulation; SEM – Standard Error of the Mean; NS – Neglect Syndrome; SC – Sensory Cueing; SPT – Smooth Pursuit Training; tDCS – Transcranial Direct Current Stimulation; VS – Visual Scanning)

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Risk of bias assessment

The assessment of the studies' risk of bias was performed using the Joanna Briggs Institute Critical Appraisal Checklist for RCTs (Chart 3). Based on the sum of the items with a positive response, 3 of the articles with bottom-up interventions[18,20,21] have a moderate level of quality, 11 articles with bottom-up or top-down interventions[1,13-15,17,19,22,24,26,27] have a high level and 2 studies with top-down interventions[16,23] present an excellent level.

The main flaws were found in questions "5 - Were those delivering treatment blind to treatment assignment?"[14,15,18,22,24,25], "6 - Were outcomes assessors blind to treatment assignment?"[15,18-22] and "11 - Were outcomes measured in a reliable way?"[1,13,25-27,16-18,20-24]. The flaws identified can generate observation and information bias, since the knowledge about the group to which the participant belongs to, can bias the therapist (question 5) and/or evaluator (question 6). In addition, a measurement is considered to be reliable (question 11) when information about the number of evaluators, training of evaluators, intra-examiner and inter-examiner reliability is reported. This requirement has only been clearly described in one study[14]; the remaining studies did not provide information that would allow their assessment.

Chart 3. Risk of bias assessment with the JBI Critical Appraisal Checklist For Randomized Controlled Trials (to be continued)

Question	*Ten Brink* et al. (2017)	*Yang et al.* (2017)	*Wu et al.* (2013)	*Mizuno* et al. (2011)	*Van Wyk* et al. (2014)	*Turton* et al. (2010)	*Cazzoli* et al. (2012)	*Kerkhoff* et al. (2014)	*Rossit* et al. (2019)	*Nyffeler* et al. (2019)	*Yi et al. (2016)*	Ferreira et al. (2011)	*Tsang* et al. (2019)	*Fong* et al. (2007)	*Machner* et al. (2014)	*Karner* et al. (2019)
1 – Was true randomization used for assignment of participants to treatment groups?	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
2 - Was allocation to treatment groups concealed?	+	+	-	+	+	+	+	+	+	+	+	?	+	+	+	+
3 - Were treatment groups similar at the baseline?	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
4 - Were participants blind to treatment assignment?	+	+	+	+	+	+	+	+	+	+	+	?	+	+	+	+
5 - Were those delivering treatment blind to treatment assignment?	+	+	-	+	?	-	+	+	-	+	?	+	+	-	?	+

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Chart 3. Risk of bias assessment with the JBI Critical Appraisal Checklist For Randomized Controlled Trials (continuation)

Question	*Ten Brink* et al. (2017)	*Yang et al.* (2017)	*Wu et al.* (2013)	*Mizuno* et al. (2011)	*Van Wyk* et al. (2014)	*Turton* et al. (2010)	*Cazzoli* et al. (2012)	*Kerkhoff* et al. (2014)	*Rossit* et al. (2019)	*Nyffeler* et al. (2019)	*Yi et al. (2016)*	Ferreira et al. (2011)	*Tsang* et al. (2019)	*Fong* et al. (2007)	*Machner* et al. (2014)	*Karner* et al. (2019)
6 - Were outcomes assessors blind to treatment assignment	-	+	+	?	+	-	+	+	-	+	+	+	+	+	?	?
7- Were treatment groups treated identically other than the intervention of interest?	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	-
8 - Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	-	+	-	+	?	-	+	+	+	?	+	+	-	+	+	-
9 - Were participants analyzed in the groups to which they were randomized?	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
10 - Were outcomes measured in the same way for treatment groups?	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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Chart 3. Risk of bias assessment with the JBI Critical Appraisal Checklist For Randomized Controlled Trials (conclusion)

Question	*Ten Brink* et al. (2017)	*Yang et al.* (2017)	*Wu et al.* (2013)	*Mizuno* et al. (2011)	*Van Wyk* et al. (2014)	*Turton* et al. (2010)	*Cazzoli* et al. (2012)	*Kerkhoff* et al. (2014)	*Rossit* et al. (2019)	*Nyffeler* et al. (2019)	*Yi et al. (2016)*	Ferreira et al. (2011)	*Tsang* et al. (2019)	*Fong* et al. (2007)	*Machner* et al. (2014)	*Karner* et al. (2019)
11 - Were outcomes measured in a reliable way?	?	?	+	?	?	?	?	?	?	?	?	?	?	?	?	?
12 - Was appropriate statistical analysis used?	?	+	+	+	?	-	+	+	+	+	-	-	+	+	+	-
13 - Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Total	8/13	11/13	10/13	11/13	9/13	8/13	12/13	12/13	10/13	11/13	10/13	9/13	11/13	11/13	10/13	8/13

(+) – Yes; (-) – No; (?) – Unclear

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Discussion

This systematic review aimed to characterize the approaches (bottom-up or top-down) with the greatest impact on ADLs in adults and in old people with NS. Sixteen studies were included, 9 of them focused on bottom-up approach techniques, 6 were focused on the top-down approaches and 1 study compares the effects of the different approaches[16]. The present systematic review seems to help to clarify that (a) different techniques in the bottom-up and top-down approaches have proved to be effective in increasing the patients' ADLs independence; (b) an improvement in NS symptoms with the implementation of these strategies does not translate into an improvement in independence in ADLs; (c) the classification in "bottom-up" and "top-down" is based on principles that are difficult to explain; (d) the choice of these approaches may be dependent on the patient's cognitive level.

In the bottom-up approach, the techniques that proved to be effective in increasing independence in ADLs were Visuomotor Feedback Training[22], Smooth Pursuit Eye Movement Training[16] and Eye Patching, when combined with Constraint-induced Therapy[14]. In turn, in the top-down approach, the techniques that proved to be effective in increasing the independence of ADLs were Visual Scanning[16,24,27], Mental Practice[16], Continuous Theta Burst Stimulation[23,26] and Transcranial Direct Current Stimulation[25], either performed alone or combined with other interventions.

In the Prism Adaptation technique[18-20] the results were controversial regarding the increase in independence in ADLs. Thus, only the study conducted by Mizuno et al. (2011)[19] reported an improvement in the independence of ADLs in participants with subacute NS, using a larger intervention dose (2 daily sessions for 5 days a week for 2 weeks). Therefore, a greater dose of intervention (for example, a greater number of daily sessions) for this technique seems to translate into a more significant effect at the level of independence in ADLs, since studies that performed only 1 daily session did not report any positive effects for ADLs[18-19].

In the analysis of the studies it was also evident that an improvement in the NS symptoms does not translate into an improvement in independence in ADLs. Such conclusion was observed in 3 different studies: Turton et al. (2010) who evaluated the Prism Adaptation technique (18) (CBS score: intervention group = positive variation of 3.5 ± 3.1; control = positive variation of 3.3 ± 2.5) (BIT-C score: Post-intervention: intervention group = positive variation of 14.8 ± 18.8; control = positive variation of 9.7 ± 15.9); in the study by Tsang et al. (2009) who applied the Eye Patching technique in isolation[17] (FIM score: Post-intervention: intervention group = 16.00 ± 14.24; control = 12.41 ± 14.21) (BIT score: Post-intervention: intervention group = 25.06 ± 30.81; control group = 8.29 ± 10.35) and in the study by Yang et al. (2017) who used the Repetitive Transcranial Magnetic Stimulation technique (top-down) in a combined way (group 1) with Sensory Cueing (bottom-up) and isolated (group 2)[1] (CBS score: Post intervention: group 1 = 14.1 ± 7.0; group 2 = 16.4 ± 5.8; control = 17.9 ± 6.5) (BIT-C score: Post intervention: group 1 = 99.6 ± 33.0; group 2 = 88.2 ± 28.7; control = 72.7 ± 33.1).

The classification of techniques in these two approaches (bottom-up and top-down) seems to have principles that are difficult to explain. In the bottom-up approach, the variety of neurophysiological based-mechanisms of techniques is considerably large. For example, the Prism Adaptation technique[18,20], as well as the Eye Patching technique[14] involves a change in the visual field, but it also integrates a visual perceptual judgment such as the Visuomotor Feedback Training technique[22]. Additionally, the PARO robot belongs to the category of interactive stimulation robots designed specifically for therapeutic purposes and in the study by Karner et al. (2019)[21], the robot was placed on the neglected side of the participant. As for the Smooth Pursuit Eye Movement Training technique, it corresponds to eye movements used to stabilize the image of an object moving in the fovea[16].

Unlike the bottom-up approach, in the top-down approach it is possible to found common characteristics in the techniques according to their neurophysiological mechanisms. Thus, the Visual Scanning technique involves visual recognition since it is inspired by behavior modification techniques and makes the individual aware of the presence of stimuli on the contralesional side, interfering with the levels of attention and information processing[29].

The Visual Scanning technique makes use of both previously acquired learning and awareness of the condition, which is not the case with the Optokinetic Stimulation and Smooth Pursuit Eye Movement Training techniques that require high levels of awareness about the condition of the individual. In addition, the Mental Practice technique consists of mentally carrying out the different stages of an action / task, requiring equally high cognitive levels[27]. As for the other techniques included in the top-down approach, Continuous Theta Burst Stimulation[23], Transcranial Direct Current Stimulation[25] and Repetitive Transcranial Magnetic Stimulation[1], these can be integrated in electrostimulation techniques based on the principle of hemispheric inter-rivalry, which can act at the level of neuromodeling either by excitation of the injured side or by inhibition of the contralesional side[1,23,25].

The process of choosing one approach for the rehabilitation of NS may also be conditioned by the necessary cognitive profile for its implementation. For example, in the top-down approach, there are techniques that involve different levels of active participation and cognitive levels, such as the Visual Scanning technique and the electrostimulation techniques. The first asks for higher cognitive levels and active levels of participation, since it requires an individual's collaboration and visual recognition of him[29].

Despite the classification in bottom-up and top-down approaches, this distribution still seems to be contradictory for some specific techniques, such as the Repetitive Transcranial Magnetic Stimulation technique[1]. According to the author of one study included in this systematic review, Yang et al. (2017)[1], and the author Carmelo (2015)[36] the mentioned technique belongs to the top-down approach, however Dintén-Fernández et al. (2019)[37] places it in the bottom-up approach. This difficulty may be due to the fact that the technique requires low levels of active participation of the individual, but leads to changes in the sensorimotor or cognitive brain processing[1].

Conclusion

From this systematic review, it is not possible to conclude which approach (bottom-up and top-down) has the greatest impact on increasing the independence of ADLs, since both include techniques that reveal positive results. From the point of view of the clinical choice between the approaches, the explanatory basis of these classifications depends on the neurophysiological mechanisms of the techniques, which demonstrates high variability and an ambiguous classification across the studies.

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Author contributions

Martins AR, Vieira A, Oliveira C, Bártolo M participated in the conception, design, research, analysis and interpretation of results and writing of the scientific article. Silva CG participated in the design, research, analysis and writing of the scientific article. Rosa M participated in the analysis and interpretation of the results and writing of the scientific article.

Competing interests

No financial, legal or political competing interests with third parties (government, commercial, private foundation, etc.) were disclosed for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.).

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