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# Impact of Non-Invasive and Top-Down Approaches On Hemispatial Neglect in Stroke Patients: A Systematic Review and Meta-Analysis.

**Noha A. Nasef [1], Gehan M. Ahmed [2], Mahmoud S. El Fakharany [3,4], Abdelaziz Abdelaziz Elsherif [2].**

[1] Department of Physical Therapy for Neuromuscular disorders and Its Surgery, Faculty of Physical Therapy, Delta University for Science and Technology, Egypt.
[2] Department of Physical Therapy for Neuromuscular disorders and Its Surgery, Faculty of Physical Therapy, Cairo University, Cairo, Egypt.
[3] Department of Physical Therapy for Pediatrics, Faculty of Physical Therapy, Cairo University, Cairo, Egypt.
[4] Faculty of Physical Therapy, ELNAHDA University

***Abstract***

***Aim: One of the most common disorders in stroke is hemispatial neglect. Regarding treatment of hemispatial neglect, there are many physiotherapy interventions including top-down, bottom-up and non-invasive approaches. In this study, we aimed to systemically examine the effect of these approaches in hemispatial neglect patient.***

***Materials and Methods: Articles were identified from 2013 to 2021 by literature searches using physiotherapy evidence base (PEDRo), google scholar and Cochrane database. Randomized trials focused on hemispatial neglect patient were included. Data were derived from the studies that were included and methodological quality of these data was evaluated using the PEDro scale. Each intervention's level of evidence was assessed using the Modified Sackett scale.***

***Results: Six trials were identified with good quality methodology. All these studies were homogeneous. Findings were analyzed in quantitative terms. This review revealed strong evidence in three articles about the effectiveness of non-invasive and also strong evidence of three articles about the unclear effect of top-down approach. Discussion: The current systematic review analyzed six randomized controlled trials, applying strict inclusion selection criteria. The present evidence supports the use of non-invasive approach in improvement of line bisection test (LBT) and star cancellation test (SCT) in hemispatial neglect patients, however, regarding the effect of top-down approach on Behavioral Inattention Test (BIT) improvement needs more studies to be able to make clinical judgment about its effect.***

***Key words***

***Hemispatial neglect; non-invasive; Top-down; stroke.***

## Introduction

Stroke is a disorder in which blood flow to the brain is restricted due to a blockage or rupture of a cerebral artery, resulting in brain cell death and paralysis on one side of the body. **[1]**. Stroke can cause impairments and disabilities that have a significant effect on a patient's ability to work. Unilateral neglect is one of the most common stroke-related disorders, which is also known as hemispatial neglect, spatial neglect, visuospatial neglect, visuospatial agnosia, and hemispatial agnosia **[2].** Hemispatial neglect refers to the failure to report, respond, or orient to meaningful stimuli applied to the side opposite a brain lesion. Patients with unilateral spatial neglect do poorly on activity daily living than patients without unilateral spatial neglect. at both admission and discharge, and they spend substantially more time in rehabilitation hospitals. The effects of unilateral spatial neglect on functional rehabilitation are detrimental, and unilateral spatial neglect rehabilitation techniques that can be used in clinical settings are required **[3].** There are a variety of techniques that can be used in stroke neurorehabilitation to aid and improve recovery. These strategies aim to enhance functional rehabilitation by promoting neuronal plasticity, relearning, and functional reorganization. Constraint-induced movement therapy, mental practice, mirror therapy, visual dysfunction therapies, and a moderately high dose of repetitive task practice have all been shown to be effective **[4].** There are also several rehabilitation methods have been developed to improve hemispatial neglect, which according to their theoretical basis can be classified into: (I) top-down approaches, (II) bottom-up approaches, (III) modulation of intracerebral inhibition processes; (IV) stimulation of arousal **[5].**

Top-down approach are focused on the patient's voluntary attempt to obey a therapist's orders. It involves of training the direction of gaze using cues on the left; this technique is still commonly used in rehabilitation units. Many systems have been created that involve differences in the nature of the stimuli, feedback or the duration, number and frequency of sessions **[5].** Repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS) and continues theta burst (cTBS) are noninvasive brain stimulation techniques. Both approaches have been used to help patients with neglect syndromes improve their clinical symptoms. The use of tDCS and rTMS in unilateral neglect is attributed to the fact that they either encourage or suppress cortical excitability and thus neuronal processing within the stimulated brain areas for time periods that outlast the stimulus cycle is the reason for their use in neglect syndromes after brain injury **[6].**

The strength of evidence regarding the clinical effectiveness of top-down and non-invasive brain stimulation techniques in treatment of hemispatial neglect after stroke is not clear. This study systematically reviewed the best evidence on the effectiveness of using these interventions for patients with hemispatial neglect after stroke. This could help directing clinical decision making by the physical therapists whether to implement those applications or not.

## Material and Methods

### Search strategy

This study was based on the recommendations of the statement on Preferred Reporting Items for Systemic Reviews and Meta-Analysis (PRISMA) **[7]**. Eligibility criteria were defined as follows: (a) Participants: hemispatial neglect after stroke patient, (b) Interventions: the study group received top-down, non-invasive approaches and traditional physiotherapy program, (c) Outcomes: Behavioral

Inattention Test, line bisection and Star Cancellation Test and (d) Study design: Randomized controlled trials (RCTs).

An electronic search was done from 2013 to 2021, in the Cochrane Central Register of Controlled Trials, PEDro, Google Scholar and PubMed databases using the following keywords: "Hemispatial neglect" and/or "Theta burst" or "Transcranial magnetic stimulation" or "Transcranial direct current stimulation" or "Sensory cueing" or "Feedback" or "Visual scanning". The search was limited to RCTs only which published from 2013 to 2021. Studies were excluded according to the following criteria: (a) Cross sectional, cohort, case control, case series, case studies and reviews, (b) Articles published in non- English language and/or (c) Published abstracts with no full-text articles available. Two authors independently evaluated each title and abstract identified in the search against the eligibility criteria. The full text was obtained for complete analysis.

**Data extraction**

Data extraction was done according to **Liberati A. et al. (2009) [8],** in which one reviewer extracted data from the included articles, and then second check was done by another reviewer. The data extraction form included authors and year of publication, the characteristics of the participant, measures of intervention, and outcomes

**Quality assessment**

Two authors applied the PEDro scale **[9]** separately to determine the quality of the trials and the third author resolved any disagreements**.**

**Data analysis**

The following classification was used for the quantitative quality rating: PEDro score < 4 indicated poor quality; 4-5 indicated fair quality; 6-8 for good quality and 9-10 indicated excellent quality. The modified Sackett scale **[10]** was used for assessing the level of evidence as follows:

• Level 1a (Strong) = Well-designed meta-analysis or 2 or more 'high' quality RCTs (PEDro Scale scores ≥ 6) that show similar findings.

• Level 1b (Moderate)= One RCT of 'high' quality (PEDro Scale score ≥ 6).

• Level 2a (Limited) = At least one 'fair' quality RCT (PEDro Scale score= 4-5).

• Level 2b (Limited)= At least one well-designed nonexperimental study: non-RCT; quasi-experimental studies; cohort studies with multiple baselines; single- subject series with multiple baselines.

• Level 3 (Consensus)= Agreement by an expert panel, a group of professionals in the field or a number of pre-post design studies with similar results.

• Level 4 (Conflicting)= Conflicting evidence of two or more equally designed studies.

• Level 5 (No evidence) = No well-designed studies: "Poor" quality RCTs with PEDro scores ≤ 3; only case studies/case descriptions or cohort studies/single subject series with no multiple baselines.

## Results

**Search results**

The search identified 203 trials from 2013 until 2021. After screening titles and abstracts, removing duplicates, articles not in English language and not randomized control trials, six studies (Bang et al. (2015), Yang et al. (2015), Seniów et al. (2016), Yang et al. (2017), Vatanparasti et al. (2019) and Rossit et al. (2019)) **[11-16]** were included in this review. Search result presented according to the flow chart (figure 1).

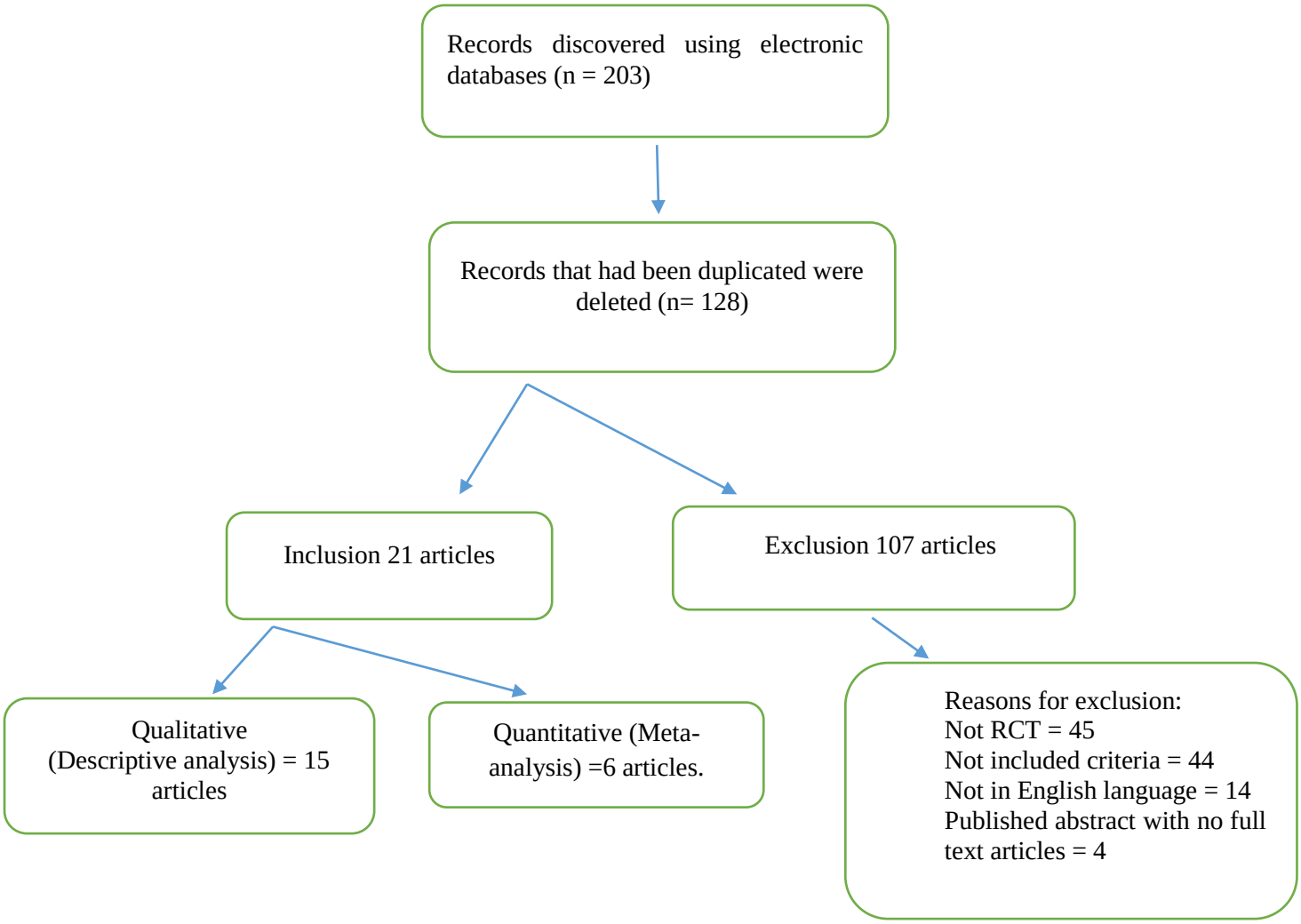


**Figure 1**: the PRISMA flow chart of the reviewed studies.

**Characteristics of the included studies**

All included studies are RCTs. The summary of the included studies is presented in Table 1. The clinical homogeneity between some of the included trials allowed the quantitative analysis of their data**.**

**Table 1.** Summary of the reviewed studies

| | Bang et al., (2015) | Yang et al., (2015) | Yang et al., (2015) | Yang et al., (2015) | Seniów et al., (2016) | Yang et al., (2017) | Vatanparasti et al., (2019) | Rossit et al., (2019) |
|---|---|---|---|---|---|---|---|---|
| Study design | RCT Level II | RCT Level II | RCT Level II | RCT Level II | RCT Level II | RCT Level II | RCT Level II | RCT Level II |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Participants | Stroke patient with Visuospatial neglect | Stroke patient with unilateral spatial neglect | Stroke patient with unilateral spatial neglect | Stroke patient with unilateral spatial neglect | Stroke patient with hemispatial neglect | Stroke patient with unilateral spatial neglect | Stroke patient with hemispatial neglect | Stroke patient with hemispatial neglect |
| NO. of participants | Control = 6<br>Study = 6 | Control = 10<br>Study =9 | Control = 10<br>Study = 10 | Control = 10<br>Study = 9 | Control = 14<br>Study = 15 | Control = 20<br>Study = 20 | Control = 7<br>Study = 7 | Control = 9<br>Study = 9 |
| Intervention (study) | tDCS and feedback training | rTMS 1 HZ | rTMS 10 HZ | Continuous TBS | Visual scanning training | rTMS and sensory cuing | Prism adaptation and cTBS | Grasp the center of the rod until balanced |
| Intervention (control) | feedback training | Sham group | Sham group | Sham group | Visual scanning training and TENS | rTMS | Prism adaptation | Grasp the rod at one side |
| Outcome of interest | Improve daily living activities and decrease neglect | Improve daily living activities and decrease neglect | Improve daily living activities and decrease neglect | Improve daily living activities and decrease neglect | Improve daily living activities and decrease neglect | Improve daily living activities and decrease neglect | Improve daily living activities and decrease neglect | Improve daily living activities and decrease neglect |
| Measure | -MVPT<br>-LBT<br>-MBI | -Star cancellation test<br>-LBT<br>-DTI | Star cancellation test<br>-LBT<br>-DTI | Star cancellation test<br>-LBT<br>-DTI | BIT | -BIT<br>-CBS<br>-FMA<br>-ARAT<br>-MBI | -Star cancellation test<br>-LBT<br>-NL<br>-figure copying test<br>-clock drawig | -BIT<br>-SIS<br>-Balloons test<br>-landmark<br>-SSA<br>-RDT |
| Component of health | Activity and participation | Activity and participation | Activity and participation | Activity and participation | Activity and participation | Activity and participation | Activity and participation | Activity and participation |

rTMS: Repetitive transcranial magnetic stimulation. tDCS: transcranial direct current stimulation. cTBS: continues theta burst. TENS: Transcutaneous electrical nerve stimulation. MVPT: Motor-Free Visual Perception Test. LBT: Line bisection test. MBI: modified Barthel index. DTI: diffusion-tensor imaging. BIT: Behavioral Inattention Test. CBS: Catherine Bergego Scale. FMA: Fugl-Meyer Assessment. ARAT: Action Research Arm Test. MBI: Modified Barthel index. NL: number of line. SIS: stroke impact scale. SSA: subjective straight-ahead. RDT: room description tasks.

**Qualitative analysis**

**Participants**

The sample size ranged from 12 to 40. There were a total of 171 patients participating across the six RCTs, diagnosed with hemispatial neglect after stroke, including both genders.

**Interventions**

The study versus the control groups in six of the included RCTs received traditional sessions of physiotherapy addition to top-down and non-invasive approaches.

**Outcome measures**

In the reviewed studies, patients were tested using Behavioral Inattention Test, line bisection and star cancellation tests to monitor the recovery of hemispatial neglect.

**Quality of the included studies and level of evidence**

The methodological quality of included six studies is presented in Table 2. The quality of the studies is good with a mean PEDro score (range 6 to 8). The six included studies had similar groups at baseline, analyzed the between-group difference.

**Table 2.** methodology assessment of studies according to the Physiotherapy Evidence Database (PEDro) scale

| Criteria | Bang et al., (2015) | Yang et al., (2015) | Seniów et al., (2016) | Yang et al., (2017) | Vatanparasti et al., (2019) | Rossit et al., (2019) |
|---|---|---|---|---|---|---|
| 1-specific eligibility criteria* | Yes | yes | yes | Yes | yes | Yes |
| 2- Random allocation of participant | Yes | yes | yes | Yes | yes | Yes |
| 3-concealed allocation | No | No | No | Yes | No | No |
| 4-similar prognosis at baseline | Yes | Yes | Yes | Yes | Yes | Yes |
| 5- blinded participants | No | Yes | Yes | Yes | Yes | Yes |
| 6- blinded therapist | No | No | Yes | No | No | No |
| 7- blinded assessor | No | No | No | No | No | No |
| 8- more than 85% follow-upfor at least | Yes | Yes | Yes | Yes | Yes | Yes |

| | | | | | | |
|---|---|---|---|---|---|---|
| one key outcome | | | | | | |
| 9-intention to treat analysis | Yes | Yes | Yes | Yes | Yes | No |
| 10- between group statistical analysis for at least one key outcome | Yes | Yes | Yes | Yes | Yes | Yes |
| 11- point estimates of variability for at least one key outcome | Yes | Yes | Yes | Yes | Yes | Yes |
| Total PEDro score ( /10) | 6 | 7 | 8 | 8 | 7 | 6 |
| Quality | Good | Good | Good | Good | Good | Good |

*Item 1 does not contribute to the total score

**Evidence of top-down and non-invasive approaches**

The result of the 6 reviewed trials (Bang et al., 2015, Yang et al., 2015, Seniów et al., 2016, Yang et al., 2017, Vatanparasti et al., 2019 and Rossit et al., 2019) **[11-16]** which investigated the effects top-down and non-invasive approaches for hemispatial patient after stroke are summarized in table 3.

**Table 3.** Summaries means of study groups and control groups and the difference between this means.

| | **Bang et al., (2015)** | **Yang et al., (2015)** | **Seniów et al., (2016)** | **Yang et al., (2017)** | **Vatanparasti et al., (2019)** | **Rossit et al., (2019)** |
|---|---|---|---|---|---|---|
| **Outcome** | Improve daily living activities and decrease neglect | Improve daily living activities and decrease neglect | Improve daily living activities and decrease neglect | Improve daily living activities and decrease neglect | Improve daily living activities and decrease neglect | Improve daily living activities and decrease neglect |
| **Means of the control group** | **line bisection Test** Pre = 10.3 Post = 5.9 | **Star cancellation test** Pre = 51.65 Post = 49.28 **line bisection Test** Pre = 61.39 Post = 53.09 | **Behavioral Inattention Test** Pre = 76.4 Post = 107.4 | **Behavioral Inattention Test** Pre = 56.0 Post = 88.2 | **Star cancellation test** Pre = 16.4 Post = 2.4 **line bisection Test** Pre = 27.6 Post = 5.6 | **Behavioral Inattention Test** Pre = 86.0 Post = 94.9 |
| **Means of** | **line** | **Star cancellation test** | **Behavioral** | **Behavioral** | **Star** | **Behavioral** |

<table>
<tr>
<td>the study group</td>
<td>bisection Test<br>Pre = 11.3<br>Post = 5.37</td>
<td>
<table>
<tr><td></td><td>pre</td><td>Post</td></tr>
<tr><td>1 HZ rTMS</td><td>52.85</td><td>27.49</td></tr>
<tr><td>10 HZ rTMS</td><td>53.14</td><td>29.01</td></tr>
<tr><td>cTBS</td><td>53.38</td><td>16.54</td></tr>
<tr><td colspan="3">line bisection Test</td></tr>
<tr><td></td><td>pre</td><td>post</td></tr>
<tr><td>1 HZ rTMS</td><td>60.87</td><td>30.02</td></tr>
<tr><td>10 HZ rTMS</td><td>63.59</td><td>32.20</td></tr>
<tr><td>cTBS</td><td>59.71</td><td>28.75</td></tr>
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</td>
<td>Inattention Test<br>Pre = 76.7<br>Post = 116.7</td>
<td>Inattention Test<br>Pre = 59.0<br>Post = 99.6</td>
<td>cancellation test<br>Pre = 21.5<br>Post = .5<br>line bisection Test<br>Pre = 33.7<br>Post = 6.7</td>
<td>Inattention Test<br>Pre = 97.1<br>Post = 123.5</td>
</tr>
<tr>
<td>Difference between means</td>
<td>line bisection Test<br>control group = -4.4<br>study group = -5.93</td>
<td>
<table>
<tr><td colspan="2">Star cancellation test</td></tr>
<tr><td>Control</td><td>-2.37</td></tr>
<tr><td>1 HZ rTMS</td><td>-25.36</td></tr>
<tr><td>10 HZ rTMS</td><td>-24.13</td></tr>
<tr><td>cTBS</td><td>-36.84</td></tr>
<tr><td colspan="2">line bisection Test</td></tr>
<tr><td>control</td><td>-8.3</td></tr>
<tr><td>1 HZ rTMS</td><td>-30.85</td></tr>
<tr><td>10 HZ rTMS</td><td>-31.39</td></tr>
<tr><td>cTBS</td><td>-30.96</td></tr>
</table>
</td>
<td>Behavioral Inattention Test<br>control group = 31<br>study group = 40</td>
<td>Behavioral Inattention Test<br>control group = 32.2<br>study group = 40.6</td>
<td>Star cancellation test<br>control group = -14<br>study group = -21<br>line bisection Test<br>control group = -22<br>study group = -27</td>
<td>Behavioral Inattention Test<br>control group = 8.9<br>study group = 26.4</td>
</tr>
</table>

**Statistical analysis:**

Six trials (Bang et al., (2015), Yang et al., (2015), Seniów et al., (2016), Yang et al., (2017), Vatanparasti et al., (2019) and Rossit et al., (2019)) **[11-16]** have homogeneity in all four components (participants, intervention, outcome and outcome measures) so three meta-analyses were performed and these meta-analysis favors the use of top-down and non-invasive approaches for hemispatial patient after stroke.

**Description and Interpretation of Forest plot:**

The Forest plot is composed of (from left to right):

1) The names of the studies arranged by publication year.
2) The data of the treatment and control groups including mean, SD and number of cases in each group.
3) The weight of each study as a % of the total of the meta-analysis (100%).
4) The difference in mean between the 2 groups + the 95%CI of the difference.
5) The publication year again.
6) On the right side, there is a figure showing the same above results. Each study is represented by a square (its size = study weight, and its center is opposite to the mean's difference) on a straight line (representing the 95%CI of the

mean's difference). The final results of the meta-analysis is represented by the black diamond (its center is the mean's difference across all studies and the tips are the 95%CI of the mean's difference across all studies).

7) The line in the middle of the graph is opposite the 0 value and it is called the equator line which means no difference between the groups. If the lines of any study and/or the diamond touch it, this means that there is no statistical difference between the 2 groups.
8) The last 2 lines written in the plot are for the heterogeneity represented by $I^2$ statistic as a % and a p value. When the p value is < 0.05, then heterogeneity is considerable across the studies and we should take the results cautiously. The 2nd line is the p value of the overall results (that are represented by the diamond in the graph). This is represented by Z value and p value. When the p value is < 0.05, this means that the overall result is statistically significant.
9) Forest plots were done using Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

**Stat analysis:**

We analyzed data from the included studies using Review Manager (RevMan – version 5.4, The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark). A formal meta-analysis was conducted for all outcomes if the data were sufficient. We expressed pooled continuous effect measures was expressed as the mean difference (MD) with 95%CI. We explored and quantified between-study statistical heterogeneity using the $I^2$ test. By default, we used the fixed effect model in all analyses. If heterogeneity was statistically significant ($p < 0.05$) or $I^2$ was > 50%, we used the Der Simonian and Laird random-effects model instead (Der Simonian and Laird, 1986). Publication bias could not be assessed due to the few number of included studies.

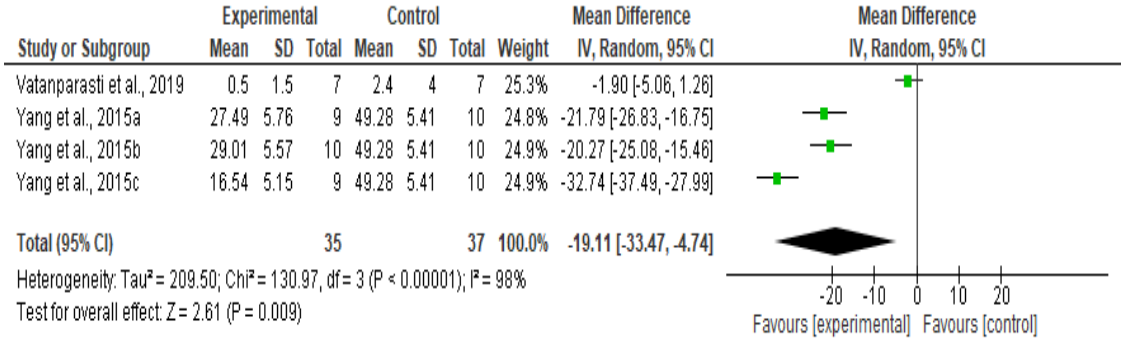


**Figure 2:** Comparison between intervention and control, outcome: 1.1 Behavioral Inattention Test (Star cancellation Test)-Non-invasive techniques

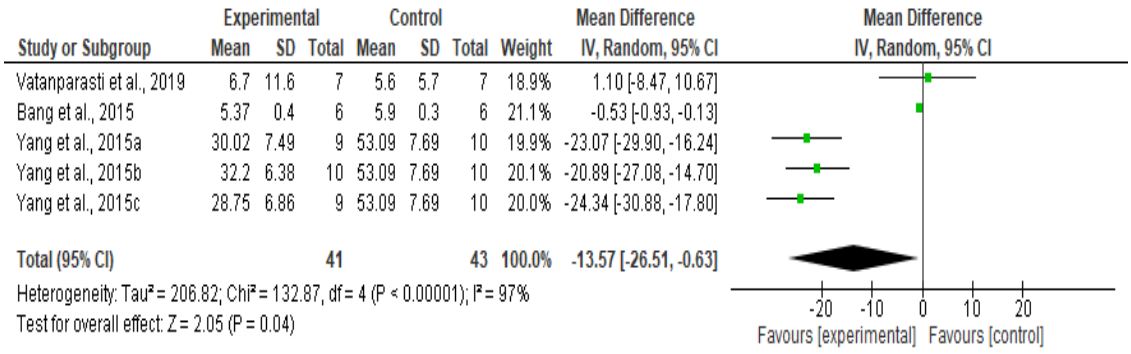


**Figure 3:** Comparison between intervention and control, outcome: 1.2 Behavioral Inattention Test (line bisection Test) Non-invasive techniques

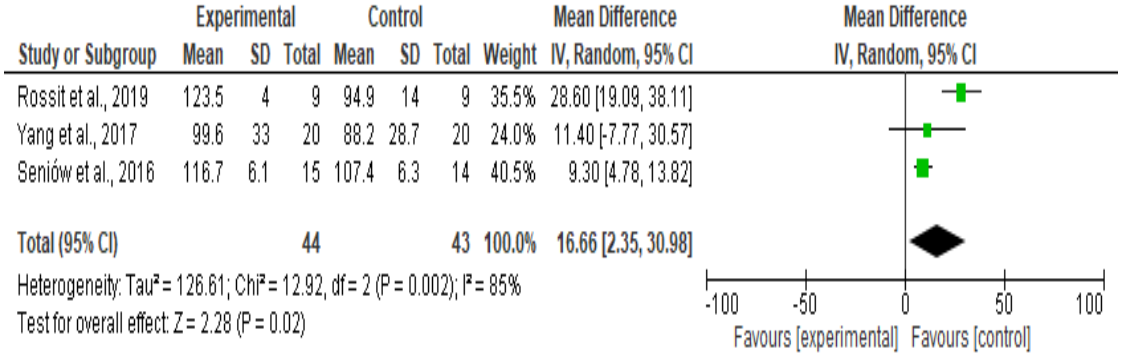


**Figure 4:** Comparison between intervention and control, outcome: 1.3 Behavioral Inattention Test (total) - Top-Down techniques

**Discussion**

The aim of the current review was to determine the effect of non-invasive approaches on line bisection and star cancellation, and also the effect of top-down on BIT score in hemispatial neglect patients after stroke. The analysis covers studies conducted between 2013 and 2021 searched using physiotherapy evidence base (PEDRo), google scholar and Cochrane database that most likely contain a large number of papers published annually. The current systematic review analyzed six randomized controlled trials, applying strict inclusion criteria. All trails satisfied at least six PEDro-scale criteria. Six studies, including Bang et al. (2015), Yang et al. (2015), Seniów et al. (2016), Yang et al. (2017), Vatanparasti et al. (2019) and Rossit et al. (2019) underwent meta-analysis **[11-16].**

The scoring of each study of the six studies with the PEDro scale is 6, 7 or 8 after collecting data. The higher the number of scores of factors measuring the study's efficiency, the greater the study's efficiency. The research design of the six studies is randomized controlled trials with evidence level two; patients involved in the six studies were hemispatial neglect after stroke.

The results of the current study revealed that non-invasive approach is favorable in improvement of star cancellation and line bisection in patients with hemispatial neglect, but more favorable for star cancellation improvement. This results are consistent with **Song et al. (2009), Lim et al. (2010) [17-18].**

Noninvasive brain stimulation techniques have previously been shown in proof of concept experiments to enhance unilateral spatial attention by modulating cortical excitability. **[19].**

After repeated magnetic stimulation, rTMS was a non-invasive application of an electrical field beyond the cranium that induced depolarization of nerve cells in the cerebral cortex and changed the excitability. **[20].** Several research on the impact of repeated transcranial magnetic stimulation (rTMS) on brain activity and unilateral spatial neglect have been published. The cTBS protocol lowered excitability in the non-affected hemisphere, resulting in a rebalancing of hemisphere excitability **[21]. Sparing et al. (2009) [22]** mentioned that Both the inhibitory action of cathodal tDCS applied over the unlesioned posterior parietal cortex (PPC) and the facilitatory effect of anodal tDCS applied over the lesioned PPC decreased symptoms of visuospatial neglect.

The results of the current study revealed that top-down approach is not favorable than control groups in improvement of BIT score in patients with hemispatial neglect. This results are consistent with **Harvey et al. (2003) [23]**; they concluded that visuo-motor training failed to find improvement on the BIT. However, **Katz et al. (2005) [24]** concluded that Virtual reality preparation can be a helpful rehabilitation tool for stroke survivors with unilateral spatial neglect.

**Conclusion**:

Our results from this analysis concluded that there is a strong evidence of using non-invasive approach is improving star cancellation and line bisection in hemispatial neglect patients and so we recommend this treatment approach for the clinical decision making by the physical therapists. However, further studies are needed to be able to decide if top-down are effective in improvement of BIT in hemispatial neglect patients or not.

**Scientific Responsibility Statement**

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

**Animal and human rights statement**

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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**Conflict of interest**

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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