Critical Review:

Are therapeutic interventions that include non-invasive brain stimulation (tDCS/rTMS) with language therapy effective at improving auditory comprehension in patients with aphasia following left-hemisphere stroke?

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This critical review examines whether incorporating NICS techniques with language therapy improves auditory comprehension abilities in patients with aphasia secondary to left-hemisphere stroke. Results of several studies provide suggestive evidence for the inclusion of NICS with language therapy. Further evidence supports that incorporating NICS techniques with language intervention enhances improvement in auditory comprehension, compared to language therapy alone. Patient candidacy and suggestions for parameters of an appropriate NICS application procedure remains unclear. Further clinical implications and results are discussed below.

Introduction

Aphasia is an acquired neurogenic communication disorder resulting from damage to the extensive network of cortical and subcortical structures in the brain, causing deficits in language modalities that may include speaking, listening, reading, and writing (Chapey, 2008). Aphasia often develops following stroke, and may have serious implications on an individual's autonomy and quality of life. Approximately 30% of individuals experiencing a cerebral stroke will acquire aphasia, with spontaneous recovery occurring in half of these cases within the first six months (Engelter et al., 2006). Spontaneous recovery without intervention is not typically expected after one year post-stroke, however, an extensive literature base has found language treatment to be efficacious for improving communication function for these patients (Holland, Fromm, DeRuyter, & Steinn, 1996).

Thomson (2000) discussed the theory that neuroplasticity and reorganization of the neural networks may account for functional recovery of language in individuals with aphasia. Non-invasive cortical stimulation (NICS), including repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) have been demonstrated to modulate the excitability, activity, and plasticity in targeted cortical regions of the brain (Nitsche et al., 2005). Therefore, there is reason to suspect that NICS techniques may facilitate recovery and potentially increase language abilities in patients with aphasia from left-hemisphere stroke. Recent research is demonstrating that NICS may be an efficacious addition to aphasia treatment, and particular gains have been noted for the improvement of naming skills in these individuals (see Mylius, Zouari, Ayache, Farhat, & Lefaucheur, 2012). However, little research has been conducted to examine the effects of NICS with language therapy for other impaired modalities associated with aphasia.

Deficits in auditory comprehension may considerably compromise an individual's ability to comprehend spoken language. Patients with aphasia demonstrating more complex deficits (e.g. global aphasia), often present with significantly compromised auditory comprehension. Furthermore, these patients have a poorer prognosis relative to other aphasia types (Chapey, 2008). Therefore, determining new techniques to facilitate auditory comprehension improvement should be a priority. NICS techniques may serve to facilitate recovery, and demonstrate clinical potential due to its non-invasive application, ease of administration, portability, and relatively low cost (Nitsche et al., 2005). Various guidelines have been implemented for the use of NICS. If followed correctly, patients are expected to incur little-to-no adverse side effects (Wasserman, 1998).

Objectives

The primary objective of this paper is to critically evaluate the current literature to determine whether the inclusion of rTMS and tDCS techniques with speech-language therapy improves auditory comprehension outcomes in a variety of patients with aphasia from left hemisphere stroke.

The secondary objective of this paper is to critically review and examine the preliminary research to determine if therapeutic interventions that include rTMS or tDCS with language therapy are more effective than language therapy alone for this population.

Methods

Search Strategy

A computer database search was conducted to find articles included in this review. PubMed, CINAHL, Medline, Google Scholar, and Scholars Portal were accessed and included the following search strategy:

[(aphasia) OR (stroke) OR (aphasia language therapy) AND (auditory comprehension) OR (auditory verbal comprehension) AND (rTMS) OR (tDCS) OR (non-invasive cortical stimulation) OR (electrical stimulation)]

The search was limited to articles written in English.

Selection Criteria

Selected articles for inclusion in this review were required to examine the effects of NICS with language therapy on auditory comprehension skills in adults with aphasia secondary to stroke. Studies were limited to patients having sustained some type of stroke of the left hemisphere. Treatment criteria were limited to papers including at least one group receiving NICS with language therapy only. One paper including a third treatment variable was not included for review.

Data Collection

Results of the search yielded eight articles that met the aforementioned criteria. Five papers examined whether NICS with language therapy was efficacious for improving auditory comprehension skills in patients with aphasia from left-hemisphere stroke. Three randomized clinical trials evaluated whether the inclusion of NICS with language therapy was more effective for improving auditory comprehension than traditional methods of language therapy alone for this population.

Results

Abo et al. (2012) conducted a non-randomized clinical trial to determine whether rTMS in conjunction with intensive language therapy improved language outcomes for 24 Japanese-speaking patients with aphasia from stroke. Patients were grouped by aphasia type and underwent fMRI to determine appropriate stimulation site (non-fluent type stimulated at inferior frontal gyrus [IFG] vs. fluent type stimulated at superior temporal gyrus [STG]). All participants were assessed pre- and post-test, and partook in 10 sessions including 40-minutes 1Hz Low Frequency (LF)-rTMS followed by 60-minutes individualized language therapy.

An appropriate Wilcoxin sign-rank test revealed significant improvement in auditory comprehension on the Standard Language Test of Aphasia (SLTA) for the non-fluent aphasia group only. The use of fMRI to localize the compensatory region to determine LF-rTMS stimulation site was a prominent strength not often included in similar designs. In doing so, the author's acknowledged that individuals may exhibit variation of the compensatory region, and thus provided control to ensure equivocal treatment of all patients. Appropriate patient grouping and analysis by factors further strengthens this study, since stroke patients present with a variety of considerations that might impact the characteristics of language impairment. This type of analysis allowed the authors to examine whether patients with a specific type of aphasia responded better to the treatment procedure, which is a useful clinical implication. Considering the study's extensive strengths, the authors provide compelling evidence that LF-rTMS with combined language therapy increases auditory comprehension for non-fluent patients with aphasia from left hemisphere stroke.

Cherney et al. (2013) conducted a single subject n-of-1 study to examine whether tDCS with combined language therapy improved language outcomes in a single participant with chronic non-fluent aphasia. A 63 year-old Cantonese first-language man with reported English proficiency underwent 30 sessions of 13-minutes 1mA cathodal tDCS to the right temporal region with 15-minutes English language treatment, followed by 75 minutes of language therapy only (computerized ORLA; 3-5 word sentences via virtual therapist). The authors noted little improvement in auditory comprehension on the Western Aphasia Battery-Revised (WAB-R) at 6-week follow up, although results did not reach significance. The researchers concluded that the patient might not have benefitted from tDCS with combined language therapy.

Careful consideration of the study's limitations should be taken before inferring efficacy. Single subject designs are restricted by a small sample size, which may contain participant biases and reduce generalizability. The participant in this case was a Cantonese first-language speaker receiving treatment in a second language. Different outcomes may have been obtained had the patient been given treatment in Cantonese, which justifies caution against generalizing findings to speakers receiving treatment in a native language. Furthermore, it is fathomable that the participant did not experience true gains, since language treatment consisted of a fixed-activity delivered by virtual therapist that did not increase in task demand or complexity. The patient may have demonstrated improvements had treatment been provided by a certified speech-language pathologist qualified in delivering increasingly challenging stimulation individualized to ongoing needs and function.

Considering limitations in the methodology and reduced generalizability, the study provides only equivocal evidence to the research question.

Jung, Lim, Kang, Sohn, and Paik (2011) conducted a retrospective single group pre- post-test study to examine whether tDCS with combined language therapy improved language function in 37 Korean participants with various types of aphasia. Patients were selected if they had received 30 minutes case-specific language treatment simultaneously with 20 minutes 1mA cathodal tDCS over the right IFG for 10 sessions. Appropriate statistical analysis showed significant evidence for improved performance on the auditory comprehension subtest of the Korean (K)-WAB. Further analysis revealed increased

overall language scores to be correlated with fluent aphasia type, hemorrhagic stroke, milder strokes, and patients in the acute phase of recovery (<30 days).

Acute patients were noted to demonstrate the greatest improvement, however the authors speculated this might be due to spontaneous recovery rather than a result of treatment. Additionally, the researchers admitted significant patient information was missing from the records, thus the participant group could not be controlled for various factors (e.g. concomitant illness). Available information revealed notable patient and medical diversity, which may introduce additional variables. Nevertheless, the researchers enforced appropriate stringent methodological criteria in selecting participants to be included in the study. A level of control was provided through grouping patients by known variables for AQ analysis, which provides clinical utility and some ability to suggest potential treatment candidacy.

Overall, the study provides suggestive evidence that tDCS with combined language therapy improves auditory comprehension in this population.

Kakuda, Abo, Uruma, Kaito, and Watanabe (2010) conducted a pre- post-test pilot study to examine whether rTMS with combined language therapy was effective in improving language for two male Japanese participants with chronic fluent aphasia from stroke. Participants received 20 minutes 1Hz LF-rTMS to left-hemisphere STG followed by 60-minutes of individualized language therapy during six daily inpatient and 12 weekly outpatient sessions lasting 1 hour. On visual inspection, the authors indicated steady improvement in auditory comprehension scores at pre-test, post-test, and six-week follow up on the SLTA for both participants, however, statistical analysis was not conducted.

The efficacy of the present design is hindered by a lack of statistical testing to determine whether reported improvements in auditory comprehension scores were significant. However, testing might not have been sensitive enough to detect significant differences as a result of the small group size. Had significance been found, low power and reduced generalizability might compromise findings. Nevertheless, statistical data would have been useful in determining if observed improvements represented a meaningful increase in auditory comprehension scores. Despite the limitations, the study holds merit in the authors' attempts in determining criteria for 'chronic' aphasia before the study, and in offering transparency by outlining SLTA scores for each patient. Because chronicity had been established, the authors concluded that the observed improvements in auditory comprehension were due to treatment.

Considering the study's design and limitations, the research provides suggestive evidence that rTMS with combined language therapy improves auditory comprehension scores in patients with aphasia from left hemisphere stroke.

Kakuda, Abo, Momasaki, and Morooka (2011) completed a pre- post-test pilot study with four patients with non-fluent aphasia from cerebral hemorrhage to evaluate the effects of language therapy with rTMS on language function. Participants underwent 18 treatments of 10-minutes 6Hz intermittent LF-rTMS followed by 20 minutes 1Hz LF-rTMS to the right IFG. Subsequent individualized language therapy targeting expressive skills commenced for 60 minutes. The authors noted an improvement greater than 5% in the auditory comprehension subtest of the SLTA for one patient. Statistical analysis was not conducted.

Similar to the previous study by Kakuda and colleagues (2010), the authors argued that statistical analysis was not required since patients were established to have 'chronic' aphasia, thus suggesting reported improvements were the result of treatment. However, statistical analyses might have provided valuable information in validating effectiveness. One further challenge was that the majority of patients presented with only minimal impairment in auditory comprehension. This poses as problem, as the potential for improvement was limited by an inability to demonstrate substantial gains. In relation to this, the language treatment in this study targeted improving expressive skills, as this was the most compromised modality. Patients may have been expected to exhibit greater improvements in auditory comprehension had it been included as a treatment target, and if participants had greater potential to demonstrate meaningful achievements.

It is of interest that one patient demonstrated gain in auditory comprehension scores despite the expectations above. Considering the small sample size, this observed improvement is noteworthy and contributes to providing a suggestive level of evidence that LF-rTMS with combined language therapy improves auditory comprehension for some individuals with aphasia.

Weiduschat and colleagues (2011) examined whether including LF-rTMS with language therapy was more effective than language therapy alone at improving language function for 10 German-speaking participants. Using a double-blind randomized clinical trial, participants were randomly assigned to a LF-rTMS over right IFG with language treatment group, or LF-rTMS over cortical vertex (sham) with language therapy group. Participants received 20 minutes 1-Hz LF-rTMS, followed by 45 minutes individualized language therapy for 10 sessions. On visual inspection most patients demonstrated improvements in auditory comprehension scores on the Aachen's Aphasia Test (AAT), although an appropriate analysis did not reach significance. However, the authors did find that participants receiving LF-rTMS with language therapy demonstrated significantly greater gains on overall

language scores, suggesting some benefit of LF-rTMS inclusion.

The present design has merit in ensuring all involved in the study were blind to research objectives, and in adequately randomizing patients to a treatment or control group. In doing so, Weiduschat and colleagues were able to conduct an appropriate analysis to demonstrate that the groups were not significantly different, thus suggesting improvements were likely a result of treatment. However, the small sample size and the inclusion of a variety of aphasia and lesion types may have affected the study's sensitivity for detecting significant improvements. A more refined criteria aimed to reduce participant variation or a larger sample size might provide further control to this study, and increase potential to provide statistical verification.

Overall, the authors propose just reasoning that including LF-rTMS in treatment had a positive effect on outcomes. Although the researchers could not offer statistical support, the study's efficacious design does provide some suggestive evidence towards the research question.

Thiel and colleagues (2013) replicated Weiduschat and associates' (2011) double blind randomized clinical trial with a larger group to determine whether patients receiving LF-rTMS with language therapy demonstrated greater language gains than patients receiving language therapy alone. Twenty-Four participants were randomly distributed to treatment groups and underwent language therapy, as previously outlined. Participants in both groups demonstrated significant gains in auditory comprehension, and an appropriate ANOVA revealed significantly greater improvements for participants treated with LF-rTMS and language therapy.

This follow-up trial served to address the limitations of Weiduschat and colleagues' (2011) study by increasing the number of participants. In doing so, the authors were able to achieve statistical significance using near identical methodology of an efficacious design. The follow up study also served to suggest reliability of the treatment method, as the observed outcomes in both implementations were relatively consistent. The reproducibility of this design is clinically useful, and overall the authors' provide compelling evidence that the inclusion of LF-rTMS with language therapy provides greater improvements in auditory comprehension function for this population.

You, Kim, Chun, Jung, and Park (2011) also conducted a double-blind randomized clinical trial to examine the effects of tDCS combined with language therapy on auditory comprehension in 21 Korean participants with sub-acute global aphasia from stroke. Patients were randomly assigned to receive ten 30-minute language therapy sessions with either 2mA anodal tDCS over left STG, 2mA cathodal tDCS over right STG, or 0mA-sham tDCS. The authors found that participants who received language therapy with right hemisphere cathodal tDCS made significantly greater gains than other patients on the auditory comprehension subtest of the K-WAB, as indicated by an appropriate repeated measures ANOVA.

One limitation of the present design lies in the methodology of examining treatment effects in sub-acute patients. The authors acknowledged that the observed improvements in auditory comprehension among all participants might be due to spontaneous recovery. Nevertheless, the researchers were able to establish statistically relevant evidence that improvements for patients receiving right hemisphere cathodal tDCS were due to the inclusion of NICS with language therapy specifically, as this group demonstrated the greatest gains. The study is further strengthened by its use of several tDCS application regions, and its methods in appropriately utilizing random distribution for assigning patients to receive differential treatments. In doing so, the authors were able to provide suggestions for candidacy and procedural treatment methodology, which offers substantial implications for clinical utility. In doing so, the study also emphasizes the importance of considering the varying effects that may occur as a result of type and site of tDCS stimulation, and the NICS procedure.

Considering the study's appropriate use of measures, methodological strengths, and relevant clinical utility, the authors offer compelling evidence that tDCS with language therapy provides significantly greater improvements in auditory comprehension for this population.

Discussion

The primary objective of this paper was to review the literature to examine whether NICS with language therapy improved auditory comprehension function in patients with aphasia. Of the five appraised papers, one study offered compelling evidence and three studies offered suggestive evidence that the combined treatment was effective (Abo et al., 2012; Jung et al., 2011; Kakuda et al., 2010, 2011). Cherney and colleagues (2013) proposed a counter-argument to this claim based on lack of findings, however, the level of evidence offered to dispute the effectiveness of NICS with language therapy was judged to be equivocal due to the study's substantial limitations.

Thus far, the overall level of evidence is suggestive that NICS with language therapy does, in some way, improve auditory comprehension outcomes for patients with aphasia. However, the previous authors were not able to comment on whether the NICS technique or language therapy was more beneficial in increasing auditory comprehension function. As such, three randomized clinical trials were included in the review to evaluate whether language therapy that included a NICS component was more effective than language therapy alone. Randomized clinical trials are beneficial for comparing the

effects of different treatments by unsystematically assigning patients to receive a specific procedure, and are therefore valuable in the present review. In this case, two groups of authors utilizing convincing designs were able to offer compelling evidence to support that language treatment including NICS techniques was significantly more beneficial in improving auditory comprehension for this population (Thiel et al., 2013; You et al., 2011). Although the study conducted by Weiduschat and colleagues (2011) was only able to offer suggestive evidence due to lack of statistical significance, their evidence was later justified in the follow-up by Thiel and associates.

Before inferring efficacy for including NICS techniques with language therapy in the treatment of aphasia, a number of important considerations should be addressed.

First, the appraised studies differed in the patient demographics and characteristics included in the design. A few authors examined the effects of treatment for patients demonstrating a specific type of aphasia, including fluent (Kakuda et al., 2010), non-fluent (Cherney, 2013; Kakuda et al., 2011), global (You et al., 2011), and non-fluent vs. fluent aphasia types (Abo et al., 2012; Jung et al., 2011). Authors examining the benefits for fluent vs. non-fluent aphasia found contradicting results, and reasons for this are currently unclear. Other authors did not control for aphasia type at all (Weiduschat et al., 2011; Thiel et al., 2013). Similarly, some studies included only patients presenting with a specified level of aphasia chronicity (e.g. acute, sub-acute, or chronic), or stroke type (e.g. infarct or hemorrhage), while other studies did not control for these variables. Generally, most studies did not control for a variety of characteristics including aphasia severity, lesion location, date of onset from stroke, and more. However, Jung and colleagues attempted to include these factors in a secondary analysis and did find evidence to suggest that these variables influenced patient outcomes. Despite this, variables associated with positive outcomes for this treatment procedure currently remains unclear.

A second consideration is that the appraised studies demonstrated robust variation in NICS application. Influential factors in the present review include stimulation type (tDCS: annodal or cathodal; rTMS: high frequency or low frequency), stimulated hemisphere (right or left), and cortical locus (IFG or STG). Selection criteria of these factors often stems from theories of interhemispheric rivalry (Kinsbourne, 1976). The studies included in this review aimed to facilitate recovery through the application of NICS, and employment was selected based on two theories: Modulating neural activation of perilesional regions in the dominant left hemisphere, or modifying activity in the compensatory right hemisphere. An in-depth discussion on the effects of recovery patterns and NICS techniques for aphasia can be found elsewhere (see Mylius et al., 2012). Many authors in the present study aimed to inhibit the homologous-damaged region of the right hemisphere in order to facilitate activation in the left hemisphere, which is a technique gaining merit in a variety of NICS studies (Cherney et al., 2013; Jung et al., 2011; Kakuda et al., 2011; Weiduschat et al., 2011; Thiel et al., 2013). All authors recognized that the NICS application procedure might influence outcomes. Thus, the procedural variability in the current literature pool raises further unanswered questions regarding the applicability and efficacy for the NICS technique.

Clinical Implications and Conclusion

Considering the above evidence, there is reason to suspect that the inclusion of NICS with language therapy is somewhat effective for improving auditory comprehension in patients with aphasia from left-hemisphere stroke, and may have potential to provide greater benefit to patients than language therapy alone. However, the inclusion of NICS into therapeutic practice is cautioned, as treatment candidacy and procedural applicability remains largely unclear.

As previously stated, the designs reviewed in this paper demonstrated exceptional diversity in the employment of treatment procedures and participant characteristics. Further research is strongly recommended to determine the variables and characteristics associated with increased improvement in auditory comprehension outcomes. Research should examine the type of aphasia that responds best to treatment, and focus on defining effective clear parameters for NICS procedures and locus of stimulation. Furthermore, designs aimed at increasing auditory comprehension specifically should be employed. The research conducted by You and associates (2011) provides useful preliminary clinical information in this area, and further studies should aim to continue this work to establish candidacy and treatment procedures.

Overall, the literature provides suggestive evidence for the effectiveness of NICS with language therapy in improving auditory comprehension abilities in patients with aphasia secondary to left-hemisphere stroke. Further research will be valuable in determining factors related to potential candidacy and treatment procedures in order to advocate for the clinical utility and applicability of NICS techniques in aphasia treatment.

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