Non-pharmacological intervention effects on apathy caused by central nervous system organic diseases
A network meta-analysis

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Abstract

Background: To evaluate the best non-pharmacological interventions on apathy in patients with central nervous system (CNS) organic diseases.

Methods: We searched PubMed, Web of Science, Embase, Cochrane Library electronic databases, China national knowledge infrastructure, Wanfang and Chinese biomedical literature database studies published from 2011 to May 29, 2021. A combination of subject words and free words were used for searching. Randomized controlled trials (RCTs) of non-pharmacological interventions for apathy in patients with central nervous system disease were included. Two researchers independently identified the eligible RCTs and extracted information. The risk of bias within each individual trial was assessed using the Cochrane Collaboration's tool. Review Manager 5.4 and ADDIS 1.16.5 were used for data analysis.

Results: A total of 5324 related studies were obtained in the initial screening, and final 8 RCTs including 334 patients were included, involving 4 non-pharmacological interventions of cognitive intervention, repetitive transcranial magnetic stimulation (rTMS), music therapy and occupational therapy. Direct comparison results showed that rTMS, cognitive intervention, and occupational therapy were superior to the conventional group \( P < .05 \). Network Meta repeated rTMS, cognitive intervention was superior to the conventional group \( P < .05 \), while the other groups did not differ from with the conventional group \( P > .05 \). The order of superiority was rTMS, cognitive intervention, occupational therapy, music therapy, and conventional group.

Conclusion: Current evidence suggests that rTMS and cognitive interventions are more effective than the conventional intervention in improving apathy in patients with CNS organic diseases. It still needs more non-pharmacological intervention studies with high quality, larger sample sizes for further exploration.

Abbreviations: AES = apathy evaluation scale, CI = confidence interval, CNS = central nervous system, OR = odds ratio, RCTs = randomized controlled trials, rTMS = repetitive transcranial magnetic stimulation.

Keywords: apathy, CNS organic disorders, network meta-analysis, non-pharmacological interventions

1. Introduction

Apathy is defined as a reduction in motivation and a disorder of goal-directed behavior\textsuperscript{[1]} mainly in terms of cognitive, behavioral and emotional changes.\textsuperscript{[2]} Apathy is a common symptom of central nervous system (CNS) organic diseases, such as stroke, Parkinson disease, dementia and mild cognitive impairment.\textsuperscript{[3–6]} Study\textsuperscript{[7]} shows that apathy is due to damage or disruption to goal-directed areas of the brain, such as the limbic system, frontal, basal ganglia, temporal, parietal, insula, occipital, et al.

Increasing evidences suggest that apathy is severely affecting patients' participation in rehabilitation,\textsuperscript{[8]} accelerating the process of cognitive decline,\textsuperscript{[9]} reducing the patient’s ability to take care of themselves,\textsuperscript{[10]} also affecting their quality of life,\textsuperscript{[11]} and even increasing the patient’s chance of suicide.\textsuperscript{[12]} The mechanism of apathy occurrence is not yet fully understood. Therefore, it is so important to find ways to improve apathy symptoms in patients with CNS organic diseases. Due to the limited efficacy of pharmacological treatment and the possible side effects,\textsuperscript{[13,14]} non-pharmacological treatments have become important for apathy.
The effects of non-pharmacological treatments have been reported in published studies. But, it is not yet clear which is the most effective. A summary of the evidence for identifying effective non-pharmacological treatments may provide an important resource for clinical practitioners. Unfortunately, the latest date of a meta-analysis about apathy symptoms was only for people with dementia, and there was a low level of confidence among the included studies.[13] Moreover, with the development of rehabilitation therapies, a number of new non-pharmacological interventions are being used in the treatment of organic diseases of the CNS with apathetic symptoms, such as repetitive transcranial magnetic stimulation (rTMS).[14] Therefore, the study aimed to explore the effect of non-pharmacological interventions in improving apathy in patients with CNS organic diseases via the methodology of network meta-analysis. We present the following article in accordance with the PRISMA reporting checklist.

2. Methods

2.1. Search strategy

The systematic review was performed according to an established protocol (PROSPERO No. CRD42021271477). The study was approved by the Ethics Committee of the Hainan Medical University. Seven English and Chinese databases, including PubMed, Web of Science, Embase, the Cochrane Library, China national knowledge infrastructure, Chinese biomedical literature database, and Wanfang database, were searched from 2011 to May 29, 2021. We searched using: “apathy OR neuropsychiatric symptoms OR non-motor symptoms” AND “stroke OR cerebrovascular accident OR cerebral infarction OR ischemic stroke OR cerebral hemorrhage OR hemorrhagic stroke OR alzheimer’s disease OR AD OR dementia OR parkinson’s disease OR PD OR multiple sclerosis OR huntington’s disease OR neurological disease OR central nervous system disease OR neurodegenerative disease OR degenerative disease.” The search was carried out using a combination of subject terms and free terms. The reference lists of included studies were also manually searched to identify any relevant articles. Articles in English and Chinese were considered to be eligible.

2.2. Inclusion and exclusion criteria

The inclusion criteria of literature were detailed following the participants, intervention, controls, outcomes, and study design. Participants: we included studies enrolling CNS organic diseases, such as stroke, Parkinson, Alzheimer disease, mild cognitive impairment, dementia, multiple sclerosis, Huntington disease. Intervention: any randomized controlled trials (RCTs) which the experimental group was given non-pharmacological interventions with no limited method of intervention. Controls: the control group was given conventional rehabilitation care, general activities or sham stimulation. Outcomes: the outcome measure was the apathy evaluation scale (AES). Study design: only RCTs in English OR Chinese were considered. The exclusion criteria: Studies included pharmacological interventions. Studies were unavailable literature data, errors, or unavailability of full text. Nonoriginal studies, including reviews, meeting abstracts, case reports, letters, or papers.

2.3. Study selection and data extraction

Two investigators (SY and XL) independently screened the literature (titles, abstracts, and full-text), then extracted the literature data from included studies using the standardized data collection form. When selecting all of the searched studies, we first remove duplicate studies through the EndNote, then read the titles and abstracts to remove the obviously irrelevant studies, and then read the full text to determine whether to include them. Data were extracted including researcher and publication date, country, sample size, disease, intervention, intervention duration, and site. Authors of respective articles were contacted to request missing or additional data for clarification where required. If the opinions were different between the 2 investigators (SY and XL), it would be resolved through discussion to reach consensus. Otherwise, the third investigator (TW) make the decision.

2.4. Assessment of methodologic quality

Eligible studies were assessed for methodologic quality by 2 independent investigators (SY and XL) at the study level using the tool recommended by the Cochrane Handbook 5.1.0. Each study was evaluated against 7 entries in the manual according to “low risk,” “high risk,” and “unclear.” If the opinions were different between the 2 investigators (SY and XL), it would be resolved through discussion to reach consensus. Otherwise, the third investigator (TW) make the decision.

2.5. Statistical analysis

Review Manager 5.4.1 was used for Direct comparison. If \( P \geq 0.1 \) and \( I^2 \leq 50\% \), then the statistical heterogeneity of included studies was considered acceptable, and a fixed-effects model was selected for analysis; if \( P < 0.1 \) and \( I^2 \geq 50\% \), then the included studies were considered to be statistically heterogeneous and a random-effects model was selected for analysis. Funnel plots were used to test the risk of bias for all included literature. ADDIS 1.16.5 was used for network Meta-analysis. We adopted a network meta-analysis methodology to derive estimates of the comparative effectiveness of each intervention against a control. An indirect effect estimate was then calculated to compare the 2 interventions, utilizing the control group as a common comparator. The network meta-analysis were reported in terms of odds ratio (OR) with a corresponding 95% confidence interval (CI). The convergence of the model was assessed using the Potential Scale Reduction Factor. When the potential scale reduction factor is close to or equal to 1, the model was considered that it had achieved good convergence efficiency and high analytical confidence. Comparisons were considered statistically insignificant when the 95% CI took a value across 0. Ranking probabilities were used to rank the interventions, with Rank 1 being the worst and Rank N being the best. \( P < 0.05 \) indicated statistical significance.

3. Results

3.1. Study selection

A total of 5324 related articles were obtained at the first beginning, and the literature was gradually screened to finally 8 RCTs studies in English (Fig. 1). There were total 334 cases, including 174 cases in the experimental group and 160 cases in the control group. The non-pharmacological interventions included cognitive interventions, rTMS, music therapy, and occupational therapy. The characteristics of included studies were shown in Table 1.

3.2. Risk-of-bias assessment

The 8 studies included in the systematic review were evaluated separately. The quality of these articles, two articles[17,18] were rated as having low risk of bias, one article[19] was unclear risk of bias, and the remaining 5 articles[20–24] were high risk of bias (Fig. 2).

3.3. Meta-analysis results

3.3.1. Direct comparison. The heterogeneity seen across studies was \( P < 0.08, \ F = 45\% \), which was analyzed by using the fixed effects model. A funnel plot was used for publication bias testing and was
found to be largely symmetrical, which was considered a low risk of publication bias. The total effect on AES of non-pharmacological interventions with routine care was −6.88 (95% CI [−8.50, −5.26]), $Z = 8.33, P < .01$. Compared with the conventional group, cognitive intervention −8.25, (95% CI [−10.56, −5.94]), $Z = 7.00, P < .001$, rTMS −7.85, (95% CI [−11.49, −4.21]), $Z = 4.23, P < .01$, and occupational therapy −4.87, (95% CI [−9.00, −0.73]), $Z = 2.31, P = .02$ had an advantage (Table 2). The result suggests that rTMS, cognitive training and occupational therapy are more effective than the conventional group in reducing the level of apathy.

3.3.2. Network meta-analysis. The random effect variance was 3.08 (95% CI [0.39, 10.13]) for the consistency test and the random effect variance was 3.10 (95% CI [0.41, 9.81])
for the inconsistency test. As the 2 results were close, this was indicating good consistency. In consideration of the 4 interventions included in this study did not form a closed loop, and the comparisons across interventions were all evidence of indirect comparisons between the interventions and the conventional group. Therefore, the consistency model was used for network meta-analysis. The PSFR factors in the consistency model were all 1, indicating that the model converged well and could effectively predict the data. Consistent results showed that all of the 4 included non-pharmacological interventions had advantages over the conventional group in improving patients’ apathy symptoms. Among these 4 interventions, rTMS −8.78 (95% CI [−16.42, −1.76]), and cognitive stimulation −8.07 (95% CI [−13.56, −2.15]) were statistically significant (P < .05), the rest were not statistically significant (P > .05). While, no statistical difference was found between the 2 comparisons of different measures (Table 3). The result suggests that rTMS, cognitive training are more effective than the conventional group in reducing the level of apathy.

The interventions were ranked by assessing the ranking probability, and the later method indicated the better effect in improving apathy symptoms in patients with neurological organic diseases. In this study, the ranking of the superiority of the interventions in improving the patient’s apathy symptom

| Study and location | Sample size T/C | Patients | Age [M(SD)] | Intervention | Duration of intervention | Site |
|-------------------|----------------|----------|-------------|--------------|-------------------------|------|
| Sardina et al, 2019 (USA) | 33/28 | Dementia | 80.6 (9.8) | Cognitive interventions (individualized cognitive domain task training, goal-oriented group activities) | 12 weeks | Nursing home |
| Savulich et al, 2017 (UK) | 21/21 | Mild cognitive impairment | 75.2 (7.4) | Cognitive intervention (iPad game) | 8 times | Hospital |
| Padala et al, 2020 (USA) | 9/10 | Alzheimer disease | 74.3 (5.7) | rTMS | 4 weeks | Hospital |
| Padala et al, 2018 (USA) | 8/8 | Mild cognitive impairment | 65.6 (9.3) | rTMS | 2 weeks | Hospital |
| Tang et al, 2018 (China) | 37/39 | Dementia | 76.4 (4.9) | Music therapy | 12 weeks | Nursing home |
| Skidmore et al, 2015 (USA) | 15/15 | Stroke | 64.9 (16.6) | Occupational therapy (metacognitive strategy training-based occupational therapy) | 6 months | Hospital |
| Treusch et al, 2014 (Germany) | 44/32 | Dementia | 82.3 (10.8) | Occupational therapy (occupational therapy training designed according to lifestyle habits, occupations, and hobbies) | 10 months | Nursing home |
| Maci et al, 2012 (Italy) | 7/7 | Alzheimer disease | 75 (12.3) | Cognitive interventions (cognitive stimulation, movement, social activities) | 3 months | Hospital or home |

C = control group, T = test group.

Figure 2. Risk of bias summary.
Table 2
Direct comparison results of the effects of different interventions in patients with CNS organic diseases.

| Interventions | MD | 95% CI | Z  | P   |
|---------------|----|-------|----|-----|
| A vs E        | −8.25 | −10.56, −5.94 | 7.00 | <.001 |
| B vs E        | −7.85 | −11.49, −4.21 | 4.23 | <.001 |
| C vs E        | −3.23 | −7.30, 0.84 | 1.55 | .12  |
| D vs E        | −4.67 | −9.00, −0.73 | 2.31 | .02  |

A = cognitive intervention, B = rTMS, C = music therapy, D = occupational therapy, E = conventional intervention.

Table 3
Effect of different interventions on indifference to CNS organic diseases (MD [95% CI]).

| A | - | - | - | - |
|---|---|---|---|---|
| B | - | - | - | - |
| C | - | - | - | - |
| D | - | - | - | - |
| E | - | - | - | - |

Table 4
Ranking probability of the effect of different intervention methods on indifference.

| Interventions | Rank 1 | Rank 2 | Rank 3 | Rank 4 | Rank 5 |
|---------------|--------|--------|--------|--------|--------|
| A             | 0.01   | 0.05   | 0.19   | 0.41   | 0.34   |
| B             | 0.01   | 0.05   | 0.15   | 0.31   | 0.48   |
| C             | 0.19   | 0.41   | 0.24   | 0.10   | 0.06   |
| D             | 0.05   | 0.27   | 0.39   | 0.19   | 0.11   |
| E             | 0.75   | 0.23   | 0.02   | 0.00   | 0.00   |

A = cognitive intervention, B = rTMS, C = music therapy, D = occupational therapy, E = conventional intervention.

advantage over the conventional group was: rTMS > cognitive intervention > occupational therapy > music therapy > conventional group (Table 4).

4. Discussion

In this network meta-analysis, we comprehensively compared 4 non-pharmacological interventions for apathy dating back to the year 2011 in order to clarify the relative efficacy and safety in patients with CNS organic diseases. The results indicated that rTMS is the most likely and the best intervention method, and cognitive intervention is the second effective intervention method. Compared with conventional rehabilitation and nursing care, the efficacy of occupational therapy and music therapy to improving apathy is not significant.

In previous meta-analysis,[24] the result showed that music therapy, cognitive interventions, multi-sensory stimulation, and pet therapy were relatively effective on apathy symptoms in people with dementia. The different results in this study may be related to the inconsistency of the population included in the study and the apathy symptom assessment scales used.

As a new treatment of apathy, some experts had suggested that rTMS may offer a new direction for the treatment of apathy,[25] but rTMS was not included in[26] study. rTMS is a neuromodulation technique which uses magnetic fields to elicit changes in the action potentials of nerve cells in the cerebral cortex to affect the area of stimulation and related areas. Sasaki et al.[27] performed 5 sessions of rTMS on chronic stroke patients with a stimulation site in the prefrontal region for 20 minutes each time at 90% relaxed motor threshold with 10 Hz stimulation for 10 seconds and 50 seconds interval, and the results also confirmed that rTMS was effective in improving apathy symptoms. However, in a study by Maruo et al,[28] the experimental group received rTMS in the M1 motor control area for 3 consecutive days at a stimulation intensity of 100% relaxed motor threshold, a frequency of 10 Hz, a time sequence of 5 seconds and an interruption of 25 seconds. No significant improvement in apathy symptoms was found in the experimental group compared to the placebo group. This shows that the efficacy of rTMS on apathy was inconsistent across studies. Our current study may be able to give clinical practitioners some informative advice.

It had been repeatedly demonstrated that high-frequency stimulation increases brain excitability.[29] In animal experiments, 10 Hz rTMS reduced neuronal apoptosis by inhibiting astrocyte polarization in ischemic rats.[30] It had been shown that high-frequency rTMS acting on the left prefrontal lobe could increase cerebral perfusion, and improve circulation, also promote metabolism. It could increase the release of dopamine in the limbic and mid-striatal areas of the midbrain,[31,32] which may play a role in reward mechanisms, reinforcement, and motivational incentives. Although there are no guidelines on specific recommendations for the treatment of apathy with rTMS currently, rTMS had opened up new directions for the treatment of apathy. More studies can be conducted to explore the optimal therapeutic dose and parameters for rTMS to improve apathy in the future.

Cognitive interventions often use cognitive stimulation or cognitive training to train patients in different cognitive fields, by using assistance tools such as paper, pencil, or computer. A study in which patients with mild to moderate Alzheimer disease with psychotic symptoms were given a 10-week cognitive intervention which consisting mainly of orientation tasks, verbal fluency tasks, shape classification, and picture-telling tasks. Compared with the control group, it showed improvement in apathy symptoms.[33] Cognitive interventions can improve attention, memory, etc, thus improving the patient's cognitive and social functioning and helping to reduce symptoms of apathy.[34] Although cognitive interventions had shown good curative effect in the treatment of apathy, it is important to design individualized training programs, and take various forms to increase the patient's interest and participation motivation to ensure the effectiveness of the intervention.

Although this study ranked the methods of non-pharmacological interventions in order of superiority, it was not possible to explain the reasons for the ranking for the time being, mainly because there were too few direct comparative studies of different non-pharmacological interventions, and most studies explored the effectiveness of a particular non-pharmacological intervention versus the conventional group in improving apathy symptoms. Differences in the effects of different non-pharmacological interventions could be carried out in the future to explore the reasons for the ranking.

Our study had limitations. First, the language of literature included in this study was Chinese and English. Second, there are numerous indicators for the evaluation of apathy symptoms, and the literature which was included in this study only using AES for assessment, so there may be other effective measures that were not included. Third, this study did not conduct subgroup analysis for diseases in the included population, which may lead to poor specificity of the results. Eventually,
there were 8 papers included, even some interventions were only included in one paper. Considering the small sample size and low-bias studies, the results may be biased. It suggests that the original study of apathy symptoms still needs to be further carried out.

5. Conclusions
In summary, current evidence suggests that rTMS and cognitive interventions may be the effective interventions in improving apathy in patients with CNS organic diseases, and the effectiveness of other interventions still needs to be further explored. It is recommended that more non-pharmacological intervention studies should be conducted in the future to explore the effects of apathy in patients with CNS organic diseases. Given the limitations of this study, the results of this analysis should be taken with a grain of salt.

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