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Attitudes towards repetitive transcranial magnetic stimulation among depressive patients and medical students

Испитивања ставова студената медицине и депресивних пацијената о репетитивној транскранијалној магнетној стимулацији

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SUMMARY

Introduction/Objective Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive and safe brain stimulation method for the treatment of patients with therapy resistant depression in adulthood. The German S3 guideline for unipolar depression recommends the use of high frequency rTMS of the left dorsolateral prefrontal cortex for depressive patients who did not respond primarily to antidepressant pharmacotherapy. Although a number of meta-analyses demonstrated its antidepressant efficacy on a high evidence level, rTMS is rarely offered to patients with mental disorders in German psychiatric hospitals.

Methods We introduced a questionnaire-based survey examining patients' (N = 122) and medical students' (N = 53) attitude toward rTMS. The questionnaire consists of 10 questions with a 5-point Likert-scale. For testing for group differences, we conducted Chi-Square tests.

Results The majority of students and patients are not aware of rTMS as a psychiatric treatment of depression, with more patients than students not being aware ($\chi^2(1) = 9.462$, $p = 0.002$; 39.3% vs. 17.0%). However, participants wish to be informed in more detail about rTMS. In general, positive attitudes cover the assumption of safety, while negative attitudes show concerns regarding the efficacy and a lack of trust in the method, mainly due to the fear of irreversible brain damage. Most participants would rather take psychiatric medication than rTMS. rTMS was assumed to be a helpful ($\chi^2(2) = 16.710$, $p < 0.001$ [patients: 32.8% vs. students: 5.7%]) and well-tolerated treatment ($\chi^2(1) = 9.110$, $p = 0.003$ [36.1% vs. 15.1%]) significantly more often by patients than by students.

Conclusion Our results show a clear need for more information about rTMS as a psychiatric treatment for patients and medical students to fight present prejudices and negative assumptions so that this treatment method with fewer side effects than medication may be used more often.

Keywords: repetitive transcranial magnetic stimulation; attitudes; depression

САЖЕТАК

Увод/Циљ Репетитивна транскранијална магнетна стимулација (pTMC) јесте метода неинвазивног и безбедног лечења одраслих пацијената оболелих од терапијски резистентне депресије. Немачки С3 водич за униполарну депресију препоручује третирање леве стране дорзолатералног префронталног кортекса високо фреквентним ТМС-ом код депресивних пацијената, који нису претходно одреаговали на антидепресивну фармакотерапију. Упркос томе што је више метаанализа указало на висок степен њеног антидепресивног дејства, репетитивна транскранијална магнетна стимулација се ретко примењује код пацијената са менталним поремећајима у немачким психијатријским установама.

Методе Истраживање ставова по питању лечења pTMC-ом спроведено је у форми анкете, а укључило је 122 пацијента и 53 студента медицине. Упитник се састојао од 10 питања, док су одговори рангирани према петостепеној Ликерт скали. За тестирање разлика у групама, спровели смо тестове χ^2.

Резултати Већина испитаника није упозната са pTMC-ом као могућом методом лечења депресије, што је израженије код пацијената него код студената ($\chi^2(1) = 9.462$, $p = 0.002$; 39.3% наспрам 17%).

Међутим, учесници су показали интересовање да буду детаљније обавештени о pTMC-у. Уопштено, позитивни ставови се углавном заснивају на претпоставци о безбедности методе, док негативни ставови указују на забринутост по питању ефикасности и недостатак поверења у ову методу, углавном због страха од неповратних можданих оштећења. Већина учесника радије би узимала психијатријске лекове него се подвргла pTMC-у. Пацијенти, у већој мери него студенти, виде ТМС као корисну методу лечења ($\chi^2(2) = 16.710$, $p < 0.001$ [пацијенти 32.8% наспрам студенти 5.7%]), која се добро подноси ($\chi^2(1) = 9.110$, $p = 0.003$ [36.1% наспрам 15.1%]).

Закључак Наши резултати јасно указују на то да постоји потреба за бољим информисањем о pTMC-у, како пацијената, тако и студената медицине, чиме би се утицало на смањење предрасуда и сумњи везаних за употребу ове методе. Узимајући у обзир препоруке водича, ова антидепресивна

метода, која има мање нуспојава него лекови, требало би да је чешће заступљена у лечењу него што је то тренутно случај.
Кључне речи: репетитивна транскранијална магнетна стимулација; ставови; депресија

INTRODUCTION

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive and safe treatment option for patients with treatment resistant depression in adulthood [1, 2]. The antidepressant efficacy of high-frequency rTMS (10-20 Hz) over the left dorsolateral prefrontal cortex (DLPFC) has been suggested in a large number of studies and meta-analyses [3–6]. It is recommended by the German S3-guidelines for unipolar depression [3] as a possible treatment for patients who are unresponsive to antidepressants.

Despite these promising results rTMS was the rarest treatment presented to patients with mental disorders in Germany in 2012 [7]. Only 9% of German psychiatric clinics offered rTMS, making it even more infrequent than electroconvulsive therapy (ECT), which was used in 43% of institutions [7].

Based on these results there appears to be a discrepancy between the evident antidepressant efficacy and tolerability of rTMS and its application in everyday psychiatric practice. One possible reason for this may include issues with health insurance coverage, as costs of an rTMS treatment on an outpatient basis are currently not covered by the German statutory health insurance. Therefore, a reimbursement is restricted to patients who are insured privately with adequate cover as well as self-payers. However, it is possible to offer rTMS as a treatment covered by German statutory health insurance for inpatients free of further costs, thus insurance coverage alone might only partly explain why this treatment is used so rarely. Lack of public knowledge about rTMS, as well as patients' and medical staffs' experiences, opinions and attitudes towards the treatment may also explain why it is so infrequently employed.

Though it is widely known that physical treatments in psychiatry such as ECT are stigmatized in the public opinion [8, 9], it is less clear how the public and patients perceive rTMS. Walter et al. [8] conducted a study examining experience, knowledge and attitudes of recipients of rTMS regarding the treatment. They found that significantly less patients remembered adverse side-effects (muscle aches, nausea or vomiting, confusion and memory

impairments) after rTMS than after ECT and psychopharmacological treatment [8]. Experience and opinions about rTMS were found to be generally positive compared to psychopharmacological treatment and ECT [8]. Moreover, there is a first questionnaire based study focusing patient's attitudes towards rTMS, which found that most of the study patients (suffering from treatment resistant depression) recommended the use of rTMS in case of depression [10]. Though these results are promising, further research is necessary to solidify these findings and to establish how patients and medical staff perceive this therapy. Thus, we set out to examine medical students' and patients' awareness and opinion about rTMS, in the hope that this knowledge will explain the current lack of interest in this treatment and to help promote it as a safe and effective way to treat depression.

METHODS

To examine patients' and students' attitudes towards rTMS treatment for depression a questionnaire was developed and used in a preceding study employing a sample of 150 depressive patients, 150 health workers and 150 healthy controls [11]. In the current retrospective questionnaire-based study, 122 depressive inpatients were recruited at the LVR Psychiatric Clinic in Düsseldorf. The patients received their diagnoses by common clinical assessment using DSM-IV criteria [12]. The patients were given the questionnaire to fill in at their own responsibility. Moreover, 53 medical students of the medical facility of the Heinrich-Heine University Düsseldorf were recruited within a university course. They filled in the questionnaire at the end of a randomly chosen medical lecture. No further inclusion or exclusion criteria were applied. There was no further randomization because of the design of the study. The questionnaire consists of 10 questions, where answers have to be given on a 5 point Likert-scale with the extremes "totally agree" and "totally disagree". The questionnaire was handed to the patients by the nursing staff and collected anonymously in sealed envelopes to eliminate potential sources of bias. The medicine students filled in the questionnaire after a university course and the patients during their inpatient stay. All participants gave their informed consent and the institutional ethics committee of the Heinrich-Heine-University Düsseldorf (No. 2807) approved the study protocol. For testing for group differences, we conducted χ^2 tests on our (originally likert-scaled) data, which is appropriate for categorical data such as our likert-scaled data. For χ^2 tests have no assumption of normal distribution, no further pre-tests for testing it were conducted. For reasons of

presentation, data is displayed using percentage. However, χ^2 tests were used on our likert-scaled data. Percentage scores were calculated summing up "totally agree" and "agree" into "yes" and "totally disagree" and "disagree" into "no." Therefore, some values do not add up to 100% due to neutral answers, which generally contains little information.

RESULTS

The students consisted of 69.2 % women and were aged between 18 and 69 years (M = 43.5, SD = 12.2). Moreover, the medical students (60.4 % women) were aged between 23 and 44 years (M = 26.0, SD = 4.63). Our results show, that the majority of students and patients are not aware of rTMS as a psychiatric treatment for depression, with patients being significantly more aware than students ($\chi^2(1) = 9.462$, $p = 0.002$; 39.3% vs. 17.0%). However, most students and patients would apply it in case of acute depression (ns), although the majority of participants do not trust rTMS (ns). Most patients and students seem to assume irreversible brain damage and brain manipulation as an adverse side effect and only 34% of students and 41% of patients are unafraid of rTMS (ns). Medication seems to be preferred over rTMS despite fewer side effects of the latter (ns). Most medical students do not perceive rTMS as a helpful treatment, whereas patient attitudes appear to be more polarized: about one third perceive it as helpful and one third have the opposing opinion. This difference is significant: $\chi^2(2) = 16.710$, $p < 0.001$ (patients: 32.8% vs. students: 5.7%). Moreover, significantly more patients than students think that rTMS as a treatment for depression is a well-tolerated method ($\chi^2(1) = 9.110$, $p = 0.003$ (36.1% vs. 15.1%). Altogether, it appears that patients have a more positive attitude towards rTMS than students do. A larger proportion of patients than of students know and are willing to receive more detailed information about rTMS (ns). See Table 1 for a detailed distribution of answers concerning attitudes towards rTMS for students and patients.

DISCUSSION

rTMS is a safe and evidence-based brain stimulation technique for patients who do not primarily respond to psychopharmacotherapy [13]. rTMS is regularly used less often than psychopharmacotherapy and even than ECT in German psychiatric hospitals (96% standard

therapy [psychopharmacotherapy] vs. 41% standard therapy [ECT] vs. 4% sometimes used [rTMS]) [7]. In the German population, ECT is generally not well known and is associated with negative attitudes [14]. Still, it is used more often than rTMS, although more negative side-effects are reported under ECT than under rTMS application [8]. In an existing report the majority of participants would prefer psychopharmacotherapy over an application of rTMS, although patients experience fewer side-effects through rTMS than through the medication [8].

In our study, we aimed to further explore the reasons for the low application rate in German psychiatric hospitals using a questionnaire assessing attitudes of patients and medical students toward rTMS. The results show that the majority of students and patients are not aware of rTMS as a psychiatric treatment for depression, with significantly more patients than students not being aware. However, participants wish to be informed in more detail about rTMS. In general, positive attitudes include the assumption of safety, while negative attitudes show concerns regarding the efficacy and a lack of trust in the method, mainly due to the fear of irreversible brain damage. Most participants would rather take psychiatric medication than rTMS. Our results could show a significant need for more information about rTMS as a psychiatric treatment for patients and medical students to fight present prejudices and negative assumptions so that this antidepressant method with fewer side effects than medication may be used more often following the guidelines.

Positive attitudes cover the assumption of safety of the method, which stands in line with the findings of multiple randomized controlled trials and meta-analyses [2, 3]. However, in general participants showed a more negative attitude toward rTMS, which contradicts the findings of Singh, Sharma [15]. Our participants stated lacking trust in the method and its efficacy and to be afraid of an application of rTMS, mainly due to irreversible brain damage. The reason might be the information deficit about rTMS as a psychiatric treatment in most participants which was likely replaced by common prejudices connected with other brain stimulation techniques such as ECT [15]. The patients in our sample have a more positive attitude towards rTMS than medical students, with significantly more assumptions about the treatment being helpful and well-tolerated than students. Our findings stand in line with a finding that patients who were treated with either sham or verum rTMS would recommend rTMS to others [10]. In their study AlHadi et al. [16] found that only 53% of the psychiatrists would agree to receive rTMS if they experienced a psychotic depressive condition, but 93%

would refer their patients for rTMS. However, they could show in their study that psychiatrists had a more positive attitude towards rTMS if they had a family member or relative who was treated with rTMS. Meta-analyses constantly concluded that a patient's experience with a brain stimulation technique (ECT) has a positive impact on attitudes toward it [9, 17]. This emphasizes the necessity of familiarity with the method and therefore a need for more detailed information for patients [14], but also medical staff in clinics [18]. Possible limitations of the study include the small number of questions within the questionnaire, the non-standardized testing conditions and the limited restricted variety in participant characteristics (only depressive patients and medical students). Therefore, the results of our study cannot be generalized to other groups without further research. Thus, future research could examine the public attitudes towards rTMS, other patient groups and medical staff.

CONCLUSION

Our results show that there is still an obvious need for more information about rTMS as a psychiatric treatment for patients and for medical students. Only a small proportion of patients and medical students is aware of rTMS as a treatment for depression and they wish to have more information about it. This mirrors existing results about a lack of public awareness of rTMS as a treatment alternative for depression. Therefore, the issue of rTMS and other brain stimulation techniques has to be covered in university lectures to expand the treatment horizon of future practitioners. Awareness of rTMS should be raised via advanced training for medical and nursing staff in hospitals, so they can offer these economical and efficient treatment options to relevant patients. Patients' doubts, prejudices and fears need to be addressed by well-informed staff or by other patients, who have already experienced rTMS.

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REFERENCES

1. Janicak PG, O'Reardon JP, Sampson SM, Husain MM, Lisanby SH, Rado JT, et al. Transcranial magnetic stimulation in the treatment of major depressive disorder: a comprehensive summary of safety experience from acute exposure, extended exposure, and during reintroduction treatment. J Clin Psychiatry. 2008; 69(2): 222-32. PMID: 18232722, DOI: 10.4088/jcp.v69n0208.
2. McClintock SM, Reti IM, Carpenter LL, McDonald WM, Dubin M, Taylor SF, et al. Consensus recommendations for the clinical application of repetitive transcranial magnetic stimulation (rTMS) in the treatment of depression. J Clin Psychiatry. 2018; 79(1). PMID: 28541649, DOI: 10.4088/JCP.16cs10905.
3. DGPPN B, KBV A. S3-Leitlinie/Nationale Versorgungsleitlinie Unipolare Depression, ed 2, 2015. 2018.
4. Lefaucheur J-P, André-Obadia N, Antal A, Ayache SS, Baeken C, Benninger DH, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). Clin Neurophysiol. 2014; 125(11): 2150-206. PMID: 25034472, DOI: 10.1016/j.clinph.2014.05.021.
5. O'Reardon JP, Solvason HB, Janicak PG, Sampson S, Isenberg KE, Nahas Z, et al. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. Biol psychiatry. 2007; 62(11): 1208-16. PMID: 17573044, DOI: 10.1016/j.biopsych.2007.01.018
6. George MS, Lisanby SH, Avery D, McDonald WM, Durkalski V, Pavlicova M, et al. Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. Arch Gen Psychiatry. 2010; 67(5): 507-16. PMID: 20439832, DOI: 10.1001/archgenpsychiatry.2010.46.
7. Blum K, Löffert S, Offermanns M, Steffen P. PSYCHiatrie Barometer Umfrage 2013. Deutsches Krankenhaus Institut Düsseldorf. 2014.
8. Walter G, Martin J, Kirkby K, Pridmore S. Transcranial magnetic stimulation: experience, knowledge and attitudes of recipients. Aust N Z J Psychiatry. 2001; 35(1): 58-61. PMID: 11270457, DOI: 10.1046/j.1440-1614.2001.00852.x.
9. Aoki Y, Yamaguchi S, Ando S, Sasaki N, Bernick PJ, Akiyama T. The experience of electroconvulsive therapy and its impact on associated stigma: a meta-analysis. Int J Soc Psychiatry. 2016; 62(8): 708-18. PMID: 27798050, DOI: 10.1177/0020764016675379.
10. Herwig U, Cardenas-Morales L, Connemann BJ, Kammer T, Schönfeldt-Lecuona C. (2010). Sham or real—Post hoc estimation of stimulation condition in a randomized transcranial magnetic stimulation trial. Neurosci Lett. 2010; 471(1): 30-33. DOI: 10.1016/j.neulet.2010.01.003
11. Arends M, Cordes J, Müller U. Einstellungen bei Patienten und in der Allgemeinbevölkerung zur repetitiven transkraniellen Magnetstimulation. Nervenheilkunde. 2006; 25(08): 674-6.
12. American Psychiatric Association (2000). Diagnostic and statistical manual of mental disorders (4th ed., Text Revision). Washington, DC; 2000.
13. Akhtar H, Bukhari F, Nazir M, Anwar MN, Shahzad A. Therapeutic efficacy of neurostimulation for depression: techniques, current modalities, and future challenges. Neurosci Bull. 2016; 32(1): 115-26. PMID: 26781880, DOI: 10.1007/s12264-015-0009-2.
14. Wilhelmy S, Rolfes V, Grözinger M, Chikere Y, Schöttle S, Groß D. Knowledge and attitudes on electroconvulsive therapy in Germany: a web based survey. Psychiatry Res. 2018; 262: 407-12. PMID: 28923432, DOI: 10.1016/j.psychres.2017.09.015.
15. Singh SM, Sharma M, Aggarwal A, Avasthi A. The knowledge, experience and attitudes of recipients of repetitive transcranial magnetic stimulation: A study from North India. Asian J Psychiatr. 2018; 31: 102-6. PMID: 29459341, DOI: 10.1016/j.ajp.2018.01.014.
16. AlHadi AN, AlShiban AM, Alomar MA, Aljadoa OF, AlSayegh AM, Jameel MA. Knowledge of and Attitude Toward Repetitive Transcranial Magnetic Stimulation Among Psychiatrists in Saudi Arabia. J ECT. 2017; 33(1): 30. PMID: 27564426, DOI: 10.1097/YCT.0000000000000349.
17. Chakrabarti S, Grover S, Rajagopal R. Electroconvulsive therapy: a review of knowledge, experience and attitudes of patients concerning the treatment. World J Biol Psychiatry. 2010; 11(3): 525-37. PMID: 20128713, DOI: 10.3109/15622970903559925.
18. Scholz-Hehn AD, Müller JC, Deml R, Methfessel I, Zilles D, Hädrich F, et al. Factors Influencing Staff's Attitude Toward Electroconvulsive Therapy: A Comparison of New Versus Experienced Electroconvulsive Therapy Clinics. J ECT. 2019; 35(2): 106-9. PMID: 30308568, DOI: 10.1097/YCT.0000000000000544.

Table 1. Distribution of answers concerning attitudes towards repetitive transcranial magnetic stimulation (rTMS) for students and patients; positive and negative answers were combined to "yes" and "no"; values do not add up to 100% due to neutral answers

Answers	Students		Patients		p
	Yes	No	Yes	No	
1. "rTMS is a efficient method."	39.5	54.7	50	43.5	0.175
2. "rTMS is a well-tolerated method."	15.1	35.8	36.1	20.5	0.003*
3. "rTMS is a safe method."	62.3	30.2	61.4	33.6	0.740
4. "rTMS treatment has few side effects."	86.8	1.9	73.0	9	0.075
5. "rTMS is a helpful treatment."	5.7	64.2	32.8	37.8	< 0.001*
6. "I am afraid of rTMS treatment."	11.3	34	18.8	41	0.154
7. "I trust in rTMS treatment."	18.9	58.5	24.6	50.8	0.592
8. "I am afraid that rTMS treatment can manipulate my brain."	22.6	35.8	26.2	44.3	0.328
9. "I am afraid that rTMS treatment can produce irreversible brain damage."	39.6	11.3	44.3	18.9	0.221
10. "I would prefer to apply rTMS rather than medication."	13.2	66.1	22.9	49.2	0.117
11. "I would apply rTMS in event of acute depression."	56.6	15.1	44.3	26.3	0.206
12. "I am aware of rTMS as a psychiatric treatment of depression."	17	83	39.3	56.6	0.002*
13. "I would like to have more information about rTMS."	49	18.9	57.4	21.4	0.249

p – value of χ^2 test;
*statistically significant

