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Letter to the Editor. Therapy of mental disorders with the use of transcranial magnetic stimulation and the limitations of the method. Commentary on the article *Transcranial magnetic stimulation (TMS) in treatment of psychiatric disorders – review of current studies*

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The article *Transcranial magnetic stimulation (TMS) in treatment of psychiatric disorders – review of current studies* by Doctor Tomasz Wieczorek et al. [1] presents to the readers of *Psychiatria Polska* the TMS method in an accessible way. Below, I refer to the issues that were presented in a debatable manner and draw attention to the matters that require analysis while developing therapies with repetitive TMS (rTMS).

The first part of the commented article concerns the description of the TMS method. Several statements contained in it regarding the operation of TMS require clarification. First, the provided description of TMS suggests that it is an influence of a magnetic field on the brain (pp. 566–567, 576). The TMS method is based on electromagnetic induction. That means TMS produces an electric field that leads to a change in the activity of nerve cells [2]. Second, the authors state that low-frequency rTMS inhibits neurons, while high-frequency excites neurons (p. 567). It is worth noting that the direction of the rTMS effect depends not only on the frequency. Even if a given rTMS protocol is employed to stimulate the same area, the effect direction is not always the same [3, 4]. The size of the effect and its direction depend, among others, on the intensity of stimulation [5], the excitability of the cortex within the stimulated area [4, 6, 7], the phases of the brain waves [8], the duration of the pro-

tocol [9], and the direction of the current flow through the coil [10, 11]. rTMS effect is influenced by the patient's activity before rTMS, during and immediately after rTMS, as well as by individual factors [12, 13]. Conclusions regarding the direction of changes in neuronal activity, derived from studies on one area of the brain, may not always be extrapolated to other areas, and conclusions from studies on healthy people do not necessarily allow predicting the effects of rTMS in patients [14]. Third, the presented definition of rTMS is narrowed down to conventional rTMS protocols and omits theta-burst stimulation (TBS), which is described as a separate TMS category (p. 567). Such a classification is inconsistent with the TMS literature, where TBS is a subtype of rTMS [15–17], which may lead to misunderstandings. Fourth, it is unfounded to claim that the TBS protocols are less demanding on the device than the conventional rTMS (p. 569). The authors argue that TBS protocols employ low intensity. A particular intensity is not a constant feature of the protocol [11, 18, 19], and TBS may overload the device more than conventional rTMS also because of the high frequency used in TBS.

The second part of the article relates to the use of rTMS in therapy. The authors inform that neurons in the right dorsolateral prefrontal cortex (DLPFC) in some patients diagnosed with depression are characterized by increased activity but decreased activity in the left (p. 568) and they refer to the assumption that in rTMS treatment the left DLPFC should be excited, while the right inhibited. It is worth noting that, paradoxically, both intermittent TBS and conventional high-frequency rTMS applied to the right DLPFC may exhibit antidepressant properties [20–22]. Moreover, the findings from neuroimaging studies do not support this assumption. It is suggested that the type of stimulation should depend on the potential lateralization of emotional processes at the individual level and factors related to the excitability and connectivity of brain networks [23]. The authors rightly highlight the importance of including control stimulation in TMS research. At the same time, it can be mentioned that the effects of rTMS therapies largely rely on non-specific factors and the placebo effect [24, 25].

The third part of the commented article deals with the safety and side effects of TMS. The authors state that the most common adverse effects of rTMS are pain or discomfort in the scalp and transient headaches after the procedure, providing values of 40% and 30%, respectively (p. 577). It is worth noting that these values apply to patients undergoing therapy for depression and the use of active rTMS [26]. There may be different estimates of the frequencies of adverse effects, depending on the group included in the study, the stimulated area, the inclusion of the placebo stimulation, the types of active TMS included, the time when the adverse effects occur, and whether the percentages relate to the number of patients or the number of TMS sessions. What is equally important, the data from the meta-analysis quoted in the commented article regarding the frequency of rTMS side effects do not constitute the average frequencies calculated based on the meta-analysis. For example, the reported 25% of rTMS-related depersonalization (p. 577) relate to three patients from one study. An additional adverse

effect that requires consideration is the possibility of obtaining neuroplasticity-like changes that are contrary to the expected ones. In some patients treated with rTMS, cases of suicidal thoughts [27–29], psychotic symptoms [30] and anxiety [31, 32] have been observed. Currently, it is difficult to assess how many such cases are the consequences of rTMS. Moreover, since the article's authors refer to the recommendation of using rTMS in the treatment of schizophrenia, despite the limited evidence of its effectiveness (p. 573) [33], the validity of this idea may be questioned. The lack of the expected rTMS effect does not indicate the absence of unwanted effects. The improvement of functioning in one area might be accompanied by a deterioration of functioning in another [34].

Another discussed issue concerns the contraindications to TMS application. They can include underage, hearing problems, psychoactive substances use, history of syncope, scalp diseases, and diseases that increase the risk of seizures. The most recent international guidelines [35] are the recommended reference point for safety issues related to TMS. At the same time, during qualification for rTMS, one can pay attention to the likelihood of the endogenous causes of disorders and, if possible, support the therapy with brain images [36], enabling precise targeting of the stimulation area and considering predictive factors [37, 38]. Moreover, the safety of rTMS operators is underinvestigated. Thus, it is suggested to limit the time spent at a distance of less than 40 cm from the coil and use hearing protection [35].

In summary, the effectiveness of rTMS depends on numerous factors, the influence of which should be taken into account in order for the results of rTMS employment to be satisfactory, minimize the occurrence of adverse effects and provide high-quality data.

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