Psychiatria Danubina, 2010; Vol. 22, Suppl. 1, pp 143–146 *Conference paper*

TREATMENT OF SHIZOPHRENIC PATIENTS AND rTMS

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SUMMARY

Introduction: *Schizophrenia (SCH) is a heterogeneous syndrome characterized by positive and negative symptoms. Despite appropriate medication, about 1/4 of patients suffer for refractory positive and/or negative symptoms, which are associated with functional handicap, increase of duration and of the number of hospitalizations. Numerous studies have suggested that the pathophysiology of auditory hallucinations (AH) is related to a hyper activity of the left temporoparietal cortex (TPC). On the other hand, negative symptoms are associated with a prefrontal hypoactivity and the efficiency of pharmacological treatments is frequently partial. Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation tool with excellent tolerability and safety. Given its hypothesized mechanisms of action and the clinical beneficial effects obtained in several types of pathology (Aleman et al. 2007), the efficacy of rTMS has been investigated for drug-resistant SCH symptoms.*

Objective: *Our objective is to expose the knowledge concerning the rTMS use in the treatment of these symptoms and to purpose a critical analysis of these data.*

Method: *a systematic review of the literature has been conducted using NIH Pubmed. The following search terms were used: TMS - rTMS - Schizophrenia - negative symptoms - hallucinations.*

Results: *Concerning the treatment of AH, 16 publications and 4 meta analyses were selected. For the negative symptoms, we retained 16 studies and 3 meta analyses. The most extensively investigated application for rTMS in SCH is the use of low-frequency stimulation to the left TPC with the aim to improve AH symptomatology. When compared to sham, this type of acute course of rTMS has been proven to induce a substantial and significant reduction in AH. But this effect does not seem long-lasting and maintenance protocols must be developed. Concerning negative symptoms, the results are less solid but we find some works which demonstrate an improvement of these symptoms while various stimulation parameters were used. Recently, new parameters of stimulation in particular the theta burst stimulation have permitted us to obtain larger effects with longer duration. The interest of these new parameters will be discussed here.*

Conclusion: *Overall, rTMS studies have demonstrated some promise in the treatment of SCH. However, more research is required to enhance rTMS efficacy and increase its beneficial effect duration and to test new therapeutic strategies in this topic.*

Key words: *rTMS - auditory hallucinations - negative symptoms - schizophrenia*

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Introduction

With a whole life prevalence of a little less than 1%, schizophrenia is a frequent and disabling pathology usually treated by pharmacological antipsychotic treatments. In spite of the efficiency of these treatments, some symptoms persist. Among positive symptoms, hallucinations (AH) and particularly hearing voices (AVH) are refractory to drug treatment in 25% of cases and negative symptoms are frequently only partly alleviated. Hence, the development of additional therapies constitutes a major step in caring for schizophrenic patients.

On a pathophysiological level, numerous studies have suggested that AH were associated with a hyperactivity of the left temporoparietal cortex (TPC) and negative symptoms with a hypoactivity of the prefrontal cortex. Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation tool with an excellent tolerability and safety profile. rTMS delivered at a 1Hz frequency (slow or low-frequency rTMS) is assumed to decrease cortical excitability In contrast, high-frequency rTMS (5-20 Hz) increases cortical excitability. During the 15 last years, given its hypothesized mechanism of action, efficacy of rTMS has been investigated for the treatment of both positive (e.g. hallucinations and delusions) and negative symptoms of schizophrenia.

Objective

Our objective is to expose the knowledge concerning rTMS use in the treatment of positive and negative symptoms of SCH and to propose a critical analysis of these data. This review summarizes the most relevant evidence in terms of efficacy and benefits effect duration according to the stimulation parameters and discusses about the progress in the particular field of new parameters of stimulation and future research in this area.

Methodology

A systematic review of the literature has been conducted using NIH Pubmed. The following search terms were used: TMS - rTMS - Schizophrenia - negative symptoms - hallucinations. The following data were analysed: number of patients - study design - parameters of treatment (frequency - technique for localisation - number of stimulations per session - rhythm of sessions). Our results are presented first in term of acute efficacy and secondly in term of maintenance protocols.

Table 1. High frequency rTMS effects on negative symptoms

Study	n subjects (frequency)	Number of pulses	Rating scales	Result
Klein (1999) (14)	31 (1Hz)	1200	PANSS HDRS	Negative
Rollnik (2000) (15)	12 (20Hz)	8 000	BPRS	Positive
Hajak (2004) (16)	20 (10Hz)	10 000	PANSS (PANSS Neg)	Positive
Jin (2006) (12)	37 (alpha TMS)	3 Hz = 1200 Alpha = 3600 20 Hz= 8000	PANSS + PANSS Neg	Positive for alpha rTMS
Goyal (2007) (17)	10 (10 Hz)	9 800	SANS HDRS	Positive
Prikryl (2007) (18)	22 (10Hz)	22 500	SANS	Positive
Holi (2004) (19)	22 (10Hz)	10 000	PANSS	Negative
Novak (2006) (20)	16 (20Hz)	12 000	PANSS	Negative
Mogg (2007)	17 (10Hz)	20 000	PANSS	Negative
Schneider (2008)	51 (1 Hz vs 10 Hz vs Placebo)	20 000	SANS	10 Hz > 1 Hz = Placebo
Cortes (2010)	35 (10 Hz)	10 000	PANSS-Neg GCI	Positive
Cohen (1999)	6 (20Hz)	8000	BPRS	Positive
Nahas (1999) (21)	8 (20 Hz)	1600	SANS	Positive
Jandl (2005) (22)	10 (10 Hz)	3500	SANS	Positive
Sachdev 2005 (23)	4 (15 Hz)	36000	PANSS	Positive

PANSS = Positive and Negative Syndrome Scale; PANSS-Neg = Negative psychopathology subscale of the Positive and Negative Syndrome Scale; SANS = Scale for Assessment of Negative Symptoms; BPRS = Brief Psychiatric Rating Scale; HDRS = Hamilton Depression Rating Scale; MDD = Patients with Majpr Depressive Disorder; SCZ = Schizophrenic patients; CGI= Clinical Global Impression

Table 2. Low frequency rTMS effects on auditory hallucinations (AH)

Study	n subjects (frequency)	Number of pulses	Rating scales	Result
Fitzgerald (2005) (24)	33 (1Hz)	9 000	PANSS AHRS	Negative
Hoffman (2003) (25)	24 (1Hz)	2 400	PANSS AHRS	Positive
Hoffman (2005) (26)	51 (1Hz)	7 290	PANSS AHRS	Positive
Vercammen 2009 (27)	38 (1Hz)	14400	PANSS AHRS	Positive Left > bilateral > Sham
Poulet (2005) (3)	10 (1Hz)	10 000	SAPS AHRS	Positive
Brunelin (2006) (4)	24 (1Hz)	10 000	AHRS	Positive
Schonfeldt-Lecuona (2004) (28)	12 (1Hz)	4 800	AHRS	Negative
Rosa (2007) (29)	11 (1Hz)	9 600	PANSS	Negative
Lee (2005) (30)	39 (1Hz)	12 000	PANSS AHRS	Positive Right = Left > Placebo
Chibbaro (2005) (31)	16 (1Hz)	3 600	SAPS AHRS	Positive

AHRS = Auditory Hallucinations Rating Scale; PANSS = Positive and Negative Syndrome Scale

Results

Concerning the treatment of AH, 16 publications and 4 meta analyses (see table 1) were selected. For the negative symptoms, we retained 16 studies and 3 meta analyses (see table 2).

In the treatment of persistent auditory hallucinations, the use of low-frequency rTMS targeting the TPC was first suggested and tested by Hoffman and colleagues (Hoffman et al. 1999). They developed extensive studies and have reported positive results in at least 5

different publications. When compared to sham, acute course of low frequency rTMS has been proven to induce a substantial and significant reduction in AH. Numerous research groups have conducted replication studies and, for example, our team published a cross over randomized study in 2005 with a positive effect for 7 patients among 10 after only a one-week treatment (Poulet et al. 2005, Brunelin et al. 2006). Reduction in AH is most often measured using the Auditory Hallucinations Rating Scale (AHRS) which is a specific scale adapted from Hoffman et al. while PANSS or SAPS do not reveal a significant effect. However, the effect described with the low frequency rTMS does not seem long-lasting (8,5 weeks on average) and maintenance protocols have been developed. We described the case of a patient for whom a protocol of treatment of two monthly sessions during the same day allowed the disappearance of AH during one year (Poulet et al. 2007). Others suggested taking back a new treatment course (10 sessions) during relapses with very interesting results (Fitzgerald et al. 2006). Others proposed a progressive spacing of the sessions with a weekly session during six weeks, followed by one session every two weeks during three months, and then a session monthly during three months (Thirthalli et al. 2008). These modalities allowed maintaining efficiency during eight months following the cure. Further studies would be needed to improve maintenance strategies.

Recently, new parameters of stimulation have been proposed. On the one hand, Dollfus et al. have published positive results from a study including 11 patients treated in an open protocol using high frequency rTMS (20Hz) (Dollfus et al. 2008). On the other hand, other teams has obtained a positive effect on AH using continuous theta burst stimulation (cTBS) (Poulet et al. 2009, Sidhoumi). Those parameters could constitute an important advance: first, in terms of the treatment duration (2 days with high 20 Hz rTMS and less than 2 minutes per session with cTBS) and second, maybe in terms of duration of the effect.

Concerning negative symptoms, the results are less robust but we found some works which demonstrate an improvement of these symptoms while using various stimulation parameters. The high-frequency stimulation of the dorsolateral prefrontal cortex (DFPLC) seems today consensual and the lateralization to the left, more adaptated to the functional neuroimaging data. The frequency of stimulation exhibiting the best clinical efficacy is 10 Hz according to the meta analyze of Freitas et al. (Freitas et al. 2009). Because alpha rhythm power is inversely correlated with the severity of the negative symptomatology, Jin et al. recommend to use a frequency adjusted to the alpha rhythm of each subject (between 8 Hz and 12 Hz) (Jin 2006). This alpha-rTMS would have a superior efficacy to the treatment using 3 Hz and 20 Hz rTMS. To increase stimulation treatment efficacy on negative symptoms we also proposed to use intermittent theta burst stimulation (iTBS) giving remarkable benefits during 6 months as published in a case report (Bor 2009).

Conclusion

The most clearly advanced application of rTMS in SCH is the treatment of refractory AH. The data supporting the use of rTMS in the treatment of negative symptoms are currently less convincing. In any case, the data we presented here open important perspectives for the use of rTMS as an additional treatment of refractory symptoms.

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