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SLOW MAGNETIC STIMULATION OF PREFRONTAL CORTEX IN DEPRESSION AND SCHIZOPHRENIA

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Abstract

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1 The authors used transcranial magnetic stimulation (TMS) of pre-frontal cortex to study mood changes in 10 depressed patients and 10 schizophrenic patients.

2 A slow rate of stimuli was used, one per 30 seconds; maximal intensity of about 2 Tesla was given for 30 stimuli, 15 on each side of the brain.

3 No side effects were seen and at least three depressed patients and two schizophrenic patients appeared to improve, at least transiently.

4 These results suggest that rapid rate TMS may not be necessary to elicit mood effects.

Keywords: depression, frontal lobe, schizophrenia, transcranial magnetic stimulation,

Abbreviations: Brief psychiatric rating scale (BPRS), diagnostic statistical manual (DSMIII-R), electroconvulsive stimulation (ECS), electro convulsive therapy (ECT), electroencephalograph (EEG), Hamilton Depression scale (HDS), Hertz (H_z), institutional review board (IRB), transcranial magnetic stimulation (TMS)

Introduction

Transcranial magnetic stimulation (TMS) of the brain is a new but widespread neurological diagnostic procedure (Hallet and Cohen, 1989). Stimulation by rapid millisecond length magnetic pulses over the motor cortex can cause muscle contraction in the contralateral arm or leg, depending on the area of motor cortex stimulated. Parkinsonian patients have been reported to show less

akinesia (enhanced reaction time) after TMS (Pascual-Leone et al., 1994a; Pascual-Leone et al., 1994b). Slow TMS was effective in a single pulse, as was rapidly repeated TMS. A preliminary trial with a single session of 30-50 single TMS stimuli of 100% intensity (≈ 2 Tesla) of 10 schizophrenic patients and 10 depressed patients over the motor cortex revealed some antidepressant effect in 3 patients and improvement in 1 chronic schizophrenic patient (Grisaru et al., 1994). Repeated daily slow TMS stimulation of motor cortex to 2 depressed patients helped one patient (Hoflich et al., 1993), and a controlled trial of low intensity vs high intensity slow TMS in 10 depressed patients treated daily for five days over the motor cortex with 250 pulses at 0.5 Hz near motor threshold revealed some clinical benefit (Kolbinger et al., 1995). More recently, George et al. (1995) and Pascual-Leone et al., (1996) have reported that rapid TMS unilaterally over left prefrontal cortex to depressed patients caused improvement in a controlled design. High frequency (10-20 Hz) and long stimulation time (20 trains of 2-10 sec each) were used but with low power (80-90% of motor threshold).

Daily TMS to rats enhances apomorphine-induced stereotypy, reverses immobility in the Porsolt swim test, and increases seizure threshold, all effects similar to ECS in rats (Fleischmann et al., 1995). Rapid TMS (25 Hz for 2 sec) has more marked effects in animal models than slow TMS (Fleischmann et al., 1994; Fleischmann et al., 1995, Fleischmann et al., 1996) but slow TMS in humans can be given at full 2-2.5 Tesla intensity, unlike rapid TMS (George et al., 1995) which cause seizures if given at full intensity and above threshold of rapidity (Pascuale-Leone et al., 1993). Thus slow TMS may have therapeutic potential and should not be ignored in favor of rapid TMS.

Since TMS over the motor cortex causes some discomforting motor movement, and since pre-frontal cortex is more often implicated in psychopathology of both depression and schizophrenia (Buchsbaum et al., 1984), the authors decided to study TMS of pre-frontal cortex in these illnesses. Some of this data has been recently reviewed (Grisaru et al., 1995).

Methods

Subjects. Ten consenting depressed patients (DSM-IIIR - Diagnostic Statistical Manual) and 10 consenting chronic schizophrenic patients (DSM-IIIR) participated after approval of the protocol by the IRB and the Ministry of Health. MAGSTIM 200 was used by an expert neurologist. Patients were evaluated with the Hamilton Depression Scale (HDS) (Hamilton, 1967) for the 10 depressed patients or Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham 1962) for the 10 schizophrenic patients before and then after 24 hr, 6 days and 28 days after a single TMS session. Ongoing antidepressant or antipsychotic treatment was not altered before TMS treatment. None of the patients had previously received TMS (Grisaru et al., 1994).

Study Procedure. Patients were given 15 stimuli over the frontal area on each side for a total of 30 stimuli in a single session. A 14 cm diameter coil was located above the orbital area on the C_3 or C_4 EEG point. Patients were given a 100% stimulus intensity, 2.5 tesla for 1 millisecond each stimulus. Stimuli were given every 30 seconds for 15 minutes. Total stimuli were 30.

Results

Tables 1 and 2 summarize the results. Among both depressed and schizophrenic patients several patients showed some improvement after the single session of TMS. Depressed patient SB reported an immediate lifting of mood within hours after TMS. His continued improvement, however, cannot be separated from concurrent antidepressant treatment. Depressed patient JR also showed an immediate lifting of mood but his continued improvement cannot be separated from concurrent antidepressant treatment. Patient DH showed increased tension and depression after the TMS session, but then improved on the standard treatment in a manner parallel to her past responses. Depressed patient MS also had an immediate lifting of mood and then continued to improve on conventional antidepressants. Depressed patient AT had three previous psychotic depressions that responded slowly to imipramine plus haloperidol. After TMS he appeared to improve more rapidly than in the past and was transferred the next day to an open ward. Patient JW had not responded to two weeks of standard antidepressants in a closed ward but seemed to respond rapidly after TMS. Patient PB showed increased tension and crying after TMS, and CB, ZK and RG had no response whatsoever.

Table 1
HDS after TMS in Depression

Name	Age	Sex	DX	Before	2 hrs after	7 days after	28 days after
SB	33	M	BP, dep	32	18	24	7
JR	27	M	UP	18	4	9	1
DH	36	F	SA, dep	30	35	28	12
MS	40	F	UP	18	2	8	20
AT	37	M	PD	31	22	20	17
CB	49	M	BP, dep	22	18	28	26
JW	42	M	PD	35	21	33	15
ZK	53	F	PD	44	43	41	40
RG	40	F	BP, dep	35	31	32	27
PB	37	F	UP	12	11	12	---

BP = bipolar; PD = psychotic depression; SA = schizoaffective, UP = unipolar

Schizophrenic patient AS had mood lifting after TMS but no lasting effect. Schizophrenic patient MJ had no immediate effect and some later improvement appeared consistent with his usual course of

illness. IZ had a marked temporary improvement the day after TMS and then rapid relapse; OZ reacted similarly. Patient LD after TMS improved rapidly concurrently with clozapine treatment despite a previous slow response to clozapine. Other schizophrenic patients showed no response to TMS.

Table 2
BPRS after TMS in Schizophrenia

Name	Age	Sex	DX	Before	24 hrs after	7 days after	28 days after
SJ	38	M	schiz	38	35	37	37
MJ	28	M	schiz	62	62	55	46
AS	39	M	schiz	52	34	46	36
IZ	31	M	schiz	49	35	42	39
SH	30	M	schiz	57	51	50	55
OZ	34	M	schiz	49	33	43	39
OB	43	F	schiz	71	71	70	---
SJ	35	M	schiz	57	53	54	40
LD	33	M	schz	57	45	34	39
EB	41	F	schiz	43	40	41	---

Discussion

This uncontrolled study cannot prove antidepressant or antischizophrenic efficacy of frontal lobe magnetic stimulation. A striking immediate lifting of mood for several hours was noted in many patients. No serious negative side effects were observed, and results appear comparable to that of motor cortex TMS (Grisaru et al., 1994; Hoflich et al., 1993; Koblinger et al., 1995) with the advantage that there is no motor discomfort. It is often emphasized that ECT requires convulsion for clinical efficacy (Potter and Rudofer, 1993). However, magnetic stimulation is more penetrating than electrical stimulation and may cause neuronal depolarization in critical brain structures without causing convulsion (Hallet and Cohen, 1989). The early history of ECT required numerous trials before the present variants of electrode placement became accepted, and TMS research is at a very early stage. Recent controlled studies in depression suggests that rapid TMS over left cortex induces a mood elevation but rapid TMS over right cortex does not (George et al., 1995; Pascual-Leone et al., 1996); this laterality will have to be studied in future clinical research. Studies of rapid TMS are usually limited to 80% of motor threshold or roughly 50% of machine intensity. The present study of slow TMS provides preliminary data on high intensity (100% machine power) TMS to frontal cortex.

Conclusion

Comparison of effects of slow TMS, as in the present study where a 100% intensity stimulus was given every 30 seconds, with rapid TMS, as in the study of George et al. (1995) where a 80% of motor threshold stimulus was given 20 times per second, will require empirical studies in the future.

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References

BUCHSBAUM MD, DELISI LE, HOLCOMB HH, CAPPELLETTI J, KING AC, JOHNSON J, HAZLETT E, DOWLING-ZIMMERMAN S, POST RM, MORIHISA J, CARPENTER W, COHEN R, PICKAR D, WEINBERGER DR, MARGOLIN R, KESSLER RM (1984). Anteroposterior gradients in cerebral glucose use in schizophrenia and affective disorders. *Arch Gen Psychiatry* **4**: 1159-1166.

FLEISCHMANN A, PROLOV K, ABARBANEL J and BELMAKER RH (1995). The effect of transcranial magnetic stimulation of rat brain on behavioral models of depression. *Brain Research* **699**: 130-132.

FLEISCHMANN A, STEPPEL J, LEON A and BELMAKER RH (1994). The effect of transcranial magnetic stimulation compared with electroconvulsive shock on rat apomorphine-induced stereotypy. *Euro Neuropsychopharmacol* **4**: 449-450.

FLEISCHMANN A, TALPALAR AE, GROSSMAN Y, SILVERBERG D and BELMAKER RH (1996). Antidepressant potential of transcranial magnetic stimulation in rat models: comparison of slow versus rapid magnetic stimulation. In: Montgomery S and Halbreich U (eds) Pharmacotherapy of Mood and Cognition. American Psychiatric Press. (In press).

GEORGE MS, WASSERMAN EM, WILLIAMS WA, CALLAHAN A, KETTER TA, BASSER P, HALLET M and POST RM (1995). Daily repetitive transcranial magnetic stimulation (rTMS) improves mood in depression. *NeuroReport* **6**: 14.

GRISARU N, ABARBANEL JM and BELMAKER RH (1995). Slow magnetic stimulation of motor cortex and frontal lobe in depression and schizophrenia. *Acta Neuropsychiatrica* (special issue). **7**: S21-S23.

GRISARU N, YAROSLAVSKY U, ABARBANEL J, LAMBERG T and BELMAKER RH (1994). Transcranial magnetic stimulation in depression and schizophrenia. *European Neuropsychopharmacology* **4**: 287-288.

HALLET M and COHEN LG (1989). Magnetism: A new method for stimulation of nerve and brain. *JAMA* **262**: 538-54.

HAMILTON M (1967). Development of a rating scale for primary depressive illness. *Br J Soc Clin Psychol* 6: 278-296.

HOFLICH G, KASPER S, HUFNAGEL A, RUHRMANN S and MOLLER HJ (1993). Application of transcranial magnetic stimulation in treatment of drug-resistant major depression - a report of two cases. *Human Psychopharmacol* **8**: 361-365.

KOLBINGER HM, HOFLICH G, HUFNAGEL A, MOLLER HJ and KASPER S (1995). Transcranial magnetic stimulation (TMS) in the treatment of major depression - a pilot study. *Human Psychopharmacology* **10**: 305-310.

OVERALL JE and GORHAM DR (1962). The brief psychiatric rating scale. *Psychol Rep* 10: 799-812.

PASCUAL-LEONE A, HOUSER CM, REESE K, SHOTLAND LI, GRAFMAN J, SATO S, VALLS-SOLE J, BRASIL-NETO JP, WASSERMANN EM, COHEN LG and HALLETT M (1993). *Electroencephalo Clin Neurophysiol* **89**: 120-130.

PASCUAL-LEONE A, RUBIO B, PALLARDO F and CATALA MD (1996). Beneficial effect of rapid-rate transcranial magnetic stimulation of the left dorsolateral prefrontal cortex in drug-resistant depression. *Lancet* **348**: 223-237.

PASCUAL-LEONE A, VALLS SOLE J, BRASIL NETO JP, CAMMAROTA A, GRAFMAN J and HALLET M (1994b). Akinesia in Parkinson's disease, part 2: Effects of subthreshold repetitive transcranial motor cortex stimulation. *Neurology* **44**: 892-898.

PASCUAL-LEONE A, VALLS SOLE J, BRASIL NETO JP, COHEN LG and HALLET M (1994a). Akinesia in Parkinson's disease, part 1: Shortening of simple reaction time with focal, single-pulse TMS. *Neurology* **44**: 884-891.

POTTER WZ, AND RUDORFER MV (1993). Electroconvulsive therapy-A modern medical procedure. *N Eng J Med* **328**: 882-883.

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