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Effect of Chronic Repetitive Transcranial Magnetic Stimulation on Regional Cerebral Blood Flow and Regional Cerebral Glucose Uptake in Drug Treatment-Resistant Depressives

A Brief Report

Andreas Conca[a] William Peschina[b] Peter König[a] Heinz Fritzsche[b] Armand Hausmann[c]

[a]Department of Psychiatry I, Regional Hospital of Rankweil, [b]Department of Nuclear Medicine, Hospital of Feldkirch, [c]Department of Psychiatry, University Clinic of Innsbruck, Austria

Key Words

Repetitive transcranial magnetic stimulation · SPECT · Cerebral blood flow · Cerebral glucose metabolism · Major depression

Abstract

Brain imaging studies have shown that repetitive transcranial magnetic stimulation (rTMS) is biologically active. The aim of the present study was to investigate the patterns of the regional cerebral glucose uptake rate (rCMRGlu) and regional ^{99m}Tc HMPAO uptake rate (regional cerebral blood flow; rCBF) during a series of therapeutic rTMS sessions at low frequency. Four drug-resistant depressed patients underwent 10 rTMS sessions as an add-on measure over 14 days. One day before and 1 day after the TMS series, 511-keV SPECT with simultaneous ^{18}F-fluorodeoxyglucose and ^{99m}Tc HMPAO measurements were carried out. All patients showed a good clinical outcome. Statistically significant common changes in rCBF and rCMRGlu patterns were found in the upper frontal regions bilaterally in terms of increased uptake rates and in the left orbitofrontal cortex in terms of decreased uptake rates of both isotopes compared to controls. However, the lateralization patterns of rCBF and rCMRGlu after rTMS treatment revealed marked differences. Thus, although no relevant changes in lateralization of the glucose uptake were observed, a clear right-sided preponderance of rCBF also in areas remote from the stimulation site was described. Therapeutic rTMS seems to influence distinct cortical regions, affecting rCBF and rCMRGlu in a homogeneous manner as well as in different ways, which are probably region dependent and illness related. The role of the stimulation coil placement site should be taken into account.

Introduction

Brain imaging studies have shown that repetitive transcranial magnetic stimulation (rTMS) is biologically active, both locally in tissue under the coil and also in remote sites, presumably through transsynaptic connec-

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Andreas Conca, MD
Department of Psychiatry
LKH-Rankweil
A–6830 Rankweil (Austria)
Tel. +43 5522 403, Fax +43 5522 403 355, E-Mail andreas.conca@lkhr.at

tions [1]. Thus, TMS at a low frequency and during acute administration reduces brain glucose metabolism globally as well as in subcortical regions [2], but also at a high frequency, TMS decreases perfusion locally and in remote areas [3]. In contrast, TMS causes a relative increase in perfusion in remote cortical and subcortical regions in a dose-dependent manner [3]. George et al. [4] found that after chronic administration, TMS at a high frequency increased brain glucose utilization globally and in areas remote from the stimulation site. To our knowledge, only one further treatment-SPECT scan study has been performed showing that TMS at a high frequency dissolved the negative baseline correlations between the severity of depression and limbic and prefrontal blood flow [5]. Examinations of blood flow and glucose metabolism in the depressed and recovered state after different somatic treatments revealed conflicting results. Thus, Wu et al. [6] hypothesized that sleep deprivation acts to reverse an abnormal metabolic overactivation in the limbic system. In contrast, Nobler et al. [7] found that electroconvulsive therapy and antidepressants may further affect regions that were abnormal at baseline – not, as may be expected, in the direction of normalization, but toward accentuated abnormality. Buchsbaum et al. [8] showed that treatment with sertraline, a selective serotonin reuptake inhibitor, normalized the metabolic rate by increasing and decreasing the uptake ratio in marked regions. The discrepancies of these findings are apparent. Methodological and technical differences, subsets of depressive disorders, pretreatment conditions, age and sex might influence the results [9]. The aim of the present study was to investigate the patterns of the regional cerebral glucose uptake rate (rCMRGlu) and regional ^{99m}Tc HMPAO uptake rate (regional cerebral blood flow; rCBF) simultaneously following a series of rTMS sessions at low frequency as an antidepressant augmentation strategy [10]. ^{99m}Tc HMPAO uptake is assumed to be proportional to the rCBF corresponding to neural activities [11], whereas ^{18}F-fluorodeoxyglucose (FDG) uptake correlates with rCMRGlu, which might reflect glial activities [12].

Patients and Methods

Patients

After approval by the local ethics committee and after receiving the patients' written informed consent, 4 depressed (3 males), aging (41.5 ± 13.7 years), right-handed, medicated inpatients were recruited. Patients were classified into stages of treatment resistance using the classification of Thase and Rush [13]; thus, all patients are labeled at least on level three. They underwent an rTMS procedure for 10 sessions, their last medication remaining unchanged. Neurological, physical and laboratory examinations were all within normal limits. As controls, 4 healthy probands matched in age (41.75 ± 16.8 years), sex and handedness were examined.

TMS Protocol

We used the commercially available Dantec 16EO5 magnetic stimulator. In each of the stimulations, TMS was applied with a circular coil over Cz (EEG 10/20 system), at 0.25 Hz, using an intensity of 80% of the maximum output (25–30% above the motor threshold of musculi abductor digiti minimi). By clockwise and counterclockwise stimulation, the left and right hemispheres were activated separately, each with a duration of 152 s (760 stimuli in total) [10, 14].

SPECT Procedure and Semiquantitative Evaluation

One day before the TMS sessions were started and 1 day after TMS was discontinued, SPECT with simultaneous ^{18}F-FDG and ^{99m}Tc HMPAO measurements was carried out. After reaching a blood glucose level of 70–100 mg%, all subjects received 750–1,100 MBq of ^{99m}Tc HMPAO and 300–550 MBq of ^{18}F-FDG intravenously and were examined in a supine position with their eyes closed and the ears unplugged. A conventional dual-head gamma camera with high-energy 511-keV collimators was used [15, 16]. Three energy windows were used for acquisition: the ^{18}F-FDG photo peak was registered at 511 keV, the ^{99m}Tc photo peak at 141 keV and Compton scatter at 170 keV. Both heads rotate 180 degrees in 6-degree steps with an acquisition time of 70 s per image. The 511-keV images were decay corrected, then the 170-keV images were subtracted from the 141-keV images, thus correcting for Compton scatter. After reconstruction and simultaneous reorientation of both studies, four summation slices for semiquantitative evaluation were processed. A standardized region overlay was semiautomatically applied. For each region of interest, the percentage of deviation of the regional mean of counts from the mean of counts of all regions was calculated. These figures (^{18}F-FDG and ^{99m}Tc HMPAO indices) were used for the statistical analyses. rCBF and rCMRGlu values were also analyzed interhemispherically by calculating the lateralization index as a percentage using the following formula: $(R + L/R - L) \times 100$.

Statistical Analyses

Uptake ratios are presented as mean values ± SD. Because of the small sample size within each group and the different sex distribution, the nonparametric Kruskal-Wallis H test comparing the uptake indices of the three groups was performed; p values corrected for ties <0.05 were considered as significant. Uptake ratios in individual patients before and after the TMS treatment were analyzed by ANOVA (repeated measure). Bonferroni correction was used to adjust the significance level; thus, the level $\alpha \leq 0.02$ was accepted as significant [17].

Results

With respect to the clinical response, all patients showed a suppression of their episode and were discharged with the identical medication as before the TMS treatment.

Changes in regional ^{18}F-FDG and regional ^{99m}Tc HMPAO uptake rates are shown in tables 1 and 2.

Table 1. Changes in regional ^{18}F-FDG uptake rates

Region of interest	Pre-TMS indices, % (n = 4)	Post-TMS indices, % (n = 4)	ANOVA (repeated measure) pre-TMS vs. post-TMS	Control indices, % (n = 4)	Kruskal-Wallis (within groups)
G. temporalis inf. R	94.5 ± 4.9	92.5 ± 8.3	F = 0.15; n.s.	93 ± 8.8	H = 0.47; n.s.
G. temporalis inf. L	96.5 ± 4.2	95 ± 6.2	F = 0.12; n.s.	99 ± 5.5	H = 0.82; n.s.
Hippocampus R	91 ± 5.1	89.5 ± 8.9	F = 0.18; n.s.	102.5 ± 2.9	H = 5.69; n.s.
Hippocampus L	92 ± 6.4	87.25 ± 6.2	F = 2.86; n.s.	95.5 ± 4.4	H = 2.69; n.s.
Thalamus R	106 ± 2.9	101.5 ± 8.4	F = 0.93; n.s.	109.25 ± 10.2	H = 2.39; n.s.
Thalamus L	106 ± 8.4	106.25 ± 6.9	F = 0.00; n.s.	105.25 ± 10.0	H = 0.16; n.s.
Basal ganglia R	105 ± 4.8	99.25 ± 11.2	F = 0.71; n.s.	109.25 ± 3.4	H = 1.97; n.s.
Basal ganglia L	109 ± 10.2	100.25 ± 4.6	F = 3.08; n.s.	109.75 ± 3.8	H = 4.80; n.s.
G. occipitalis inf. R	114 ± 12.6	110.25 ± 9.5	F = 2.26; n.s.	110.75 ± 9.3	H = 0.13; n.s.
G. occipitalis inf. L	115.75 ± 7.1	109.5 ± 9.5	F = 9.24; n.s.	106 ± 9.0	H = 2.44; n.s.
G. temporalis sup. R	102.75 ± 2.2	99.75 ± 6.3	F = 1.32; n.s.	98 ± 4.5	H = 1.39; n.s.
G. temporalis sup. L	103.5 ± 1.2	100.5 ± 4.0	F = 2.50; n.s.	107.75 ± 7.7	H = 3.21; n.s.
G. orbitofrontalis R	96.75 ± 3.9	94.75 ± 1.7	F = 1.26; n.s.	101.5 ± 2.1	H = 6.09; $p < 0.05$[1]
G. orbitofrontalis L	99.5 ± 2.5	93.25 ± 2.1	F = 31.78; $p < 0.02$	102.75 ± 5.4	H = 7.94; $p < 0.02$[1]
G. frontalis sup3. R	97.25 ± 7.5	97.75 ± 6.9	F = 3; n.s.	104.5 ± 3.5	H = 3.59; n.s.
G. frontalis sup3. L	100.25 ± 10.9	96.25 ± 7.2	F = 2.01; n.s.	107 ± 5.0	H = 3.53; n.s.
G. frontalis sup2. R	90.75 ± 2.6	95.75 ± 3.0	F = 4.29; n.s.	93.25 ± 9.3	H = 2.1; n.s.
G. frontalis sup2. L	90.25 ± 1.3	94.25 ± 5.1	F = 2.67; n.s.	91.25 ± 10.5	H = 1.5; n.s.
G. frontalis med. R	94.25 ± 2.4	97 ± 3.6	F = 13.44; n.s.	102 ± 2.3	H = 6.54; $p < 0.04$[2]
G. frontalis med. L	94 ± 1.8	96.5 ± 1	F = 8.33; n.s.	101.5 ± 3.8	H = 7.59; $p < 0.03$[2]
G. centralis 2 R	91.25 ± 2.2	96.5 ± 2.9	F = 9.52; n.s.	95.25 ± 7.6	H = 3.58; n.s.
G. centralis 2 L	93 ± 2.6	100 ± 5.9	F = 3.16; n.s.	98.25 ± 2.5	H = 5.34; n.s.
G. parietalis inf. R	100.5 ± 5.7	103 ± 1.4	F = 0.50; n.s.	93.25 ± 9.6	H = 4.35; n.s.
G. parietalis inf. L	96.25 ± 2.5	95.75 ± 2.5	F = 0.06; n.s.	102.5 ± 5.4	H = 4.3; n.s.
G. occipitalis sup. R	123.25 ± 14.4	118.25 ± 7.9	F = 0.29; n.s.	111 ± 5.7	H = 1.51; n.s.
G. occipitalis sup. L	119.75 ± 10.1	120.75 ± 10.7	F = 0.02; n.s.	104 ± 5.4	H = 3.19; n.s.
Suppl. motor area R	95.75 ± 3.9	101.5 ± 2.5	F = 11.42; n.s.	86 ± 9.13	H = 7.50; $p < 0.03$[1]
Suppl. motor area L	92.5 ± 5.1	99.25 ± 2.1	F = 4.06; n.s.	81.75 ± 11.0	H = 6.52; $p < 0.04$[1]
Primary motor area R	90.25 ± 3.3	97.5 ± 1.3	F = 21.94; $p < 0.02$	87.5 ± 5.5	H = 7.65; $p < 0.03$[1]
Primary motor area L	90.25 ± 3.7	95 ± 4.9	F = 13.05; n.s.	83.25 ± 7.4	H = 5.15; n.s.
Somatosensory area R	110.25 ± 2.9	113.75 ± 2.5	F = 3.27; n.s.	98 ± 10.0	H = 7.82; $p < 0.02$[1]
Somatosensory area L	106.75 ± 4.7	110.5 ± 2.9	F = 9; n.s.	100.5 ± 8.9	H = 4.63; n.s.

Values are mean ± SD. n.s. = Not significant.
[1] Controls versus post-TMS (subtest of Kruskal-Wallis).
[2] Controls versus pre-TMS (subtest of Kruskal-Wallis).

The lateralization indices for ^{99m}Tc HMPAO and ^{18}F-FDG uptake revealed changes only in rCBF after rTMS treatment, indicating a marked right-sided preponderance also in remote brain structures such as the hippocampal region; thus, the lateralization index in controls (−0.2) and prior to treatment (−1.1) changed to a lateralization index of +1.7 at the end of rTMS therapy.

Discussion

Despite the consistent limitations within intrinsic technical areas of the SPECT studies, brain imaging procedures contribute essentially to our understanding of brain function and the impact of treatment strategies on cerebral activities [9]. Comparing the patients' ^{99m}Tc HMPAO and ^{18}F-FDG uptake ratios at baseline with the control values, only a moderate hypofrontality [9] was observed in ^{18}F-FDG uptake in the gyri frontales me-

Table 2. Changes in regional ^{99m}Tc HMPAO uptake rates

Region of interest	Pre-TMS indices, % (n = 4)	Post-TMS indices, % (n = 4)	ANOVA (repeated measure) pre-TMS vs. post-TMS	Control indices, % (n = 4)	Kruskal-Wallis (within groups)
G. temporalis inf. R	91 ± 5.1	95.75 ± 7.8	F = 2.3; n.s.	97.25 ± 4.4	H = 0.087; n.s.
G. temporalis inf. L	93.5 ± 4.4	94.5 ± 3.1	F = 0.74; n.s.	100 ± 4.7	H = 3.988; n.s.
Hippocampus R	96.75 ± 1.7	100 ± 7.7	F = 0.725; n.s.	100.5 ± 4.7	H = 1.467; n.s.
Hippocampus L	98.25 ± 4.0	94.75 ± 9.3	F = 0.703; n.s.	98.5 ± 1	H = 0.01; n.s.
Thalamus R	117 ± 3.56	119.25 ± 18.9	F = 0.05; n.s.	107.5 ± 10.5	H = 2; n.s.
Thalamus L	113.5 ± 7.32	117.75 ± 15.2	F = 0.161; n.s.	110.5 ± 11.3	H = 0.184; n.s.
Basal ganglia R	110 ± 4.32	105.5 ± 10.8	F = 0.739; n.s.	110.75 ± 12.8	H = 0.762; n.s.
Basal ganglia L	108.75 ± 6.5	110 ± 6.5	F = 0.061; n.s.	110.5 ± 2.1	H = 0.127; n.s.
G. occipitalis inf. R	118 ± 8.37	108 ± 11.4	F = 30; $p < 0.01$	116 ± 8.2	H = 1.423; n.s.
G. occipitalis inf. L	118.25 ± 7.93	108.25 ± 9.7	F = 28.571; $p < 0.02$	105.75 ± 14.8	H = 2.672; n.s.
G. temporalis sup. R	105 ± 4.55	99.25 ± 7.9	F = 2.779; n.s.	99.25 ± 7.3	H = 1.511; n.s.
G. temporalis sup. L	102 ± 5.77	95.5 ± 7.14	F = 4.333; n.s.	104.75 ± 4.2	H = 3.64; n.s.
G. orbitofrontalis R	97 ± 3.46	95 ± 6.1	F = 0.558; n.s.	99.75 ± 3.0	H = 1.933; n.s.
G. orbitofrontalis L	97 ± 2.3	91.75 ± 3.3	F = 7.391; n.s.	100.5 ± 4.2	H = 6.146; $p < 0.05$[1]
G. frontalis sup3. R	96 ± 5.8	96.25 ± 6.1	F = 0.024; n.s.	100 ± 6.7	H = 1.37; n.s.
G. frontalis sup3. L	99.75 ± 11.0	91.5 ± 6.9	F = 7.116; n.s.	100.75 ± 6.1	H = 3.254; n.s.
G. frontalis sup2. R	90.25 ± 4.9	97.25 ± 4.9	F = 3.585; n.s.	92.5 ± 8.5	H = 2.92; n.s.
G. frontalis sup2. L	91.5 ± 3.7	92.75 ± 4.1	F = 0.904; n.s.	91.75 ± 7.3	H = 0.304; n.s.
G. frontalis med. R	94 ± 5.0	98.25 ± 4.3	F = 5.594; n.s.	96.75 ± 7.7	H = 1.225; n.s.
G. frontalis med. L	91 ± 1.8	93 ± 3.7	F = 1.846; n.s.	99.25 ± 5.4	H = 4.832; n.s.
G. centralis 2 R	96.5 ± 1.3	98 ± 3.6	F = 0.931; n.s.	98.25 ± 8.8	H = 0.556; n.s.
G. centralis 2 L	91.75 ± 5.0	96.25 ± 5.2	F = 18.692; $p < 0.03$	100 ± 5.1	H = 4.371; n.s.
G. parietalis inf. R	9.25 ± 3.8	97.25 ± 7.1	F = 0.982; n.s.	95 ± 9.4	H = 1.145; n.s.
G. parietalis inf. L	93 ± 6.1	91 ± 14.0	F = 0.174; n.s.	100.5 ± 3.3	H = 2.711; n.s.
G. occipitalis sup. R	107 ± 8.4	102.75 ± 11.7	F = 0.248; n.s.	104 ± 5.4	H = 1.341; n.s.
G. occipitalis sup. L	106.5 ± 7.6	106 ± 9.8	F = 0.005; n.s.	105.5 ± 4.0	H = 0.185; n.s.
Suppl. motor area R	96.25 ± 3.3	105.5 ± 4.7	F = 38.383; $p < 0.01$	88 ± 4.2	H = 9.302; $p < 0.01$[1]
Suppl. motor area L	92 ± 3.8	100.75 ± 1.5	F = 17.417; $p < 0.03$	84 ± 6.7	H = 8.435; $p < 0.02$[1]
Primary motor area R	96 ± 6.5	105.5 ± 6.6	F = 38.383; $p < 0.01$	95.5 ± 4.2	H = 5.712; n.s.
Primary motor area L	92.75 ± 3.8	96.75 ± 5.3	F = 4.8; n.s.	94.75 ± 5.7	H = 1.188; n.s.
Somatosensory area R	101.75 ± 4.4	104.75 ± 7.7	F = 0.406; n.s.	94.5 ± 8.9	H = 2.577; n.s.
Somatosensory area L	9.5 ± 6.3	100.5 ± 5.8	F = 0.353; n.s.	99 ± 7.4	H = 0.01; n.s.

Values are mean ± SD. n.s. = Not significant.

[1] Controls versus post-TMS (subtest of Kruskal-Wallis).

diales bilaterally, which disappeared after TMS treatment. This pattern of cerebral metabolism is in accordance with studies reporting that normalized values correlate with a good clinical outcome [4, 8, 9], but contrasts with recently published results suggesting that the antidepressant response to rTMS might vary as a function of stimulation frequency and may depend on pretreatment cerebral metabolism. Thus, the better response to 20-Hz rTMS was associated with greater baseline global hypometabolism. Conversely, for 1-Hz treatment, the response tended to be associated with global hypermetabolism [2]. We did not find further significant differences for the activities of either tracer comparing the patients in a depressed state and the controls. This metabolic pattern might reflect the influence of previous and current drug trials. However, our findings revealed significant differences in regional tracer uptake between patients in remission and controls. Thus, in patients in remission, the glucose utilization increased significantly close to the coil placement in bilateral prefrontal regions and right-sided

sensomotoric regions, though a decrease in glucose uptake in both gyri frontales inferiores remote from the coil placement site was observed. ^{99m}Tc HMPAO activities showed a similar pattern, but involved only the bilateral prefrontal regions and the left gyrus frontalis inferior, similar to electroconvulsive therapy action [7]. Additionally, a clear right-sided preponderance of rCBF was observed. This phenomenon may support the hypothesis that TMS also affects cortical and subcortical areas remote from the stimulation site, presumably through transsynaptic connections [1–4]. In individual patients, the ^{99m}Tc HMPAO activities before and after the rTMS treatment were decreased in the inferior part of the visual cortices (areas 17 and 18). This observation corresponds partially to the findings indicating that sertraline medication in responders decreases the uptake ratio in the right occipital area 19 toward normalization [8]. Our findings suggest that chronic rTMS at a low frequency induced significantly higher ^{99m}Tc HMPAO activities under the coil stimulation site (left lateral premotor cortex, both supplementary motor areas and the right primary motor cortex) comparable to the effects of acute TMS [18]. Furthermore, the pattern of both tracers within patients indicates that rTMS at a low frequency as an augmentation therapy modulates neuronal and glial cell metabolism in a selective and region-dependent manner.

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