Transcranial magnetic stimulation in anxiety disorders

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ABSTRACT

rTMS is a recently introduced method capable of altering cortical excitability beyond the time of stimulation. It has been employed in several psychiatric disorders with variable degrees of efficacy. In this study 28 patients with anxiety disorders, with inadequate response to oral medications, and 12 normal controls were included. Among the patient group, twenty two continued the study. So we ended up by 34 subjects divided into three groups: The ***first group*** *was subjected to rTMS and consisted of 12 patients (8 females and 4 males , age range 22-35yrs) with anxiety disorder: 8 with generalized anxiety disorder, 3 with panic disorder and 1 with generalized anxiety disorder and panic attacks. A* ***second group*** *of 10 patients: 7 with generalized anxiety disorder and 3 with panic disorder was sham- treated. All patients fulfilled the ICD –10 symptom check list criteria. Hamilton anxiety rating scale HARS was applied to all patients before starting and after finishing the rTMS sessions. A* ***third group*** *of normal 12 age-matched controls was studied for determination of cortical motor threshold and MEP amplitude.* ***TMS procedure:*** *Determination of the cortical motor threshold (CMT) to all three groups. rTMS technique was applied for patient group 1 only. Sham stimulation was done to patient group 2.* ***Results:*** *The treatment was generally tolerated with no serious side effects.* ***Cortical motor threshold and amplitude: (CMT & CMA)*** *CMT was lower in the patient groups ranging from 25-55% of the output stimulus intensity (mean 46.15%) as compared to the control group ranging from 50-85% (mean 68.3%), which showed statistical significance (p: 0.00004). The mean amplitude of the motor evoked response was higher in the patient group (1507.1uv) than the control group (1179.5 uv) , however not reaching statistical significance. Hamilton Anxiety Rating Scale (HARS) was applied to all participants prior to treatment sessions and after the last session. First group (real treated): showed statistically significant improvement on the HARS, while the sham-treated group showed non significant improvement. Mean duration of improvement lasted for 4 weeks ± 6 days.* ***Conclusion:*** *Patients with generalized anxiety disorder and panic disorder showed an increased cortical excitability than normal controls. Patients receiving real rTMS showed significant and lasting improvement than those who were sham-treated.* ***(Egypt J. Neurol. Psychiat. Neurosurg., 2004, 41(2): 423-431).***

INTRODUCTION

Anxiety disorders are the most common psychiatric disorders, found in 10-30% of the general population. Anxiety disorders can be subdivided into several types based on clinical characteristics and response to psychopharmacologic agents. These major categories include panic disorder, post-traumatic stress disorder, generalized anxiety disorder, social phobia, and obsessive compulsive disorder.[1]

The emotional experiences that we perceive as fear, anger, and contentment reflect an interplay between higher brain centres and subcortical regions such as the hypothalamus and the amygdala. This is illustrated in patients in whom the prefrontal cortex or the cingulated gyrus has been removed. These patients are no longer bothered by pain as a sensation, they exhibit appropriate autonomic reactions, but the sensation is not felt as a powerful unpleasant experience.[2]

Thus, noxious and pleasurable stimuli have dual effects. First, they trigger autonomic and endocrine responses, integrated by subcortical structures, that immediately alter internal states, thereby preparing the organism for attack, flight, sex, or other adaptive behaviours. These behaviours are relatively simple to execute and require no conscious control. Thereafter, a second set of mechanisms come into play, involving the cerebral cortex. Cortical processing of emotionally significant stimuli results in a conscious experience of emotion as well as in signals to lower centres that can suppress or enhance the somatic manifestations of emotions.[3]

Many aspects of our primary emotional responses are learned, and during this learning visceral feedback probably has an important role. But with experience we depend increasingly on cognition to evaluate the significance of our environment, while visceral sensations probably play a less important role.[2] The anatomical connections of the amygdala with the temporal (cingulate gyrus) and frontal (prefrontal) association cortices provide the means by which visceral sensations trigger a rich assortment of associations and narratives, which represent the cognitive interpretation of emotional states.[1]

Antonio Damasio has suggested that when we think about the potential consequences of a behaviour the memory of our emotional state (visceral experiences) in similar circumstances may provide useful information for evaluating the behaviour. The memory may activate ascending noradrenergic and cholinergic projections of the brain stem and basal forebrain, thereby activating the cortex and replicating the conscious sensations of the remembered emotional state, bypassing the feedback of the autonomic nervous system. This may be the basis of what we refer to as "gut feelings".[2]

The right hemisphere plays a major role in this aspect as its structural organization might account for its crucial role in emotional experience; in addition to the greater contiguity and interconnectivity of units involved in different aspects of information processing, the right hemisphere also shows a greater density of connections with the limbic system and, therefore, is better equipped for emotional processes that require the ability to integrate external and internal information into a unified percept.[3]

The lateralization patterns of neuromodulator projection systems have shown that the noradrenergic projection system is under greater control of the right hemisphere, while the dopaminergic system seems under control of the left hemisphere. As a consequence, the right hemisphere is involved in phasic arousal, while the left hemisphere is involved in tonic arousal. Increased left hemisphere activation may result in anxiety or hostility states, while increased right hemisphere activation may result in states of mood elation. The concept of increased/decreased activation is generally a relative one; in laterality studies, increased left activation implies decreased right activation, which means that either primary left hyperactivation or right hypoactivation may result in anxiety states.[4]

In panic disorder the majority of investigations reporting laterality findings indicate that temporolimbic circuits of the right hemisphere and regions functionally connected to them might be more involved than the homologous regions of the left hemisphere; however it remains controversial whether the pathogenesis of panic disorder involves a reduced or an increased activity of these right hemisphere regions. A right hemisphere overactivity is mainly supported by functional imaging studies as increased blood flow in the temporal cortex during the attacks and increased activity in the right prefrontal cortex between attacks.[5,6,7]

rTMS: (repetitive transcranial magnetic stimulation)

TMS facilitates non invasive stimulation of the cerebral cortex. The development of stimulators capable of discharging at different rates has expanded the applications of TMS in cognitive and behavioural sciences. Depending on the stimulation frequency, intensity and duration rTMS can transiently inhibit or facilitate the function of the cortical region.

Hypothesis:

Guided by these basic mechanisms which underlie anxiety disorders, we can postulate that modulation of cortical excitability might affect anxiety, rTMS could be one method of modulating cortical excitability. In a previous research employing rTMS in obsessive compulsive disorder, the first symptom to improve was anxiety[8], and this supports the hypothesis of the current study.

Aim of the work:

1. To study the state of cortical excitability in patients suffering from anxiety disorders.
2. To test the efficacy of repetitive transcranial magnetic stimulation in amelioration of symptoms in anxiety disorders.

MATERIALS AND METHODS

The study started by forty subjects: 28 patients with anxiety disorders, with inadequate response to oral medications, and 12 normal controls. All subjects gave a written consent for the procedure which was explained to them without suggesting any therapeutic expectation. Oral medications were continued in all patients. Among the patient group, six subjects were not regular on sessions and thus excluded, while the other twenty two continued the study. So we ended up by 34 subjects divided into three groups:

The ***first group*** was subjected to rTMS and consisted of 12 patients (8 females and 4 males, age range 22-35yrs) with anxiety disorder: 8 with generalized anxiety disorder, 3 with panic disorder and 1 with generalized anxiety disorder and panic attacks.

A ***second group*** of 10 patients: 7 with generalized anxiety disorder and 3 with panic disorder was sham- treated. All patients fulfilled the ICD –10 symptom check list criteria. Hamilton anxiety rating scale HARS was applied to all patients before starting and after finishing the rTMS sessions.

A ***third group*** of normal 12 age-matched controls was studied for determination of cortical motor threshold and motor evoked potential (MEP) amplitude.

TMS procedure:

1. Determination of the cortical motor threshold (CMT): TMS was done using Dantec Maglit stimulator with an 8-shaped coil, held over the motor area of the right hemisphere,and recording was obtained from the abductor pollicis brevis of the left hand with the target muscle at rest. Cortical motor threshold was defined as the minimal stimulus intensity needed to evoke a response > 20 uv in amplitude in 3/5 trials.[9] This procedure was done for patient and control groups.
2. MEP amplitude was determined as peak to peak amplitude.
3. rTMS technique was applied for patient group 1 only, using the same coil, at 80% of the predetermined motor threshold specified for each patient. 10 Hz were delivered for 2 seconds per minute for 10 trains. The coil was placed over the right lateral prefrontal cortex as previously defined as 5cm anterior and 2cm inferior to the optimal motor cortex site for producing an abductor pollicis brevis contraction with single pulses.[10] The sessions were done three days a week, for two weeks.

Sham stimulation was done to patient group 2, with the coil held at 45 degrees to the scalp surface without direct contact. This produces a similar sensation in the scalp but appears not to stimulate the brain being ineffective in producing a motor evoked potential.[11]

RESULTS

Twenty two patients continued the study. The treatment was generally tolerated with no serious side effects.

Cortical motor threshold and amplitude: (CMT & CMA)

CMT was lower in the patient groups ranging from 25-55% of the output stimulus intensity (mean 46.15%) as compared to the control group ranging from 50-85% of the output stimulus intensity (mean 68.3%), which showed statistical significance (p: 0.00004). The mean amplitude of the motor evoked response was higher in the patient group (1507.1uv) than the control group (1179.5 uv), however not reaching statistical significance (Figs.1 & 2, Table 1, Graphs 1 & 2).

rTMS:

Among the first group of 12 (rTMS treated), two patients (16%) reported headache after the procedure that responded to regular analgesics with a muscle relaxant. Ten patients (83%) reported a tendency for sleep lasting for hours after the stimulation, which they considered a beneficial effect rather than a side effect, having an initial complaint of insomnia. In the second group of 10 sham treated patients, only one (10%) complained of mild headache, no other complaints were reported in this group.

Hamilton Anxiety Rating Scale (HARS) was applied to all participants prior to treatment sessions and after the last session. The results were as follows:

First group (real treated): Six patients (50%) showed a reduction of HARS by 50% than baseline assessment appreciable only after completion of sessions.

Among the first group the starting mean HARS score was 31 and after completion of sessions it showed a mean value of 16, which is a statistically significant difference (p: 0.0002). Improvement was noted first on insomnia and tension after the first to the second sessions, where some patients described a sense of relaxation and tendency to sleep, then by the third or forth sessions reaction to stressful situations decreased in severity together with improvement of autonomic and somatic manifestations of anxiety, and lastly by the fifth to the sixth sessions mood depression started to improve together with intellectual functions and the ability to tolerate daily activities.

Individual symptoms that showed appreciable improvement:

- anxious mood starting by 4 ending by 2.
- tension starting by 3 and ending by1.
- Insomnia starting score by a mean of 3 and ending by 1
- behaviour at interview starting by 2 ending by 0.
- autonomic symptoms starting by 3 ending by 1.

Improvement was assessed weekly thereafter and lasted for an average of 4 weeks ± 6 days. It is worthmentioning that in three patients improvement lasted for 6 months, with discontinuation of therapy in two of them, to recur at a lower HARS score after 6 months improving on mild anxiolytics.

Second group (sham treated): Starting mean HARS score was 33 and score after sham sessions was 26. Although there was a change from baseline yet not statistically significant (p: 0.1). Symptoms most improved were anxious mood, and tension starting by a mean of 4 and ending by 2. Mean duration of improvement lasted for 2 weeks ± 4 days.

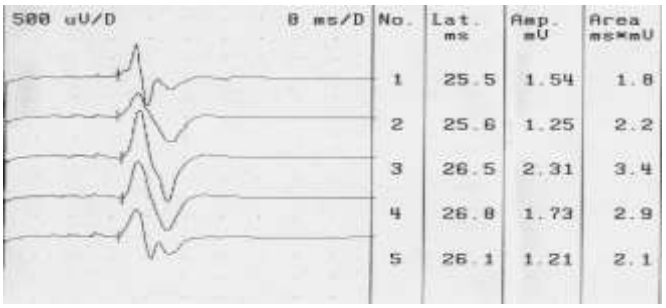


Fig. (1): Motor evoked response from the right cortex in a normal control (amplitude is shown).

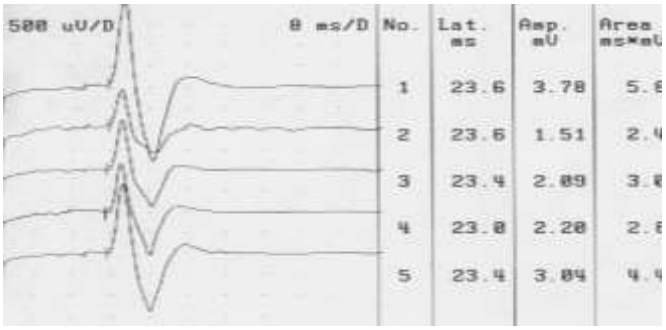
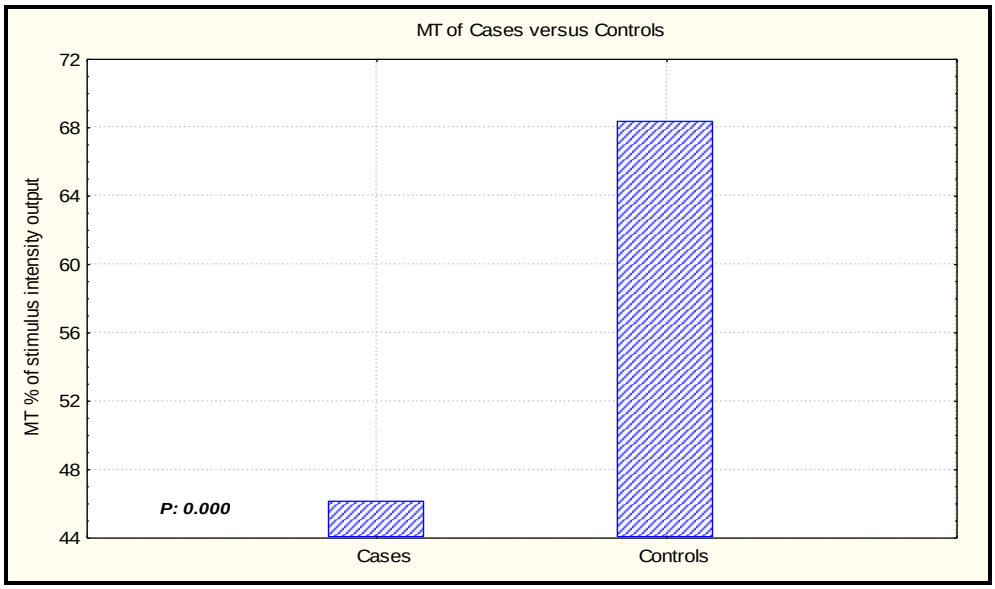


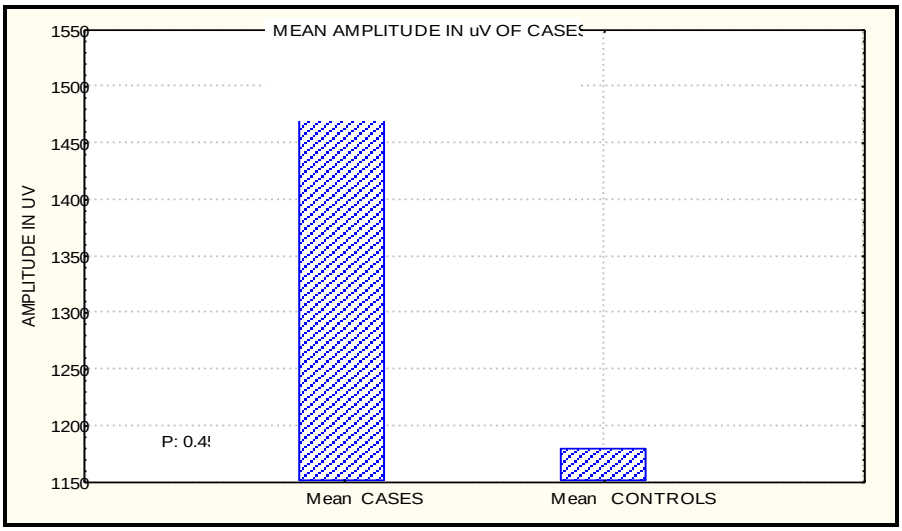
Fig. (2): Motor evoked response from the right cortex in patient with anxiety disorder.

Table 1. CMT and MUP amplitude in cases and controls.

Cases		Controls	
CMT (%)	**Amplitude (uv)**	**CMT (%)**	**Amplitude (uv)**
55	600	80	250
45	600	85	1600
65	940	80	2500
40	800	70	1900
45	2094	85	1500
40	3000	50	188
25	4000	50	345
50	2500	65	1243
40	490	60	2460
35	1563	55	430
45	5500	65	1545
30	700	75	194
55	1234		
30	740		
45	500		
40	325		
50	1220		
65	620		
80	3200		
35	845		
60	936		
40	750		
Mean 46.15% SD ± 13.1	Mean 1507.1 SD ± 1345.5	Mean 68.3% SD ± 12.85	Mean 1179.5 SD ± 873.6



Graph (1): Mean motor threshold (mt) of cases vrs controls.



Graph (2): Mean amplitude of motor evoked response of cases vrs controls.

DISCUSSION

The results of this study can be formulated as:

- Central motor conduction studies support the idea that patients with anxiety disorders have a lower cortical motor threshold and higher amplitude of motor units than normal controls, denoting increased cortical excitability.
- None of the treated groups showed any significant side effects.
- Patients treated with real rTMS showed lasting signifincant symptom improvement.
- Patients treated with sham TMS showed non-significant improvement less lasting than the first group, which still needs to be explained.
- As regards the finding of increased cortical excitability, this agrees with previous studies that found decreased intracortical inhibition in patients with obsessive compulsive disorder.[10] This also can be explained in view of the pathophysiologic mechanisms underlying anxiety mentioned above.

  Many studies showed right hemisphere overactivation, as demonstrated by increased blood flow[5,6,7]. The current study shows over activation rather by a more direct method, relying on cortical excitability.
- None of our patients showed any significant side effects to necessitate ending treatment. The incidence of headache was higher (16%) as compared to other studies (5-10%)[12], possibly because our group of patients was a potentially headache prone sample. rTMS has proved to be safe in most studies. It is painless, does not require anaesthesia, is not coupled with the induction of seizures (when safety criteria are followed)[12], and has few risks and cognitive side-effects[13].
- rTMS can produce effects that last after the stimulation period. This was first demonstrated in the motor system. Rapid rTMS, at frequencies of 5 hz and higher , will transiently enhance motor excitability[14], whereas slow rTMS of 1 hz, will transiently depress excitability[15]. The mechanisms of these changes are unclear, yet the analogies to long-term potentiation and long-term depression are apparent.

The treatment of mood disorders is the area in which TMS has attracted the most interest to date in psychiatry. In 1994 it was proposed that the prefrontal cortex (PFC) might be a more effective target for TMS.[16] This idea was based on the evidence of a link between the response to ECT and

changes in PFC function[17] as well as imaging studies reporting abnormalities in this area in depressed patients.[18] The first published studies applying focal stimulation of the PFC appeared in 1995 and 1996.[19,11,20] These studies produced promising results with rapid rate stimulation of the left PFC, while others using different stimulation parameters reported limited clinical effects.[21] More recent studies applied slow rate stimulation of the right PFC.[22]

On the other hand, the efficacy of rTMS in anxiety disorders did not gain much concern. rTMS has been tried in a few studies for the treatment of OCD with variable results.[23,24] These studies were based on findings suggestive of hyperfrontality in OCD, and accordingly they suggested that right prefrontal stimulation possibly disrupted compulsion related activity.

In a randomized trial of left and right prefrontal and midoccipital stimulation in 12 patients with obsessive compulsive disorder, it was found that a single session of right prefrontal rTMS decreased compulsive urges for 8 hours, but there was no effect on anxiety or obsessions[10]. Others reported that the condition of two patients with posttraumatic stress disorder improved during open treatment with 1 Hz rTMS over the right frontal cortex.[24] Grisaru et al 1998, similarly stimulated 10 patients with posttraumatic stress disorder and found decreased anxiety.[25] Feinsod et al 1998 applied 1hz in patients with schizophrenia and noticed significant reduction in their total Brief Psychiatric Rating Scale scores and the authors reported that this was because of a reduction in anxiety and restlessness rather than in psychotic symptoms.[26] To date no studies concerned with TMS in generalized anxiety disorder or panic disorder could be found, so that the results of the current study cannot be compared to other literature in this field.[27] Yet they can be interpreted in view of previous research on the pathophysiology of anxiety and panic disorders[5,6,7]. Examples of abnormalities suggesting either a hypoactivation or a hyperactivation of the right hemisphere in patients with panic disorder are reported[28,29]. Another recent study suggested that patients with panic disorder showed hyperactivation of the right hemisphere neural networks in early stages of information processing, and a reduced efficiency of these networks in later stages.[30]

These basic mechanisms when coupled with the findings in the current study of increased cortical excitability in anxiety disorders could at least partially explain the clinical response to modulation of brain excitability by rTMS.

Sham-treated patients showed some degree of improvement and this agrees with other studies where some sham conditions have been shown to produce significant cortical activity.[31]

Conclusion:

This study demonstrates a direct evidence of increased cortical excitability in anxiety disorders which can throw more light on pathophysiology and give some implications on treatment. rTMS is a safe, well-tolerated technique of treatment which produces lasting effects in patients non responsive to medications. However, the finding of cortical hyperexcitability and the clinical response to rTMS need to be verified by further research on a larger sample of patients. Also whether cortical hyperexcitability is a cause or a result of the disease process needs to be clarified. rTMS techniques still wait to be standardized as regards the stimulation frequency, intensity, duration and number of sessions. The possibility of repetition of the sessions with disease exacerbations still requires more intensive research.

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الملخص العربي

التنبية المغناطيسى عبر الدماغ فى اضطرابات القلق

يعتبر التنبية المغناطيسى عبر الدماغ احد وسائل تعديل عتبة القشرة المخية.

إجراءات البحث:

استكمل البحث على 22 مريضا ممن استوفوا تشخيص اضطراب القلق، و12 حالة ضابطة من الأصحاء. المجموعة الأولى: 12 مريضا عولجوا بالتنبية المغناطيسى المتكررعبر الدماغ. المجموعة الثانية: 10 مرضى عرضوا للتنبية المتكرر المصطنع. وقد اجرى للجميع اختبار هاميلتون للقلق قبل وبعد الجلسات. أما المجموعة الثالثة (الضابطة) 10 من الأصحاء. أجرى للثلاث مجموعات التنبية المغناطيسى عبر الدماغ لتحديد العتبة الحركية للقشرة المخية.

النتائج:

- وجد أن العتبة الحركية أقل لدى مجموعتى المرضى (46,15%) عن المجموعة الضابطة (68,3%) بدلالة إحصائية.
- أظهرت المجموعة الأولى تحسنا ذى دلالة احصائية على مقياس هاميلتون فى حين أن المجموعة الثانية أظهرت تحسنا غير دال إحصائيا.
- استمر التحسن فى حدود أربعة اسابيع 6ايام.