**International Journal of ChemTech Research**
CODEN (USA): IJCRGG, ISSN: 0974-4290, ISSN(Online):2455-9555
Vol.10 No.5, pp 418-426, 2017

# The Effect of Different Frequencies of Transcranial Magnetic Stimulation Combined with Aeropic Exercise on Cognitive Function in Stroke Patients

***[1]Abdulaleem Abdulfattah Atteya, [2]Ebtisam Mohamed Fhamy, [3]Hebatallah Raafat Mohamed Rashad, [1]Tahani FathiMousMousa, [2]Sandra Mohamed Ahmed**

[1]Faculty of Physical Therapy, Cairo University, Cairo, Egypt
[2]Neurology, Cairo University, Cairo, Egypt
[3]ClinicalNeurophysiology, Cairo University, Cairo, Egypt

**Abstract :** Repetitive transcranial magnetic stimulation (rTMS) holds promise as a therapeutic tool in cognitive impairment in stroke. The aim of this study to evaluate the effect of different frequencies of transcranial magnetic stimulation combined with aerobic exercise on cognitive function in stroke patients. Thirty right hand stroke patients, right side hemiparesis of both gender classified into three equal groups, (GI) received (10 Hz) frequency of rTMS combined with aerobic exercise and physiotherapy program while (GII) received (5Hz) frequency of rTMS combined with aerobic exercise and physiotherapy and (G III) received aerobic exercise and physiotherapy program. All patients evaluated by using Addenbrooke Cognitive Examination Revised for cognitive function and Transcrinal Doppler (TCD)for blood flow velocity in affected middle cerebral arterypre and post treatment and Neurophysiological evaluations included the intensity of motor threshold in each patient in both group (GI and GII) before the first session. There were significant differences in blood flow velocity in affected side(left MCA) in group (I, II and III) with a percentage of improvement (19.68, 10.98 and 7.35%), respectively. There were significant differences in addenbrookes cognitive examination within group (I, II and III) with a percentage of improvement (30.29, 26.92 and 17.79%), respectively and there were significant positive correlation (*P*>0.05) between improvement percentage of blood flow velocity in affected side of MCA and improvement percentage of total addenbrookes cognitive examination in groups I (10 HZ) and II (5 HZ), but a no correlation (P>0.05) was observed in group III (aerobic exercise).In our study we demonstrated that rTMS combined with aerobic exercise play a major role in increasing blood flow velocity which Reflect in improvement cognitive function in stroke patients mainly high frequency (10HZ).

**Keywords :** Stroke, Repetitivetranscranial magnetic stimulation, Aerobic exercise, Cognitive function.

## Introduction

Cognition is the set of all mental abilities and processes related to knowledge, attention, memory , judgment, evaluation, reasoning , "computation", problem solving, decision making, comprehension and production of language[1]. Cognitive function reflects a set of processes that allow for the perception of a stimulus and the extraction of information in order to guide thoughts and actions to ultimately achieve a desired goal [2].Cognitive impairments after stroke can occur in isolation or concomitantly with physical impairments [3].Cognitive impairment can make it difficult for the stroke survivor to follow treatment guidelines and can limit functional recovery[4].Estimates of the prevalence of cognitive impairment after stroke range from 11.6 to 56.3% [5].Almost two thirds of these patients are affected by mild cognitive impairment [6]. The incidence of cognitive deficit increases threefold after stroke and about 25% of stroke patients develop dementia. Some of the patients recover completely from physical disability after the stroke but are often unable to cope with activities of daily life because of cognitive impairment[7]. Cognitive assessments should evaluate different cognitive domains, including testing for language, neglect, praxis and more global cognitive function including memory, motor speed, executive function and attention. Addenbrooke's cognitive examination (ACE) is a brief, simple and reliable cognitive test. The test used for determine mild cognitive impairment and dementia [8].

Transcranial Doppler (TCD) and transcranial color Doppler (TCCD) are types of Doppler ultrasonography that measure the velocity of blood flow through the brain's blood vessels by measuring the echoes of ultrasound waves moving transcranially (through the cranium)[9].Transcranial Doppler (TCD) was used to assess cognition by measuring cerebral blood flow velocity during cognition tasks in normal subject. The result showed that during the video gam, both middle cerebral arteries and posterior cerebral artery had selective increase in the mean blood flow velocity compared with ipsilateral anterior [10].

Physical activity benefits cognitive as a whole. Specifically, however, executive control processes (such as working memory, multitasking or planning) are more positively affected in comparison to other regions of the brain. This demonstrates the direct link between the improvement in memory processes and aerobic exercise. The prefrontal cortex is primarily responsible for supporting executive control processes, and studies suggest exercise may be used as an intervention to prevent age-related decline in executive control and memory [11].

Transcranial magnetic stimulation (TMS) Is non-invasive brain stimulation techniques. These techniques interact with spontaneous brain activity and related sensory-motor and higher order cognitive abilities. Transcranial magnetic stimulation uses a coil to deliver a brief (≐200 to 300 ms) and powerful (0.2 to 4.0 T) magnetic pulse to the scalp. The stimulation-induced effects of TMS depend on several technical parameters, including the intensity and number of stimulations (i.e., frequency), the coil orientation, and the locality and depth of stimulation. The effects also depend on a number of variables related to the stimulated subject, including age, eventual pharmacological treatments and the state of the subject [12]. When TMS was directed over the primary motor cortex, the discharges induced the activation of the corticospinal tract, which produced a peripheral motor response known as the motor evoked potential (MEP). Since the discovery of TMS, this technique has been used to investigate the state of cortical excitability, the excitability of the cortico-cortical or corticospinal pathway[13]. TMS studies on humans were initially focused on the motor system because the effects of TMS on the motor system are easily discernible from peripheral muscles. In the motor cortex, the activation of pyramidal neurons by TMS has been suggested to predominantly occur via interneurons in the superficial cortical layers[14]. TMS that it is possible to evaluate the state of motor cortex excitability by measuring what is known as the motor threshold The motor threshold, which reflects the global excitability of the corticospinal motor pathway, has been defined as the intensity of TMS that produces an identifiable MEP of ≐50 mV in at least five out of ten TMS pulses [15]. Although threshold in human adults is largely independent of age, gender and hemisphere, it varies with different target muscles[16]. In the mid-1990s, technological advances allowed the delivery of rhythmic trains of magnetic pulses in a rapid sequence up to a 100-Hz repetition rate, which was referred to as repetitive TMS (rTMS). Studies have shown that rTMS interacts with cortical activity more effectively than TMS. Therefore, new applications began evaluating the potential benefits of rTMS in the treatment of psychiatric disorders [17]. In recent years, rTMS has been rapidly developed as a potential therapeutic tool in many other clinical fields [18]. Several studies in normal subjects have suggested that TMS may lead to enhanced cognitive performance. In healthy subjects, most of these effects were transient (in the range of minutes), but repeated TMS in follow-up sessions, in concert with learning and plasticity processes, may prolong the facilitating effects beyond the end of the stimulation period and provide important opportunities for long lasting positive effects[19]. Some preliminary data have shown improved picture naming or word repetition performance in vascular aphasia [20], primary progressive aphasia [21] and Alzheimer’s disease [22]. Repetitive TMS can also be used to improve performance in sensory extinction [23]and unilateral neglect associated with stroke [24].

## Materials and Methods

Thirty right hand stroke patients ,right side hemiparesis of both gender participated in this study, ages ranged from 40 to 65 years (mean age 52,00± 9.00), mean patient's duration (18.30 ±11.30 month), mild cognition impairment according to MMSE and mild degree of spasticity (grade 1 & 1+) according to Modified Ashworth scale. The patients were classified into three equal groups. (GI) received (10 Hz) frequency of rTMS combined with aerobic exercise and physiotherapy program, while (GII) received (5Hz) frequency of rTMS combined with aerobic exercise and physiotherapy and (GIII) received aerobic exercise and physiotherapy program. The patients selected from out –patient clinic of neurology department in Kaser El Aini Hospital, Cairo University and from Outpatient clinic of Faculty of physical Therapy, Cairo University in period from June 2016 to March 2017. The whole procedure was explained for every patient and the Patients signed on informed consent before beginning of study to insure complete satisfaction. Neurological assessment done throughout history taking from patients or near relative, general medical examination and physical examination conducted to each patient according to assessment sheet of Neurology Department, Faculty of physical Therapy, Cairo University. Addenbrooke s cognitive examination Revised test ACE-R was conducted at a comfortable sitting position on chair with back support and suitable seat height compared to the table in front of the patient. The patients were asked to write and draw by the non-affected hand if they can't do this by the affected one. Reading items were written and drawn in clear and suitable font and size. All items were assessed and scores were record for each item and then the total score were calculated. Assessment of cerebral blood flow velocity (middle cerebral arteries) by Transcranial Doppler, The patient was asked to remove any clothing, jewelry, or other objects that may interfere with the scan. The patient was lie on an examination table ,supine position examined with operator at head. At the start of the examination , the transtemporal acoustic bone window was checked for adequate ultrasonic beam penetration(if failed , the patient was considered inappropriate for the TCD examination and excluded from the study. Once the cerebral arteries were adequately visualized the detailed TCD protocol for both sides was performed. The left middle cerebral artery wasinsonate through the temporal window. The window was located by applying liberal amount of acoustic coupling gel to the hair and skin of the temporal region in front and above the external auditory meatus**.**Slowly moving the transducer around to allow the point of best transmission to be identified. The technologist was used all possible comfort measures and completes the procedure as quickly as possible to minimize any discomfort .The highest signal was sought at a depth ranging from 50-55mm. Maximum velocity ,mean velocity, pulsatility index(PI) and Resistance Index(RI) were recorded bilaterally and compared with normative data And Neurophysiological evaluations included the intensity of motor threshold of rTMS was determined in each patient before the first session in **GI** and **GII**.

The Patients in **(G1)** were treated by high frequency (10HZ) of transcrinal magnetic stimulation applied overthe left DLPFC ,combined with aerobic exercise and physiotherapy program. High frequency (10HZ) rTMS with Magstim rapid magnetic stimulator, connected with a figure –of-eight coil with diameter of 70mm. The patients were seated in a chair that allow them to keep their arms and hands relaxed . The intensity of motor threshold of rTMS was determined in each patient before first session, using single –pulse stimulation over the primary motor cortex at the hot point of first dorsal interosseus muscle .The motor threshold represented the lowest intensity required to elicit a motor evoked potential in 50% of successive trials or to produce a visible movement of the thumb, wrist or fingers in at least half of 10 stimulation in a fully relaxed muscle. Each rTMS session was consisted of 6 trains, with train duration(10second ,number of plus 600 ), Each patient given high frequency (10HZ) and 90% of motor thresholds intensity over the dorsolateral prefrontal cortex (DLPFC). The total duration of rTMS session was 6minutes Treatment sessions for each patient (five times per week for two weeks). The stimulation parameters were chosen according to current safety guidelines **Physiotherapy program** (stretching exercise , strengthening exercise, PNF ,then aerobic exercise will performed on treadmill. Before starting the training procedure each patient was instructed to wear comfortable shoes and stand with erect back as much as possible. The exercise on treadmill was performed under supervision of therapist to ensure correct and accurate application of exercise intensity and duration ,Speed, all patients were walk on a treadmill at1.0 m/s (low speed)**.**The first five minute of each session was dedicated to warming up exercise on treadmill followed physical activity exercise for 10min, and finally cooling down for five minute. With gradually decreased of speed until reaching the resting heart rate. All patients were provided with a progressive exercise prescription based on 50-70% of their predicted max heart rate .The heart rate was monitored continuously with polar pulse rate.

**G (II)** received (5Hz) frequency of rTMS over the left DLPFC .Each rTMS session was consisted of 6 trains,( with train durationn10second number of pluse300), and same model of aerobic exercise was performed on treadmill and same physiotherapy program and **G(III**) received same model of aerobic exercise was performed on treadmill and same physiotherapy program. Total session of aerobic exercise and physiotherapy program was one hour for all groups.

## Result

The obtained data was collected and statistically analyzed and compared with measurable variable **In Table (1**)t-test :significant differences in blood flow velocity (Left MCA) within group I (P=0.001; P<0.05), group II (P=0.0001; P<0.05) and group III (P=0.017; P<0.05) with a percentage of improvement (19.68, 10.98 and 7.35%), respectively

**Table (1): Mean values of blood flow (Left) within each group.**

| **Item** | **Blood flow (Left)** | | | | | |
|---|---|---|---|---|---|---|
| | **Group I (10 HZ)** | | **Group II (5 (HZ)** | | **Group III (Aerobic exercise)** | |
| | **Before** | **After** | **Before** | **After** | **Before** | **After** |
| **Mean ±SD** | 44.20 ±3.99 | 52.90 ±5.87 | 42.80 ±8.17 | 47.50 ±8.27 | 40.80 ±2.65 | 43.80 ±4.66 |
| **Min. – Max.** | 39.0 – 53.0 | 44.0 – 61.0 | 30.0 – 53.0 | 36.0 – 59.0 | 36.0 – 45.0 | 40.0 – 54.0 |
| **Mean difference** | 8.70 | | 4.70 | | 3.00 | |
| **Improvement %** | 19.68% | | 10.98% | | 7.35% | |
| **t-value** | 5.178 | | 9.485 | | 2.935 | |
| **P-value** | 0.001 | | 0.0001 | | 0.017 | |
| **Significant** | **S** | | **S** | | **S** | |

In **Table (2)** (ANOVA test) No significant differences in before blood flow (Left) (P=0.390; P>0.05), while there were significant difference in after blood flow (Left) (P=0.014; P<0.05) among groups I (10HZ), II (5HZ) and III (aerobic exercise).

**Table (2): Mean values of blood flow (Left) among three groups (I, II and III).**

| **Item** | **Blood flow (Left)** | |
|---|---|---|
| | **Before** | **After** |
| **Group I (10 HZ)** | 44.20 ±3.99 | 52.90 ±5.87 |
| **Group II (5 HZ)** | 42.80 ±8.17 | 47.50 ±8.27 |
| **Group III (Aerobic exercise)** | 40.80 ±2.65 | 43.80 ±4.66 |
| **F-value** | 0.975 | 5.035 |
| **P-value** | 0.390 | 0.014 |
| **Significant** | **NS** | **S** |

**Table (3)**:The statistical analysis revealed that the significant difference of the means of after blood flow (Left) was observed between group I and III (P=0.0.004; P<0.05).

**Table (3): Post hoc multiple comparison test (LSD) for after blood flow (Left).**

| Means | Groups | I (10HZ) | II (5HZ) | III (Aerobic exercise |
|---|---|---|---|---|
| **52.90** | **I (10HZ)** | | 0.072 | 0.004* |
| **47.50** | **II (5HZ)** | | | 0.210 |
| **43.80** | **III (Aerobic exercise** | | | |

*****: Donates pairs of groups significantly different at (P ≤ 0.05).

In **Table (4)** significant differences in addenbrookes cognitive examination within group I (P=0.005; P<0.05), group II (P=0.005; P<0.05) and group III (P=0.005; P<0.05) with a percentage of improvement (30.29, 26.92 and 17.79%), respectively.

**Table (4): Mean values of addenbrookes cognitive examination within each group.**

| **Item** | **Addenbrookes cognitive examination** | | | | | |
|---|---|---|---|---|---|---|
| | **Group I (10 HZ)** | | **Group II (5 (HZ)** | | **Group III (Aerobic exercise)** | |
| | **Before** | **After** | **Before** | **After** | **Before** | **After** |
| **Mean ±SD** | 20.80 ±1.75 | 27.10 ±2.33 | 20.80 ±2.25 | 26.40 ±2.59 | 20.80 ±1.87 | 24.50 ±2.71 |
| **Min. – Max.** | 19.0 – 23.0 | 23.0 – 30.0 | 18.0 – 23.0 | 23.0 – 29.0 | 18.0 – 23.0 | 21.0 – 28.0 |
| **Mean difference** | 6.30 | | 5.60 | | 3.70 | |
| **Improvement %** | 30.29% | | 26.92% | | 17.79% | |
| **Z-value** | 2.810 | | 2.840 | | 2.825 | |
| **P-value** | 0.005 | | 0.005 | | 0.005 | |
| **Significant** | **S** | | **S** | | **S** | |

**Table (5)** (ANOVA test):No significant differences in before addenbrookes cognitive examination (P=1.000; P>0.05), while there were significant difference in after addenbrookes cognitive examination (P=0.048; P<0.05) among groups I (10HZ), II (5HZ) and III (aerobic exercise).

**Table (5):** Mean values of addenbrookes cognitive examination among three groups (I, II and III).

| **Item** | **Addenbrookes cognitive examination** | |
|---|---|---|
| | **Before** | **After** |
| **Group I (10 HZ)** | 20.80 ±1.75 | 27.10 ±2.33 |
| **Group II (5 HZ)** | 20.80 ±2.25 | 26.40 ±2.59 |
| **Group III (Aerobic exercise)** | 20.80 ±1.87 | 24.50 ±2.71 |
| **F-value** | 0.00 | 2.780 |
| **P-value** | 1.000 | 0.048 |
| **Significant** | **NS** | **S** |

**In Table (6)** significant difference of the means of addenbrookes cognitive examination was observed between group I and III (P=0.031; P<0.05).

**Table (6): Post hoc multiple comparison test (LSD) for addenbrookes cognitive examination.**

| Means | Groups | I (10HZ) | II (5HZ) | III (Aerobic exercise |
|---|---|---|---|---|
| **27.10** | **I (10HZ)** | | 0.545 | 0.031* |
| **26.40** | **II (5HZ)** | | | 0.107 |
| **24.50** | **III (Aerobic exercise** | | | |

*****: Donates pairs of groups significantly different at (P ≤ 0.05).

**Table (7):**Significant positive correlation (*P*>0.05) between improvement percentage of blood flow (right and left) and improvement percentage of total addenbrookes cognitive examination in groups I (10 HZ) and II (5 HZ), but a no correlation (P>0.05) was observed in group III (aerobic exercise).

**Table (7): Correlation coefficients betweenaddenbrookes cognitive examination and blood flow (Right and left) in each group**.

| Item | Blood flow (Left) | | |
|---|---|---|---|
| | Correlation coefficient (r) | P-value | Significant |
| **Group I (10 HZ)** | 0.792 | 0.006 | **S** |
| **Group II (5 HZ)** | 0.684 | 0.027 | **S** |
| **Group III (Aerobic exercise)** | -0.224 | 0.534 | **NS** |

## Disscussion:

In The present study the patient's age were maximally limited to 65 years in order to minimize the effect of age on cognition function of the participated patients. It was proved that 3% of population over 65 years had cognitive impairment and the prevalence of the cognitive decline after stroke would increase exponentially as age increases after 65 years old [25]. In this study, the limited number of females compare to males was due to low incidence of stroke of females compare to males in this age. It was previously documented that men's stroke incidence is 41% greater than women's stroke incidence and that male/female ratio is 5:4 at ages 55-65[26]. The results showed that group I(10HZ) frequency rTMS applied to the left DLPFC was high significant improvement in total score ACER test and high significant improvement in blood flow velocity (the left MCA) Followed by group II (5HZ) and group III (Aerobic exercise respectively). This improvement may attributed to physiological effect of high frequency of magnetic stimulation combined with aerobic exercise on brain and increase oxygen consumption ,reduce blood pressure and resting heart rate, strengths heart muscle which reflect on its pumping efficiency leading to increase cerebral blood flow . Agreement with this study Peter et al[26] reported there was a maximal increase of CBFV in the middle cerebral artery (MCA) of 3.6% and 5.6% during 10 Hz and 20 Hz stimulation, respectively. This increase was only seen on the stimulated left hemisphere. It is likely that the increase of CBFV is due to dilatation of the small resistance vessels rather than due to vasoconstriction of the MCA.Cotelli et al. and Devi et al., [27] supported this study when they applied daily high frequency rTMS over the left DLPFC of patients with AD .They found that real rTMS improved performance in cognitive tests with improvements in language abilities and general cognitive abilities. Vanderhasselt et al., [28]found when stimulated the left dorsolateral prefrontal cortex (DLPFC) in the patients that had them perform a switching task that required the control of attention between visual and auditory cues. It was found patients that received active stimulation had improved reaction times, whereas those that received sham stimulation. Our study found there was positive improvement in group II and group III but less than group I may be attributed to complexity of some training mainly language training and need long of time to activate cortical areas and increase blood flow. Kim et al[29] disagree with our study when reported that was a positive effect on mood, but the study was not powered to detect any measurable effect on cognition and had nosignificant effect on any cognitive function parameter in group applied high5-10frequency repetitive transcranial magnetic stimulation over the left dorsolateral prefrontal cortex (DLPFC) in contrast, resulted in significantly lower Beck Depression Inventory scores post stroke patients. At the end of result there were significant positive correlation between improvement percentage of blood flow and improvement percentage of total addenbrookes cognitive examination in groups I (10 HZ) and II (5 HZ), but a no correlation ($P>0.05$) was observed in group III (aerobic exercise) may be due to the improvement in blood flow in group III not enough to increase improvement in cognitive function like group (I &II).

Ainslie et al.,[30]found aerobic exercise and physiotherapy program was proved to promote angiogesis, increase in capillary density and improved daily living activity, gait grasp function but not play positive role in improvement function. Ploughman et al.,[31] recently reported that a single session of treadmill exercise improved grasping function in the hemiparetic hand but not cognitive function for chronic stroke. Quaney et al., [32]examined the effects of an aerobic training program on cognitive function and reported in addition to physical benefits, the aerobic exercise may improve cognitive function in stroke survivors. Thus, it was concluded that high rTMS play a major role in increasing blood flow velocity which reflect in improvement cognitive function in stroke patients. **Peter et al.,[26]** supported our study when reported there was a maximal increase of CBFV in the middle cerebral artery (MCA) of 3.6% and 5.6% during 10 Hz and 20 Hz stimulation, respectively. This increase was only seen on the stimulated left hemisphere.

## Conclusion

In our study we demonstrated that rTMS combined to aerobic exercise play a major role in increasing blood flow velocity which reflect in improvement cognitive function in stroke patients mainly high frequency(10HZ).

## Reference

1. Blomberg, O. "Concepts of cognition for cognitive engineering International Journal of Aviation Psychology 21 (1): 85–104..1080/10508414.2011.537561. 2011
2. Purves, D., Cabeza, R., Huettel, S.A., LaBar, K.S., Platt, M.L., Woldorff, M.G. of Principles Cognitive Neuroscience (2nd.ed ) Sunderland MA: Sinauer Associates Inc.2013
3. Leśniak, M., Bak, T., Czepiel, W., Seniów, J., &Członkowska, A. Frequency and prognostic value of cognitive disorders in stroke Dementia and Geriatric patients. Cognitive Disorders, 26(4), 356-363.2008
4. Cumming, T. B., Marshall, R. S., & Lazar, R. M. (2013). Stroke, cognitive deficits, and rehabilitation: Still an incomplete picture International Journal of Stroke, 8(1), 38-45. ,Das S, Paul N, Hazra A, et al. Cognitive Dysfunction in Stroke Survivors: A Community-Based Prospective Study from Kolkata, India. J Stroke Cerebrovasc Dis 2013 ;p 22:1233-42.
5. Patel, M. D., Coshall, C., Rudd, A. G., & Wolf e, C. D. A. Cognitive impairment after stroke: Clinical determinants and its associations with long-term stroke outcomes Journal of the American Geriatrics Society, 50(4), 700-706 2002..
6. Sachdev PS, Chen X, Brodaty H, Thompson C, Altendorf A, Wen W The determinants and longitudinal course of post-stroke mild cognitive impairment. J IntNeuropsychol Soc15:915–923.. 2009;
7. Titianova E, Velcheva I, Stamenov Treatment of Acute Ischemic Stroke with Thrombolysis in Bulgaria. Neurosonology and Cerebral Hemodynamics 2010;p 14-9(1)6,New Insights for the Healthcare Professional 2013
8. Alexandrov AV, Joseph M: Transcranial Doppler; An Overview of its Clinical Applications. The Internet Journal of Emergency and Intensive Care Medicine 2000; Vol4 N1
9. Kelley RE, ChangJY, ScheinmanNJ, LevinBE, DuncanRC, Lee SC. Transcranial Doppler assessment of cerebral flow velocity during cognitive tasks. Stroke journal of American heart association:23pp9-14.1992
10. Sharon plowman, Denise Smith, Eexersice Physiotherapy for Health, Fitness and Performance. Lippo Williams& Wilkins 2007;p.61.

11. Miniussi, C., Ruzzoli, M., & Walsh, V. (2010). The mechanism of transcranial magnetic stimulation in cognition. Cortex, 46(1), 128–130
12. Rothwell, J. C., Day, B. L., Thompson, P. D., Dick, J. P., & Marsden, C. D.. Some experiences of techniques for stimulation of the human cerebral motor cortex through the scalp. Neurosurgery, 1987.20(1), 156–163.
13. Di Lazzaro, V., Thickbroom, G. W., Pilato, F., Profice, P., Dileone, M., Mazzone, P., et al.. Direct demonstration of the effects of repetitive paired-pulse transcranial magnetic stimulation at I-wave periodicity. Clinical Neurophysiology, 2007 ;p 118(6), 1193–1197.
14. Rossini, P. M., Barker, A. T., Berardelli, A., Caramia, M. D., Caruso, G., Cracco, R. Q., et al.. Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: Basic principles and procedures for routine clinical application. Report of an IFCN committee. 1994
15. Rossini, P. M., Desiato, M. T., &Caramia, M. D.. Age-related changes of motor evoked potentials in healthy humans: Non-invasive evaluation of central and peripheral motor tracts excitability and conductivity. Brain Research, 1992 ;p 593(1), 14–19.
16. George, M. S., Padberg, F., Schlaepfer, T. E., O’Reardon, J. P., Fitzgerald, P. B., Nahas, Z. H., et al.. Controversy: Repetitive transcranial magnetic stimulation or transcranial direct current stimulation shows efficacy in treating psychiatric diseases (depression mania, schizophrenia, obsessive–compulsive disorder, panic, posttraumatic stress disorder). Brain Stimulation, p 2(1), 14–21.2009;.
17. Mally, J., & Stone, T. W. New advances in the rehabilitation of CNS diseases applying rTMS. Expert Reviews in Neurotherapy, 7(2), 165–177. 2007
18. Miniussi, C., Cappa, S. F., Cohen, L. G., Floel, A., Fregni, F., Nitsche, M. A., et al.. Efficacy of repetitive transcranial magnetic stimulation/transcranial direct current stimulation in cognitive neurorehabilitation. Brain Stimulation, 1(4), 326–336. 2008
19. Naeser, M. A., Martin, P. I., Lundgren, K., Klein, R., Kaplan, J., Treglia, E., et al.. Improved language in a chronic nonfluent aphasia patient after treatment with CPAP and TMS. Cognitive and Behavioral Neurology, 23(1), 29–38.2010
20. Finocchiaro, C., Maimone, M., Brighina, F., Piccoli, T., Giglia, G., &Fierro, B. A case study of Primary Progressive Aphasia: Improvement on verbs after rTMS treatment Neurocase, 12(6), 317–321. 2006.
21. Cotelli, M., Fertonani, A., Miozzo, A., Rosini, S., Manenti, R., Padovani, A., et al. Anomia training and brain stimulation in chronic aphasia. Neuropsychological Rehabilitation, 2011 ;p 21(5), 717–741.
22. Oliveri, M., Rossini, P. M., Filippi, M. M., Traversa, R., Cicinelli, P., Palmieri, M. G., et al.. Time-dependent activation of parieto-frontal networks for directing attention to tactile space. A study with paired transcranial magnetic stimulation pulses in right-braindamaged patients with extinction. Brain, 123(Pt 9), 1939–1947.2000
23. Shindo, K., Sugiyama, K., Huabao, L., Nishijima, K., Kondo, T., & Izumi, S. Long-term effect of low-frequency repetitive transcranial magnetic stimulation over the unaffected posterior parietal cortex in patients with unilateral spatial neglect. Journal of Rehabilitation Medicine, 38(1), 65–67. 2006.
24. Gorelick PB, Scuteri A, Black SE, et al. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the american heart association/american stroke association. Stroke;p4 2:2672-713 .2011
25. PeterW. PecuchStefan, Evers Here ,W. Folkerts ,Nikolaus Michael .Volker AroltThe cerebral hemodynamics of repetitive transcranial magnetic stimulation. European Archives of Psychiatry and Clinical Neuroscience, Volume 250, Issue 6, pp 320–324.2000
26. Cotelli M, Calabria M, Manenti R, Rosini S, Zanetti O, Cappa SF, Miniussi C (2010b) Improved language performance in Alzheimer disease following brain stimulation. J NeurolNeurosurg Psychiatry Jun 23 (epub ahead of print)
27. Vanderhasselt MA, De Raedt R, Baeken C, Leyman L, D’haenen H (2006) The influence of rTMS over the left dorsolateral prefrontal cortex on Stroop task performance. Exp Brain Res 169(2):279–282 (epub 2006 Jan 18)
28. Kim BR, Kim DY, Chun MH, Yi JH, Kwon JS: Effect of repetitive transcranial magnetic stimulation on cognition and mood in stroke patients.American Journal of Physical Medicine & Rehabilitation: - Volume 89 - Issue 5 - pp 362-368:2010
29. Ainslie PN, James D, Keith P. Elevation in cerebral blood flow velocity with aerobic fitness through healthy human ageing. J physiology;586p:4005-4010.2008

30. Ploughman M, McCarthy J, Bosse M, Sullivan H, Corbett D. Does treadmill exercise improve performance of cognitive or upper extremity tasks in people with chronic stroke? A randomized cross-over trial. Arch Phys Med Rehabil.;89:2041–20430 . 2008
31. Quaney, B. M., Boyd, L., McDowd, J. M., zahner, L. H., He, J., Mayo, M. S., &Macko R. F, (2009). Aerobic exercise improves cognition and motor function poststroke. Neurorehabilitation and Neural Repair, 23

*****