

## TRANSCRANIAL MAGNETIC STIMULATION (TMS) APPLICATION IN SPORT MEDICINE: A BRIEF REVIEW

FIorenzo MOSCATELLI<sup>1,§</sup>, ANNA VALENZANO<sup>1,§</sup>, VINCENZO MONDA<sup>2</sup>, MARIA RUBERTO<sup>3</sup>, GIUSEPPE MONDA<sup>1</sup>, ANTONIO I. TRIGGIANI<sup>1</sup>, EMANUELE MONDA<sup>1</sup>, SERGIO CHIEFFI<sup>2</sup>, INES VILLANO<sup>2</sup>, LUCIA PARISI<sup>4</sup>, MICHELE ROCCELLA<sup>4</sup>, ANTONIETTA MESSINA<sup>2,7</sup>

<sup>1</sup>Department of Clinical and Experimental Medicine, University of Foggia, Foggia, Italy - <sup>2</sup>Department of Experimental Medicine, Università degli Studi della Campania "Luigi Vanvitelli", Italy - <sup>3</sup>Department of Medical-Surgical and Dental Specialties, Second University of Naples, Italy - <sup>4</sup>Department of Psychological, Pedagogical and Educational Sciences, University of Palermo, Italy

§ *Fiorenzo Moscatelli and Anna Valenzano equally contributed to manuscript*

### ABSTRACT

*Since 1985, transcranial magnetic stimulation (TMS) has been used for non-invasive exploration of motor control in humans and for a wide range of applications in all ages of life. This brief review examined briefly the potential interest in sport medicine.*

**Keywords:** TMS, transcranial magnetic stimulation, motor cerebral cortex, athletes.

DOI: 10.19193/0393-6384\_2017\_3\_062

**Received** November 30, 2016; **Accepted** February 02, 2017

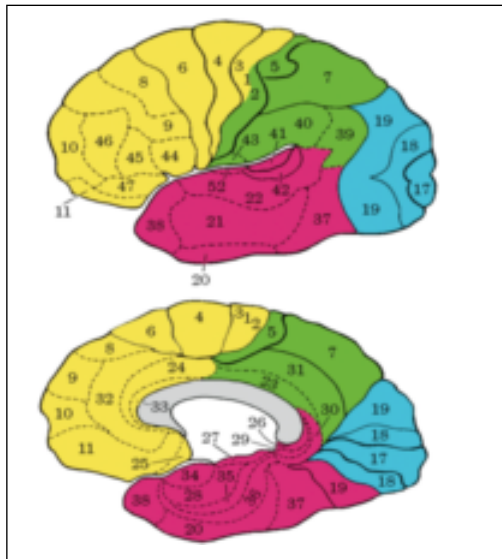
### Introduction

The primary motor cortex (M1) is identified as Brodmann area 4 (Fig.1), and located in dorsal part of the precentral gyrus and anterior bank of the central sulcus, M1 is thicker and with lower cell density than other cortical area. The main output cells are the large pyramidal cells in lamina V and smaller cells in lamina III. M1 contains large corticospinal neurons which send long axons down the spinal cord to synapse onto alpha motor neurons which connect to the target muscle.

Among the numerous non-invasive techniques and tools to explore and investigate the human cortical cortex, transcranial magnetic stimulation (TMS) contributed to understand how brain networks build and optimize the motor programs

responsible for motor performance<sup>(1-14)</sup>. TMS is a method for noninvasive focal brain stimulation, where localized intracranial electrical currents, large enough to depolarize a small population of neurons, are generated by rapidly changing extracranial magnetic fields. TMS can be applied in single pulses, pairs of pulses, or repeated trains of pulses (rTMS). Following standardized guidelines and procedures, human studies with adults and children have demonstrated TMS procedures to be safe and well tolerated. When single pulse TMS is applied in primary motor cortex (M1) at suprathreshold intensities, it activates corticospinal outputs, producing a twitch in a peripheral muscle (a motor evoked potential (MEP), which can be used as an index of corticospinal excitability. Trains of repeated TMS pulses (rTMS) at various stimula-

tion frequencies and patterns can induce a lasting modification of activity in the targeted brain region, which can outlast the effects of the stimulation itself.



**Figure 1:** In this figure it is possible to observe the different Brodmann areas. The human primary motor cortex (M1), usually identified as Brodmann area 4, is located in dorsal part of the precentral gyrus and anterior bank of the central sulcus.

The after effects of rTMS are thought to relate to activity-dependent changes in the effectiveness of synaptic connections between cortical neurons, reflecting cortical plasticity mechanisms. Single and paired pulse TMS protocols are exclusively used for investigational purposes, while rTMS protocols can be used both in investigational and therapeutic applications. Repetitive physical training is generally considered as a principal strategy for acquiring a motor skill, and this process can elicit cortical motor representational changes referred to as use-dependent plasticity. In training settings, physical practice combined with the observation of target movements can enhance cortical excitability and facilitate the process of learning<sup>(15-30)</sup>.

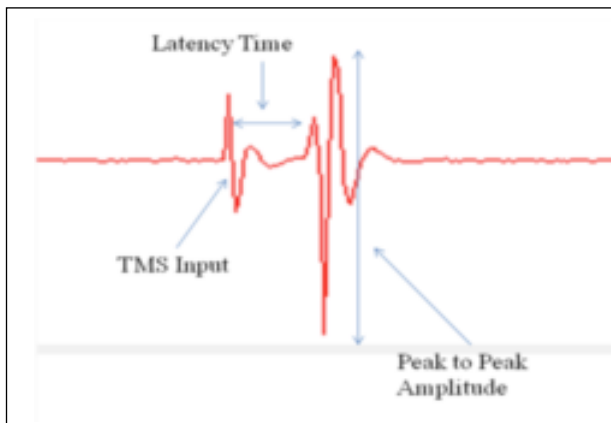
TMS has been used to study intracortical, cortico-cortical, and cortico-subcortical interactions<sup>(15-30)</sup>. Peripheral nerve stimulation can depolarize neuronal membranes similarly to stimulation parameters in central nervous system: short pulses with a duration of less than 1 ms and with an amplitude of few milliamperes. Transcranial methods for brain stimulation face the problem of delivering such a stimulus across the high resistance barrier of the periencephalic layers, including scalp, skull, meninges and cerebrospinal fluid. TMS has been

used to study the human nervous system within clinical populations; mechanisms of fatigue in small, isolated muscle groups; corticospinal contributions during human gait and acute neural adaptations following strength training. Transcranial brain stimulation, at present primarily with several forms of noninvasive electrical cortical stimulation, is under active investigation in child neurology and psychiatry, particularly in disorders where focal cortical over- or under-activation is presumed to be part of the pathophysiology<sup>(31-35)</sup>. While a number of transcranial neurostimulation techniques have been developed, two are undergoing the most active investigation: TMS and transcranial direct current stimulation (tDCS).

In TMS, intracranial electrical currents are induced in the cortex by a fluctuating extracranial magnetic field, whereas in tDCS constant electrical currents are conducted to the brain via scalp electrodes. Both techniques share a capacity to modulate regional cortical excitability, and both are well-tolerated by children and adults<sup>(36-40)</sup>. TMS in particular stands out among noninvasive brain stimulation techniques in that it has experimental, diagnostic, and therapeutic potential. With TMS, an operator may either measure or modulate cortical excitability. A rapidly growing body of research attests to the utility of TMS as a valuable tool for the study of normal neurophysiology, and to the safety and efficacy of TMS in clinical conditions where repetitive TMS (rTMS) is applied to either enhance or depress regional cortical excitability and distributed activity in specific brain networks<sup>(41-50)</sup>.

In classic TMS experiments, stimulation is delivered to the primary motor cortex (M1), and motor evoked potentials (MEPs) from a muscle or set of muscles are recorded with surface electromyography (EMG) electrodes. The intensity of TMS is typically given as a multiple or percentage of the threshold intensity for evoking MEPs of a certain amplitude in a specified fraction of a series of consecutive trials in a hand muscle (Fig 2).

Studies show that in human the resting motor threshold varies greatly, thus are critical the measures of intensity that take into account the biological efficacy of the stimulus in the individual subject. The threshold for eliciting MEPs in a muscle is most often used as the unit of stimulus intensity, and subsequently is usually to stimulate the brain over the threshold (110%-120% of motor threshold) to investigate MEPs response<sup>(28)</sup>.



**Figure 2:** Motor evoked potential (MEP).

TMS induces electrical currents in the brain via Faraday's principle of electromagnetic induction<sup>(29)</sup>. Put simply, Faraday discovered that a pulse of electric current sent through a wire coil generates a magnetic field. The rate of changes of this magnetic field determines the induction of a secondary current in a nearby conductor. With regard to TMS, an electric pulse, which grows to peak strength and diminishes back to zero in a short period of time (<1 ms), is sent through the conductive wiring within the TMS coil. The rapid fluctuation of this current produces a magnetic field perpendicular to the plane of the coil that similarly rise (up to about 2.5 T) and falls rapidly in time. This rapidly fluctuating magnetic field passes unimpeded through the subject's scalp and skull and induces a current in the brain in the opposite direction of the original current<sup>(30-33)</sup>.

In general, TMS is unique among the neurostimulation methods in its roles as a therapeutic intervention as well as an experimental and diagnostic tool. Three TMS protocols have been used extensively to study, measure, and modulate cortical excitability using Single Pulse TMS (the cortex is stimulated once to elicit an evoked response), Paired-Pulse TMS (paradigms provide measures of intracortical inhibition and facilitation, thought to be mediated by gamma-aminobutyric acid (GABA)-ergic and glutamatergic activity, respectively) and more over<sup>(51-67)</sup>.

### **Facilitation**

When TMS is performed with the target muscle steadily contracting, it shows different results than when the muscle is relaxed. Muscle contraction has three main effects<sup>(34)</sup>: the threshold for evoking the motor response is reduced, the latency of the MEP is shortened, and the amplitude of the

MEP is markedly increased<sup>(35)</sup>. These facilitatory effects can also be induced simply by the subject's thinking about the maneuver or contraction of another muscle (either on the same or opposite side), but the extent of facilitation is less than that induced by contraction of the target muscle<sup>(36)</sup>.

The underlying mechanisms for facilitation are not entirely understood but likely include increased cortical and spinal excitability<sup>(37)</sup>. With voluntary contraction, the resting potential of the anterior horn cell (AHC) is closer to threshold, requiring less temporal summation of descending volleys, which means that the discharge can occur at an earlier I or D wave, thus shortening the onset latency. Furthermore, with increasing force, according to the Henneman size principle, larger and faster conducting spinal motoneurons will be recruited, thus shortening the onset latency. The increase of the compound muscle action potential amplitude indicates recruitment of a greater number of spinal motoneurons. This could also be due to increased spinal excitability, increased synchronization of spinal motoneuron firing, or an increasing number of I waves bringing more AHCs to threshold.

### **TMS as a tool to investigate cortical excitability in athletes**

As a non-invasive technique, TMS and neuroimaging techniques have been largely used to investigate adaptive changes in human motor cortex, contributing to understand how brain networks can optimize motor programs responsible for coordination of muscle activity involved in complex motor learning<sup>(31,59)</sup>.

Currents used by TMS cause activity in specific parts of the brain, with minimal discomfort also in children, allowing the study of neural functions, interconnections and dysfunctions. TMS can stimulate deep neural structures such as motor cortex, and allows to investigate the brain integrity to muscle pathway and functionality of cortical network. In this light, motor evoked potential (MEP) from peripheral muscles and motor cortex excitability become relevant in TMS studies.

The repetitive practice of simple movements such as fingers ballistic movements highlighted motor cortex adaptations with similarity to motor learning processes. The improvement in task performance was accompanied by an immediate increase in MEP response, and cross-sectional studies have revealed comparable changes among indi-

viduals with varying degrees of motor skills. TMS could be suitable for investigating the effect of acute exercise, considering the augmented amplitudes of MEP as result of acute exercise bouts, substantiating the increased neuronal excitability during fatigue<sup>(60-80)</sup>.

In sport competition, the fatigue has large influence in performance, while fatigue refers to any exercise inducing loss of ability to exert force or power with a muscle or a muscle group<sup>(46-50)</sup>, due to changes in the excitability of the motor pathway both at central and peripheral levels<sup>(51-53)</sup>. When subject performs the maximal voluntary contraction, component fatigue is ascribed not only to peripheral factors but also to central factors that play a role in the decline in force which results from a sub optimal output from the primary motor cortex, which ultimately leads to sub-optimal firing rates of motor neurons. When a subject performs an incremental exhaustive exercise, there is a rapidly decrease in muscle phosphocreatine and ATP, as well as an accumulation of metabolites like pyruvate and lactate<sup>(54-60)</sup>.

TMS study in sports-specific motor activities are still scarce, although TMS may open new windows in many different research areas in sport science disciplines. Kinesiology-related research issues for which TMS has already been, or could potentially be applied, include: (i) post-exercise facilitation, (ii) central fatigue, (iii) sensorimotor integration and co-ordination, and (iv) neuronal plasticity. When a subject performs a weak voluntary contraction of a muscle, the corticospinal pathway to that muscle is facilitated<sup>(74)</sup>.

As already mentioned, most facilitatory effects occur at low contraction forces. Additionally, higher MEP potentiation has been reported for precision movements as compared to general grip tasks, presumably because of the larger involvement of pyramidal tract neurons in such tasks<sup>(75)</sup>. A spread of facilitatory effects has also been shown during a voluntary contraction of neighbouring ipsilateral or homonymous contralateral muscles, but other reports give opposing<sup>(40)</sup>. Besides the immediate influence of the voluntary motor activity, there are also prolonged postexercise MEP potentiation effects<sup>(76)</sup>.

TMS has also been used to assess supraspinal fatigue of isolated working small muscle groups quantifying the contribution of central processes to fatigue of limb locomotor muscles.

Moreover, TMS can be used to investigate physiological states other than fatigue, as showed by the fact that neuromuscular adaptation readily occurs as a result of resistance exercise training<sup>(15)</sup>. The primary motor cortex (M1) is heavily involved in voluntary contraction of skeletal muscle and shows a high degree of plasticity, or capacity to change quickly, with motor practice<sup>(38,41)</sup>, and classically 20 min practice of a ballistic pinching task can elicit a significant improvement in task performance. The improvement in task performance was accompanied by an immediate increase in corticospinal response (MEP), demonstrating that M1 has an adaptive role in the consolidation of motor tasks.

Therefore, TMS enables a greater understanding of the behaviour of the corticospinal tract in 'top-down' paradigms, where the effect of motor skills on corticospinal plasticity and neuromuscular adaptation can be examined.

## References

- 1) Messina G, De Luca V, Viggiano A, Ascione A, Iannaccone T, Chieffi S, Monda M. Autonomic nervous system in the control of energy balance and body weight: personal contributions. *Neurol Res Int.* 2013; 1-5. doi:10.1155/2013/639280.
- 2) Monda M, Messina G, Vicidomini C, Viggiano A, Mangoni C, De Luca B. Activity of autonomic nervous system is related to body weight in pre-menopausal, but not in postmenopausal women. *Nutr Neurosci.* 2006; 9(3-4): 141-5.
- 3) Monda M, Viggiano A, Viggiano A, Viggiano E, Messina G, Tafuri D, De Luca V. Sympathetic and hyperthermic reactions by orexin A: Role of cerebral catecholaminergic neurons. *Regul Pept.* 2007; 139(1-3): 39-44. doi:10.1016/j.regpep.2006.10.002.
- 4) Messina G, Dalia C, Tafuri D, Monda V, Palmieri F, Dato A, Russo A, De Blasio S, Messina A, De Luca V, Chieffi S, Monda M. Orexin-A controls sympathetic activity and eating behavior. *Front Psychol.* 2014; 5: 997. doi:10.3389/fpsyg.2014.00997.
- 5) Monda M, Messina G, Mangoni C, De Luca B. Resting energy expenditure and fat-free mass do not decline during aging in severely obese women. *Clin Nutr.* 2008; 27(4): 657-9. doi:10.1016/j.clnu.2008.04.005.
- 6) Monda M, Viggiano A, Viggiano A, Mondola R, Viggiano E, Messina G, Tafuri D, De Luca V. Olanzapine blocks the sympathetic and hyperthermic reactions due to cerebral injection of orexin A. *Peptides.* 2008; 29(1): 120-126. doi:10.1016/j.peptides.2007.10.016.
- 7) Esposito M, Serpe FP, Diletti G, Messina G, Scortichini G, La Rocca C, Baldi L, Amorena M, Monda M. Serum levels of polychlorinated dibenzo-p-

- dioxins, polychlorinated dibenzofurans and polychlorinated biphenyls in a population living in the Naples area, southern Italy. *Chemosphere*. 2014; 94: 62-69. doi:10.1016/j.chemosphere.2013.09.013.
- 8) De Luca V, Viggiano E, Messina G, Viggiano A, Borlido C, Viggiano A, Monda M. Peripheral amino Acid levels in schizophrenia and antipsychotic treatment. *Psychiatry Investig*. 2008; 5(4): 203-8. doi:10.4306/pi.2008.5.4.203.
  - 9) Messina G, Vicidomini C, Viggiano A, Tafuri D, Cozza V, Cibelli G, Devastato A, De Luca B, Monda M. Enhanced parasympathetic activity of sportive women is paradoxically associated to enhanced resting energy expenditure. *Auton Neurosci Basic Clin*. 2012; 169(2): 102-106. doi:10.1016/j.autneu.2012.05.003.
  - 10) Monda M, Viggiano A, Viggiano A, Viggiano E, Messina G, Tafuri D, De Luca V. Quetiapine lowers sympathetic and hyperthermic reactions due to cerebral injection of orexin A. *Neuropeptides*. 2006; 40(5): 357-63. doi:10.1016/j.npep.2006.07.003.
  - 11) Viggiano A, Vicidomini C, Monda M, Carleo D, Carleo R, Messina G, Viggiano A, Viggiano E, De Luca B. Fast and low-cost analysis of heart rate variability reveals vegetative alterations in noncomplicated diabetic patients. *J Diabetes Complications*. 2009; 23(2): 119-123. doi:10.1016/j.jdiacomp.2007.11.009.
  - 12) Di Bernardo G, Messina G, Capasso S, Del Gaudio S, Cipollaro M, Peluso G, Casale F, Monda M, Galderisi U. Sera of overweight people promote in vitro adipocyte differentiation of bone marrow stromal cells. *Stem Cell Res Ther*. 2014; 5(1): 4. doi:10.1186/scrt393;
  - 13) Viggiano A, Nicodemo U, Viggiano E, Messina G, Viggiano A, Monda M, De Luca B. Mastication overload causes an increase in O<sub>2</sub> - production into the subnucleus oralis of the spinal trigeminal nucleus. *Neuroscience*. 2010; 166(2): 416-421. doi:10.1016/j.neuroscience.2009.12.071.
  - 14) Viggiano A, Chieffi S, Tafuri D, Messina G, Monda M, De Luca B. Laterality of a second player position affects lateral deviation of basketball shooting. *J Sports Sci*. 2013; (October 2013): 37-41. doi:10.1080/02640414.2013.805236;
  - 15) Chieffi S, Iavarone A, Iaccarino L, La Marra M, Messina G, De Luca V, Monda M. Age related differences in distractor interference on line bisection. *Exp Brain Res*. 2014; 232(11): 3659-64. doi:10.1007/s00221-014-4056-0.
  - 16) Chieffi S, Iachini T, Iavarone A, Messina G, Viggiano A, Monda M. Flanker interference effects in a line bisection task. *Exp Brain Res*. 2014; 232(4): 1327-1334. doi:10.1007/s00221-014-3851-y.
  - 17) Monda M, Messina G, Scognamiglio I, Lombardi A, Martin GA, Sperlongano P, Porcelli M, Caraglia M, Stiuso P. Short-term diet and moderate exercise in young overweight men modulate cardiocyte and hepatocarcinoma survival by oxidative stress. *Oxid Med Cell Longev*. 2014; 2014. doi:10.1155/2014/131024.
  - 18) Triggiani AI, Valenzano A, Ciliberti MA, Moscatelli F, Villani S, Monda M, Messina G, Federici A, Babiloni C, Cibelli G. Heart rate variability is reduced in underweight and overweight healthy adult women. *Clin Physiol Funct Imaging*. 2015. doi:10.1111/cpf.12281.
  - 19) Messina G, Monda V, Moscatelli F, Valenzano A.A., Monda G, Esposito, T., Blasio, S.D., Messina, A., Tafuri, D., Barillari, M.R., Cibelli, G., Chieffi, S., Varriale, B., Monda, M. Role of orexin system in obesity. *Biol Med*. 2015; 7(4). doi:10.4172/0974-8369.1000248.
  - 20) Messina G, Palmieri, F., Monda V, Messina A, Dalia, C., Viggiano, A., Tafuri, D., Messina, A., Moscatelli, F., Valenzano, A., Cibelli, G., Chieffi, S., Monda, M. Exercise Causes Muscle GLUT4 Translocation in an Insulin-Independent Manner. *Biol Med*. 2015;s3. doi:10.4172/0974-8369.1000s3007.
  - 21) Valenzano A, Moscatelli F, Triggiani AI, Capranica L, De Ioannon G, Piacentini MF, Mignardi S, Messina G, Villani S, Cibelli G. Heart-Rate Changes After an Ultraendurance Swim From Italy to Albania: A Case Report. *Int J Sports Physiol Perform*. 2016; 11(3): 407-9. doi:10.1123/ijsp.2015-0035.
  - 22) Moscatelli, F., Messina, G., Valenzano, A., Petito, A., Triggiani, A.I., Ciliberti, M.A.P., Monda, V., Messina, A., Tafuri, D., Capranica, L., Cibelli, G., Monda, M. Relationship between RPE and Blood Lactate after Fatiguing Handgrip Exercise in Taekwondo and Sedentary Subjects. *Biol Med*. 2015. doi:http://dx.doi.org/10.4172/0974-8369.1000s3008.
  - 23) Rinaldi B, Guida F, Furiano A, Donniacuo M, Luongo L, Gritti G, Urbanek K, Messina G, Maione S, Rossi F, de Novellis V. Effect of Prolonged Moderate Exercise on the Changes of Nonneuronal Cells in Early Myocardial Infarction. *Neural Plast*. 2015; 2015:265967. doi:10.1155/2015/265967.
  - 24) Messina, G., Viggiano, A., Tafuri, D., Palmieri, F., De Blasio, S., Messina, A., De Luca, A., Chieffi, S., Monda, M. Role of orexin in obese patients in the intensive care unit. *J Anesth Clin Res*. 2014; 5(3). doi:10.4172/2155-6148.1000395.
  - 25) Messina, G., Zannella, C., Monda, V., Dato, A., Liccardo, D., De Blasio, S., Valenzano, A., Moscatelli, F., Messina, A., Cibelli, G., Monda, M. The Beneficial Effects of Coffee in Human Nutrition. 2015; 7(4). doi:10.4172/0974-8369.1000.
  - 26) Messina A, De Fusco C, Monda V, Esposito M, Moscatelli F, Valenzano A, Carotenuto M, Viggiano E, Chieffi S, De Luca V, Cibelli G, Monda M, Messina G. Role of the Orexin System on the Hypothalamus-Pituitary-Thyroid Axis. *Front Neural Circuits*. 2016; 10:66. doi:10.3389/fncir.2016.00066.
  - 27) Mazzeo, F., Motti, M.L., Messina, G., Monda, V., Ascione, A., Tafuri, D., Palmieri, F., Messina, A., Monda, M. Use of nutritional supplements among south Italian students of physical training and sport university. *Curr Top Toxicol*. 2013; 9: 21-26.
  - 28) Chieffi, S., Iavarone, A., La Marra, M., Messina, G., Dalia, C., Viggiano, A., De Luca, V., Monda, M. Vulnerability to Distraction in Schizophrenia. *J PSYCHIATRY*. 2015; 18(2). doi:10.4172/1994-8220.1000228;
  - 29) Esposito, T., Viggiano, An., Viggiano, Al., Viggiano, E., Giovane, A., Varriale, B., Messina, G., De Luca, V., Monda, M. ICV injection of orexin A induces synthesis of total RNA and mRNA encoding preorexin in various cerebral regions of the rat. *J Therm Biol*. 2006; 31(7): 527-532. doi:10.1016/j.jtherbio.2006.07.002.
  - 30) Messina G, Di Bernardo G, Viggiano A, De Luca V, Monda V, Messina A, Chieffi S, Galderisi U, Monda M. Exercise increases the level of plasma orexin A in

- humans. *J Basic Clin Physiol Pharmacol.* 2016; 27(6): 611-616. doi:10.1515/jbcp-2015-0133.
- 31) Viggiano E, Monda V, Messina A, Moscatelli F, Valenzano A, Tafuri D, Cibelli G, De Luca B, Messina G, Monda M. Cortical spreading depression produces a neuroprotective effect activating mitochondrial uncoupling protein-5. *Neuropsychiatr Dis Treat.* 2016; 12: 1705-10. doi:10.2147/NDT.S107074.
- 32) Moscatelli F, Messina G, Valenzano A, Monda V, Viggiano A, Messina A, Petito A, Triggiani AI, Ciliberti MA, Monda M, Capranica L, Cibelli G. Functional Assessment of Corticospinal System Excitability in Karate Athletes. *PLoS One.* 2016; 11(5): e0155998. doi:10.1371/journal.pone.0155998.
- 33) Messina, G., Valenzano, A., Moscatelli, F., Triggiani, A.I., Capranica, L., Messina, A., Piombino, L., Tafuri, D., Cibelli, G., Monda, M. Effects of Emotional Stress on Neuroendocrine and Autonomic Functions in Skydiving. *J PSYCHIATRY.* 2015; 18(4). doi:10.4172/2378-5756.1000280.
- 34) Moscatelli F, Valenzano A, Petito A, Triggiani AI, Ciliberti MAP, Luongo L, Carotenuto M, Esposito M, Messina A, Monda V, Monda M, Capranica L, Messina G, Cibelli G. Relationship between blood lactate and cortical excitability between taekwondo athletes and non-athletes after hand-grip exercise. *Somatosens Mot Res.* 2016; 33(2): 137-44; doi:10.1080/08990220.2016.1203305.
- 35) De Fusco C, Messina A, Monda V, Viggiano E, Moscatelli F, Valenzano A, Esposito T, Sergio C, Cibelli G, Monda M, Messina G. Osteopontin: Relation between Adipose Tissue and Bone Homeostasis. *Stem Cells Int.* 2017; 2017:4045238. doi: 10.1155/2017/4045238.
- 36) Villano I, Messina A, Valenzano A, Moscatelli F, Esposito T, Monda V, Esposito M, Precenzano F, Carotenuto M, Viggiano A, Chieffi S, Cibelli G, Monda M, Messina G. Basal.
- 37) Forebrain Cholinergic System and Orexin Neurons: Effects on Attention. *Front Behav Neurosci.* 2017 Jan 31; 11: 10. doi: 10.3389/fnbeh.2017.00010;
- 38) Fiorelli A, Messina G, Chiodini P, Costanzo S, Viggiano A, Monda M, Vicidomini G, Santini M. Cardiac Autonomic Changes After Thoracic Sympathectomy: A Prospective, Randomized Study. *Ann Thorac Surg.* 2017 Jan; 103(1): 216-224. doi: 10.1016/j.athoracsur.2016.10.055.
- 39) Messina G, Chieffi S, Viggiano A, Tafuri D, Cibelli G, Valenzano A, Triggiani AI, Messina A, De Luca V, Monda M. Parachute Jumping Induces More Sympathetic Activation Than Cortisol Secretion in First-Time Parachutists. *Asian J Sports Med.* 2016 Mar 8; 7(1): e26841. doi: 10.5812/asjms.26841.
- 40) Esposito M, Gimigliano F, Barillari MR, Precenzano F, Ruberto M, Sepe J, Barillari U, Gimigliano R, Militerni R, Messina G, Carotenuto M. Pediatric selective mutism therapy: a randomized controlled trial. *Eur J Phys Rehabil Med.* 2016 Nov 10.
- 41) Messina, G., Viggiano, E., Monda, V., Messina, A., Moscatelli, F., Valenzano, A., Tafuri, D., de Luca, V., Cibelli, G., Monda, M. Neuroprotection and acidosis induced by cortical spreading depression. *Neuropsychiatr Dis Treat.* 2016; 12: 3193-3194.
- 42) Mazzeo, F., Monda, M., Messina, G., Santamaria, S., Messina, A., Montesano, M., Monda, V., Tafuri, D. Doping in Italy: An analysis of its spread in ten years. *Biol Med.* 2016; 8: 1000263 doi: 10.4172/0974-8369.1000263.
- 43) Monda, V., Valenzano, A., Moscatelli, F., Messina, A., Piombino, L., Zannella, C., Viggiano, E., Monda, G., De Luca, V., Chieffi, S., Villano, I., Tafuri, D., Russo, L., Dalia, C.; Viggiano, A., Cibelli, G., Messina, G., Monda, M. Modifications of activity of autonomic nervous system, and resting energy expenditure in women using hormone-replacement therapy. *Biol Med.* 2016; 8(5): 1000306 doi: 10.4172/0974-8369.1000306.
- 44) Aurilio, C., Pace, M.C., Passavanti, M.B., Pota, V., Sansone, P., Barbarisi, M., Rossi, A., Coaccioli, S., Chieffi, S., Messina, G., Monda, M. Chronic pain pharmacological treatment in patients with depressive disorders. *African Journal of Psychiatry* 2015; 18(5): 1000307 doi: 10.4172/2378-5756.1000307.
- 45) Messina, G., Viggiano, A., Chieffi, S., Viggiano, E., Tafuri, D., De Luca, V., Messina, A., Monda, M. Neuroleptic drugs affect sympathetic and thermogenic reactions to orexin A. *African Journal of Psychiatry* 2014; 17(6): 1000172 doi: 10.4172/Psychiatry.1000172.
- 46) Precenzano F, Ruberto M, Parisi L, Salerno M, Maltese A, Vagliano C, Messina G, Di Folco A, Di Filippo T, Michele Roccella. Executive functioning in preschool children affected by autism spectrum disorder: a pilot study. *Acta Medica Mediterranea*, 2017, 33: 35-39; DOI: 10.19193/0393-6384\_2017\_1\_005.
- 47) Precenzano F, Lombardi P, Ruberto M, Parisi L, Salerno M, Maltese A, D'alessandro I, Della Valle I, Magliulo RM, Messina G, Roccella M. Internalizing symptoms in children affected by childhood absence epilepsy: a preliminary study. *Acta Medica Mediterranea*, 2016, 32: 1749-1753; DOI: 10.19193/0393-6384\_2016\_6\_158.
- 48) Iavarone A, Patruno M, Galeone F, Chieffi S, Carlomagno S. Brief report: error pattern in an autistic savant calendar calculator. *J Autism Dev Disord.* 2007 Apr; 37(4): 775-9.
- 49) Precenzano F, Ruberto M, Parisi L, Salerno M, Maltese A, D'alessandro I, Grappa MF, Magliulo RM, Messina G, Roccella M. Borderline intellectual functioning and parental stress: an Italian case-control study. *Acta Medica Mediterranea*, 2016, 32: 1761-1765; DOI: 10.19193/0393-6384\_2016\_6\_160.
- 50) Ruberto M, Precenzano F, Parisi L, Salerno M, Maltese A, Messina G, Roccella M. Visuomotor integration skills in children affected by obstructive sleep apnea syndrome: a case-control study. *Acta Medica Mediterranea*, 2016, 32: 1659; DOI: 10.19193/0393-6384\_2016\_5\_146.
- 51) Esposito M, Precenzano F, Sorrentino M, Avolio D, Carotenuto M. A Medical Food Formulation of Griffonia simplicifolia/Magnesium for Childhood Periodic Syndrome Therapy: An Open-Label Study on Motion Sickness. *J Med Food.* 2015 Aug; 18(8): 916-20. doi: 10.1089/jmf.2014.0113.
- 52) Esposito M, Gallai B, Parisi L, Roccella M, Marotta R, Lavano SM, Mazzotta G, Patriciello G, Precenzano F, Carotenuto M. Visuomotor competencies and primary monosymptomatic nocturnal enuresis in prepubertal

- aged children. *Neuropsychiatr Dis Treat.* 2013; 9: 921-6. doi: 10.2147/NDT.S46772.
- 53) Esposito M, Parisi P, Miano S, Carotenuto M. Migraine and periodic limb movement disorders in sleep in children: a preliminary case-control study. *J Headache Pain.* 2013 Jul 1; 14:57. doi: 10.1186/1129-2377-14-57;
- 54) Carotenuto M, Gimigliano F, Fiordelisi G, Ruberto M, Esposito M. Positional abnormalities during sleep in children affected by obstructive sleep apnea syndrome: the putative role of kinetic muscular chains. *Med Hypotheses.* 2013 Aug;81(2): 306-8. doi: 10.1016/j.mehy.2013.04.023.
- 55) Esposito M, Gallai B, Parisi L, Roccella M, Marotta R, Lavano SM, Gritti A, Mazzotta G, Carotenuto M. Maternal stress and childhood migraine: a new perspective on management. *Neuropsychiatr Dis Treat.* 2013;9:351-5. doi: 10.2147/NDT.S42818.
- 56) Esposito M, Carotenuto M. Intellectual disabilities and power spectra analysis during sleep: a new perspective on borderline intellectual functioning. *J Intellect Disabil Res.* 2014 May; 58(5): 421-9. doi: 10.1111/jir.12036.
- 57) Esposito M, Roccella M, Parisi L, Gallai B, Carotenuto M. Hypersomnia in children affected by migraine without aura: a questionnaire-based case-control study. *Neuropsychiatr Dis Treat.* 2013; 9: 289-94. doi: 10.2147/NDT.S42182.
- 58) Carotenuto M, Esposito M. Nutraceuticals safety and efficacy in migraine without aura in a population of children affected by neurofibromatosis type I. *Neurol Sci.* 2013 Nov; 34(11): 1905-9.
- 59) Carotenuto M, Gallai B, Parisi L, Roccella M, Esposito M. Acupressure therapy for insomnia in adolescents: a polysomnographic study. *Neuropsychiatr Dis Treat.* 2013; 9: 157-62. doi: 10.2147/NDT.S41892.
- 60) Esposito M, Pascotto A, Gallai B, Parisi L, Roccella M, Marotta R, Lavano SM, Gritti A, Mazzotta G, Carotenuto M. Can headache impair intellectual abilities in children? An observational study. *Neuropsychiatr Dis Treat.* 2012;8:509-13. doi: 10.2147/NDT.S36863.
- 61) Carotenuto M, Esposito M, D'Aniello A, Ripa CD, Precenzano F, Pascotto A, Bravaccio C, Elia M. Polysomnographic findings in Rett syndrome: a case-control study. *Sleep Breath.* 2013 Mar;17(1):93-8. doi: 10.1007/s11325-012-0654-x. Erratum in: *Sleep Breath.* 2013 May; 17(2): 877-8.
- 62) Esposito M, Carotenuto M, Roccella M. Primary nocturnal enuresis and learning disability. *Minerva Pediatr.* 2011 Apr; 63(2): 99-104.
- 63) Carotenuto M, Esposito M, Pascotto A. Migraine and enuresis in children: An unusual correlation? *Med Hypotheses.* 2010 Jul; 75(1): 120-2. doi: 10.1016/j.mehy.2010.02.004.
- 64) Perillo L, Esposito M, Caprioglio A, Attanasio S, Santini AC, Carotenuto M. Orthodontic treatment need for adolescents in the Campania region: the malocclusion impact on self-concept. *Patient Prefer Adherence.* 2014 Mar 19; 8: 353-9. doi: 10.2147/PPA.S58971.
- 65) Carotenuto M, Esposito M, Precenzano F, Castaldo L, Roccella M. Cosleeping in childhood migraine. *Minerva Pediatr.* 2011 Apr; 63(2): 105-9.
- 66) Verrotti A, Casciato S, Spalice A, Carotenuto M, Striano P, Parisi P, Zamponi N, Savasta S, Rinaldi VE, D'Alonzo R, Mecarini F, Ritaccio AJ, Di Gennaro G. Coexistence of childhood absence epilepsy and benign epilepsy with centrotemporal spikes: A case series. *Eur J Paediatr Neurol.* 2017 Feb 14. pii: S1090-3798(17)30105-8. doi: 10.1016/j.ejpn.2017.02.002.
- 67) Toldo I, Rattin M, Perissinotto E, De Carlo D, Bolzonella B, Nosadini M, Rossi LN, Vecchio A, Simonati A, Carotenuto M, Scalas C, Sciruicchio V, Raieli V, Mazzotta G, Tozzi E, Valeriani M, Cianchetti C, Balottin U, Guidetti V, Sartori S, Battistella PA. Survey on treatments for primary headaches in 13 specialized juvenile Headache Centers: The first multicenter Italian study. *Eur J Paediatr Neurol.* 2016 Dec 31. pii: S1090-3798(16)30299-9. doi: 10.1016/j.ejpn.2016.12.009.
- 68) Matricardi S, Spalice A, Salpietro V, Di Rosa G, Balistreri MC, Grosso S, Parisi P, Elia M, Striano P, Accorsi P, Cusmai R, Specchio N, Coppola G, Savasta S, Carotenuto M, Tozzi E, Ferrara P, Ruggieri M, Verrotti A. Epilepsy in the setting of full trisomy 18: A multicenter study on 18 affected children with and without structural brain abnormalities. *Am J Med Genet C Semin Med Genet.* 2016 Sep; 172(3): 288-95. doi: 10.1002/ajmg.c.31513.
- 69) Carotenuto M, Esposito M, Cortese S, Laino D, Verrotti A. Children with developmental dyslexia showed greater sleep disturbances than controls, including problems initiating and maintaining sleep. *Acta Paediatr.* 2016 Sep; 105(9): 1079-82. doi: 10.1111/apa.13472.
- 70) Franzoni E, Matricardi S, Di Pisa V, Capovilla G, Romeo A, Tozzi E, Pruna D, Salerno GG, Zamponi N, Accorsi P, Giordano L, Coppola G, Cerminara C, Curatolo P, Nicita F, Spalice A, Grosso S, Pavone P, Striano P, Parisi P, Boni A, Gobbi G, Carotenuto M, Esposito M, Cottone C, Verrotti A. Refractory absence seizures: An Italian multicenter retrospective study. *Eur J Paediatr Neurol.* 2015 Nov; 19(6): 660-4. doi: 10.1016/j.ejpn.2015.07.008.
- 71) Morandi A, Bonnefond A, Lobbens S, Carotenuto M, Del Giudice EM, Froguel P, Maffei C. A girl with incomplete Prader-Willi syndrome and negative MS-PCR, found to have mosaic maternal UPD-15 at SNP array. *Am J Med Genet A.* 2015 Nov; 167A(11): 2720-6. doi: 10.1002/ajmg.a.37222.
- 72) Pasquali D, Carotenuto M, Leporati P, Esposito M, Antinolfi L, Esposito D, Accardo G, Carella C, Chiovato L, Rotondi M. Maternal hypothyroidism and subsequent neuropsychological outcome of the progeny: a family portrait. *Endocrine.* 2015 Dec; 50(3): 797-801. doi: 10.1007/s12020-015-0564-3.
- 73) Esposito M, Precenzano F, Sorrentino M, Avolio D, Carotenuto M. A Medical Food Formulation of Griffonia simplicifolia/Magnesium for Childhood Periodic Syndrome Therapy: An Open-Label Study on Motion Sickness. *J Med Food.* 2015 Aug; 18(8): 916-20. doi: 10.1089/jmf.2014.0113.
- 74) Esposito M, Gallai B, Roccella M, Marotta R, Lavano F, Lavano SM, Mazzotta G, Bove D, Sorrentino M, Precenzano F, Carotenuto M. Anxiety and depression levels in prepubertal obese children: a case-control study. *Neuropsychiatr Dis Treat.* 2014 Oct 3; 10: 1897-902. doi: 10.2147/NDT.S69795.
- 75) Carotenuto M, Parisi P, Esposito M, Cortese S, Elia M.

- Sleep alterations in children with refractory epileptic encephalopathies: a polysomnographic study. *Epilepsy Behav.* 2014 Jun; 35:50-3. doi: 10.1016/j.yebeh.2014.03.009.
- 76) Esposito M, Marotta R, Roccella M, Gallai B, Parisi L, Lavano SM, Carotenuto M. Pediatric neurofibromatosis 1 and parental stress: a multicenter study. *Neuropsychiatr Dis Treat.* 2014 Jan 22;10:141-6. doi: 10.2147/NDT.S55518.
- 77) Esposito M, Ruberto M, Gimigliano F, Marotta R, Gallai B, Parisi L, Lavano SM, Roccella M, Carotenuto M. Effectiveness and safety of Nintendo Wii Fit Plus™ training in children with migraine without aura: a preliminary study. *Neuropsychiatr Dis Treat.* 2013; 9: 1803-10. doi: 10.2147/NDT.S53853.
- 78) Esposito M, Gimigliano F, Ruberto M, Marotta R, Gallai B, Parisi L, Lavano SM, Mazzotta G, Roccella M, Carotenuto M. Psychomotor approach in children affected by nonretentive fecal soiling (FNRFS): a new rehabilitative purpose. *Neuropsychiatr Dis Treat.* 2013; 9: 1433-41. doi: 10.2147/NDT.S51257.
- 79) Esposito M, Parisi L, Gallai B, Marotta R, Di Dona A, Lavano SM, Roccella M, Carotenuto M. Attachment styles in children affected by migraine without aura. *Neuropsychiatr Dis Treat.* 2013; 9: 1513-9. doi: 10.2147/NDT.S52716.
- 80) Esposito M, Gallai B, Parisi L, Castaldo L, Marotta R, Lavano SM, Mazzotta G, Roccella M, Carotenuto M. Self-concept evaluation and migraine without aura in childhood. *Neuropsychiatr Dis Treat.* 2013; 9: 1061-6. doi: 10.2147/NDT.S49364.

---

*Corresponding author*

ANTONIETTA MESSINA, MD; Ph.D  
Department of Experimental Medicine,  
Section of Human Physiology, and Clinical Dietetic Service  
Università degli Studi della Campania "Luigi Vanvitelli"  
Via Costantinopoli 16  
80138 Naples  
(Italy)