

# High frequency heart rate variability evoked by repetitive transcranial magnetic stimulation over the medial prefrontal cortex: A preliminary investigation on brain processing of acute stressor-evoked cardiovascular reactivity

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## ABSTRACT

**Introduction:** Transcranial Magnetic Stimulation (TMS) is a non-invasive technique for brain stimulation. Repetitive TMS (rTMS) over the medial Prefrontal Cortex (mPFC), Brodmann Area 10 (BA10) may stimulate transynaptically perigenual Anterior Cingulate Cortex (pACC, BA 33), insula, amygdala, hypothalamus and connected branches of the Autonomic Nervous System (ANS) involved in stressor-evoked cardiovascular reactivity. Stressors are associated with an increase in sympathetic cardiac control, a decrease in parasympathetic control, or both, and, consequently, an increase in systolic/stroke volume, total vascular impedance/resistance and heart rate, a decrease of baroreflex sensitivity, *i.e.*, an increase in blood pressure/arterial tension. **Objectives and Aims:** The present work aims, using TMS and accordingly to Gianaros modeling, based on functional neuroimaging studies and previous neuroanatomical data from animal models, to probe the connectivity of brain systems involved in stressor-evoked cardiovascular reactivity and to explore TMS potential as a tool for detection and stratification of individual differences concerning this reactivity and hemoreological risk factors correlated with the development of Coronary Heart Disease (CHD). **Methods:** Both subjects, a 52 years old male and a 40 years old female with previous increased Low Frequency (LF)/High Frequency (HF) Heart Rate Variability (HRV) ratios

(respectively, 4.209/3.028) without decompensated cardiorespiratory symptoms, gave informed consent, and ethico-legal issues have been observed. Electroencephalographic (EEG) monitoring has been performed for safety purposes. Immediately after administration, over the mPFC, of 15 pulses of rTMS, during 60 second, with an inductive electrical current, at the stimulating coil, of 85.9 Ampère per µsecond and 66 Ampère per µsecond, respectively, for male and female subjects (a “figure-of-eight” coil and magnetic stimulator MagLite, Dantec/Medtronic, have been used), HRV spectrum analysis (cStress software) has been performed (during 5 minutes, in supine position). **Results:** In both subjects, LF power, HF power and LF/HF ratio results, before and after rTMS administration, pointed towards sympathetic attenuation and parasympathetic augmentation (respectively, in male/female subject: decreased LF power—65.1 nu/69.3 nu, before rTMS; 56.1 nu/41.6 nu, after rTMS; increased HF power—15.5 nu/22.9 nu, before rTMS; 30.9 nu/45.5 nu, after rTMS). **Conclusions:** In this preliminary investigation, the existence of a link between “mind” and heart’s function has been put in evidence, through a reversible “virtual” lesion, of brain systems involved in cardiovascular control, caused by TMS. Repetitive TMS over mPFC decreased brain function involved in stressor-evoked cardiovascular reactivity, suggesting the importance of TMS in the management of stress-related cardiovascular disorders.

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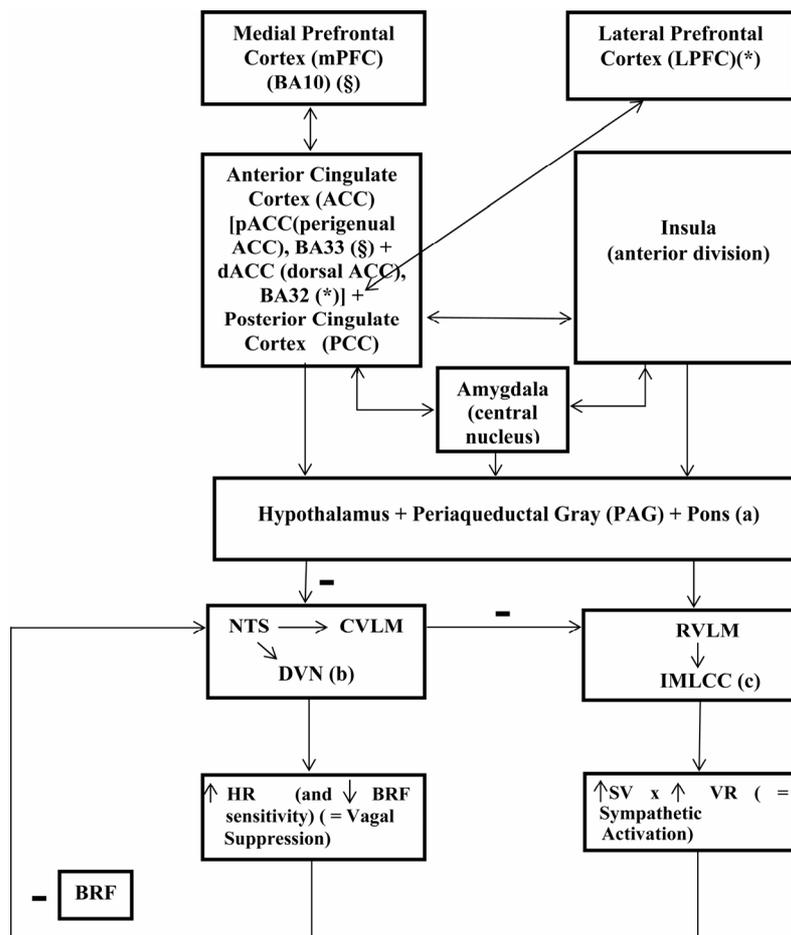
**Keywords:** Repetitive Transcranial Magnetic Stimulation (rTMS); Medial Prefrontal Cortex (mPFC); Anterior Cingulate Cortex (ACC); Amygdala; Autonomic Nervous System (ANS); Heart's Conducting System; Acute Sressor-Evoked Cardiovascular (Blood Pressure) Reactivity; Heart Rate Variability (HRV)

**1. INTRODUCTION**

**1.1. Acute Sressor-Evoked Cardiovascular Reactivity (Figure 1)**

Through neuroimaging studies, it has been made correlations between brain areas involved in individual blood

pressure (cardiovascular) reactivity and Coronary Heart Disease (CHD). Perigenual Anterior Cingulate Cortex (pACC), the affective division of cingulate cortex, is connected to circuits of the orbital and medial Prefrontal Cortex (mPFC), insula, amygdala, hypothalamus, Periaqueductal Gray (PAG), pons, medulla and the (pre-sympathetic) Inter-Medio-Lateral Cell Column of the spinal cord (IMLCC), and it supports stressor-evoked autonomic/cardiovascular reactivity [1-3]. Dorsal Anterior Cingulate Cortex (dACC), the cognitive-motor division of cingulate cortex, is connected to adjacent circuitry of the lateral PFC, motor/supplementary motor cortex and posterior parietal cortex, supports functions related with

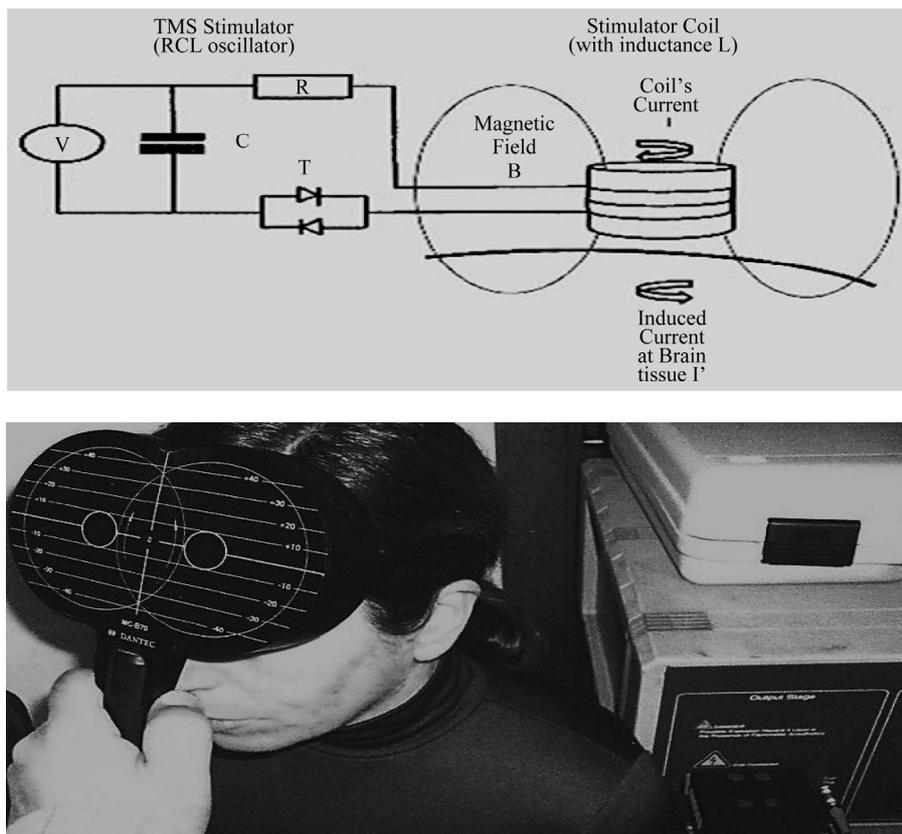


**Figure 1.** Processing of stressor-related information (stressor-evoked blood pressure/cardiovascular reactivity) by brain systems. Blood Pressure (BP) is a result of a multiplication consisting of three factors: Stroke Volume (SV), Heart Rate (HR) and Total Vascular Resistance (VR) (these factors are increased by stress). Baroreflex Feedback (BRF) and relations between (a), (b) and (c) blocks are inhibitory/negative (-) influences; the other relations are excitatory/positive influences. BA, Brodmann Area; NTS, Nucleus Tractus Solitarius; CVLM, Caudal Vento-Lateral Medulla; DVN, Dorsal Vagal Nucleus; NA, Nucleus Ambiguus; RVLM, Rostral Vento-Lateral Medullary; IMLCC, Inter-Medio-Lateral Cell Column; §, BA10 connects directly to BA33; \*, LPFC connects directly to BA32 (Model adapted from Peter Gianaros, 2008, with Elsevier and author's expressed permissions).

attention, executive control and conflict and error monitoring [4], and processes emotion-related physiologic reactivity and subjective distress—awareness of subjective emotional experiences [5], pain-related anxiety [6] and intentional regulation of autonomic activity [7]. Posterior Cingulate Cortex (PCC) supports evaluative processes related to cognition and emotion; research of Gianaros *et al.* revealed that processing of stressors by PCC may indirectly modulate autonomic/cardiovascular reactivity, through connections with pACC and dACC [8]. The insula, particularly the anterior division, presents efferent and afferent connections similar to those of ACC, *i.e.*, with amygdala, hypothalamus, thalamus, PAG, pons, Nucleus Tractus Solitarius (NTS) and medullary and brainstem areas that control pre-autonomic nuclei innervating peripheral target organs [9,10]; afferent projections from peripheral target organs provide insula with a “viscerotopic” map of the body [11]. Accordingly to Gianaros and Critchley, insula activation has been associated with stressor-evoked blood pressure reactivity [8, 12-19]. The amygdala is involved in the rapid assignment of emotional salience to environmental events [20-23]; its central nucleus sends information concerning behavioral adaptive changes and physiologic adjustments, through the stria terminalis, to lateral and paraventricular hypothalamic nuclei and to PAG, medullary, and pre-autonomic nuclei; the central nucleus of amygdala is also connected to dACC, pACC and insula [24-26]. The amygdala regulates BP reactivity through its interference with the Baroreflex (BRF). The BRF—a negative feedback control mechanism, for adjustment of Heart Rate (HR), Cardiac Output (CO) and Vascular Resistance (VR), in order to maintain Blood Pressure (BP) within a homeostatic range—relies on afferent projections, from cardiopulmonary mechanoreceptors and chemoreceptors, that signal changes in BP to the NTS: afferent activation of the NTS activates vagal nuclei in the medulla and, through signaling with the Caudal Ventro-Lateral Medulla (CVLM), inhibits pre-sympathetic nuclei in the Rostral Ventro-Lateral-Medulla (RVLM) and IMLCC. The amygdala can gate BRF, through inhibitory projections to the NTS and excitatory projections to the RVLM [27-29]. The ACC and insula can also gate the BRF, on exposure to acute stressors, allowing BP to exceed its regulatory set point [27,28,30]. Bernston *et al.* hypothesized that the amygdala and networked cortical areas may underlie individual cardiovascular reactivity by linking stressor-related processing with BRF suppression [27]. Resting levels of High-Frequency Heart Rate Variability (HF-HRV), an indicator of cardiac parasympathetic activity linked to cardiovascular disease risk, have been associated with PCC BOLD activation to grief-related stimuli in bereaved individuals [31,32].

## 1.2. Transcranial Magnetic Stimulation (TMS) (Figure 2)

Neuronal stimulation using TMS is achieved via the principles of electromagnetic induction. A stimulating coil is placed over the surface of the scalp, and, when the stimulator unit is discharged, a large current is transferred into the coil, generating a magnetic field, which induces a current within proximate electro-conductive tissues and generates action potentials in cortical neurons. The depth and focality of stimulation is influenced by the size and shape of the stimulating coil: with “figure-of-eight” coil, the magnetic field peaks along the intersection of the two windings. Single-pulse TMS, delivered individually (not coupled with another pulse), is used to: measure aspects of cortico-motor excitation and inhibition; map cortical representation; examine central motor encoding and conduction time; create temporary virtual lesions (disrupting cortical activity), useful in cognitive neuroscience studies [33-38]. Repetitive TMS (rTMS) is used to alter neuronal excitability of a specific region of the cortex, influencing cortical plasticity, and their effects depend upon the stimulation parameters applied. Determining stimulation intensity as a percentage of the resting stimulation-evoked motor threshold (the lowest stimulus intensity that gives rise to a 50  $\mu$ V evoked response, in the relaxed target muscle 50% of the time, following a train of at least 6 stimuli) reduces the effects of individual variability of motor cortex excitability [39-45]. Stimulation’s frequency is the most determinant of rTMS effect on cortical excitability. Low-frequency rTMS (1 Hz or less), at motor threshold intensities, suppresses cortical excitability, and the duration of this inhibitory effect is similar to the application’s one; high frequency, suprathreshold, stimulation, however, increases cortical excitability, and this period of hyperexcitability may last for minutes [46-50]. In healthy controls and in persons with neuropsychiatric disorders, rTMS can change cortical excitability that lasts beyond the stimulation’s period, and these effects may arise through Kindling/Long Term Potentiation (LTP) and Quenching/Long Term Depression (LTD) mechanisms in horizontal intracortical cells; also cortical stimulation propagates to secondarily connected cortical areas). Low-frequency rTMS, due to its resulting suppression of cortical excitability, is a potential treatment for disorders characterized by cortical hyperexcitability (e.g., Tourette’s syndrome); high-frequency rTMS is a potential treatment for motor and psychiatric disorders characterized by reduced cortical excitability (e.g., stroke, Parkinson’s disease, depressive disorders). A large number of these studies involve stimulation of the left Dorsolateral Prefrontal Cortex (DLPFC), because early rTMS investigations suggested a relationship between major



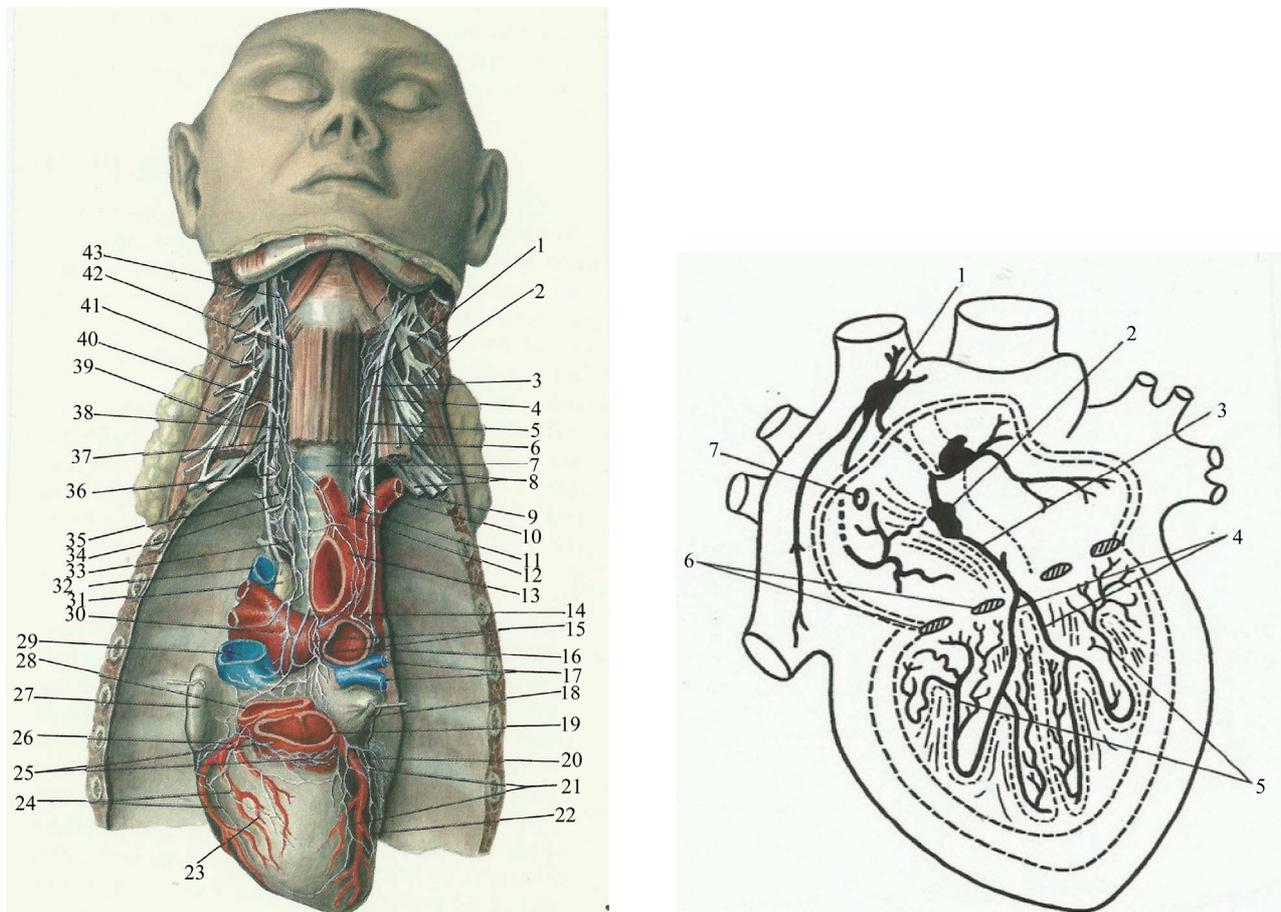
**Figure 2.** Top: Basic Transcranial Magnetic Stimulation (TMS) power electronics circuit. The TMS electronics circuit is a RCL oscillator, and consists of a Capacitor (with Capacitance  $C$ ), a Thyristor switch ( $T$ ), a stimulating coil (with Inductance  $L$ ) and a Resistance  $R$  (in the coil, cables). The Capacitor is first charged to some Kilovolt, and then discharged through the Coil, by gating the Thyristor into a conducting state. The resulting damped sinusoidal current pulse  $I$  has a peak value of 5 - 10 Kiloampere. Down: Magnetic Stimulator and “figure-of-eight” inductive stimulating coil, positioned over subject’s medial Prefrontal Cortex (mPFC).

depression and relative underactivity of the left DLPFC [51-58]. The most clinically effective rTMS parameters and the optimal site for stimulation in Stress related Disorders are not currently known. The target area of cortical stimulation for any TMS study should be determined according to the theorized underlying neurophysiology and the treatment goal. Procedures can be implemented to monitor for early detection of seizures and/or minimize risk of seizures—electroencephalography and/or electromyography monitoring can be used to check for signs of spread of excitation and after-discharges [59, 60].

### 1.3. Heart’s Innervation and Conducting System [61] (Figure 3)

The extracardiac nervous part comprises nerve conductors, connecting heart’s nervous system with central nervous system, and with nervous structures of other organs. The intracardiac nervous system integrates nerve plexuses and endings. Cardiac innervation has sources

the branch of the sympathetic trunk and the branches of the cervical and thoracic parts of the vagus nerve. Three cardiac nerves—superior, middle and inferior—arise on the each side from the ganglia and interganglionic connections of the sympathetic trunk. The superior cervical cardiac nerve originates from the superior cervical plexus, and it is an isolated trunk, composed of branches joined into a single nerve in the lower part of the neck. The middle cervical cardiac nerve arises from the middle cervical ganglion. The inferior cervical cardiac nerve arises from the inferior cervical or stellate ganglion, it is represented by, at least, one trunk, and, frequently, it communicates with the branches of the vagus nerve. The vagus nerves and their branches (the superior laryngeal and the recurrent laryngeal nerves) give rise to the superior and inferior cardiac branches. The superior cardiac branches originate from the trunk of the vagus nerve immediately below the ganglion nodosum and from the superior laryngeal nerve. The highest branch is called the depressor nerve (Zion’s nerve). The inferior cardiac



**Figure 3.** Functional anatomy of heart's innervation and conducting system. Left: Nerves of heart. (1) Left superior cervical cardiac nerve; (2) Left cervical plexus; (3) Left sympathetic trunk; (4) Left vagus nerve; (5) Left phrenic nerve; (6) Anterior scalene muscle; (7) Trachea; (8) Left brachial plexus; (9) Left subclavian artery; (10) Left inferior cervical cardiac nerve; (11) Brachiocephalic trunk; (12) Left common carotid artery; (13) Arch of aorta; (14) Left recurrent laryngeal nerve; (15) Anterior atrial plexus; (16) Left pulmonary artery; (17) Pulmonary veins; (18) Left atrial auricle; (19) Pulmonary trunk; (20) Left coronary artery; (21) Left anterior plexus; (22) Left ventricle; (23) Right ventricle; (24) Right anterior plexus; (25) Ganglion field in the region of conus arteriosus; (26) Right coronary artery; (27) Right atrial auricle; (28) Aorta; (29) Superior vena cava; (30) Right pulmonary artery; (31) Lymph node; (32) Azygos vein; (33) Right inferior cervical cardiac nerve; (34) Right recurrent laryngeal nerve; (35) Right inferior cardiac branch; (36) First thoracic ganglion; (37) Inferior cervical ganglion of right sympathetic trunk; (38) Right superior cardiac branch; (39) Right phrenic nerve; (40) Right vagus nerve; (41) Right sympathetic trunk; (42) Superior cervical cardiac nerve; (43) Superior laryngeal nerve (adapted from V. Vorobiev). Right: Conducting system of heart. (1) Sinoatrial node; (2) Atrioventricular node; (3) Bundle of His; (4) Branch of bundle of His; (5) Network of Purkinje's fibers; (6) Coronary sinus; (7) Heart valve (adapted from F. Volynskii) (in Atlas of Thoracic Surgery, by Boris V. Petrovsky, Mosby Company, Toronto, 1979).

branches form from the trunk of the vagus nerve and from the recurrent laryngeal nerve in the lower part of the neck and in the mediastinum. The cardiac nerves and branches arising from the sympathetic and vagus nerves, repeatedly intertwining, form nerve plexuses along the length of the large vessels. The conducting system of the heart is composed of special muscle fibers which can transmit impulses from the nerve apparatus to all groups of the heart muscles, and are syncytially connected with one another, forming ganglia and bundles. The sinoatrial system consists of the Keith-Flack sinus node—situated in the wall of the right atrium under the epicardium between the right auricula and the superior vena cava—and

two inconstant bundles (Wenckebach's and Schenberg's bundles). The atrioventricular system consists of the Aschoff-Tawara node and the atrioventricular bundle of His and its two branches. The Aschoff-Tawara atrioventricular node is situated in the posteroinferior part of the interatrial septum above the orifice of the coronary sinus. Lower down, the node is continuous with the bundle of His, which penetrates the membranous part of the interventricular septum and divides into the right and left branches (limbs). Both branches descend to the apex of the heart along the septal surfaces, dividing into terminal branches, Purkinje's fibers, which spread in the fibers of the myocardium. The sinoatrial and atrioventricular parts

of the conducting system are connected with one another by nerve pathways, which accomplish the complicated and versatile contact of the conducting system with all the nerve apparatuses of the heart. The automatic rhythm of the cardiac contraction originates in the sinoatrial Keith-Flack node (pacemaker), and impulses from it spread, in the musculature of the atria, to the Aschoff-Tawara node, and, from there, along the bundle of His, to the musculature of the ventricles. Within a functional perspective, at the sinoatrial Keith-Flack node it converges the antagonistic modulatory parasympathetic (vagal) and the sympathetic nervous (ANS) tonus, translated, namely, into Heart Rate Variability (HRV).

## 2. PRELIMINAR INVESTIGATION ON BRAIN PROCESSING OF ACUTE STRESSOR-EVOKED CARDIOVASCULAR REACTIVITY, USING REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (rTMS) OVER THE MEDIAL PREFRONTAL CORTEX (mPFC, BA 10)

### 2.1. Methods

A 52 years old male and a 40 years old female with previ-

ous increased Low Frequency (LF)/High Frequency (HF) Heart Rate Variability (HRV) ratios (respectively, 4.209/3.028) without decompensated cardiorespiratory symptomatology, gave informed consent, and ethico-legal issues have been observed. Electroencephalographic (EEG) monitoring has been performed for safety purposes. Immediately after administration, over the mPFC, of 15 pulses of rTMS, during 60 second, with an inductive electrical current, at the stimulating coil, of 85.9 Ampère per µsecond and 66 Ampère per µsecond, respectively, for male and female subjects (a “figure-eight” coil and magnetic stimulator MagLite, Dantec/Medtronic, have been used), HRV spectrum analysis (cStress software) has been performed (during 5 minutes, in supine position).

### 2.2. Results (Table 1)

In both subjects, LF power, HF power and LF/HF ratio results, before and after rTMS administration, pointed towards sympathetic attenuation and parasympathetic augmentation (respectively, in male/female subject: decreased LF power—65.1 nu/69.3 nu, before rTMS; 56.1 nu/41.6 nu, after rTMS; increased HF power—15.5 nu/22.9 nu, before rTMS; 30.9 nu/45.5 nu, after rTMS).

**Table 1.** Heart Rate Variability (HRV) spectrum analysis before (left) and after (right) administration of rTMS. High Frequencies (HF) Power increased and Low Frequencies (LF) Power decreased, contributing for decreased LF/HF ratio in both subjects (sympathetic attenuation and parasympathetic activation).

Measure	Unit	Value	Subject 1	Measure	Unit	Value
TopPeak	Hz	0.0033	Spectral	TopPeak	Hz	0.0131
VLFPeak	Hz	0.0393	Spectral	VLFPeak	Hz	0.0131
LFPeak	Hz	0.0426	Spectral	LFPeak	Hz	0.0425
HFPeak	Hz	0.341	Spectral	HFPeak	Hz	0.3399
TotPower	ms <sup>2</sup>	8688.1	Spectral	TotPower	ms <sup>2</sup>	12375
VLFPower	ms <sup>2</sup>	3330.1	Spectral	VLFPower	ms <sup>2</sup>	7629.9
LFPower	ms <sup>2</sup>	3490.4	Spectral	LFPower	ms <sup>2</sup>	2664
HFPower	ms <sup>2</sup>	829.2	Spectral	HFPower	ms <sup>2</sup>	1465.3
LFPower	n.u.	65.1	Spectral	LFPower	n.u.	56.1
HFPower	n.u.	15.5	Spectral	HFPower	n.u.	30.9
LF/HF	ratio	4.209	Spectral	LF/HF	ratio	1.818
Beats	count	418	Time Domain	Beats	count	432
MeanNN	ms	765	Time Domain	MeanNN	ms	722.1
SDNN	ms	129.8	Time Domain	SDNN	ms	177.6
MeanHR	l/min	78.4	Time Domain	MeanHR	l/min	83.1
SDHR	l/min	27.8	Time Domain	SDHR	l/min	36.5
NN50	count	108	Time Domain	NN50	count	199
pNN50	%	25.9	Time Domain	pNN50	%	46.2
SDSD	ms	80.5	Time Domain	SDSD	ms	118.4
RMSSD	ms	80.5	Time Domain	RMSSD	ms	118.4

## Continued

Measure	Unit	Value	Subject 1	Measure	Unit	Value
TopPeak	Hz	0.0033	Spectral	TopPeak	Hz	0.0066
VLFPeak	Hz	0.0033	Spectral	VLFPeak	Hz	0.0066
LFPeak	Hz	0.0498	Spectral	LFPeak	Hz	0.063
HFPeak	Hz	0.2952	Spectral	HFPeak	Hz	0.1758
TotPower	ms <sup>2</sup>	188.8	Spectral	TotPower	ms <sup>2</sup>	1158.2
VLFPower	ms <sup>2</sup>	154.4	Spectral	VLFPower	ms <sup>2</sup>	346.6
LFPower	ms <sup>2</sup>	23.8	Spectral	LFPower	ms <sup>2</sup>	337.3
HFPower	ms <sup>2</sup>	7.8	Spectral	HFPower	ms <sup>2</sup>	369.1
LFPower	n.u.	69.3	Spectral	LFPower	n.u.	41.6
HFPower	n.u.	22.9	Spectral	HFPower	n.u.	45.5
LF/HF	ratio	3.028	Spectral	LF/HF	ratio	0.914
Beats	count	409	Time Domain	Beats	count	386
MeanNN	ms	682.1	Time Domain	MeanNN	ms	754.1
SDNN	ms	19.9	Time Domain	SDNN	ms	43.6
MeanHR	1/min	88	Time Domain	MeanHR	1/min	79.6
SDHR	1/min	2.6	Time Domain	SDHR	1/min	3.8
NN50	count	0	Time Domain	NN50	count	9
pNN50	%	0	Time Domain	pNN50	%	2.3
SDSD	ms	6.6	Time Domain	SDSD	ms	47.4
RMSSD	ms	6.6	Time Domain	RMSSD	ms	47.4

### 2.3. Discussion

The actual study results on the neural correlates of stressor-evoked cardiovascular reactivity, using TMS, although limited, are consistent with Lane *et al.* correlational study [32]. Those results suggest that transient disruption/virtual lesion of brain circuitries involved in stress information processing and stressor-evoked cardiovascular reactivity may allow individual stratification concerning risk for the development of Coronary Heart Disease (CHD). It detects persons more prone to develop CHD, particularly those which brain circuitries involved in stressor-evoked cardiovascular reactivity may be already affected by subclinical cerebrovascular lesions (e.g., “vascular depression”). The most clinically effective rTMS parameters and the optimal site for stimulation in Stress related Disorders are not currently known. The target area of cortical stimulation for any TMS study should be determined according to the theorized underlying neurophysiology and the treatment goal.

### 3. CONCLUSIONS

In this preliminary investigation, the existence of a link between “mind” and heart’s function has been put in evidence, through a reversible “virtual” lesion, of brain systems, involved in cardiovascular control, caused by Transcranial Magnetic Stimulation (TMS). Repetitive

TMS over medial Prefrontal Cortex (pmPFC) decreased brain function involved in stressor-evoked cardiovascular reactivity, and suggested the importance of TMS in the management of stress-related cardiovascular disorders. More controlled research is needed for an integrated understanding of the pathogeny of essential hypertension, partially explained through kindling/Long Term Potentiation (LTP) mechanisms of brain neural networks involved in stressor-evoked cardiovascular reactivity, which may be quenched through the administration of repetitive Transcranial Magnetic Stimulation (rTMS).

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