



**UNIVERSITY OF THESSALY**  
**SCHOOL OF HEALTH SCIENCES**



**FACULTY OF MEDICINE**

**HEAD AND NECK SURGERY DEPARTMENT**  
**ENT DEPARTMENT**

Clinical Director: Bizakis Ioannis

---

**PhD Thesis**

**“The evaluation of electroacupuncture in the management of motion sickness syndrome in healthy male adults, in a double blinded study.”**

By

**OURANIA FYDANAKI**  
Ophthalmology registrar, MD

Submitted with the aim to fulfil part of the requirements of the PhD title acquisition  
Larisa, 2019



© 2019 OURANIA FYDANAKI

The approval of the Phd thesis by the Faculty of Medicine of the School of Health Sciences does not declare the approval of the the author's believes (according to the article 202, paragraph 2 of N.5343/1932).



Approved by the members of the Examination Committee (07/05/2019)

**1st Examiner: Ioannis Hajiioannou**, Associate Professor of Otorhinolaryngology

**2<sup>nd</sup> Examinaer: Eythymios Dardiotis**, Associate Professor of Neurology

**3<sup>rd</sup> Examiner: Ioananis Bizakis**, Professor of Otorhinolaryngology

**4<sup>th</sup> Examiner: Eftychia Kapsalaki**, Associate Professor of Radiology

**5<sup>th</sup> Examiner: Georgia Xiromerisiou**, Associate Professor of Neurology

**6<sup>th</sup> Examiner: Konstantinos Paterakis**, Associate Professor of Neurosurgery

**7<sup>th</sup> Examiner: Konstantinos Fountas**, Professor of Neurosurgery

**“The evaluation of electroacupuncture in the management of motion sickness syndrome in healthy male adults, in a double blinded study.”**

**OURANIA FYDANAKI**

University of Thessaly, Faculty of Medicine, 2019

**Three-membered Consultation Committee**

- 1. Ioannis Hajioannou**, Associate Professor of Otorhinolaryngology – Head and Neck Department, ENT Department, University of Thessaly, Larisa (**Supervisor**)
- 2. Ioananis Bizakis**, Professor of Otorhinolaryngology – Head and Neck Department, ENT Department, University of Thessaly, Larisa
- 3. Eythymios Dardiotis**, Associate Professor of Neurology, Neurology Department, University of Thessaly, Larisa

**«Η αξιολόγηση του ηλεκτροβελονισμού στην αντιμετώπιση του συνδρόμου της κινήτωσης σε υγιείς άρρενες ενήλικες μέσω διπλής τυφλής μελέτης»**

**ΟΥΡΑΝΙΑ ΦΥΔΑΝΑΚΗ**

Πανεπιστήμιο Θεσσαλίας, Τμήμα Ιατρικής, 2019

**Τριμελής Συμβουλευτική Επιτροπή**

- 1) **Ιωάννης Χατζιωάννου**, αναπληρωτής καθηγητής Ωτορινολαρυγγολογίας, ΩΡΛ κλινική, Πανεπιστήμιο Θεσσαλίας (**Επιβλέπων**)
- 2) **Ιωάννης Μπιζάκης**, καθηγητής Ωτορινολαρυγγολογίας, ΩΡΛ κλινική, Πανεπιστήμιο Θεσσαλίας
- 3) **Ευθύμιος Δαρδιώτης**, επίκουρος καθηγητής Νευρολογίας, Νευρολογική κλινική, Πανεπιστήμιο Θεσσαλίας





## Greek abstract

**Σκοπός:** Η κινήτωση είναι η κύρια αιτία των συμπτωμάτων σχετιζόμενων με την ναυτία κατά τη διάρκεια παθητικής κίνησης σε χρήση μέσων μεταφοράς. Ο σκοπός αυτής της μελέτης είναι η εκτίμηση της επίδρασης του ηλεκτροβελονισμού ως προς τη μείωση των συμπτωμάτων σχετιζόμενων με την κινήτωση.

**Υλικά και Μέθοδοι:** Οι εθελοντές της μελέτης κατανεμήθηκαν τυχαία σε τρεις ομάδες: Ομάδα Α με θεραπευτικό ηλεκτροβελονισμό, ομάδα Β με sham ηλεκτροβελονισμό και Ομάδα Γ χωρίς καμία θεραπεία αποτελώντας την ομάδα ελέγχου. Μετά από μία συνεδρία ηλεκτροβελονισμού οι εθελοντές εκτέθηκαν σε ναυσιογόνα ερεθίσματα μέσω μίας περιστρεφόμενης καρέκλας. Τα συμπτώματά τους μετρήθηκαν με τη χρήση της ελληνικής έκδοσης ενός ερωτηματολογίου εκτίμησης των συμπτωμάτων κινήτωσης (MSAQ) τροποποιημένο από τον Γιάνναρο.

**Αποτελέσματα:** Σε αυτή τη μελέτη 56 εθελοντές έλαβαν μέρος, 55 εκ των οποίων ολοκλήρωσαν τη διαδικασία. Τα συμπτώματα και των τριών ομάδων ήταν αυξημένα μετά την έκθεση αυτών στα ναυσιογόνα ερεθίσματα. Ο μέσος όρος των ολικών συμπτωμάτων ήταν 53,3 για την ομάδα Α, 53,8 για την ομάδα Β και 68,1 για την ομάδα Γ. Η διαφορά βρέθηκε μερικώς στατιστικά σημαντική στη σύγκριση της ομάδας Α και Γ, καθώς και μεταξύ των ομάδων Β και Γ, ειδικά όσον αφορά στην ομάδα των περιφερικών συμπτωμάτων όπως μετρήθηκε με το παραπάνω ερωτηματολόγιο κατά Γιάνναρος.

**Συμπεράσματα:** Το αποτέλεσμα της παρούσας μελέτης δηλώνει ότι οι συμμετέχοντες που έλαβαν θεραπευτικό ή sham ηλεκτροβελονισμό τείνουν να έχουν λιγότερα συμπτώματα κινήτωσης σε σχέση με τους εθελοντές που δεν έλαβαν κάποια θεραπεία.

**Λέξεις κλειδιά:** κινήτωση, ηλεκτροβελονισμός, ερωτηματολόγιο, ερεθισμός τύπου Coriolis



## English abstract

**Objective:** Motion sickness is the main cause of nausea-related symptoms during passive motion in transportation. The aim of this study was to evaluate the effects of electroacupuncture (EA) for the reduction of motion sickness symptoms.

**Materials and Methods:** Study participants were randomly assigned into three groups: Group A, therapeutic EA; Group B, sham EA; and group C, a control group. After an EA session, participants were exposed to a motion stimulus, using a rotating chair. Their symptoms were measured using the Greek version of the Gianaros Motion Sickness Assessment Questionnaire (MSAQ).

**Results:** In this study 56 volunteers participated, 55 of which completed the procedure. All 3 groups of subjects showed increases in their motion sickness symptoms after exposure to the motion stimulus. The mean total symptom score for Group A was 53,3, for Group B it was 53,8, and in Group C was it 68,1. This difference is partially statistically significant when comparing Group A or B with Group C, especially in a peripheral group of symptoms, as measured by the Gianaros MSAQ.

**Conclusions:** The results of the present study suggest that participants who received therapeutic or sham EA prior to motion stimulation tended to have fewer motion sickness symptoms in comparison with their counterparts, who were not given any therapy.

**Keywords:** motion sickness, electroacupuncture, questionnaire, Coriolis stimulation



### **THREE-MEMEBERED CONSULTATION COMMITTEE**

1. IOANNIS HAJIIOANNOU, ASSOCIATE PROFESSOR (SUPERVISOR)
2. IOANNIS BIZAKIS, PROFESSOR
3. EYTHYMOS DARDIOTIS, ASSOCIATE PROFESSOR

### **SEVENTH-MEMBERED EXAMINATION COMMITTEE**

1. IOANNIS HAJIIOANNOU, ASSOCIATE PROFESSOR (SUPERVISOR)
2. IOANNIS BIZAKIS, PROFESSOR
3. EYTHYMOS DARDIOTIS, ASSOCIATE PROFESSOR
4. EFTYCHIA KAPSALAKI, ASSOCIATE PROFESSOR
5. GEORGIA XIROMERISIOU, ASSOCIATE PROFESSOR
6. KONSTANTINOS PATERAKIS, ASSOCIATE PROFESSOR
7. KONSTANTINOS FOUNTAS, PROFESSOR

### **ΤΡΙΜΕΛΗΣ ΣΥΜΒΟΥΛΕΥΤΙΚΗ ΕΠΙΤΡΟΠΗ**

1. ΙΩΑΝΝΗΣ ΧΑΤΖΗΙΩΑΝΝΟΥ, ΕΠΙΚΟΥΡΟΣ ΚΑΘΗΓΗΤΗΣ
2. ΙΩΑΝΝΗΣ ΜΠΙΖΑΚΗΣ, ΚΑΘΗΓΗΤΗΣ
3. ΕΥΘΥΜΙΟΣ ΔΑΡΔΙΩΤΗΣ, ΕΠΙΚΟΥΡΟΣ ΚΑΘΗΓΗΤΗΣ

### **ΕΠΤΑΜΕΛΗΣ ΕΞΕΤΑΣΤΙΚΗ ΕΠΙΤΡΟΠΗ**

1. ΙΩΑΝΝΗΣ ΧΑΤΖΗΙΩΑΝΝΟΥ, ΑΝΑΠΛΗΡΩΤΗΣ ΚΑΘΗΓΗΤΗΣ
2. ΙΩΑΝΝΗΣ ΜΠΙΖΑΚΗΣ, ΚΑΘΗΓΗΤΗΣ
3. ΕΥΘΥΜΙΟΣ ΔΑΡΔΙΩΤΗΣ, ΕΠΙΚΟΥΡΟΣ ΚΑΘΗΓΗΤΗΣ
4. ΕΥΤΥΧΙΑ ΚΑΨΑΛΑΚΗ, ΑΝΑΠΛΗΡΩΤΡΙΑ ΚΑΘΗΓΗΤΡΙΑ
5. ΓΕΩΡΓΙΑ ΞΗΡΟΜΕΡΗΣΙΟΥ, ΕΠΙΚΟΥΡΗ ΚΑΘΗΓΗΤΡΙΑ
6. ΚΩΝΣΤΑΝΤΙΝΟΣ ΠΑΤΕΡΑΚΗΣ, ΑΝΑΠΛΗΡΩΤΗΣ ΚΑΘΗΓΗΤΗΣ
7. ΚΩΝΣΤΑΝΤΙΝΟΣ ΦΟΥΝΤΑ, ΚΑΘΗΓΗΤΗΣ



Dedicated to my parents and my sister

Dedicated to Nikos, without whom I wouldn't be who I am today. He just flew away from Larisa 2 years ago and never came back...





## ACKNOWLEDGMENTS

First of all, I would like to sincerely thank my supervisor doctor, Panagiotis Kousoulis, in 120 Training Wing Hellenic Airforce Department in Kalamata, where I had my first job as a junior doctor. He contributed in the conception of the idea of this study, with the aim to find a non-pharmacological prevention treatment for junior pilots who suffered with motion sickness related to flight. He played also a major role in the conduction of this study, as he actively participated in the study and thus this study constitutes a double blind study.

Moreover, I would like to thank my professor Ioannis Hajjiannou, who with his kindness and his professionalism helped me to initiate and the conclude my thesis. He stood by me in all the difficulties I have been through the last few years of our co-operation with patience and support. He always had the answer in my questions and the solution in my problems.

Furthermore, I would like to thank the commanders, Mr Theodoros Lagios and Mr Konstantinos Chinis, of 120 Training Wing in Kalamata, where this study took place, who supported our efforts and encouraged military personnel to participate voluntarily in our study. They also had the kindness to offer two days off in the participants in order to attract more attention and participation.

Finally, I want to thank my family, my parents and my sister, who supported me all these years to finish my studies, not only financially but also and mainly psychologically.



## SHORT CURRICULUM VITAE

### OURANIA FYDANAKI

#### Personal details

First name: Ourania  
Last name: Fydanaki  
Date of birth: 08/08/1986  
Nationality: Greek  
Home Address: 295 The Hayes Apartments, CF10 1EF, Cardiff  
Telephone number (mobile): 0030 6987534517, 0044 (0)7400803473  
e-mail: [raniafida@yahoo.gr](mailto:raniafida@yahoo.gr)  
GMC reference number: 7550318  
Athens Medical Association number: 078604

#### Qualifications

2014-today PhD student at University of Thessaly, Larisa, Greece

2004-2010 Ptychion Iatrikes, Medical Degree (MD), Aristotle University of Thessaloniki, (Very Good-mark 8.17/10.0), Greece

2004- 2010 Diploma of Military School of Combat Support Officers, Thessaloniki, Greece (Captain today)

2001-2004 High School Degree, General High School of Doxato, Drama, Grade: 19,8

#### Working Experience

01/08/2018 – today Clinical Fellow in ophthalmology, Aneurin Bevan University Health Board, Royal Gwent Hospital, Newport, UK

23/10/2017-31/07/2018 LAS post in ophthalmology (ST3 level), Aneurin Bevan University Health Board, Royal Gwent Hospital, Newport, UK

21/10/2016-26/09/2017 Resident in Ophthalmology (training post), University Clinic, General Hospital “G. Gennimatas”, Athens, Greece

02/10/2015-20/10/2016 Junior Resident in Ophthalmology (training post), 251 General Hospital of Airforce, Surgical Services, Department of Ophthalmology, Athens, Greece

05/09/2011-1/10/2015 Medical Service Doctor in Flight Training Wing/ Medical Service - Crew member of a helicopter AB-205 in Search and Rescue Missions, Kalamata, Greece

01/11/2010-04/09/2011 Junior/ Trainee Doctor in 251 General Hospital of Airforce in the Section of Operations- Training- Organization-Research/Training Center for Airforce Medical Staff

06/2011-07/2011 Medical Doctor in Special Olympic Games, Athens, Greece

### **Publications**

1) Recovery of corneal clarity after DMEK followed by Rebubbling versus uneventful DMEK,  
K. Droutsas, A. Lazaridis, **O.Fydanaki**, E. Giallourous, I. Georgalas, G. Kymionis, W. Segundo, Cornea, 2018 Jul;37(7):840-847

2) Electroacupuncture Could Reduce Motion Sickness Susceptibility in Healthy Male Adults: A Double-Blinded Study  
**O. Fydanaki**, P. Kousoulis, E. Dardiotis, I. Bizakis, I. Hajjiioannou, MEDICAL ACUPUNCTURE Volume 29, Number 6, 2017, DOI: 10.1089/acu.2017.1246

3) Psychometric properties of the Greek version of the Gianaros Motion Sickness Assessment Questionnaire  
P. Kousoulis, A. Pantes, G. Alevetsovitis, **O. Fydanaki**, Aerosp Med Hum Perform.2016; 87(11):954-957

4) How cost-worthy is the Hellenic Airforce investment on health disorders prevention: policy comparison between flying and non-flying personnel  
Alevetsovitis, I. Katsou, V. Moutevelis, **O. Fydanaki**, P. Prezerakos, BMMR, VOL 16, No 1, 2013

5)Acute barotitis media in flight: pathophysiology, symptoms, prevention and treatment  
**O.Fydanaki**, G. Alevetsovitis, L. Agelakis, V. Moutevelis, BMMR, VOL 16, No 1, 2013

### **Abstracts/Presentations**

2018 Wales, UK, Welsh Ophthalmic Forum, Orbital inflammatory lesion secondary to cavernous sinus teratoma excision. A case report

2018 ESCRS, Vienna, Austria, The safety and efficacy of a tele-clinic in ophthalmic emergencies (poster)

2018 51th Panhellenic Ophthalmology Congress, Thessaloniki, Greece “The use of I-RING® pupil expander for the management of the intra-operative floppy iris syndrome and small pupils”

2018 51th Panhellenic Ophthalmology Congress, Thessaloniki, Greece “Orbital inflammatory lesion secondary to cavernous sinus teratoma excision. A case report”

2018 51th Panhellenic Ophthalmology Congress, Thessaloniki, Greece “The safety and efficacy of a tele-clinic in ophthalmic emergencies”

2018 32<sup>nd</sup> International Congress of Hellenic Society of Intraocular Implant and refractive surgery, Athens “Cataract surgery using the Malyugin ring 6.25mm in a patient with small pupil and posterior synechiae.”

2017 22<sup>nd</sup> BMMC Congress, Belgrad “Electroacupuncture may reduce motion sickness susceptibility in healthy male adults. Results of a double blind study.”

2017 9<sup>th</sup> Health Congress of Messinia, Greece “Electroacupuncture may reduce motion sickness susceptibility in healthy male adults. Results of a double blind study.”

2015 7<sup>th</sup> Health Congress of Messinia, Greece, Development and application of a new method in desensitization of motion sickness in Greek trainee pilots of Hellenic Airforce

2013 18<sup>th</sup> Congress of Balkan Military Medical Committee, How Cost-worthy is the Hellenic AirForce’s Investment on Health Disorders Prevention: Policy Comparison between Flying-non Flying Personnel

## **Foreign Languages**

English	Excellent level IELTS, SCORE 8/9, C1 Level, British Council (2016) Proficiency in English, University of Michigan (2002)
German	Good Level Zentrale Mittelstufenprüfung (2002)

## Contexts

Acknowledgements.....	16
Short Curriculum Vitae.....	18
General part.....	24
Motion sickness review.....	25
Historical perspective.....	25
Vestibular Overstimulation theory.....	26
“Sensory conflict” theories.....	26
Adaptation mechanisms.....	28
Sensory rearrangement, sensory conflict and neural mismatch.....	30
Discussion of the sensory conflict theory.....	31
Advances in “sensory conflict” theory.....	32
Non-sensory conflict theories.....	33
Symptoms of Motion Sickness.....	36
Acupuncture review.....	39
Historical review of Traditional Chinese Medicine and acupuncture.....	39
Acupuncture theories.....	42
Acupuncture technique.....	45
Indications and use of acupuncture.....	47
How it works – Proposed Mechanisms.....	51
Advantages of acupuncture.....	54
Contraindications of acupuncture.....	55

Complications of acupuncture.....	56
Specific part.....	58
Introduction.....	59
Material and Methods.....	59
Results of initial study.....	62
Discussion.....	64
Results of final study.....	69
Potential clinical and practical applications.....	79
Conclusions.....	80
Appendices.....	82
References.....	88





## GENERAL PART

---

## **Motion sickness review**

Motion sickness is a syndrome which results when the subject is exposed to real or apparent motion. Virtually anyone can present with motion sickness when exposed to a stimulus which is sufficient in magnitude and duration. The signs and symptoms have been recognized from the ancient years and in our days, the syndrome is very well described. However, when it comes to the aetiology of the syndrome, the scientific community has not reached a consensus. Several theories have been suggested, but none of them can explain the syndrome as a whole. The large numbers of papers that have been published trying to shed some light on the mystery of the aetiology of motion sickness show that there still is long way before the final answer is found. The purpose of this article is to present the different theories that have been proposed and discuss their strengths and weaknesses.

### **Historical perspective**

The first reference to motion sickness can be found in Homer's *Odyssey*. The term "nausea" comes from the Greek word "naus" which means "a ship" and Hippocrates has written that "sailing on the sea proves that motion disorders the body", a statement which was very progressive at the time. However, it was in the beginning of the nineteenth century that the first theories on the aetiology and pathophysiology of motion sickness were introduced(1). Whiting (1838) suggested that movement of the human body irritates the gastric mucosa and induces vomiting(1). In 1874, Bennett suggested that the battering received by the liver during motion was the reason for an increased excretion of bile into the stomach, which in turn induced emesis(1). Other scientists like Lesson (1878) and Whitham (1887) said that motion sickness results from changes of the cerebral vascular flow which irritated the brain cells in the region of the vomiting centre within the medulla oblongata(2, 3).

All the above theories, termed by Reason and Brandt as "blood and guts theories", were interesting, but oversimplified the phenomenon(2). Their biggest drawback is that they did not take into consideration the fact that an impaired vestibular system gives renders the subject immune to motion sickness and that the vestibular system is an essential element for the development of the syndrome.

Irwin (1881) was the first who stressed the importance of the vestibular system and suggested that motion sickness has close connection with the equilibrium. He was also the first to observe that a form of "conflict" – which he named "discord" – might

take place in the generation of sea sickness. He wrote: “In the visual vertigo of seasickness there appears to be a discord between the immediate or true visual impressions and a certain visual habit or visual sense of the fitness and order of things, which passes into consciousness as a distressing feeling of uncertainty, dizziness and nausea.” However, he argued that the primary cause of seasickness was “irritative hyperaemia” of the semi-circular canals caused by the changing force components acting upon the head(4).

### **Vestibular Overstimulation theory**

Between 1945 and 1960, plenty of knowledge was gathered about the vestibular system and its functions. The dominant theory at that time was that motion sickness was caused when the vestibular system was excessively stimulated by head movement accelerations. Scientists believed that motion sickness could be predicted just by analysing the magnitude, axis, and frequency of the motion and its impact on the vestibular system. Some also gave a bigger role to the otolith organs and believed that the semi-circular canals were not as significant. De Witt in 1953 wrote: “Seasickness is caused by the overstimulation of the otolith system. The part played by the other organs in the determination of the position of the body is only secondary” (5).

The “vestibular overstimulation theory” is a significant step forward to understanding the aetiology of motion sickness because it recognizes that the vestibular system has an essential role. However, it fails to explain the appearance of symptoms in situations of visually induced motion sickness and in cases where there is no direct vestibular stimulus (i.e. the individual is stationary). An example is that of “simulator sickness”, where instructor pilots can be made to experience motion sickness by performing aerobatics in the simulator. Here, it is the absence of an expected vestibular stimulus, rather than the presence of an excessive vestibular stimulus that is the cause of the sickness. One could also say that, in these cases, the provocative stimulus seems to be more related to the visual, and less to the vestibular component of stimulation. Moreover, the theory does not explain the appearance of motion sickness occurring immediately after the cessation of a provocative motion stimulus to which the individual has become adapted, e.g. after return on earth from space travel. Finally, the vestibular system is “excessively” stimulated when people engage in everyday activities like running, dancing and jumping without having motion sickness. On the other hand, there are some very mild vestibular stimuli that produce motion sickness like the sea waves, while on the other hand, strong stimuli can be tolerated without symptoms.

### **“Sensory conflict” theories**

Claremont (1931) was the first who observed that motion sickness occurs when the sensory information from one set of senses is different than the information from

another set(6). He was the first to suggest that a form of “sensory conflict” is present, but did not mention anything about the underlying physiologic mechanisms. Since then, numerous authors such as Hill (1936) and Kirkner (1949) considered this “sensory conflict hypothesis”(7, 8).

A major advance in the “sensory conflict” theory was the identification of “intrasensory conflict”. In the initial publications - prior to 1960 - “conflict signals were assumed to result from a direct comparison of signals provided by different sensory modalities” (intersensory conflict) e.g. "the signals from the eye and ear do not agree”. However, papers from scientists like Lansberg(1963) and Guedry (1964) suggested that in several situations that provoke motion sickness, a conflict existed within the same modality e.g. the canal – otolith conflict inside the labyrinth(9, 10).

Another improvement on the theory came from Reason and Brandt (1975) and Reason (1978) who elaborated on the idea of sensory conflict(2, 11). They explained the idea of past vs. present sensory information conflict and suggested a hypothesis summarized by their statement that: “all situations which provoke motion sickness are characterized by a condition of sensory rearrangement, in which the motion signals transmitted by the eyes, the vestibular system and the non-vestibular proprioceptors are at variance not only with one another, but also -and this is the crucial factor- with what is expected on the basis of past experience or exposure history”.

Given that perspective, Reason and Brandt described two “sensory rearrangement” conditions:

- a. an intersensory rearrangement between visual and inertial (vestibular and non-vestibular proprioceptors) signals and
- b. an intrasensory rearrangement between canal and otolith signals.

For each of these conditions they describe three different types of “sensory conflicts” as seen in the Table 1.

	<b>Visual (A) - Inertial (B)</b>	<b>Canal (A) – Otolith (B)</b>
<b>Type 1 A and B</b>	1. watching waves over the side of a ship 2. looking out of the side or rear windows of a moving vehicle 3.making head movements while wearing some optical device that distorts vision	1. head movements made about some axis other than that of bodily rotation – cross coupled angular accelerations 2. Low frequency oscillations: between 0.1-0.3 Hz.
<b>Type 2 (A not B)</b>	1. “Cinerama sickness” 2. Operating a fixed-base vehicle simulator with a moving visual	1. Weightless flight, “space sickness” 2. Calorific stimulation of the outer

	display- “simulator sickness”.	ear. 3.Positional alcoholic nystagmus associated with alcohol and heavy water
<b>Type 3 (B not A)</b>	1. Reading a map in moving vehicle. 2. Riding in a vehicle without external visual reference. 3. Being swung in an enclosed cabin.	1. Rotation about an Earth- horizontal axis. 2. Any rotation about an off- vertical axis.

Table 1: Some Everyday and Laboratory Examples of the Six Kinds of Sensory Rearrangement that can Provoke Motion Sickness. Reason and Brandt (1975)(2)

### Adaptation mechanisms

The initial “sensory conflict” theories tried to describe the characteristics of the circumstances in which motion sickness occurs, but they did not clarify where the conflict takes place. The first ideas on this issue came from Von Holst(12) and Held(13).

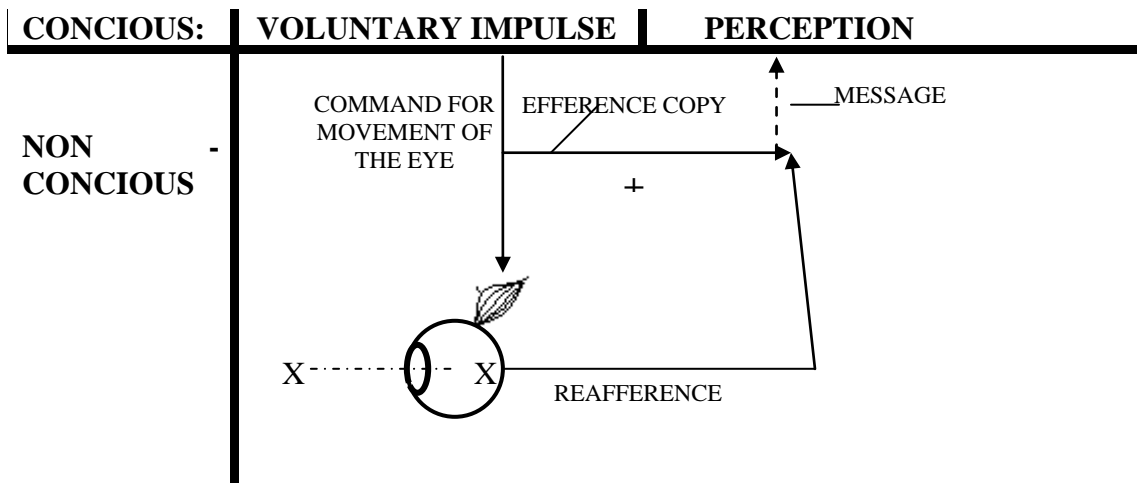


Fig 1. Von Holst’s efference copy/reafference mechanism(12)

Von Holst introduced the efference copy/re-fference mechanism (Fig 1). He used the term “efference” to describe the command signal to some effector organ (e.g. muscle). He claimed that whenever an “efference” is initiated, “it leaves an image of itself (the efference-copy), somewhere in the central nervous system, which retains the important informational characteristics of the command signal”. The muscular

activity that occurs, produces feedback sensory information (re-afference) - as opposed to sensory information from external sources (ex-afference). The “re-afference” is then compared with the “efference copy” like “the negative of a photograph to the print” and when they are matched, the copy is erased and no further activity occurs. If they are not matched, “a mismatch signal is generated which produces further corrective motor activity”(12).

Held described a slightly different mechanism (Fig 2). He suggested that there is a “Correlation Storage” which stores “previous combinations of concurrent efferent and re-afferent signals”. The current efferent and re-afferent signals are sent to the Correlation storage, where they reactivate the stored re-afferent traces combined with them. A Comparator is then responsible to compare the current re-afferent signal with the reactivated re-afferent trace. The contribution of the theory is that a re-afferent signal/copy is stored in the Correlation storage instead of being erased and may serve for future comparisons, thus providing an explanation for adaptation(13).

Reason described a very similar model, which he called “neural mismatch hypothesis”(11). Two structural components are introduced: a “Neural Store” unit that stores previously experienced efferent/re-afferent pairs and a “Comparator Unit”. When a movement occurs, the efferent signal is transmitted to the “Neural Store” to trace already stored re-afferent signals combined with the current movement. The traced re-afferent signal is then sent to the “Comparator Unit” where it is compared with the incoming sensory inputs. If these two sets of information do not match, a “mismatch signal” is generated which leads to the motion sickness syndrome. According to Reason, the higher the mismatch signal, the higher the symptom severity(11). As Reason clearly stated “with continued exposure to the rearranged environment the contents of the Neural Store are updated until eventually adaptation is complete and no mismatch is found”(11). It is interesting to point out the similarity between Held’s and Reason’s model. The basic contribution of these two models is that they stressed the importance of past vs. present pattern comparison, whereas former scientists only recognized sensory conflicts happening simultaneously (e.g. visual-vestibular, canal-otolith conflicts).

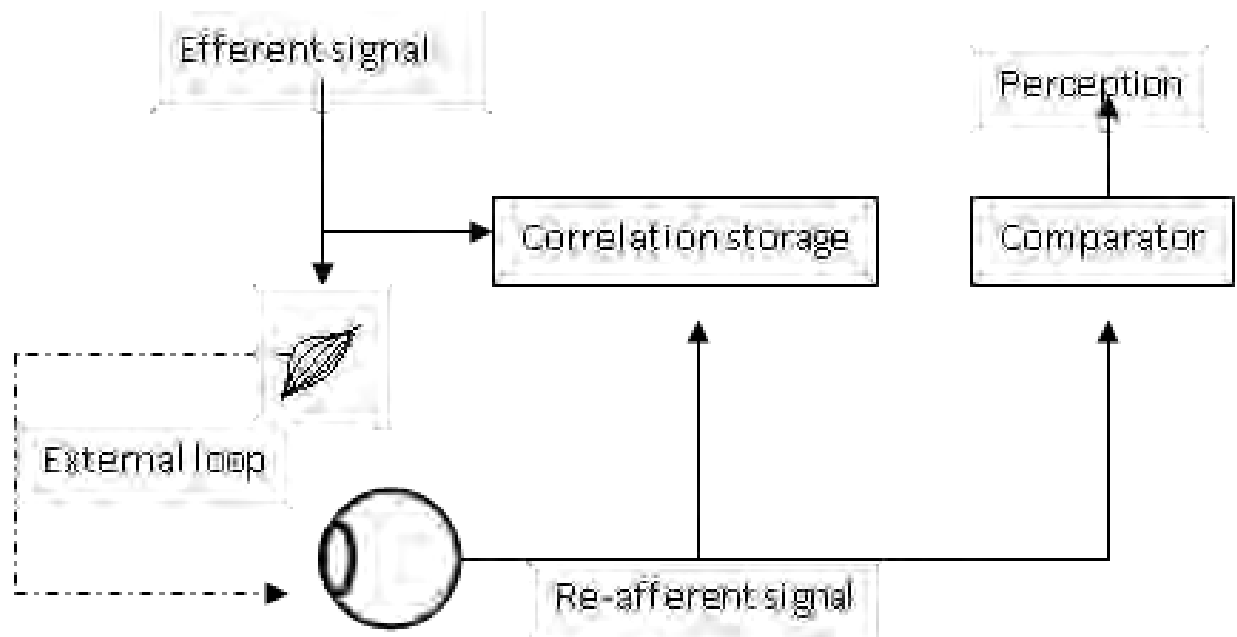


Fig 2: Held 's "Correlation Storage" model (1961)

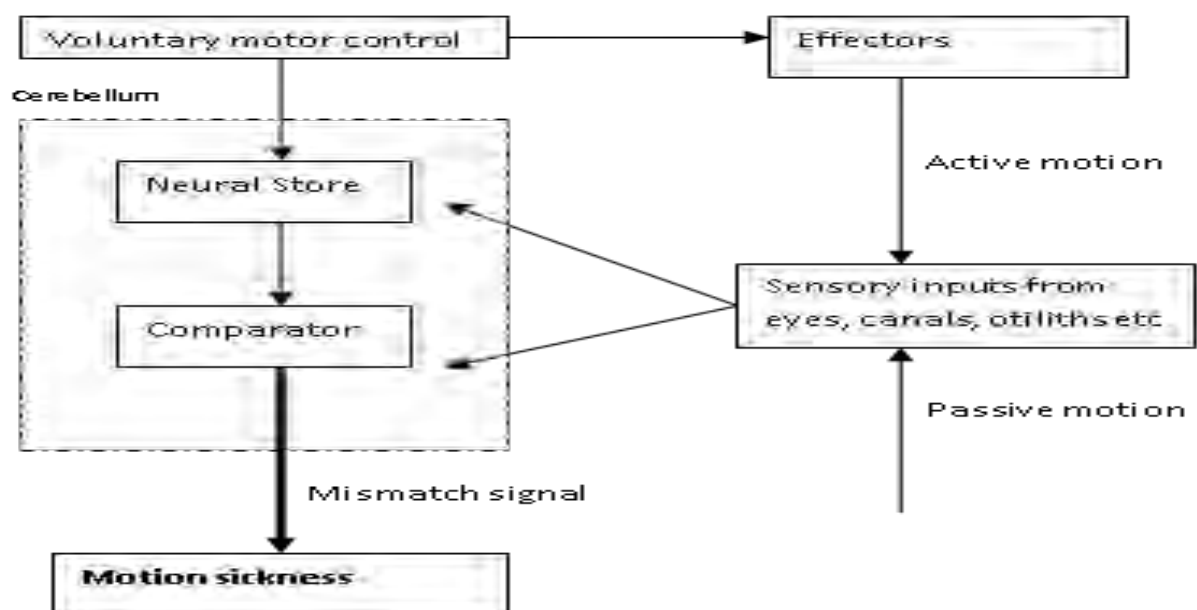


Fig 3. The basic structural components of the neural mismatch model (Reason, 1978)(11)

### Sensory rearrangement, sensory conflict and neural mismatch

At this point it is appropriate to try to clarify the three terms which are often confused in literature. The term "sensory rearrangement" was first used by Held (1961) to



describe “experimental situations in which the information arriving at one set of receptors is systematically distorted so that they are incompatible when compared with information arriving at functionally related receptors”(13). The prism spectacles that distort the retinal image and the Slow Rotating Room that was used in several experiments are examples of conditions characterized by “sensory rearrangement”. Therefore, the term “sensory rearrangement” describes the overall situation in which the “sensory conflict” takes place.

As we described above, according to Reason, when the “sensory conflicts” are evaluated by the brain (neural store, comparator), it produces in turn a “mismatch signal”, which is finally responsible for producing the motion sickness syndrome(2, 11). Guedry (1991) uses the term “neural mismatch” as a broader concept than “sensory conflict”. According to him, the term “neural mismatch” is preferable to the term “sensory conflict” for situations provoking motion sickness(14). The term “sensory conflict” is the correct term to use for "Coriolis cross-coupled" stimulation because both the canals and the otoliths send contradictory information. However, a number of nauseogenic motions are characterized by presence of sensory information from one set of organs, without concomitant information from another sensor. One can mention as an example the head movements made during weightlessness which generate normal semicircular without the usually coupled information from the otolithic sensors.

Although these terms are often confused in literature, what is most often seen is the term “sensory conflict” being used to describe the whole group of theories based on this concept, while the term “neural mismatch” is used to refer specifically to Reason’s model.

We will summarize with Reason’s statement: “The sensory rearrangement notion sought to answer the question: what is the essential characteristic of the nauseogenic stimulus? The neural mismatch notion, attempts to explain why the sickness reactions occur when they do, and why they diminish with continued exposure. Together it is argued, they constitute an adequate theory of motion sickness”.

### **Discussion of the sensory conflict theory**

The “sensory conflict” theory is extremely useful, especially because it provides a qualitative approach of the causes of motion sickness. It provides a framework for understanding all motion sickness subtypes e.g simulator sickness, sea sickness, space sickness, car sickness, air sickness, even some nauseating vestibular diseases, as a result of one common “sensory conflict” mechanism. Since it suggests a mechanism, it can also lead to the adoption of some useful preventive measures. It has been shown in practice that preventive measures which, according to the theory, reduce the “sensory conflict” can also reduce the incidence of motion sickness in the subjects. The greatest advancement with the “sensory conflict” theory is that it identifies the

contributing sensory systems, how they interact with each other and how this relates to the sensory rearrangement concept.

However, the sensory conflict theory is not a quantitative theory and cannot be used to measure sensory conflict, nor does it comment on the significance of the several possible conflicts. The theory can be used to anticipate whether the immersion in some motion environments could be nauseogenic, but it cannot predict the magnitude of the symptoms using information like the magnitude, the duration or the axes of motion.

Moreover, although the theory attributes a major role to the vestibular system, it does not explain why such a conflict is unable to provoke the symptoms in individuals with damaged vestibular system. The theory also does not explain why the endpoint of the syndrome is vomiting instead of, for example, defecation or sneezing. The theory would be broadly correct, even if the sensory conflict produced one of those symptoms instead of vomiting.

As Griffin (1991) stated: “The sensory conflict theory cannot be tested by experiment since, while it provides a framework for what has been observed, it makes no precise predictions. Since the theory cannot be disproved, it may be assumed to be either broadly correct, or irrelevant. The theory does not make quantitative predictions. Indeed, it implies that such predictions cannot be made. The effects of changes to the quantity or quality of motion stimuli cannot, therefore, be inferred from the sensory conflict theory”(15).

### **Advances in “sensory conflict” theory**

#### **Reflex-Response theory of motion sickness**

Griffin has suggested that the aetiology of motion sickness might be partially explained in terms of inappropriate (i.e. unnecessary, unsynchronized, delayed, or opposing) reflex responses to movements(15). Reflex responses happen normally but only after the human sensory systems detect motion. In cases where the motion signals are incorrectly interpreted, the development of new reflexes is necessary. According to Griffin, “motion sickness is assumed to arise from the “conflict” between inappropriate reflex responses”. The theory is therefore centered on “response conflict” rather than “sensory conflict”. According to Griffin, as we do not know how to measure the sensory conflict, we could instead measure indicators of response conflict. The theory provides a different point of view and is not incompatible in a broad sense with the sensory conflict theory. It may be also helpful to understand why the syndrome needs some time of motion exposure to develop and an additional time for the recovery.

## Otolith Tilt - translation reinterpretation hypothesis

While on the ground, the otolith organs are stimulated by the linear accelerations to the horizontal axis (linear motion) or to the vertical axis (head tilt), and both are interpreted in relation to gravity. On the other hand, in space, with the absence of gravity, there is no point in the body using information of head tilt. Therefore, the brain adapts to the weightless environment by interpreting all otolith receptor output as linear motion. More specifically, “the nervous system reinterprets signals from the otolith organs to represent fore-aft or left-right linear acceleration rather than pitch or roll of the head with respect to the vertical”. When astronauts return to earth, and for a period of time, and before the re-adaptation to an environment where gravity exists, this reinterpretation of otolith responses persists. It is suggested that this reinterpretation of the otolith signals is nauseogenic.

The basic underlying mechanism that explains motion sickness in space appears to be some type of sensory conflict. When on ground, signals from the otolith receptors are combined by respective signals from the semi-circular canals and the eyes. In the absence of gravity, the signals from the otolith organs are expected to contradict with the ones from the semi-circular canals and the eyes. More specifically, after a roll or pitch head movement, the eyes would indicate the movement, but without the respective appropriate signal from the otolith organs. It has been reported by astronauts that, during the initial period of space flight, specifically pitch head movements produce motion sickness symptoms. These reports are supportive of the sensory conflict notion to space motion sickness and of the otolith tilt-translation interpretation hypothesis(16, 17). The otolith tilt-translation interpretation hypothesis could be seen as a refinement or support to the all-embracing sensory conflict theory.

## A mathematical model of sensory conflict

To address some of the deficiencies in Reason’s “neural mismatch” theory(2, 11), Oman (1982, 1990) proposed his version of the sensory – motor conflict theory from a mathematical modeling perspective(18, 19). The model incorporated and extended Reason’s hypothesis and was synthesized by application of “observer theory” concepts from control engineering. He tried to use these concepts to explain how the CNS actively controls body movement processing the neural information it receives from a limited set of noisy sensory signals. The “actual sensory input” and the “expected sensory input” are represented as vectors and the difference between them is related with the sensory conflict signal. Although the author himself describes his mathematical model as heuristic, it does represent a first attempted transition from a qualitative to a quantitative and therefore, more predictive model. The complete analysis of Oman’s model is beyond the scope of this presentation.

## The subjective vertical (SV) theory

In 1998, Bles et al introduced the subjective vertical theory as an evolution to Oman's model(20, 21). They define the term "subjective vertical" as "the internal representation of gravity" and they state: "All situations which provoke motion sickness are characterized by a condition in which the sensed-vertical as determined on the basis of integrated information from the eyes, the vestibular system and the non-vestibular proprioceptors is at variance with the expected vertical as predicted on the basis of previous experience" (20). Like Oman, they see the "sensed vertical" and the "expected vertical" as vectors. They believe that the vector difference between the "sensed vertical" and the "expected vertical" represents the conflict that causes motion sickness. It is therefore one step forward from Oman, who sees the conflict as the vector difference between the "actual sensory input" and the "expected sensory input" as a whole. They also hypothesize that not only the magnitude, but also the direction of the difference vector may affect the severity of motion sickness. The authors also try to answer why the subjective vertical is so important that, when it is at stake, it leads to motion sickness. One explanation could be that the vertical is critical for the body to maintain the upright position and another could be that the body needs that information to keep the cardiac output adequate for each body position. They also used the model to successfully predict the amount of motion sickness for vertical motions and they believe that it could expand to allow predictions of all possible three-dimensional movements. The theory, if correct, would be an important step forward, because it explains motion sickness using only one provocative conflict instead of the many types of sensory rearrangements of the classic sensory conflict theory.

### **Non-sensory conflict theories**

#### Poison theory

We noted earlier that although the "sensory conflict" type theories explain some of the characteristics of motion sickness they do not explain why it finally leads to emesis instead of any other symptom. Treisman tries to explain this question by the following theory(22). According to him, there are four different kinds of defense against having poisons in the stomach: (1) "rejection by taste", (2) vomiting caused by "effects on the stomach lining", (3) vomiting caused by "stimulation of appropriate chemoreceptors" when a poison is absorbed in the blood and (4) vomiting caused by "early or minimal physiological disturbances produced by absorbed toxins." The latter is the key point of Treisman's theory. He hypothesizes that motion may affect the same mechanisms in the brain that are affected by toxins. It is known that in everyday life, there is a constant need for coordination of the sensory information from the eyes, the labyrinth system and the proprioceptors, that in turn control the limb and eye movements. Treisman suggested that disruption in this activity would "constitute an ideal warning system for detecting early central effects of neurotoxins." Treisman's theory states that this activity is in fact disrupted by certain motions, and that the disruption is interpreted as "an early physiological disturbance produced by absorbed toxins", so that vomiting results.

There is evidence that Treisman's theory is valid. It has been suggested that the central nervous system of orientation in space and detection of motion have an additional function of detecting and responding to certain poisons. An experiment was done by Money and Cheung (1983) using intramuscularly administered poisons. This

showed that, animals with a surgically damaged vestibular system did not exhibit emetic response to some specific poisons given intramuscularly. The same poisons when given by the same route before the surgical procedure, with an intact vestibular system, induced vomiting. Of course, the removal of the vestibular apparatus also also caused immunity to motion sickness. This implies that “the vestibular system is involved both in circumstances of motion sickness and also in circumstances of poisoning with certain toxic chemicals”. Under this perspective, motion sickness has a meaning. As Money states: “In a motion sickness situation the brain says: ‘This unusual requirement for recalibration is such that my vestibular system must be sending me false information; therefore I have probably been poisoned by something I ate and I should vomit’.”(23).

### Spatial orientation and motion sickness

Guedry et al (1998) have hypothesized an interesting relationship between motion sickness and the development of the spatial orientation mechanism(24). They state that “at any given stage of development, during head movements, unique patterns of canal-otolith signals are produced and irrespective of whether a movement is efficient or inefficient, vestibular signals will be part of the total associated pattern of sensory information”. During some movements, conflict between canal and otolith signals or other senses may be produced and result in an unpleasant nauseogenic sensation. The authors suggest that the unpleasant sensation resulting from conflicting vestibular signals is innate. Thus, the innate displeasure that is the result from movement that produce vestibular conflict would discourage the development of those programs. It is known that this succession of pleasure-displeasure is a part of the evolution and development of human behaviour. As far as motion sickness is concerned, pleasure and displeasure could be the reason behind the training of the spatial orientation system which is, day after day, developed and conditioned embracing perceptual-motor programs that are efficient in the motion environment of the individual and discouraging ineffective ones. This hypothetical mechanism explains why motion sickness results during exposure to motion environments that the subjects are not used to and provides a reason why adaptation to motion sickness occurs after spending some time in this environment and new perceptual-motor programs are developed.

### Eye movement hypothesis

Ebenholz et al (1994) described a hypothesis that sustained eye movements such as nystagmus, stimulate cells within the vestibular nucleus, which then initiate vagal activity responsible for motion sickness symptoms, such as emesis. The hypothesis is based on a connection between the vestibular and vagal nuclei(25).

A variety of eye movements, like saccades, smooth pursuit or nystagmus, are produced during motion or simulation of motion. The well documented vestibular ocular reflex (VOR) is believed to stabilize the images in the retina during head movements and shows that there is a connection between the vestibular system and

the eye(26). There is evidence that applying force such as traction to the extra-ocular muscles induces vomiting. Moreover, a vagal stimulation has been suggested to explain the oculo-cardiac reflex resulting in bradycardia during strabismus surgery(27).

The hypothesis is that in any motion sickness situation, reflexive and voluntary muscle movements are generated, afferent signals from the muscles to the vagal nuclei are produced and result in a vagus nerve stimulation, which leads to the development of symptoms. The theory suggests a new role of the vestibular system for the generation of motion sickness syndrome, especially the development of the autonomic symptoms like pallor, sweating, nausea and alteration in peristalsis. The theory implies that the vestibular system has a key, but mediating role whenever motion sickness occurs. This theory however cannot explain why motion sickness occurs in blind subjects(28).

### Postural Instability theory

The basic idea behind the theory of Stoffregen and Riccio (1991) is that one of the primary goals in humans is to maintain postural stability in the environment(29). They define the term “postural control” as “the coordinated stabilization of all body segments” and the term “postural stability” as “the state in which uncontrolled movements of the perception and action systems are minimized”. According to them, postural instability does not mean a complete loss of postural control (like falling), which is more often found in literature. On the contrary, stability may be degraded rather than lost as a whole and instability may persist over long periods of time, without necessarily leading to loss of control.

Their central hypothesis is that postural instability precedes motion sickness and that “prolonged postural instability is the cause of motion sickness”. Among several corollary hypotheses is the suggestion that “Symptoms may...scale directly to the magnitude of instability” They also propose that “reductions in demands on postural control should reduce the incidence or severity of motion sickness”. Motion sickness will appear when an individual tries to maintain postural control when he enters a demanding environment. On the other hand, when he reduces his postural demands and stops trying to achieve postural control, motion sickness is suggested to be reduced. Resting the head and lying down are given as examples of ways to reduce the demands on postural control.

This theory does not have many supporters. It is not a quantitative theory and there is much uncertainty of how to measure stability and instability. However, there are few studies supporting the idea that postural instability, as measured by increases in the variability, range and velocity of postural motion, precedes visually induced motion sickness(30, 31). There are also limited indications that measurements of postural instability could predict which individual will experience mild symptoms of visually induced motion sickness(31). On the other hand, two studies performed by Warwick-

Evans et al found no evidence to support the hypothesis that reducing the demands of postural control reduces the incidence or severity of motion sickness(32). Moreover, there are situations that provoke motion sickness, but do not require postural control e.g. the passenger in the back seat of a car. The theory also did not make any claims regarding the symptoms associated with motion sickness.

## Symptoms of Motion Sickness

Motion sickness symptoms are not restricted to the nausea or vomiting that many people have in mind. There are several other types of symptoms that are related to this condition. Graybiel et al back in 1968 categorised motion sickness according to the type and the severity of symptoms experienced. The main symptoms reported were nausea, skin pallor, cold sweating, increased salivation, drowsiness, dizziness and pain/headache. They also identify five different levels of severity(33).

**DIAGNOSTIC CATEGORIZATION OF DIFFERENT LEVELS OF SEVERITY OF ACUTE MOTION SICKNESS**

Category	Pathognomonic 16 points	Major 8 points	Minor 4 points	Minimal 2 points	AQS* 1 point
<u>Nausea syndrome</u>	Vomiting or retching	Nausea* II, III	Nausea I	Epigastric discomfort	Epigastric awareness
<u>Skin color</u>		Pallor III	Pallor II	Pallor I	Flushing
<u>Cold sweating</u>		III	II	I	
<u>Increased salivation</u>		III	II	I	
<u>Drowsiness</u>		III	II	I	
<u>Pain</u>					Headache
<u>Central nervous system</u>					Dizziness: Eyes closed ≥ II Eyes Open III

\*AQS = Additional qualifying symptoms. \*III = severe or marked, II = moderate, I = slight.

Levels of Severity Identified by Total Points Scored				
Frank Sickness	Severe Malaise	Moderate Malaise A	Moderate Malaise B	Slight Malaise
(S)	(M III)	(M IIA)	(M IIB)	(M I)
≥ 16 points	8 - 15 points	5 - 7 points	3 - 4 points	1 - 2 points

Figure 4. Diagnostic categorization of different levels of severity of motion sickness according to Graybiel et al(33).

About 30 years later, Golding et al published a new questionnaire for quantification and categorization of motion sickness symptoms. In this questionnaire, apart from the aforementioned symptoms of motions sickness, were introduced also heat sensation, stomach discomfort and fatigue(34).

In 2001, Golding at al modified the above questionnaire of Golding and divided the symptoms of motion sickness into four main categories: gastroenterological, Central Nervous System (CNS), Peripheral Nervous System (PNS) and sopite symptoms(35). In the former type nausea related symptoms were included, while in the CNS group symptoms of dizziness and faint were part of it. In the PNS symptoms' group sweating (cold or warm) and the feeling of heat or cold were participating. The sopite symptoms were newly introduced and included the feeling of nervousness, drowsiness, fatigue and anxiousness (see appendix 1).





## **Acupuncture review**

Acupuncture is one of the oldest medical treatment methods all over the world, originating from China, has been used as a therapeutic intervention for the treatment of various diseases and symptoms for more than 2500 years and it is still in use today. This medical philosophy and practice is challenging the basis of our understanding of health and illness. Nowadays, that both the patients and the medical world tries to investigate more towards non-invasive or non-pharmacology dependent treatments, acupuncture as well as other alternative medical options became increasingly popular not only among Chinese populations but also in Western world too. Thus, many health practitioners such doctors and physiotherapists include and combine acupuncture in the daily practice to enhance patients' treatment.

### **Historical review of Traditional Chinese medicine and acupuncture**

Traditional Chinese medicine started back to 17-11<sup>th</sup> century BC, when Shang dynasty was in power. At the time, diseases could not be understood and they were thought to be caused by magical components. People of the time tended to use needles made of various materials like stones and bones and treated both alive and ceased

patients(36). The “Yellow Emperor’s Classic of Internal Medicine” was the earliest formal try of organisation of treatment and diagnostic methods in acupuncture and was formed with questions and answers(37). Chronologically it is placed about 100BC. This was also the time that Qi, which is the energy among the meridians, was first perceived and started to be the main treatment target, although there were not used any specific acupoints which started to be used later in the treatment of acupuncture.



Figure 5. Needles made from bones, chronologically place 10,000~4,000 years ago during the New Stone Age, from exhibition in Shanghai TCM Museum in China

Following the above period, acupuncture started to develop and being organised as people tried to understand it in a deeper level. It was at the time that Han Dynasty was in power, about 200 BC to 200 AD, when acupuncture had its major structural formation(36) Well established and used until nowadays theories such as the “five elements” and the “Yin-Yang” perceived and developed during Han’s years in a try to understand the various causes of the diseases which would lead to a better confrontation or prevention of them. Since then, a more logical expansion and explanation of acupuncture was given, distinguishing acupuncture from magic and the unexplained, although these theories were not widely adapted and older theories and methods of acupuncture had their own supporters and believers(36).

The first needles which resemble the current ones we use today, were found about fifty years ago, when archaeologists opened the tomb of one of the Han Dynasty Princes’, Liu Sheng, chronologically located at the beginning of the dynasty; about 113BC(36). These needles are known as the “nine needles” were made from gold and silver materials. In that tube, various other medical devices of the time were found, that is why the needles’ use is not completely understood, as they could be used for other medical purposes apart from acupuncture, like drainage of different body cavities(36).

In other tombs of the same period, the first acupuncture documents were found. These were the Mawangdui and Zhangjiaoshan tombs, placed chronologically in the second

century BC as well. In these documents the first documentation of the early meridians perception takes place, which are called “mai” at the time, and are used in the medical practice, although there were no mentioning of the use of acupuncture itself(36). Evidence of acupuncture as we know it today was found about one century later than that in the Shiji’s historical records, in which acupuncture with the use of needles is mentioned, although the known theories of Qi and meridians were not. Shiji reported the treatment of a presumed deceased prince at that time with the insertion of a needle in his head, which in fact may not even be acupuncture treatment, and represent any other medical practice(36).

In the following years, the progressive evolution of acupuncture in combination with moxa, herbs and other treatments, comprised the major part of traditional medicine(38). Evidence of the acupoints and the known acupuncture that we use today, date back into 15<sup>th</sup> century, in bronze statues that have been found from that period(38). A more formal attempt for documentation and organisation of the acupoints was made during Song Dynasty, when the “Illustrated Manual of Points for Acupuncture and Moxibustion on a Bronze Statue with Acupoints” was developed. This represents the first formal anatomical documentation of acupoints still in use today(39).



Figure 6. This bronze statue, which dates in 15<sup>th</sup> century, depicts the anatomical location of acupoints.

The first published text was made in the years of Ming Dynasty (1368-1644) and is called “The Great Compendium of Acupuncture and Moxibustion”, opening a new era for acupuncture. This document analysed the meridian system and all of the acupoints in use today, and also the methodology of acupuncture with the main purpose to heal any alterations in the flow of the Qi(40). An interesting fact is that in China the traditional medicine was based only on observing people and their diseases,

as it was not allowed to dissect dead people and anatomy apart from the obvious to the human eye was not developed(37)

For almost the two following centuries, from about the middle of the 17<sup>th</sup> century to the beginning of the 19<sup>th</sup> century, the acupuncture lost its previous glory and status. Doctors and many of the eminent people of the time started to think that acupuncture, together with many surgical techniques, were insignificant and useless skills. In this perception, contributed the fact that Emperor Dao Guang, stated in 1822 that acupuncture and moxa treatment were not appropriated types of treatment for a royal and that they should be abandoned, acupuncture stayed out of the spotlight for a long time(38). Since then, the application of acupuncture and moxibustion were forbidden in China officially by the government, as they were trying to develop a more western medicine practice instead. Similarly, the government of Japan also forbidden the use of acupuncture in 1876. Thus, Imperial Medical Academy of China did not deal with acupuncture treatment until later in 1911, when acupuncture started to come again in the light(41).

The Western world contacted acupuncture initially during the 16<sup>th</sup> century, not by medical community like doctors or medical practitioners, but by the missions performed by Jesuits in China. Since then, acupuncture started to spread in the western world too, and many popular physicians in Europe were using acupuncture at the end of the 19<sup>th</sup> century. In particular, at that time acupuncture became quite developed in France. One of the known practitioners who favour acupuncture in France, George Soulie DeMorant, published his book on acupuncture treatment in 1939 being one of the first acupuncture documents in Europe(40). On the other side of the world, in the United States, acupuncture also started to gain field in the medical practice. Specifically, acupuncture was initially documented as a treatment of musculoskeletal pain in a document printed in 1822 by Sir William Osier, including acupuncture by this way in the western medicine(40).

In the middle of the 20<sup>th</sup> century, communism status of China resulted in difficulties to get medical supplies from the West, including medicines and medical equipment. Because of this fact the government decided to find another way to treat their people and so they revitalized the traditional medicine for that, which had been forgotten for many years(42). With this “back to the roots” step they could face the demanding needs of medical solutions of their increasing population of their country against the not supporting West(41). The Western world and particularly United States started to favour upon traditional Chinese medicine at the beginning of 1970s, when President Richard Nixon visited China. This visit was the end of Chinese isolation and the beginning of the recognition of acupuncture again among the popular medical techniques(41).

## Acupuncture theories

Qi, as mentioned above, plays a major role in the traditional Chinese medicine theory. It represents the energy which is believed to flow into the meridians. The balanced circulation of Qi through the body is correlated with the existence of good health of people, while any obstruction of this circulation leads to various medical health problems. The main target of acupuncture is the restoration of the unobstructed flow of Qi through the needle insertion(43). However, this energy type, resembling fluid, circulation in the body is not only a Chinese belief and people at that time from different places had similar beliefs. In particular, in ancient Greece, two of the eminent theorists Praxagoras and Erasistratus suggested the theory that energy, called pneuma, which in Greek represents part of the soul -something not visible and not defined-, was the one flowing in the vessels of the body(44). This is one of the reasons why traditional Chinese medical theory is believed to have been inspired by the ancient Greece, where medicine was evolved at that time. As aforementioned above, the history of Qi started to develop about 100BC, which is later than the development of ancient Greek medical evolution.

Another basic part of the acupuncture theory is the “Five elements”, essential both for the diagnosis and the treatment. This theory was developed during the Han Dynasty years, when a boost of the acupuncture evolution took place(36). According to the theory of “Five elements” there are five different basic material by which the universe is formed. These are the following: wood, fire, earth, metal and water(45, 46). Each of these elements is recognised by various characteristics, such as specific related meridians, flavour, emotions, colours and climate condition. For example, the wood represents the Liver and Gall Bladder meridian, and is characterised by the green colour, sour taste, anger and wind. These five materials should be in balance among each other and any shortage or excess of any of them would affect the materials which neighbour with the affected one in the circle of the “Five elements”, with a cascade of reaction resulting in disease. This balance among the circle of “Five elements” applies not only individually but also to every aspect of the whole world as well(45).



Figure 7. The “Five elements” circle.

According to traditional Chinese medical theory, the Yin and the Yang were the two opposite and always connected energies that initiated the universe. Similarly, with the previously aforementioned “Five element” theory, Yin and Yang are believed to be part of everyone and everything and that the balance of these two is related to good health(46). Yin represents the female component, while Yang is the male component. None of these could vanish the other, and even in situations with excess Yin there is always a Yang part and vice versa. Connected to the previous theories of acupuncture, Yin and Yang are thought to flow together with Qi and blood within the body. Any imbalance between the two leads to Qi stagnation which in turn will result in disease and health disorders, which could be either generalised or specialised to particular organ(46). Yin-Yang, Qi and blood circulated through the meridians, invisible “vessels” in the body, and any obstruction in this circulation should be treated accordingly in order to prevent or treat the related health problem. In acupuncture, this is performed with the needle insertion into specific acupoints selected after the diagnosis of the initial cause(47).

The disease concept as known in Western medicine was not the same as in traditional Chinese medicine. For instance, according to the acupuncture theory, various different types of fever are recognised and diagnosed based in the theory of “five elements”. Fevers were mainly characterised of the climate condition of the element affected on them. Thus, the diagnosis of these fevers was related to cold, heat, humidity, dryness and wind problems. Even, fever related to diseases which are now known to be caused by infections, were diagnosed as above and related to climate imbalance among the five elements(46).

Today, acupuncture is well established and the anatomical location of the acupoints is clear. There are twelve basic meridians from the toes to the head of the body, but also accessory meridians and internal branches exists in order to complete the circulation of Qi in every part of the external and internal part of the body(39, 47). The names of the meridians do not correlate to the internal organ of the same name. The main twelve meridians are the following and act in pair: lung, large intestine, stomach, spleen, heart, small intestine, bladder, kidney, pericardium, gallbladder, liver and triple warmer(48). The latter is thought to be related to temperature balance between different parts of the body.

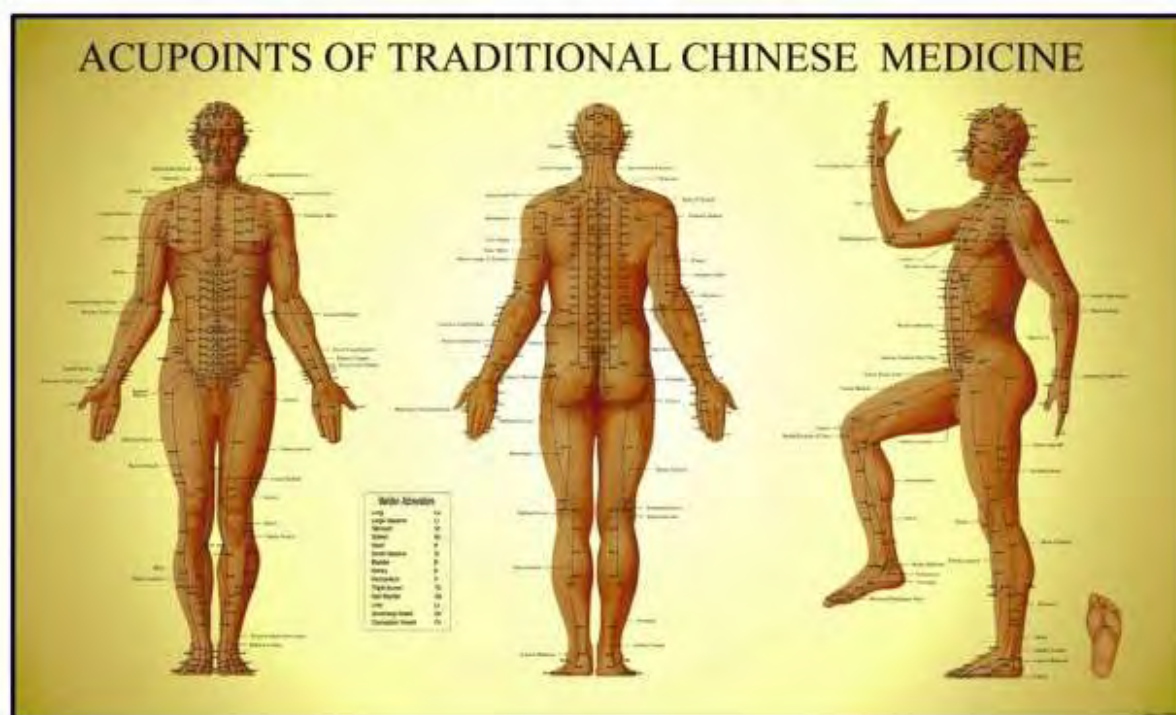


Figure 8. Meridians and acupoints chart.

In all of the meridians in traditional Chinese medicine there are specific acupuncture points, the needling of them is involved the treatment process. The main and basic acupoints are part of the twelve meridians described above but many other various acupoints are used outside these meridians. In total, there are 361 basic acupoints plus the various other acupoints outside the main meridians. The anatomical identification of the former is well established and recognised by many authors and acupuncture charts as in figure above demonstrate them specifically. The extra acupoints are not well specified and differences among various practices exist(47). The acupoints are believed to be the more superficial to the skin anatomical points along the meridians, the needling of which can affect the Qi circulating in these meridians. Apart from the treatment, acupoints are also used in the diagnosis process in acupuncture as the reflexes of them could give signs of the health problem involved(49). The needles' insertion in the body following the diagnosis process is thought to solve any Qi flow obstruction and this leads to the disease healing procedure. A patient who receives acupuncture is believed to understand the healing effect of acupuncture even by the time of needle insertion in a phenomenon called The Chi. This could involve slight anaesthesia, heat, slight pain, electrical current or tension sensation at the point where the needle is inserted(50). However, the Teh Chi, although it is connected to the effectiveness of acupuncture, it is not always required for it and many practitioners do not try to obtain that as it requires mainly deeper acupuncture, which could be more painful and connected with more complications as well(51).



The main acupuncture model is the one related strongly to the roots of traditional Chinese practice and the Qi, Yin-Yang and “Five elements” theory that were the basis of the development of acupuncture. However, in our days that acupuncture is developed in the western world under the scope of the evidenced based medical practice, many western mainly practitioners base their acupuncture practice to the proven mechanisms according to its’ neurological, biochemical and other well established effects on the human body.(43) In the latter model, the trigger points play a significant role, especially for muscle related pain, and many practitioners tend to identify them based on charts and manual palpation and then treat them (<http://www.triggerpoints.net/>). The accurate identification of these trigger points and the needling of them, reinforced with manual or electrical irrigation, lead to the relaxation of the affected muscle which obviously releases the pain in the area(52) It has been found that acupoints are characterised by low electrical impedance and include both skin and muscle component. In the majority of cases the traditional Chinese acupuncture points coincide with the trigger points(53) Each physician and acupuncturist select the methods of their treatment depending of their training and their own preferences.

### **Acupuncture technique**

Traditional Chinese medicine differs from the western model that we are used to today in many ways. One of the major positives about acupuncture in the evaluation of the body and soul as whole unit that should be treated regardless of the particular isolated organ which may be affected, which consists of a holistic approach to medical health problems and is far away from today’s subspecialisation trend(54). The word acupuncture itself is a combination of the Latin words “acus”, which is something sharp, and the word puncture, which is the insertion, and in conclusion acupuncture is the treatment using the insertion of needles(46). Acupuncture is a medical healing method comprising of the insertion of needles of various sizes, shapes and materials into the acupoints in the skin and muscles of the whole body from toes to head(47). The needles can be inserted only for few seconds, or inserted several times to the same point in few seconds, they could stay for few minutes to half an hour and this is the usual technique. They can also be irrigated during their staying inside the body with different types of methods. This could include manual stimulation(55) or this electrical stimulation using various electrical devices developed and even with the use of usual syringe needles with injectable fluid like anaesthetic or water for injection depending on the protocol used(50).

The traditional Chinese medicine apart from acupuncture includes other healing treatments as well and the one which is closely connected with acupuncture is moxibustion. In the latter method, specific dry cones of a specific herb called *Artemisia vulgaris*, are placed in the same skin points of the body as in acupuncture, with or without the presence of needle at the same time, and they are set on fire. The small burns that they produce to the applied skin is believed to be therapeutic(46). Many acupuncturists use moxa in their everyday practice in few selected points of their treatment as is it believed to reinforce the acupuncture effect.

The needling technique became more defined and organised as far as the insertion, direction, depth, speed and ways of retaining or withdrawing it even back to 13<sup>th</sup> century. One of the eminent acupuncture practitioners of that time Dou Han Qing organised and documented the various needling techniques and suggested many ways with the aim to eliminate the discomfort and increase the speed of needle insertion at the same time(38). Other practitioners of acupuncture focused on the improvement of the sterilisation process, as only recently single use sterile needles were introduced for acupuncture, while other dealt mainly with the complications, such as broken needles(38)(51). The acupuncture needles made of steel, still in use in our days, developed later probably during the 18<sup>th</sup> to 19<sup>th</sup> century.

Nowadays, there are several types of acupuncture needles that the acupuncturist can use. The most common type of needles in use today is the fine stainless steel needles. Silver and gold needles, similarly to the initial ones, still exist today but only rarely and only for specific indications are used in our days. There is a wide selection of sizes, lengths and widths of acupuncture needles today and depending to the area of needling practitioners choose the more suitable ones. All of them are very fine, sterile, single use and disposable ones. Some of them are accompanied by plastic tube guides and others are not. Their length could vary from few millimetres to few centimetres and their diameter is less than 0,4 mm generally. During the acupuncture procedure, the needles are inserted into the skin or even deeper to the muscle depending on the area treated. In a recent study, C. Wang et al found no difference in the efficacy between deep traditional and superficial acupuncture and thus recommended the use of more superficial acupuncture technique as a way to decrease the pain or adverse reaction of a more deeper technique(51).The accurate acupoint needling is preceded by a palpation of the presumed area, and the practitioner inserts the needle where a small cavity is presented(47).

Auricular acupuncture is an established medical technique in the eastern and western countries and works in isolation or in conjunction with the body acupuncture. Developed mainly during the last 70 years, auricular acupuncture treatment restricts its application to the ears according to anatomical maps. Each point is believed to correspond to an anatomical organ or area and the stimulation of it affects them indirectly. This stimulation could be performed with various methods including needles, just pressure with fingers, probes or herbs (acupressure), electrical current or laser(56). Different types of needle are usually used for auricular acupuncture, which include smaller and finest needles, such as intradermal or press needles. Intradermal needles are very fine and short and are used mainly for the ear. They are inserted about 1-3 mm depth and could be left in place for a few days, being covered with a waterproof tape. The press needles are also short and they are inserted into the skin of the ear via a press system. All of these needles are sterile and they can promote continuous stimulation to the points selected by leaving them in place for 1 to 4 days(57).

## Indications and use of acupuncture

Acupuncture is nowadays increasingly popular not only in Asian but also in Western world. Its popularity raised suddenly in Western world particularly after the visit of President of United States Nixon in 1972(42). At that time also, New York Times presented an article of one of his journalists who covered the above visit in China, describing the benefit he gained having himself acupuncture treatment for post-operative pain(41).

In 1996, the World Health Organization (WHO) set the recognised indication and criteria of acupuncture which were published, along with a review of acupuncture methods and use in order to establish an accepted methodology and indications list, which was not existing until that time(58). One year later, the National Institute of Health of United States (NIH) stated that acupuncture was a safe medical technique effective against various medical conditions and from that time acupuncture gained wide acceptance among medical world(41).

According to WHO there are fourteen well recognised indications that acupuncture treatment is beneficial(58). These are the following:

Pain	Infections
Neurological disorders	Respiratory disorders
Digestive disorders	Blood disorders
Urogenital disorders	Gynaecological and obstetric disorders
Cardiovascular disorders	Psychiatric disorders and mental disturbances
Paediatric disorders	Sense organ disorders
Skin diseases	Cancers

Pain is the most common indication for acupuncture. Its lack of adverse effects and safety, highlight acupuncture as the medical treatment preferred as monotherapy or combined with medication treatment not only for acute but mainly for chronic pain. It has been found that its success rate is equivalent of that of morphine(58). Much research has been done on this field. For instance C. Wang et al found that the application of acupuncture treatment on trapezius muscle decreased the pain symptoms of the patients, which were “dose depended” as the beneficial effect increased as the applications of acupuncture increased during the fourth week of the patients’ treatment(51). Moreover, X. Zhang et al noticed in their meta-analysis on the acupuncture treatment for fibromyalgia that acupuncture and electroacupuncture found to be significantly effective compared to the control groups with lasting results and that they were also found to be superior in comparison with the common used pharmacological treatment(59). Also, Siqueira et al, evaluating 34 runner athletes with knee pain reported that after a 5-week course of acupuncture treatment the treated limb acquired 47% strength, while the non-treated knee gained only 6%. The above outcomes, which were also documented with electromyography, resulted in a total reduction of the knee pain almost 50% (60).

Different types of pain could be addressed with acupuncture and while the musculoskeletal pain may be the commonest indication it is not the only one. In a recent study about the acupuncture’s effectiveness for acute migraine, S. Farahmand et al found that the analgesic effect of acupuncture was statistically significant during the first hour of treatment compared to the controlled group and they proposed that it can be used safely in the treatment for this condition combined with common treatments(61). Moreover, acupuncture was found to be effective against postherpetic neuralgia. In particular, Wang et al in their meta-analysis concluded that acupuncture treatment showed a tendency of better results in comparison with the common medication control group(62). Another interesting application of electroacupuncture for neuropathic pain and an example is demonstrated through an animal trial. J. Wang et al noticed a statistical significant improvement in induced neuropathic pain of sciatic nerve in rats starting from day two after treatment, and that electroacupuncture frequently applied could lead to the reduction of the activation of astrocytes in the spinal cord which are linked to the improvement of this type of pain(63). Outstandingly, acupuncture has been compared even to strong pain-relief medication such as morphine and has been found comparable or even more beneficial. K. Beltaief et al studied 115 patients with renal colic diagnosis and evaluated in two separate groups the monotherapy of either acupuncture or intravenous morphine. In the acupuncture group, patients had a half an hour acupuncture treatment, while in the medication group they had intravenous morphine every five minutes until the decline of pain at least to the half of its initial intensity. In this study, acupuncture effectiveness was of the same level as morphine treatment, but apart from the less adverse effects that it was connected, it reached its analgesic effect earlier than the medication group, which was also reported greater(64).

Pain related to cancer conditions can be a real challenge, being reinforced by the fact that cancer patients are already overtreated and sometimes resistant to further treatment. Acupuncture could provide assistance in these cases without adding more side effects to these patients. These patients could also be complicated by other cancer related or drug related symptoms, which reduce the quality of their daily life. Xu et al in their study, including patients suffering from hepatocellular carcinoma, reported the positive effect of electroacupuncture which was comparable to the fentanyl used control group and was important even from the third day postoperatively(65). Another study depicted also the benefit of acupuncture in pain relief in patients with cervical cancer. Meng et al studied two different acupuncture protocols in sixty-four cervical cancer patients and they found a superiority of trigger points technique in comparison to the common general pain relief acupuncture protocol in the two weeks interval after the beginning of the treatment(66). Moreover, G. Lopez et al, studied 375 cancer patients with different type of cancer and resulted that acupuncture could decrease not only the pain related to their condition but help in various other symptoms too. In particular they found that, related pain, xerostomia and nausea symptoms were significantly reduced to more than 50% of their initial intensity(67). Positive effect of acupuncture was also found in the occurring of hot flashes, fatigue and tingling sensation in these patients of the above study.

The traumatic and post-operative pain is another important chapter in the indications of acupuncture and it is well recognised and frequently used. In a recent study, the application of electroacupuncture was found to reduce the postoperative pain in patients after hemorrhoidectomy even as soon as six hours after the operation in comparison with the control group who received only sham acupuncture. The benefit of acupuncture in the above study was more evident in the first day postoperatively, when the pain is more severe and thus the authors recommend the electroacupuncture in treatment of postoperative pain in these cases(68). Moreover, acupuncture could be considered in patients who are not suitable for further painkiller use. For example, Bosco et al applied intensive electroacupuncture with frequency of 23-70 Hz in two patients who had partial and complete mastectomy for breast tumour. Both of the patients had hepatic cirrhosis and it was not safe for them to get stronger painkiller in order to undergo the surgery. The application of electroacupuncture was performed prior to and after the surgery with significant results as both of the patients could tolerate the postoperative pain without taking any strong painkillers like opioids(69). Thus, the authors suggest that electroacupuncture should be considered in cases that the drug reduction is important.

Acupuncture could also be applied in a variety of gastrointestinal problems with great results, sparing serious side effects. For example, W. Sun et al reported a case of a young lady patient with postoperative ileus after having caesarean section, in whom acupuncture was drastically beneficial and helped her to mobilize her intestine as soon as thirty minutes after the first session(70). This result is really promising as non-pharmacological methods are preferable for breastfeeding women who have just delivered their babies. Moreover, currently the effect of acupuncture on many gastrointestinal problems is under investigation. For example, researchers in China are investigating the effectiveness of acupuncture towards irritable bowel syndrome and the results are expected to be published soon(71). Furthermore, the transcutaneous

electrostimulation of specific acupoints showed beneficial results in the management of constipation caused by the use of opioids. Zhu et al found that daily electrostimulation of specific acupoints in cancer patients treated with opioids for their pain control with daily electrostimulation treatments for two weeks, had the similar efficacy as lactulose medication used per os in the control group(72).

A specific part of gastrointestinal applications of acupuncture is the nausea of many causes, based on which we decided to induce our own study about motion sickness. Albooghobeish et al, studying 122 women who underwent laparoscopy surgery for gynaecological causes resulted that acupuncture was more beneficial compared to medication control group. In specific, the patient who received acupuncture had about one third less nausea symptoms than their counterpart who received conventionally metoclopramide, and despite the fact that metoclopramide group reported about 10 fold more postoperative nausea and vomiting symptoms, the rate of vomiting itself was equal in both groups(73). Moreover, Van den Heuvel et al in the study resulted that acupuncture and acustimulation mainly in the acupoint P6 show beneficial effect in the nausea and vomiting symptoms of pregnant women and that the lack of the possible harmful adverse effects on the foetuses that the equivalent medication has, it is worth continuing the research on this field(74).

Acupuncture has various other implications in many medical subspecialties including gynecology and obstetrics. Xu et al in their meta-analysis, including almost 600 women, resulted in the benefit of acupuncture in patient with endometriosis. They found that acupuncture was effective in a statistically significant level in the pain control related to the condition and that also resulted in the decline of CA-125 blood levels(75). Moreover, in another meta-analysis S. Sung found that when acupuncture was combined with the usual pain control medication resulted in greater benefit in female patients with chronic pelvic pain when compared to treatment only with medication, and thus proposed as adjunctive treatment for this disease(76). Acupuncture showed also promising results in difficult managing gynecological conditions like cervical dystonia. Bega et al, applied acupuncture in 5 patients with uncontrolled cervical dystonia as adjunctive to their main treatment with BOTOX injections and all of them reported an overall improvement in the severity of their symptoms(77).

Another interesting domain of acupuncture is also the neurological related diseases. Tu et al in their study concluded that acupuncture is beneficial for a variety of neurological conditions characterized by alterations in the glutamate levels in the central nervous systems. Thus, they suggested that acupuncture could be helpful in the management of anxiety and depression disorders, as well as sleeping difficulties, Alzheimer disease and schizophrenia(78). Anxiety of different causes is believed to be addressed effectively with acupuncture. Samadi et al studied 131 women giving birth and the noticed that acupressure at a single specific acupoint for half an hour, resulted in the reduction of the stress of the patients during their labour. The comparison was performed with a control group that received usual treatment and the results were statistically significant in favour to the acupressure group(79).

Addictions condition is another important sector of acupuncture application, as in isolation or association with other modalities can achieve impressive results. Zeng et al found that 3 weekly session electroacupuncture for one month succeeded to reduce the withdrawal symptoms of previous drug addict patients after being treated with methamphetamine, decreasing all the symptoms connected to that such as stress and depressive mood(80). Obesity treatment with acupuncture and electroacupuncture has great results as well. Y. Zhang et al in their study found that only few sessions of acupuncture on obese patients result in the significant decrease of their weight in comparison with the control groups following only related diet(81). Moreover, similar results were found in another meta-analysis of acupuncture treatment for the latter indication. Particularly, K. Zhang et al reported that up to two months sessions of acupuncture resulted in the lower levels of body weight, body mass index and body fat mass in obese patients, when compared to control groups. What was interesting in the last study was that the patients from the acupuncture group presented also lower levels of serum lipids(82).

The indication of use for the auricular acupuncture are about the same as in the traditional acupuncture. Asher et al in their systematic meta-analysis found that auricular acupuncture reported significant benefit in the treatment of different types of pain, especially in the postoperative pain and they concluded that auricular acupuncture could be beneficial for the treatment of pain mainly regarding patient non responding to pharmacological treatment(56). Moreover, Garner et al noted in their study that the application of auricular acupuncture could relieve pain and insomnia in comparison to the usual pain treatment and that this treatment could be even applied to military staff in order to reduce the uncontrolled use of opioid medication(57). Temporomandibular myofascial pain is another area that the acupuncture could be applied with beneficial results. More specifically, Lopez-Martos et al resulted in a statistically significant benefit both of dry acupuncture and combined with electrostimulation in the reduction of the pain in patient affected by the above disorder. The results were constantly superior to the control group until the end of the follow up period of the patients lasting more than one month(83). Auricular acupuncture was found also to have positive results in the treatment of obesity. H. Oto et al noted a statistically significant weight loss in patients who received acupuncture treatment in comparison to their control group counterparts. In their study the authors proposed also that this effect is possibly attributed to the reduced ghrelin level that the patients of the acupuncture group tended to have as a result of their treatment(84).

### **How it works – Proposed Mechanisms**

The mechanisms of acupuncture and electroacupuncture are still vague today. In traditional Chinese acupuncture in ancient years, the correlation of the acupuncture of specific points to the treatment of allocated body sites and organs including visceral organs was also noticed. In this observational report is based the meridian system and the development of the acupoints as well as the theory among them(39). In the tradition of Chinese medicine, the energy blockage, which is called Qi stagnation, is responsible for the cause of the diseases According to this theory, energy, called Qi,

which is flowing along the meridians is blocked at any point of this flow and this should be diagnosed and treated accordingly(85). Nowadays, many researchers try to identify the reason of acupuncture effectiveness and many studies are still held based on these unclear mechanisms. The main area of research in Western world the pain management using acupuncture and how this could be better understood. Many interesting theories were proposed for this reason.

One of the oldest proposed theories, is the gate control theory. According to this, there are separate inhibitory and transmittory nerve fibres, which are both in correlation to the spinal cord. The sensation of pain is the result of the stimuli imbalance of the aforementioned fibres(85). This theory is not very popular anymore as it could not explain the variety of the acupuncture indications.

Another one of them has been suggested by C. Li et al, who reported brain functional MRI in patients who had dry needle acupuncture as treatment for Bell's palsy. They found that the brain responses to acupuncture differed along the various pathological stages of the disease. The brain responses were greater in the later stage, while they were normal during the early and recovered stage to the levels of the healthy controls(86). Thus, they proposed that the acupuncture effect could be linked to the brain functional status. This results was also consistent with the findings of R. Zhang et al, who noticed that electroacupuncture stimulates the central nervous system in a different way in control groups and units in pain in animal models, according to different involvement of the opioid receptors in the reduction of pain of the above groups(87).

One among the popular theories of mechanism of acupuncture and electroacupuncture is the injury of the site of acupuncture with or without current cause. It is believed that the needle insertion into an acupoint results in flowing current within the myelin sheath of the nerves and causes a myelinated neural circuit AA(85). We have already reported that the acupoints are characterised by low electrical impedance and include both skin and muscle component(53). In particular Gabyoglu et al believe that the acupuncture stimulation affects also possibly the skin receptors of touch and pressure, muscle fibres or even tendon and pain pressure receptors. Thus, any type of injury that the needle could cause to the acupoints, mechanical, electrical or magnetic, induces perturbation of the current in the nearby myelinated nerve. S Chang in his review article suggests that this could also be reinforced by the fact that the acupuncture injury could also cause electromagnetic effects in the acupoints treated as the impedance of them can be altered in such a way that the brain can no longer recognise the source of pain according to this impedance matching/mismatching theory(85). In particular it is believed that the acute pain and its short duration may not have cause great deviation of the impedance of the site of pain and this is the reason why acute pain could be treated easier than chronic, as the acupuncture could alter this impedance easier. Cabyoglu at al believe that the analgesic effect of acupuncture



results from the inhibitory action on neural activity of the dorsal periaqueductal grey region and the formation of the brainstem (53).

Another important proposed mechanism of the acupuncture and electroacupuncture action is the neurochemical factors related that could also cause the centrally controlled effects. It has been proved in previous studies that biochemical molecules, such as opioids, serotonin, norepinephrine, cytokines and other transmitters, play an important role in this procedure(87). The analgesic effect in this mechanism is performed by the inhibition of the pain signals that are introduced to the nervous system. It is believed that the stimulation of a needle in an acupoint can irrigate the pain receptors and result in the production of endogen opioids, enkephalins and serotonin by the brain, which can contribute to the pain relief(53). N. Dimitrov et al, studying the effect of acupuncture on rats, found that the needle stimulation of ST36 resulted in degranulation of mast cell locally with the release of 5-HT and serotonin confirmed with immunohistochemistry. They also proposed this serotonin tissue increase as one probable local action of acupuncture(88). T.K. Lim et al in their study refer also that the stimulation of the needles can cause changes in the structure of fibroblasts that can potentially lead to ATP release. This in turn can attribute in the adenosine and several purines formation, and all of them can result in the inhibition of pain via the purinergic receptors(89). On the other hand T.Y. Yang et al found using immunohistochemistry, that acupuncture alleviated lipopolysaccharide-induced anxiety behaviour, changes using dry needling in ST41 in rat models by suppressing serotonin transporter(90). The most important role of all these bioactives seem to play the opioids as they promote a chemical cascade which results in the reduction of pain. They are also responsible of activation of the norepinephrine and serotonin, which also contribute in the alleviation of pain(87).

Another interesting finding in the review of mechanisms of electroacupuncture is the specific frequency of major results. A better improvement of pain in protocols which included lower frequency of electrostimulation in comparison to higher ones has been found. 10 Hz electrostimulation provides better control of pain and 2-10 Hz contribute in the alleviation of hyperalgesia more than higher frequency(87). This is the reason why most studies involving treatment of pain prefer lower frequencies. Zhao et al for example in the study to alleviate hyperalgesia in rats with electroacupuncture, they preferred a frequency of 2 Hz, 1-3 mA in ST36 and SP6 with significant results.

In our days, taking into advantage the medical technological facilities available, researchers also tried to find the source of acupuncture effectiveness using neuroimaging and other radiological modalities. T. Parrish et al depicted using fMRI in their study, that acupuncture stimulated specific cortical areas are related to the acupoints used. In particular in the acupuncture group, in whom BL60 for visual stimulation and K3 for auditory stimulation acupoints was used, a corresponding stimulation in the related brain areas was found(91). On the contrary, in the sham group, no stimulation was recorded. The effect of acupuncture on the brain can also be reinforced by several other studies. For instance, Zheng et al found in their study that the acupuncture of Liv3 and LI4 in patient with Alzheimer disease produced significant changes in the brain activity depicted by fMRI scan, and also resulted in

hippocampal connectivity(92). Claunch et al presented also relative specificity in the stimulation of acupoints commonly used for pain relief, showing a trend to activate particular limbic-paralimbic areas. Specifically, they triggered manually LI4, ST36 and LV3 and examined their healthy subjects with subsequent fMRI, which showed deactivated regions in the medial prefrontal, medial parietal and medial temporal lobes in quite similar patterns and overlap(93). In a similar result with the last study arrived also K. Hui et al, who studied the same popular acupoints, adding that the haemodynamic changes were affected by the psychophysical factors as well(94).

According to Stux et al, the actual mechanism of acupuncture could be the combination of all the above referred to as three-level system. After the stimulation of the muscle the electrical signal travels to the spinal cord, midbrain and hypothalamus-pituitary and the stimulation of them results in the reduction of pain. While the spinal cord secretes enkephalins and dynorphins to inhibit the afferent signals, the midbrain uses the enkephalins along with monoamines, serotonin and norepinephrine to block the pain related to spinal cord. At the third level of control stand the hypothalamus and pituitary gland, which secrete  $\beta$ -endorphins into CSF and serum and can induce pain relief centrally(95).

Acupuncture and particular electroacupuncture is also beneficial in the management of obesity. F Wang et al in the study concluded that the low frequency at about 2 Hz that electroacupuncture tended to result in the increase of weight loss related to reduction of appetite(96). They also found that electroacupuncture resulted in the decrease of the levels of the cholesterol and triglycerides in the plasma, as well as related to increase levels of anorexigenic peptides such as aMSH and CART.

## **Advantages of Acupuncture**

The advantages of acupuncture are the following:

1. Acupuncture is applicable nowadays for different medical conditions and the list of indications is considered non-exhausted as new applications of acupuncture are investigated by researchers. It could be applied as part of various medical specialisations such as surgery, pain management, orthopaedics, gynaecology, anaesthesiology and many others(58).
2. Acupuncture training is easily achievable and courses all over the world are held for this reason.
3. Acupuncture is cheaper than conventional western medicine. This fact could be considered not only in the developed world in order to decrease the amount of money spent on medicines, but could also be considered in the developing world where there

is lack of medical supplies and limited financial sources. In the latter environment, acupuncture could provide medical support within the increased population among a wide variety of indications as above.

4. Limited contraindications (see below).

5. Acupuncture is regarded as a safe medical technique. It can cause only few minor side effects, such as minimal bleeding or bruising, and this is the reason that it is preferred in patients who cannot tolerate medication or are already overtreated, particularly for painful diseases, which is one of the major indications of acupuncture. It has been proved that acupuncture could be almost as effective as morphine, but being safer than this. The safety and non-pharmacological treatment that acupuncture provides is a significant reason to apply it isolated or in conjunction with other medication, even when its success rate is not at the same level as with the main proposed pharmacological treatment(58).

### Contraindications

The absolute contraindications are established by the Guidelines AACP (Acupuncture Association of Chartered Physiotherapists 2017) are the following(97):

General	Local
Sepsis	Local swelling
Treatment of not investigated seizure	Infection
<i>Acute stroke, as it could cause cerebral blood overflow</i>	Tumour area
Unstable mental status	Uncontrolled movements
<i>Young patients, although there is not specific age limit</i>	Previous lymph node removal

Needle phobia	Spinal tumours/metastasis

### **Complications of acupuncture**

The complications of acupuncture as established by the Guidelines AACP are the following(97):

Bleeding and bruising	Nausea
Mild aggravation of symptoms	Faint
Mild pain	Stuck, bent or broken needle
Drowsiness	Headache
Dizziness	Allergy or infection
Allocated pain	pneumothorax

Most of the above complications are minimal, temporal and easily treatable when an appropriate sterile acupuncture technique is used by a well-trained physician. The most important risk of acupuncture is the pneumothorax when applying needling in the thoracic cavity. The above risk is really low accounting for about 0.0002%(97) of patients having acupuncture and is even less when the appropriate technique is followed. In the suspicion of pneumothorax the patient needs urgent medical and surgical evaluation and should be referred urgently to the closed Accident and Emergency Department.



## SPECIFIC PART

---

|

## **INTRODUCTION**

Motion sickness is a syndrome caused when a person is exposed to certain types of motion and often occurs during passive motion in vehicles that are means of transport. Body acceleration applied to a person not accustomed to it is considered a main eliciting factor. The cause, according to the prevailing hypothesis, is ambivalent stimuli sent to the brain by the body's sensory receptors, the vestibular and visual systems. Major signs and symptoms of motion sickness include nausea, vomiting, pallor, cold sweating, drowsiness, headache, increased salivation, and hyperventilation(33).

Acupuncture is a type of therapy that involves applying mechanical stimulation to various body points using needles. Electroacupuncture (EA) entails the application of an electric current to the fitted needles by means of a special device. Previous studies have shown benefits from the application of acupuncture and EA for prevention of and therapy for nausea from other causes, such as chemotherapy- induced nausea(98, 99), postoperative nausea(100-102), and pregnancy- related nausea in the first semester(99, 103) The present study was designed to research the effect of EA on the symptoms of motion sickness.

## **MATERIALS AND METHODS**

The sample in this study consisted of asymptomatic young males of the Hellenic Air Force, ages 18–30. The sample consisted of 20 people. The study took place in the 120 Flight Training Wing Medical Service (in Kalamata, Greece). Participation in the study was voluntary, according to the World Medical Association Declaration of Helsinki. All participants signed informed consent for their participation in the study. Ethical approval was obtained by the Hellenic Air Force Directorate of Health and University of Thessaly Ethics Committee.

The following staff categories were excluded from the study:

1. Pilots of any experience level, because they are considered already adapted to complex motion sickness stimuli

2. Subjects who had received acupuncture or EA treatment in the past for any reason
3. People who had medical histories active diseases that could affect their tolerance to motion sickness (e.g., chronic gastrointestinal or ear–nose–and–throat problems)
4. Subjects who had consumed alcohol within the last 24 hours prior to the examination
5. Subjects who reported <6hours sleep the night before.

The participants were randomly assigned into 1 of 3 groups:

1. Group A, who were subjected to therapeutic EA
2. Group B, who were subjected to sham EA and were used as a first control group
3. Group C, who did not receive any therapy and were used as the second control group.

Prior to each session, the medical history of each participant was taken. In cases of drug use, illness, or any other pathologic conditions, the procedure was postponed for the particular participant until resolution of the condition occurred.

Application of therapeutic EA and sham EA to the participants in Groups A and B, respectively, was performed by acupuncture trained Investigator A (O.F.) and took place half an hour prior to the motion-exposure procedure.

The acupuncture points used were PC 6 (Pericardium 6), ST 36 (Stomach 36), and LI 4 (Large Intestine 4) bilaterally. EA was applied on needles in PC 6 and ST 36 bilaterally, while, in the LI 4 point only manual acupuncture was applied. The aforementioned protocol is compatible with the recent study of Han et al., who studied the effectiveness of EA treatment for gastroesophageal disease(104).

Sterile, disposable, stainless-steel needles were used, with a guide that was 0.25 x 0.25 mm. They were inserted about 1 cm below the skin surface. Once the needles were positioned at points PC 6 and ST 36, they were connected to a pair of cables of



an EA device on the same side to complete the electrostimulation. EA was applied via an ES-160 EA device (ITO Co., Ltd., Tokyo, Japan) for 20 minutes at pre-set program 1. In the selected electrostimulation program, the frequency ranges between 1 and 6 Hz, while the phase durations of the electrical waves are between 50 and 300  $\mu$ s. There are 5 different consecutive modes used in this program: (1) constant; (2) fast + slow; (3) burst; (4) sweep; and (5) constant. The maximum output current used was low, between 1 and 16 mA (the peak output current of the device is 32mA) and the stimulation intensity was adjusted depending on the degree of each participant's tolerance (mean level of 10–14 mA). This is according to the practice of Han et al.'s study, in which the same EA device and the same method for the current were used(104). However, Han et al. preferred to use a mixed electric current at a frequency of 2–6 Hz and the “fast + slow” mode of the ES-160 of ITO(104).

Sham acupuncture is nontherapeutic acupuncture at nontherapeutic points, but using the same needles as when applying therapeutic acupuncture. The participants were not able to distinguish the difference between conventional and sham EA, despite the fact that no electricity ran through the needles for the latter. In the present study sham acupuncture was applied to nontherapeutic points through superficial needling near acupuncture points LI 13 (Large Intestine 13) and GB 32 (Gall Bladder 32). When applying sham acupuncture, the EA device's cables were connected to the placed needles; yet, no electrical stimulation was applied.

Half an hour after the end of the EA procedure, the participants were exposed to a Coriolis-type stimulus to induce motion sickness by using a rotating chair under the supervision of Investigator B (P.K.). Coriolis stimulation simultaneously engages two of the three semi-circular canals of the ears and occurs when there is a sudden movement of the participant's head on one axis in space, while the participant is in rotation on another axis. This illusion gives the impression that there is rotation on the third axis in space. It has been shown that this Coriolis illusion can disorientate a participant easily and generate motion sickness(105).

In the present study, the rotation of the motor-driven chair was always clockwise, stable, and pre-set at 10 revolutions per minute. The head of each participant was aligned with the rotation axis, after the adjustment of the seat and the headrest, as was described in a previous study(106). There was a type of seatbelt used for the protection of the volunteers. During the rotation, the participants were exposed to limited visual stimuli; the participants were placed in a barely lit room and were asked to keep their eyes shut. This practice enhanced the disorientation of the volunteers, as vision is the major input for orientation. The participants followed computer-recorded commands to make specific head movements (right roll, front pitch, left roll, and back pitch) every 30 seconds.

Before the start of the session and immediately after its end, motion sickness symptoms were measured using the Greek version of the Gianaros Motion Sickness Assessment Questionnaire (MSAQ)(35), which had been translated and validated in a previous study(106) The MSAQ is comprised of 16 questions, covering four clusters of symptoms: (1) gastrointestinal (GSTR); (2) central nervous system (CNS); (3) peripheral nervous system (PNS); and (4) sopite (SOP)–related symptoms. Each symptom was given ratings of 1 (not at all) to 9 (severe). A total score is produced (MSAQ-Total) and four subscale scores (MSAQ-GSTR, MSAQ-CNS, MSAQ-PNS and MSAQ-SOP). Two types of measures of motion sickness severity were used for the present study:

(1) MSAQ scores (total and sub-scale scores) after motion exposure

(2) The difference in MSAQ scores before and after the exposure.

In addition, during the rotation and after each head movement, total subjective motion sickness symptoms were measured based on a scale from 1 to 7, according to the practice of Golding and Kerguelen (1 = no symptoms and 7 = maximum nausea–vomiting intensity)(107). The session ended either when the participant reached maximum intensity of nausea symptoms or vomiting level, or wished to interrupt the process (7 in the Kerguelen scale) or had completed 20 minutes of motion exposure. The times reached by the volunteers in the rotating procedure was assessed and compared among the 3 groups.

## **RESULTS OF THE INITIAL STUDY**

The sample of this study initially consisted of 20 subjects, 8 of whom were assigned to Group A, 6 to Group B, and 6 to Group C. All participants completed the Greek version of the Gianaros MSAQ(106) without any need for assistance. The mean time required to complete the questionnaire was about 3 minutes (range: 2–4 minutes).

The variables that were researched -GSTR, CNS, PNS, SOP, and TOTAL- result from summing up the responses to the relevant questions of the Gianaros questionnaire. In the current analysis, the reliability of the scales (Likert scales) was tested with a Cronbach’s a statistic. After motion exposure, the statistics were estimated at levels

ranging from 0.74 (SOP) to 0.93 (TOTAL), implying that the internal consistency of the data was at least satisfactory.

The basic descriptive measures of the variables showed that their mean values, as well as their ranges and dispersions (standard deviations), increased considerably after application of the motion procedure.

To further this analysis, the increase in the symptom severity in the total score and in all subscale scores was compared by comparing Group A versus Group B, Group A versus Group C, and Group B versus Group C. The bi-group differences were evaluated on the basis of a nonparametric Mann–Whitney U-test (for two independent samples). No statistically significant differences were found at baseline before motion stimuli was applied. However, after motion exposure, when comparing Group A to Group C, it was found that the differences in the elevated values of the variables TOTAL, PNS, and SOP were statistically significant (with the last one marginally so). With respect to SOP, a statistically significant difference at level 0.01 was also found when comparing Group A to Group B. The results of the analysis are presented in Table 2.

Test Statistics for Group A vs Group C						
	GASTR	KNS	PNS	SOP	TOTAL	
Mann-Whitney U	13.000	13.000	8.000	9.500	7.000	
Z	-1.425	-1.423	-2.079	-1.884	-2.197	
Asymp. Sig. (2-tailed)	0.154	0.155	0.038	0.060	0.028	
Exact Sig.	.181	0.181	0.043	0.059	0.029	
Test Statistics for Group A vs Group B						
	GASTR	KNS	PERIF	SOP	TOTAL	
Mann-Whitney U	21.000	14.500	19.500	10.500	15.500	
Z	-0.389	-1.232	-0.582	-1.754	-1.100	
Asymp. Sig. (2-tailed)	0.698	0.218	0.560	0.079	0.271	
Exact Sig.	0.755	0.228	0.573	0.081	0.282	
Test Statistics for Group B vs Group C						
	GASTR	KNS	PERIF	SOP	TOTAL	
Mann-Whitney U	8.500	16.500	8.500	17.500	11.500	
Wilcoxon W	29.500	37.500	29.500	38.500	32.500	
Z	-1.529	-0.241	-1.537	-0.080	-1.043	
Asymp. Sig. (2-tailed)	0.126	0.810	0.124	0.936	0.297	
Exact Sig.	0.132	0.818	0.132	0.937	0.31	

Table 2. Mann–Whitney Nonparametric U test for Two Independent Samples. Asymp., asymptomatic; sig., significance; GSTR, gastrointestinal; CNS, central nervous system; PNS, peripheral nervous system; SOP, sopite

As the motion sickness symptoms of each person was measured twice (i.e., before and after exposure; paired observations), the significance of the changes was evaluated on the basis of a Wilcoxon test for two related samples. The results are presented in Table 3 and show that, in all cases (i.e., all variables and all groups), the changes are statistically significant at the level of 0.05.

		Test Statistics <sup>a</sup>				
		GASTR	KNS	PNS	SOP	TOTAL
Group A	Z	-2.524 <sup>b</sup>	-2.201 <sup>b</sup>	-2.521 <sup>b</sup>	-2.032 <sup>b</sup>	-2.521 <sup>b</sup>
	Asymp. Sig. (2-tailed)	0.012	0.028	0.012	0.042	0.012
Group B	Z	-2.201 <sup>b</sup>	-2.214 <sup>b</sup>	-1.826 <sup>b</sup>	-1.997 <sup>b</sup>	-2.201 <sup>b</sup>
	Asymp. Sig. (2-tailed)	0.028	0.027	0.048	0.046	0.028
Group C	Z	-2.207 <sup>b</sup>	-2.201 <sup>b</sup>	-2.207 <sup>b</sup>	-1.992 <sup>b</sup>	-2.207 <sup>b</sup>
	Asymp. Sig. (2-tailed)	0.027	0.028	0.027	0.046	0.027
a. Wilcoxon Signed Ranks Test						
b. Based on negative ranks.						

Table 3. Significance of Changes in Values of the Variables Before and After Motion Exposure: Wilcoxon Nonparametric Test for Paired Samples. <sup>a</sup>Wilcoxon signed-rank test. <sup>b</sup>Based on negative ranks. Asymp., asymptomatic; sig., significance; GSTR, gastrointestinal; CNS, central nervous system; PNS, peripheral nervous system; SOP, sopite

The average times of exposure to motion stimulus by group are shown in Table 4. The greatest mean time (17.5 minutes) appeared to be achieved by the participants in Group B. To test for the differences in the mean times of exposure among the 3 groups, the F-test (one-way analysis of variance; ANOVA) was used.

		Test Statistics <sup>a</sup>				
		GASTR	KNS	PNS	SOP_	TOTAL_
Group A	Z	-2.524 <sup>b</sup>	-2.201 <sup>b</sup>	-2.521 <sup>b</sup>	-2.032 <sup>b</sup>	-2.521 <sup>b</sup>
	Asymp. Sig. (2-tailed)	0.012	0.028	0.012	0.042	0.012
Group B	Z	-2.201 <sup>b</sup>	-2.214 <sup>b</sup>	-1.826 <sup>b</sup>	-1.997 <sup>b</sup>	-2.201 <sup>b</sup>
	Asymp. Sig. (2-tailed)	0.028	0.027	0.048	0.046	0.028
Group C	Z	-2.207 <sup>b</sup>	-2.201 <sup>b</sup>	-2.207 <sup>b</sup>	-1.992 <sup>b</sup>	-2.207 <sup>b</sup>
	Asymp. Sig. (2-tailed)	0.027	0.028	0.027	0.046	0.027
a. Wilcoxon Signed Ranks Test						
b. Based on negative ranks.						

Table 4. Time of exposure to motion stimulus: descriptive statistics by Group

The assumptions of the techniques (homogeneity of variances and normality of variables) were evaluated on the basis of the Levene test and Shapiro–Wilk statistics, respectively. Examination of the mean differences between groups in A versus B, in A versus C, and in B versus C was carried out using a Tukey posthoc multiple comparison test. The results of the whole procedure are presented in Table 5. These findings indicated that the assumptions of the one-way ANOVA were fulfilled and the estimated F-statistic (7.036) was statistically significant (at a level of 0.006).

However, the difference in the mean times between groups A and B was not statistically significant ( $P=0.575$ ); on the contrary, comparisons between Group C and each of the other two groups (A and B) showed that the relevant differences were statistically significant.

Test of Homogeneity of Variances				
Levene Statistic	df1	df2	Sig.	
3.067	2	17	0.073	
Test of Normality: Shapiro-Wilk statistic				
	Statistic	df	Sig.	
Group A	0.827	8	0.055	
Group B	0.807	6	0.068	
Group C	0.938	6	0.647	
One-Way ANOVA: F-test				
	Sum of Sq. (df)	Mean Square	F	Sig.
Between Groups	305.085 (2)	152.543	7.036	0.006
Within Groups	368.552 (17)	21.68		
Total	673.637 (19)			
Tukey test: Post Hoc Multiple Comparisons				
(I) Group	(J) Group	Mean Difference (I-J)	Std. Error	Sig.
A	B	-2.5625	2.5146	0.575
	C	7.1042	2.5146	0.030
B	A	2.5625	2.5146	0.575
	C	9.6667	2.6882	0.006
C	A	-7.1042	2.5146	0.030
	B	-9.6667	2.6882	0.006

Table 5. Test for Differences in the Mean Times of Exposure to Motion Stimulus Among Groups. df, difference; Sig., significance; ANOVA, analysis of variance; SE, standard error. Comparisons of all possible pairs of sub-groups (I and J) of the factor variable under investigation include tests of mean differences between groups (A,B), (A,C), (B,A), (B,C), (C,A), (C,B)

## DISCUSSION

The main purpose of this study was to evaluate EA pre-therapy as a beneficial nonpharmaceutical method for the treatment of motion sickness. The initially recorded differences are relatively small and partially statistically significant. However, promising findings were observed. No difference was found in the gastrointestinal and central nervous systems. A statistically significant difference was observed in the peripheral and total symptoms in the comparison between Group A and Group C, while the difference in SOP-related symptoms was only marginally significant. The volunteers in Group A mentioned less sweating or cold sweating symptoms, as well as less flushing and heat sensations in comparison to their Group C counterparts. Given that peripheral symptoms are attributed to sympathetic nervous system activation, it is possible, that acupuncture alters autonomic nervous system activity in a certain way. The difference in total symptoms was mainly attributed to the peripheral subtotal.

The results of this study cannot be clearly understood, because the pathophysiology mechanisms of acupuncture are still in debate. Tjen-A-Looi et al. studied cats and found that EA at PC 6 and LI 4 decreased premotor sympathetic cardiovascular neuronal activity in the rostral ventral lateral medulla by 41% and 12%(108), respectively(108). Yang et al. suggested that manual and laser acupuncture at PC 6 and ST 36 in rats enhanced gastric motility and increased heart rate, while EA in the former induced an increase in low-frequency/ high-frequency in heart rate variability (HRV)(109). Those results were attributed to sympathetic nerve activity and were partially compatible with the results found in a study by Hideaki et al. The latter studied 16 healthy individuals using HRV testing and found that EA at LI 4 and LI 11 bilaterally increased sympathetic nerve activity immediately, while parasympathetic nerve activity was induced 20 minutes later(110). However, although there have been efforts to identify the accurate mechanism of acupuncture in several studies, this field remains unclear and more studies are needed.

The acupuncture points used in the present study (PC 6, ST 36, and LI 4) were selected because they had been used in the past for treatment of nausea. Dundee et al., in a review article, proposed the PC 6 antiemetic action in postoperative morning sickness, cancer chemotherapy, and travel sickness(99) and Alizadeh et al. discussed the use of points for preventing postoperative nausea and vomiting (PONV)(101). ST 36 is a point that is thought to promote the regulation of the gastric activity. Sallam et al. studied rats with the aim of finding a potential treatment for chemotherapy-induced delayed emesis; the treatment proposed was EA via chronically implanted electrodes, and the researchers found that a combination of EA of PC 6 and ST 36 points was

superior to PC6 only(98). LI 4 is one of the most-researched and significant acupuncture points. It has analgesic and spasmolytic effects and it is frequently used in combination with ST 36 or PC 6(101, 104)..

In previous studies, acupuncture or EA produced relief of nausea symptoms(99, 100, 102). For example, Dundee et al, in a series of studies with more than 500 female patients, found a significant reduction in PONV only by stimulating PC6(99). The lack of anti-nausea effect of EA in the present study, which is effective for the treatment of nausea of other causes, such as chemotherapy-induced and postoperative nausea, might indicate that there are different pathophysiology mechanisms in the development of nausea in motion sickness.

One major concern of the present investigators was to ensure proper study blinding. Investigator A (O.F.) conducted the EA procedure and investigator B (P.K.) supervised the motion exposure procedure. Investigator B (P.K.) was not aware of the participants' division into groups. Group A and B participants were not able to distinguish whether they were subjected to therapeutic or sham EA, because both were applied with the same method. For the above reasons, the comparison between Groups A and B was, in effect, a double-blinded study. Group C participants were aware that they had not received any therapy prior to the motion exposure. They were used as a control group in order to research the possibility of a placebo effect of sham EA. Every effort was made to ensure that the participants did not inform Investigator B about which groups they were in. Thus, the comparison between Groups A or B with Group C, also, was in effect, a single-blinded study.

The MSAQ scores and sub-scores before the exposure were similar in all 3 groups, indicating that all subjects had the same starting point, with respect to their motion sickness symptoms. This was expected, as the experiment was conducted under appropriate conditions (double-blinded study) to safeguard the random sample selection. Any slight differentiations noticed could have resulted from the small sample. Therefore, any differences in the MSAQ scores observed had to be attributed to the exposure to rotating motion and the influence of the EA therapy. The MSAQ scores increased in a statistically significant way after the procedure in all 3 groups of participants. This meant that all 3 groups were exposed to a stimulus of adequate intensity to produce measurable physiologic effects.

Quantifying the physiologic effects and the motion sickness symptoms is inherently difficult and this might contribute to the variable results seen in motion sickness studies. Scientists generally rely on subjective measures and questionnaires for these studies(101). Motion sickness has usually been assessed with a questionnaire by Graybiel et al., which ranges the symptoms from slight malaise (1–2 points) up to frank sickness (> 16 points)(33). Muth et al. proved that there was no correlation of



high doses of ondansetron and dimenhydrinate with prevention of motion sickness(111) using the same MSAQ as in the present study. It is worth mentioning that this is the first time that the Greek-validated version of MSAQ was used in a study(106).

Regarding the time spent by the participants on the rotating chair being submitted to the Coriolis stimuli, the comparison among the 3 groups was interesting. Group B tended to be more resistant to nausea stimuli, while Group A was the second more durable group. However, there was no statistically significant difference between Groups A and B. On the contrary, Group C spent statistically significant less time being rotated in comparison with both Groups A and B. This result reinforces the suggestion that EA and EA procedures affect and reduce motion sickness symptoms. The lack of a statistically important difference between the first two groups might have been the result of a placebo effect or the consequence of the small sample size of the participants.

Therefore, a major limitation of reporting results of this study was the small sample size. The small sample reflected a difficulty in recruiting, which could be attributed to the lack of information of Greek citizens about EA procedures. Moreover, the inclusion criteria were relatively strict, and only young adult males were allowed to take part in the study.

However, the finding of reducing motion sickness symptoms in the twenty-volunteers sample was striking enough to allow for publication in Medical Acupuncture journal(112).

## **RESULTS OF THE FINAL STUDY**

In further advancing the study, the sample size has been increased to the number of 56 participants. The supplementary results seem to confirm the preliminary data as the pre-treatment with electro-acupuncture has been proven to reduce partially the symptoms of motions sickness. Particularly, the early statistical analysis proves that both therapeutic and sham electroacupuncture has statistically significant benefit in the peripheral nervous system related motion sickness symptoms in comparison to the control group who received no treatment.

Data

Our dataset comprised of 56 persons who underwent special test before and after motion exposure. 55 volunteers completed the procedure, while one wished to stop during the procedure without completing it and was excluded from the study. From the former 19 were included in A group, 17 in B group and 19 in C group. Several statistical tests were performed. The variables of main interest assigned to the following variable names: GASTR, KNS, PNS and SOP.

#### Internal consistency of the data

The variables under research are GASTR, KNS, PNS, SOP and TOTAL are conducted summing up the responses to the relevant questions of the Giannaros Questionnaire(35). In our analysis the reliability of the scales (Likert scales) was tested on the basis of the Cronbach's Alpha statistic. The after motion exposure the values of the Cronbach's Alpha were estimated at levels ranging from 0.754 (SOP) to 0.933 (GASTR). The internal consistency of the data is satisfactory with respect to SOP, good with respect to KNS and PNS and excellent with respect to GASTR. Cronbach's Alpha statistic was also estimated for the total Giannaros after motion score (referred to as TOTAL) and the corresponding result is excellent, too. The exact values of the overall reliability analysis of the variables of interest are presented in Table 6.

<b>Variable</b>	<b><i>Cronbach's Alpha</i></b>
GASTR	0.933 (excellent)
KNS	0.845 (good)
PNS	0.824 (good)
SOP	0.754 (satisfactory)
TOTAL	0.933 (excellent)

Table 6. Reliability of the data used in the analysis: *Cronbach's Alpha* after motion exposure

#### Basic descriptive measures

The basic descriptive measures of the variables under investigation are presented in Table 7.1 and Table 7.2. The results show that the mean vales as well as their ranges and dispersion (standard deviations) increased considerably after the application of the motion procedure and this holds for all variables of interest.

To test the significance of the changes (increases) in the mean values of the variables a paired-observation t-test was carried out as the changes refer to the same individual participating in the study.

To assess the changes of the variables achieved before and subsequently after the motion exposure process we employed a t-test analysis for paired observations as the same individuals are measured in two different points of time. For the overall sample (N = 55 cases) the results of the analysis are presented in Table 8 and imply that in all cases the differences in the mean values of the variables estimated before and after the motion exposure are very statistical significant.

More specific and detailed statistical analysis by Group of individuals are presented in next section.

<b>Descriptive Statistics: before motion exposure</b>						
	N	Range	Min	Max	Mean	Std. Dev.
Giannaros_Before_GASTR	55	7	4	11	4.44	1.167
Giannaros_Before_KNS	55	5	5	10	5.64	1.267
Giannaros_Before_PNS	55	2	3	5	3.18	.434
Giannaros_Before_SOP	55	25	4	29	6.91	3.879
Giannaros_before_TOTAL score	55	35	16	51	20.16	5.480

Table 7.1. Descriptive statistics of the variables used in the analysis: measures obtained before motion exposure

<b>Descriptive Statistics: after motion exposure</b>						
	N	Range	Min	Max	Mean	Std. Dev
Giannaros_After_GASTR	55	32	4	36	18.60	10.631
Giannaros_After_KNS	55	36	5	41	18.78	10.447

Giannaros_After_PNS	55	23	3	26	11.04	6.774
Giannaros_After_SOP	55	22	3	25	10.60	6.181
Giannaros_after_TOTAL score	55	95	16	111	58.96	29.102

Table 7.2. Descriptive statistics of the variables used in the analysis: after motion exposure

		Mean	Std. Dev.	SE Mean	t	df	Sig.
Pair 1	GASTR(A) – GASTR (B)	14.164	10.694	1.442	9.822	54	.000
Pair 2	KNS(A) – KNS(B)	13.145	10.438	1.407	9.340	54	.000
Pair 3	PNS(A) – PNS(B)	7.855	6.748	.910	8.632	54	.000
Pair 4	SOP(A) – SOP(B)	3.691	6.055	.816	4.521	54	.000
Pair 5	TOTAL(A) - TOTAL(B)	38.800	29.013	3.912	9.918	54	.000

Table 8. Paired observation t-test statistics examining the difference in the mean values of the variables of interest achieved after (A) motion exposure compared to the corresponding values observed before (B) motion exposure.

### Comparisons between groups on individuals

To further our analysis, we compared the difference (actually increase) in the symptom severity in the total score and in all subscale scores by comparing bi-group changes involving all possible combinations that is changes of Group A vs Group B, changes of Group A vs Group C and changes of Group B vs Group C. The response variables represent Likerts scales and moreover after statistical exploration analysis the normality assumption was not meet for any of the variables and sub-groups. Hence, the bi-group differences were evaluated on the basis of the non-parametric Mann-Whitney U-test (applied for two independent samples in compared pair of groups).

The estimated statistics are shown in Tables 8.1, 8.2 and 8.3 It should be noted that no statistically significant differences were found at the beginning of the study, i.e. before motion exposure (results are not presented here). However, after motion exposure, the results reveal the following:

Comparing Groups A & B, no statistical significance differences were found for any of the variables of interest

Comparing Groups B & C, only variable PNS meets the statistical significance level of 0.05 ( $p < 0.05$ )

Comparing Group A & Group C we found that the only difference in the elevated values of the variables refers to PNS which is statistically significant at level 0.05 ( $p < 0.05$ )

Ranks				
	group	N	Mean Rank	Sum of Ranks
GASTR	A	19	16.97	322.50
	C	19	22.03	418.50
	Total	38		
KNS	A	19	17.47	332.00
	C	19	21.53	409.00
	Total	38		
PNS	A	19	15.71	298.50
	C	19	23.29	442.50
	Total	38		
SOP	A	19	18.84	358.00
	C	19	20.16	383.00
	Total	38		
TOTAL	A	19	16.45	312.50
	C	19	22.55	428.50
	Total	38		

Test Statistics and significance levels					
	GASTR	KNS	PNS	SOP	TOTAL
Mann-Whitney U	132.500	142.000	108.500	168.000	122.500
Wilcoxon W	322.500	332.000	298.500	358.000	312.500
Z	-1.403	-1.126	-2.113	-.367	-1.694
Asymp. Sig. (2-tailed)	.160	.260	<b>.035</b>	.714	.090

Table 8.1 Mann-Whitney non-parametric U test for two independent samples: mean ranks and test statistics for Group A vs Group C

Ranks				
	group	N	Mean Rank	Sum of Ranks
GASTR	A	19	18.29	347.50
	B	17	18.74	318.50
	Total	36		
KNS	A	19	17.29	328.50
	B	17	19.85	337.50
	Total	36		
PNS	A	19	19.26	366.00
	B	17	17.65	300.00
	Total	36		
SOP	A	19	18.37	349.00
	B	17	18.65	317.00
	Total	36		
TOTAL	A	19	18.11	344.00
	B	17	18.94	322.00
	Total	36		

Test Statistics and significant levels					
	GASTR	KNS	PNS	SOP	TOTAL
Mann-Whitney U	157.500	138.500	147.000	159.000	154.000
Wilcoxon W	347.500	328.500	300.000	349.000	344.000
Z	-.127	-.732	-.465	-.080	-.238
Asymp. Sig. (2-tailed)	.899	.464	.642	.937	.812

Table 8.2 Mann-Whitney non-parametric U test for two independent samples: mean ranks and test statistics for Group A vs Group B

Ranks				
	group	N	Mean Rank	Sum of Ranks

GASTR	B	17	15.76	268.00
	C	19	20.95	398.00
	Total	36		
KNS	B	17	17.85	303.50
	C	19	19.08	362.50
	Total	36		
PNS	B	17	14.12	240.00
	C	19	22.42	426.00
	Total	36		
SOP	B	17	18.00	306.00
	C	19	18.95	360.00
	Total	36		
TOTAL	B	17	15.94	271.00
	C	19	20.79	395.00
	Total	36		

Test Statistics and significance levels					
	GASTR	KNS	PNS	SOP	TOTAL
Mann-Whitney U	115.000	150.500	87.000	153.000	118.000
Wilcoxon W	268.000	303.500	240.000	306.000	271.000
Z	-1.477	-.349	-2.373	-.270	-1.380
Asymp. Sig. (2-tailed)	.140	.727	<b>.018</b>	.787	.168

**Table 8.3 Mann-Whitney non-parametric U test for two independent samples: mean ranks and test statistics for Group B vs Group C**

Changes before and after motion exposure by group of individuals

Table 9.1 and Table 9.2 show the mean values of the variables GASTR, KNS, PNS, SOP and TOTAL before and after the motion exposure and the corresponding changes (increases) as well as inference tests by group. As the motion of each person is measured twice i.e. before and after exposure (paired observations) the significance of the changes is evaluated on the basis of the Wilcoxon test for two related samples.

The descriptive results by group of persons are presented in Table 9.1 and show that in all cases (i.e. all variables and all groups) the changes between the two points of time are positive implying increases in each composite variable; for overall sub-group (that is with respect to the variable TOTAL) the changes are higher in Group C (48.68) followed by Group B (35.94) and finally by Group A (31.47). The application of the Wilcoxon non parametric test for paired samples resulted in the estimated Z-statistics which are presented in Table 9.2; the results imply that all changes (that is differentials among all groups and across all variables under investigations) are statistically significant at the level of 0.05 ( $p < 0.05$ ).

Group	Variable	N	Before (B)	After (A)	Difference (A - B)
A	GASTR	19	4.74	16.63	11.89
	KNS	19	6.16	16.68	10.53
	PNS	19	3.26	9.74	6.47
	SOP	19	7.63	10.21	2.58
	TOTAL	19	21.79	53.26	31.47
B	GASTR	17	4.29	17.24	12.94
	KNS	17	5.71	19.00	13.29
	PNS	17	3.00	8.35	5.35
	SOP	17	6.18	10.71	4.53
	TOTAL	17	19.18	55.12	35.94
C	GASTR	19	4.26	21.79	17.53
	KNS	19	5.05	20.68	15.63
	PNS	19	3.26	14.74	11.47
	SOP	19	6.84	10.89	4.05



	TOTAL	19	19.42	68.11	48.68
--	-------	----	-------	-------	-------

Table 9.1 Mean values of the variables under investigation before and after motion exposure by group of individuals

Test Statistics <sup>a</sup>						
Group		GASTR(A) GASTR(B)	KNS(A) KNS(B)	PNS(A) PNS(B)	SOP(A) – SOP(B)	TOTAL(A) TOTAL(B)
1	Z	-3.412 <sup>b</sup>	-3.206 <sup>b</sup>	-3.298 <sup>b</sup>	-2.139 <sup>b</sup>	-3.551 <sup>b</sup>
	Asymp. Sig. (2-tailed)	.001	.001	.001	.032	.000
2	Z	-3.409 <sup>b</sup>	-3.299 <sup>b</sup>	-3.065 <sup>b</sup>	-2.451 <sup>b</sup>	-3.517 <sup>b</sup>
	Asymp. Sig. (2-tailed)	.001	.001	.002	.014	.000
3	Z	-3.727 <sup>b</sup>	-3.724 <sup>b</sup>	-3.683 <sup>b</sup>	-2.728 <sup>b</sup>	-3.784 <sup>b</sup>
	Asymp. Sig. (2-tailed)	.000	.000	.000	.006	.000

a. Wilcoxon Signed Ranks Test

b. Based on negative ranks.

Table 9.2 Test statistics and significance of the changes in the values of variables before (B) and after (A) motion exposure: Wilcoxon non parametric test for paired (related) samples

### Time of exposure

The average times of exposure to motion stimulus by Group of interest are shown in Table 10. The greatest mean time (17.765 minutes) appears to be achieved by the participants of Group B followed by participants of Group A (mean time = 15.947) and finally by participants of Group C (mean time = 12.579). Overall (i.e. for the total of 55 cases) the mean time of exposure to motion stimulus was 15.345 minutes.

To test for the differences in the mean times of exposure between the three groups of interest we could not employ the F-test (one-way analysis of variance) as the appropriate tests performed in exploration data analysis proved that the assumptions of the homogeneity of variances and the normality distribution of variables were not

Group	N	Mean Rank
A	19	30.32
B	17	32.47
C	19	21.68
Total	55	

Group	N	Mean	Std. Deviation	Std. Error	Minimum	Maximum
A	19	15.947	5.2172	1.1969	4.0	20.0
B	17	17.765	3.4826	.8447	8.0	20.0
C	19	12.579	6.7046	1.5381	2.0	20.0
Total	55	15.345	5.6845	.7665	2.0	20.0

valid (the inferences were evaluated on the basis of the Levene test and Shapiro-Wilk statistics respectively).

Hence the examination of the differences between groups was carried out using the Kruskal-Wallis non-parametric test for k-independent samples. The results are presented in Table 11 and reveal that the differences in time of motion exposures between the three groups of participants are statistically significant at 10% level of significance ( $p < 0.1$ )

Table 10. Time of exposure to motion stimulus: descriptive statistics by Group

Test Statistics <sup>a,b</sup>	
	time
Chi-Square	5.100
df	2
Asymp. Sig.	.078

a. Kruskal Wallis Test  
b. Grouping Variable: group (A, B, C)

Table 11. Test for differences in the times of exposure to motion stimulus between Groups of interest

## **POTENTIAL CLINICAL AND PRACTICAL APPLICATIONS**

The results of this study are promising in the management of motion sickness in several fields.

Firstly, the concept of this study was inspired by the increased number of motion sickness symptoms among the junior pilots mainly in their first year of training in the Hellenic Airforce. This sometimes results even to change in the careers of these trainees. For this reason, we believe that with the electroacupuncture treatment, these incidences could be decreased and trainees susceptible to motion sickness, could continue following their dreaming career of a pilot. Since, as our study demonstrated, only a group of the symptoms of motion sickness is affected (the peripheral nervous systems symptoms) the acupuncture treatment could be combined with other possible techniques in order to reduce the total symptoms.

Secondly, many people travelling by various means of transportation find also difficulties in the management of motion sickness and they usually tend towards pharmacological approaches. These people, especially those with more prominent their peripheral nervous system symptoms related to motion sickness, could also be benefited by the application of electroacupuncture.

Last but not least, other professionals from various background exposed to travelling by passive motion with different means of transportation with similar motion sickness symptoms could have electroacupuncture treatment, as a non-pharmacological and without serious adverse effects method.

## **CONCLUSIONS**

The results of this study suggest that individuals who were subjected to therapeutic EA prior to motion stimulation tended to have fewer motion sickness symptoms in comparison with their counterparts who were not subjected to the same therapy.

Indeed, this tendency showed, a statistically significant result, especially with regard to peripheral symptoms. Therefore, we are optimistic that a novel field of potential clinical applications of electroacupuncture for treating motion sickness, can be further strived in the future.

## APPENDICES

---



Appendix 1. Greek version of the Gianaros Motion Sickness Assessment  
Questionnaire (MSAQ)

## Δήλωση συμμετοχής

**ΤΙΤΛΟΣ ΕΡΕΥΝΗΤΙΚΗΣ ΕΡΓΑΣΙΑΣ:** Αξιολόγηση εφαρμογής του ηλεκτροβελονισμού στη αντιμετώπιση του συνδρόμου της κινήτωσης σε υγιείς άρρενες ενήλικες, μέσω διπλής τυφλής μελέτης.

### ΕΡΕΥΝΗΤΕΣ:

Υποδος (Υ1) Φυδανάκη Ουρανία (Υγειονομική Υπηρεσία 120 ΠΕΑ)

Επνος (Υ1) Κουρούλης Παναγιώτης (Γραφείο Αεροπορικής Ιατρικής 120 ΠΕΑ)

### ΚΕΝΤΡΙΚΗ ΥΠΟΘΕΣΗ:

Η εφαρμογή του ηλεκτροβελονισμού σύμφωνα με τις διεθνείς πρακτικές αυξάνει την αντοχή των ατόμων στην κινήτωση, όταν εφαρμοστεί πριν από την έκθεσή τους σε ναυσιγόνο κινητικό περιβάλλον.

### ΙΣΤΟΡΙΚΟ – ΣΤΟΧΟΙ

Η κινήτωση είναι ένα σύνδρομο που συναντάται όταν ένα άτομο εκτεθεί σε κινητικά ερεθίσματα στα οποία δεν είναι προσαρμοσμένο. Θεωρείται ότι προκαλείται από αντικρουόμενα ερεθίσματα που στέλνονται στον εγκέφαλο από τους αισθητηριακούς υποδοχείς του σώματος, του έσω ωτός και των οφθαλμών. Στα κύρια συμπτώματά της ανήκουν η ναυτία, η ωχρότητα, ο κρύος ιδρώτας, ο έμετος, η ζάλη, η κεφαλαλγία, η σιελόρροια και το λιποθυμικό επεισόδιο.

Λαμβάνοντας υπόψη τα θετικά οφέλη του βελονισμού και ηλεκτροβελονισμού στην πρόληψη και θεραπεία της ναυτίας διαφόρων αιτιών – όπως ναυτία από χημειοθεραπεία, μετεγχειρητική, καθώς και του πρώτου τριμήνου της κύησης- κρίθηκε σκόπιμο να διερευνηθεί η χρήση των παραπάνω μεθόδων στην πρόληψη και αντιμετώπιση της ναυτίας που προκαλείται από την κινήτωση.

### ΣΗΜΑΣΙΑ – ΧΡΗΣΙΜΟΤΗΤΑ – ΣΗΜΑΝΤΙΚΑ ΣΗΜΕΙΑ

Η προτεινόμενη μελέτη είναι πρωτότυπη και δεν έχει επαναληφθεί στον Ελλαδικό χώρο. Επιπλέον, η εφαρμογή ηλεκτροβελονισμού για την αντιμετώπιση της κινήτωσης δεν έχει εφαρμοστεί ποτέ σύμφωνα με τη διεθνή βιβλιογραφία.

Από την μελέτη θα διερευνηθεί ο ρόλος του ηλεκτροβελονισμού στην πρόληψη και θεραπεία της κινήτωσης. Δεδομένου ότι η αεροναυτία (κινήτωση λόγω έκθεσης στην κίνηση του αεροσκάφους) είναι ιδιαίτερα συχνή σε εκπαιδευόμενους ικάρους, ένα θετικό αποτέλεσμα της μελέτης αυτής θα μπορούσε να φανεί ιδιαίτερα χρήσιμο στην Πολεμική Αεροπορία.

### ΕΜΠΙΣΤΕΥΤΙΚΟΣ ΧΑΡΑΚΤΗΡΑΣ ΤΩΝ ΠΡΟΣΩΠΙΚΩΝ ΔΕΔΟΜΕΝΩΝ

Οι μελετητές δεσμεύονται ότι τα δεδομένα της μελέτης (ονοματεπώνυμο και μετρήσεις) θα χρησιμοποιηθούν για τα συμπεράσματα της μελέτης και μόνο, και ότι δε θα αποδεδειχτούν για χρήση από τρίτους, συμπεριλαμβανομένων και των υπηρεσιών και γραφείων της Πολεμικής Αεροπορίας που δεν έχουν σχέση με τη μελέτη. Η μελέτη είναι επώνυμη για πρακτικούς λόγους χειρισμού των δεδομένων και όχι για ατομική αξιολόγηση των συμμετεχόντων. Τα συμπεράσματα που θα προκύψουν από τη στατιστική επεξεργασία θα είναι συνολικά και όχι ατομικά για κάθε συμμετέχοντα.

### ΕΘΕΛΟΝΤΙΚΗ ΣΥΜΜΕΤΟΧΗ

Η συμμετοχή στη μελέτη είναι εθελοντική. Ο κάθε συμμετέχοντας μπορεί να διακόψει τη συμμετοχή του οποιαδήποτε στιγμή αυτός το επιθυμήσει χωρίς να υπάρξει καμία συνέπεια για την πράξη αυτή. Οι μελετητές θα καταβάλουν κάθε προσπάθεια ώστε η μη συμμετοχή ή η διακοπή της συμμετοχής να είναι εμπιστευτικού χαρακτήρα.

### ΧΟΡΗΓΗΣΗ ΦΑΡΜΑΚΩΝ

Δεν θα υπάρξει σε κάποιο στάδιο της μελέτης χορήγηση φαρμάκων για οποιοδήποτε λόγο.

*Διάβασα το ανωτέρω κείμενο προσεκτικά και κατανόησα τον τρόπο της μελέτης και τη σημασία της συμμετοχής μου. Μου δόθηκε χρόνος να κάνω ερωτήσεις ώστε να μου λυθούν όλες οι απορίες. Δέχομαι να συμμετέχω εθελοντικά στη μελέτη.*

Ονοματεπώνυμο \_\_\_\_\_

Υπογραφή \_\_\_\_\_

## Appendix 2. The form of the voluntary declaration of the participants



Ερωτηματολόγιο μέτρησης της κινήτωσης (GOLDING-KERQUELEN)																									
Ονοματεπώνυμο:																									
Ημερομηνία εξέτασης:																									
Συμπτώματα																									
Μεγάλη τάση για έμετο-έμετος - θέλω να σταματήσω																									
Μέτρια τάση για έμετο αλλά μπορώ να συνεχίσω																									
Ήπια προς μέτρια τάση για έμετο																									
Ήπια τάση για έμετο																									
Λίγα συμπτώματα (π.χ. δυσφορία στο στομάχι) αλλά όχι τάση για έμετο																									
Οποιοδήποτε σύμπτωμα όσο μικρό κι αν είναι																									
Κανένα σύμπτωμα																									
+	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	5min	20min		
																									STOP

Appendix 3. Golding-Kerguelen Questionnaire of motion sickness



## REFERENCES

---



1. Huppert D, Benson J, Brandt T. A Historical View of Motion Sickness-A Plague at Sea and on Land, Also with Military Impact. *Frontiers in neurology*. 2017;8:114-.
2. Reason JT, Brand JJ. *Motion sickness*: Academic press; 1975.
3. Koselka M. A cognitive behavioral intervention for seasickness. UNIFORMED SERVICES UNIV OF THE HEALTH SCIENCES BETHESDA MD, 2000.
4. Irwin J. THE PATHOLOGY OF SEA-SICKNESS. *The Lancet*. 1881;118(3039):907-9.
5. de Wit G. Seasickness;(motion sickness) a labyrinthological study. *Acta otolaryngologica Supplementum*. 1953;108:7.
6. Claremont C. The psychology of seasickness. *Psyche*. 1931;11:86-90.
7. Hill J. The Care of the Sea-Sick. *Br Med J*. 1936;2(3955):802-7.
8. Kirkner FJ. Psychophysiological studies of motion sickness and airsickness. *Journal of comparative and physiological psychology*. 1949;42(4):273-85.
9. Lansberg MP. Canal-sickness: fact or fiction? *Industrial medicine & surgery*. 1963;32:21-4.
10. Guedry FE, Jr. Visual Control of Habituation to Complex Vestibular Stimulation in Man. *Acta Otolaryngol*. 1964;58:377-89.
11. Reason JT. Motion sickness adaptation: a neural mismatch model. *Journal of the Royal Society of Medicine*. 1978;71(11):819-29.
12. Von Holst E. Relations between the central nervous system and the peripheral organs. *British Journal of Animal Behaviour*. 1954.
13. Held R. Exposure-history as a factor in maintaining stability of perception and coordination. *The Journal of nervous and mental disease*. 1961;132:26-32.
14. GUEDRY F. Motion sickness and its relation to some forms of spatial orientation: Mechanisms and theory. 1991 30. 1991.
15. GRIFFIN M. Physical characteristics of stimuli provoking motion sickness. 1991 32. 1991.
16. Young LR, Oman CM, Watt DG, Money KE, Lichtenberg BK. Spatial orientation in weightlessness and readaptation to earth's gravity. *Science*. 1984;225(4658):205-8.
17. Parker DE, Reschke MF, Arrott AP, Homick JL, Lichtenberg BK. Otolith tilt-translation reinterpretation following prolonged weightlessness: implications for preflight training. *Aviat Space Environ Med*. 1985;56(6):601-6.
18. Oman CM. A heuristic mathematical model for the dynamics of sensory conflict and motion sickness. *Acta oto-laryngologica Supplementum*. 1982;392:1-44.
19. Oman CM. Motion sickness: a synthesis and evaluation of the sensory conflict theory. *Canadian journal of physiology and pharmacology*. 1990;68(2):294-303.
20. Bles W, Bos JE, de Graaf B, Groen E, Wertheim AH. Motion sickness: only one provocative conflict? *Brain Res Bull*. 1998;47(5):481-7.
21. Bos JE, Bles W. Modelling motion sickness and subjective vertical mismatch detailed for vertical motions. *Brain Res Bull*. 1998;47(5):537-42.
22. Treisman M. Motion sickness: an evolutionary hypothesis. *Science*. 1977;197(4302):493-5.
23. Money KE, Cheung BS. Another function of the inner ear: facilitation of the emetic response to poisons. *Aviat Space Environ Med*. 1983;54(3):208-11.
24. Guedry FE, Rupert AR, Reschke MF. Motion sickness and development of synergy within the spatial orientation system. A hypothetical unifying concept. *Brain Res Bull*. 1998;47(5):475-80.

25. Ebenholtz SM, Cohen MM, Linder BJ. The possible role of nystagmus in motion sickness: a hypothesis. *Aviat Space Environ Med.* 1994;65(11):1032-5.
26. Lappe M, Hoffmann KP. Optic flow and eye movements. *International review of neurobiology.* 2000;44:29-47.
27. Bloch M. Oculocardiac reflex: 'My heart just stopped'. *Emergency medicine Australasia : EMA.* 2018;30(4):592-3.
28. Graybiel A. Susceptibility to acute motion sickness in blind persons. *Aerosp Med.* 1970;41(6):650-3.
29. Riccio GE, Stoffregen TA. An ecological Theory of Motion Sickness and Postural Instability. *Ecological Psychology.* 1991;3(3):195-240.
30. Stoffregen TA, Smart LJ, Jr. Postural instability precedes motion sickness. *Brain Res Bull.* 1998;47(5):437-48.
31. Smart LJ, Jr., Stoffregen TA, Bardy BG. Visually induced motion sickness predicted by postural instability. *Human factors.* 2002;44(3):451-65.
32. Warwick-Evans LA, Symons N, Fitch T, Burrows L. Evaluating sensory conflict and postural instability. *Theories of motion sickness. Brain Res Bull.* 1998;47(5):465-9.
33. Graybiel A, Wood CD, Miller EF, Cramer DB. Diagnostic criteria for grading the severity of acute motion sickness. *Aerosp Med.* 1968;39(5):453-5.
34. Golding JF. Motion sickness susceptibility questionnaire revised and its relationship to other forms of sickness. *Brain Res Bull.* 1998;47(5):507-16.
35. Gianaros PJ, Muth ER, Mordkoff JT, Levine ME, Stern RM. A questionnaire for the assessment of the multiple dimensions of motion sickness. *Aviat Space Environ Med.* 2001;72(2):115-9.
36. Ramey D, Buell PD. A true history of acupuncture. *Focus on Alternative and Complementary Therapies.* 2004;9(4):269-73.
37. White A, Ernst E. A brief history of acupuncture. *Rheumatology.* 2004;43(5):662-3.
38. Ma K-W. The Roots and Development of Chinese Acupuncture: From Prehistory to Early 20Th Century. *Acupuncture in Medicine.* 1992;10(1\_suppl):92-9.
39. Lee IS, Lee SH, Kim SY, Lee H, Park HJ, Chae Y. Visualization of the Meridian System Based on Biomedical Information about Acupuncture Treatment. *Evidence-based complementary and alternative medicine : eCAM.* 2013;2013:872142.
40. Kaplan G. A Brief History of Acupuncture's Journey to the West. *The Journal of Alternative and Complementary Medicine.* 1997;3(supplement 1):s-5-s-10.
41. Tanaka TH. *History of Acupuncture.* 2019.
42. Hong GG. Acupuncture: The historical basis and its US practitioners. *Laboratory Medicine.* 1998;29(3):163-6.
43. Ahn CB, Jang KJ, Yoon HM, Kim CH, Min YK, Song CH, et al. A study of the Sa-Ahm Five Element acupuncture theory. *Journal of acupuncture and meridian studies.* 2009;2(4):309-20.
44. Pioreschi P. *A History of Medicine: Primitive and ancient medicine:* Horatius Press; 1996.
45. Ma Z, Jia C, Guo J, Gu H, Miao Y. Features analysis of five-element theory and its basal effects on construction of visceral manifestation theory. *Journal of traditional Chinese medicine = Chung i tsa chih ying wen pan.* 2014;34(1):115-21.
46. Veith I. Acupuncture in traditional Chinese medicine. An historical review. *California medicine.* 1973;118(2):70-9.

47. Langevin HM, Yandow JA. Relationship of acupuncture points and meridians to connective tissue planes. *Anat Rec.* 2002;269(6):257-65.
48. Products A. *Atlas of Acupuncture points.* 2017.
49. Lin LL, Wang YH, Lai CY, Chau CL, Su GC, Yang CY, et al. Systems biology of meridians, acupoints, and chinese herbs in disease. *Evidence-based complementary and alternative medicine : eCAM.* 2012;2012:372670.
50. Furlan AD, van Tulder MW, Cherkin DC, Tsukayama H, Lao L, Koes BW, et al. Acupuncture and dry-needling for low back pain. *Cochrane Database Syst Rev.* 2005(1):CD001351.
51. Wang CC, Huang TH, Chiou KC, Chang ZY. Therapeutic Effect of Superficial Acupuncture in Treating Myofascial Pain of the Upper Trapezius Muscle: A Randomized Controlled Trial. *Evidence-based complementary and alternative medicine : eCAM.* 2018;2018:9125746.
52. Itoh K, Saito S, Sahara S, Naitoh Y, Imai K, Kitakoji H. Randomized trial of trigger point acupuncture treatment for chronic shoulder pain: a preliminary study. *Journal of acupuncture and meridian studies.* 2014;7(2):59-64.
53. Cabyoglu MT, Ergene N, Tan U. The mechanism of acupuncture and clinical applications. *The International journal of neuroscience.* 2006;116(2):115-25.
54. Wang WJ, Zhang T. Integration of traditional Chinese medicine and Western medicine in the era of precision medicine. *Journal of integrative medicine.* 2017;15(1):1-7.
55. Silva de Camargo P, Lima CR, de Andrade ERML, Silva Santos AT, Rodrigues Hernandez JW, Silva AM. The Effect of Auricular and Systemic Acupuncture on the Electromyographic Activity of the Trapezius Muscle with Trigger Points-A Pilot Study. *Journal of acupuncture and meridian studies.* 2018;11(1):18-24.
56. Asher GN, Jonas DE, Coeytaux RR, Reilly AC, Loh YL, Motsinger-Reif AA, et al. Auriculotherapy for pain management: a systematic review and meta-analysis of randomized controlled trials. *Journal of alternative and complementary medicine.* 2010;16(10):1097-108.
57. Garner BK, Hopkinson SG, Ketz AK, Landis CA, Trego LL. Auricular Acupuncture for Chronic Pain and Insomnia: A Randomized Clinical Trial. *Medical acupuncture.* 2018;30(5):262-72.
58. Organization WH. *Acupuncture: review and analysis of reports on controlled clinical trials: World Health Organization; 2002.*
59. Zhang XC, Chen H, Xu WT, Song YY, Gu YH, Ni GX. Acupuncture therapy for fibromyalgia: a systematic review and meta-analysis of randomized controlled trials. *Journal of pain research.* 2019;12:527-42.
60. Siqueira APR, Beraldo LM, Krueger E, Ulbricht L. Reduction in Knee Pain Symptoms in Athletes Using an Acupuncture Protocol. *Acta ortopedica brasileira.* 2018;26(6):418-22.
61. Farahmand S, Shafazand S, Alinia E, Bagheri-Hariri S, Baratloo A. Pain Management Using Acupuncture Method in Migraine Headache Patients; A Single Blinded Randomized Clinical Trial. *Anesthesiology and pain medicine.* 2018;8(6):e81688-e.
62. Wang Y, Li W, Peng W, Zhou J, Liu Z. Acupuncture for postherpetic neuralgia: Systematic review and meta-analysis. *Medicine.* 2018;97(34):e11986.
63. Wang JY, Gao YH, Qiao LN, Zhang JL, Duan-Mu CL, Yan YX, et al. Repeated electroacupuncture treatment attenuated hyperalgesia through suppression of spinal glial activation in chronic neuropathic pain rats. *BMC complementary and alternative medicine.* 2018;18(1):74.

64. Beltaief K, Grissa MH, Msolli MA, Bzeouich N, Fredj N, Sakma A, et al. Acupuncture versus titrated morphine in acute renal colic: a randomized controlled trial. *Journal of pain research*. 2018;11:335-41.
65. Xu L, Wan Y, Huang J, Xu F. Clinical analysis of electroacupuncture and multiple acupoint stimulation in relieving cancer pain in patients with advanced hepatocellular carcinoma. *J Cancer Res Ther*. 2018;14(1):99-102.
66. Meng F-F, Feng Y-H. A pilot study of acupuncture at pain acupoints for cervical cancer pain. *Medicine*. 2018;97(52):e13736-e.
67. Lopez G, Garcia MK, Liu W, Spano M, Underwood S, Dibaj SS, et al. Outpatient acupuncture effects on patient self-reported symptoms in oncology care: a retrospective analysis. *Journal of Cancer*. 2018;9(19):3613-9.
68. Wu J, Chen B, Yin X, Yin P, Lao L, Xu S. Effect of acupuncture on post-hemorrhoidectomy pain: a randomized controlled trial. *Journal of pain research*. 2018;11:1489-96.
69. Bosco F, Cidin S, Maceri F, Ghilli M, Roncella M, De Simone L. An integrated approach with homeopathic medicine and electro-acupuncture in anaesthesiology during breast cancer surgery: Case reports. *Journal of pharmacopuncture*. 2018;21(2):126-31.
70. Sun W, Li M, Lin T, Sun Z, Zhuang Z, Wen J, et al. Effectiveness of acupuncture for recovery of flatulence after cesarean section: A case report. *Medicine*. 2018;97(50):e13352.
71. Pei LX, Geng H, Chen H, Wu XL, Chen L, Zhou JL, et al. Acupuncture for irritable bowel syndrome: study protocol for a multicenter randomized controlled trial. *Trials*. 2018;19(1):529.
72. Zhu HD, Gong Z, Hu BW, Wei QL, Kong J, Peng CB. The Efficacy and Safety of Transcutaneous Acupoint Interferential Current Stimulation for Cancer Pain Patients With Opioid-Induced Constipation: A Prospective Randomized Controlled Study. *Integrative cancer therapies*. 2018;17(2):437-43.
73. Albooghobeish M, Mohtadi A, Saidkhani V, Fallah H, Behaein K, Nesionpour S, et al. Comparison Between Effects of Acupuncture and Metoclopramide on Postoperative Nausea and Vomiting after Gynaecological Laparoscopy: A Randomized Controlled Trial. *Anesth Pain Med*. 2017;7(5):e12876.
74. Van den Heuvel E, Goossens M, Vanderhaegen H, Sun HX, Buntinx F. Effect of acustimulation on nausea and vomiting and on hyperemesis in pregnancy: a systematic review of Western and Chinese literature. *BMC complementary and alternative medicine*. 2016;16(1):13.
75. Xu Y, Zhao W, Li T, Zhao Y, Bu H, Song S. Effects of acupuncture for the treatment of endometriosis-related pain: A systematic review and meta-analysis. *PLoS One*. 2017;12(10):e0186616.
76. Sung SH, Sung AD, Sung HK, An TE, Kim KH, Park JK. Acupuncture Treatment for Chronic Pelvic Pain in Women: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Evidence-based complementary and alternative medicine : eCAM*. 2018;2018:9415897.
77. Bega D, Park K, Grimone A, Lin F, Ring M. Acupuncture as Adjuvant Therapy for the Management of Cervical Dystonia. *Medical acupuncture*. 2018;30(4):198-203.
78. Tu CH, MacDonald I, Chen YH. The Effects of Acupuncture on Glutamatergic Neurotransmission in Depression, Anxiety, Schizophrenia, and Alzheimer's Disease: A Review of the Literature. *Frontiers in psychiatry*. 2019;10:14.



79. Samadi P, Alipour Z, Lamyian M. The Effect of Acupressure at Spleen 6 Acupuncture Point on the Anxiety Level and Sedative and Analgesics Consumption of Women during Labor: A Randomized, Single-blind Clinical Trial. *Iranian journal of nursing and midwifery research*. 2018;23(2):87-92.
80. Zeng L, Tao Y, Hou W, Zong L, Yu L. Electro-acupuncture improves psychiatric symptoms, anxiety and depression in methamphetamine addicts during abstinence: A randomized controlled trial. *Medicine*. 2018;97(34):e11905.
81. Zhang Y, Li J, Mo G, Liu J, Yang H, Chen X, et al. Acupuncture and Related Therapies for Obesity: A Network Meta-Analysis. *Evidence-based complementary and alternative medicine : eCAM*. 2018;2018:9569685.
82. Zhang K, Zhou S, Wang C, Xu H, Zhang L. Acupuncture on Obesity: Clinical Evidence and Possible Neuroendocrine Mechanisms. *Evidence-based complementary and alternative medicine : eCAM*. 2018;2018:6409389.
83. Lopez-Martos R, Gonzalez-Perez LM, Ruiz-Canela-Mendez P, Urresti-Lopez FJ, Gutierrez-Perez JL, Infante-Cossio P. Randomized, double-blind study comparing percutaneous electrolysis and dry needling for the management of temporomandibular myofascial pain. *Medicina oral, patologia oral y cirugia bucal*. 2018;23(4):e454-e62.
84. Ito H, Yamada O, Kira Y, Tanaka T, Matsuoka R. The effects of auricular acupuncture on weight reduction and feeding-related cytokines: a pilot study. *BMJ Open Gastroenterology*. 2015;2(1):e000013.
85. Chang S. The meridian system and mechanism of acupuncture--a comparative review. Part 2: mechanism of acupuncture analgesia. *Taiwanese journal of obstetrics & gynecology*. 2013;52(1):14-24.
86. Li C, Yang J, Sun J, Xu C, Zhu Y, Lu Q, et al. Brain Responses to Acupuncture Are Probably Dependent on the Brain Functional Status. *Evidence-Based Complementary and Alternative Medicine*. 2013;2013:14.
87. Zhang R, Lao L, Ren K, Berman BM. Mechanisms of acupuncture-electroacupuncture on persistent pain. *Anesthesiology*. 2014;120(2):482-503.
88. Dimitrov N, Atanasova D, Tomov N, Sivrev D, Lazarov N. Acupuncture causes serotonin release by mast cells. *Romanian journal of morphology and embryology = Revue roumaine de morphologie et embryologie*. 2017;58(3):961-8.
89. Lim TK, Ma Y, Berger F, Litscher G. Acupuncture and Neural Mechanism in the Management of Low Back Pain-An Update. *Medicines*. 2018;5(3).
90. Yang TY, Jang EY, Ryu Y, Lee GW, Lee EB, Chang S, et al. Effect of acupuncture on Lipopolysaccharide-induced anxiety-like behavioral changes: involvement of serotonin system in dorsal Raphe nucleus. *BMC complementary and alternative medicine*. 2017;17(1):528.
91. Parrish TB, Schaeffer A, Catanese M, Rogel MJ. Functional magnetic resonance imaging of real and sham acupuncture. Noninvasively measuring cortical activation from acupuncture. *IEEE engineering in medicine and biology magazine : the quarterly magazine of the Engineering in Medicine & Biology Society*. 2005;24(2):35-40.
92. Zheng W, Su Z, Liu X, Zhang H, Han Y, Song H, et al. Modulation of functional activity and connectivity by acupuncture in patients with Alzheimer disease as measured by resting-state fMRI. *PLoS One*. 2018;13(5):e0196933.
93. Claunch JD, Chan S-T, Nixon EE, Qiu WQ, Sporko T, Dunn JP, et al. Commonality and specificity of acupuncture action at three acupoints as evidenced by FMRI. *The American journal of Chinese medicine*. 2012;40(4):695-712.

94. Hui KK, Napadow V, Liu J, Li M, Marina O, Nixon EE, et al. Monitoring acupuncture effects on human brain by fMRI. *Journal of visualized experiments : JoVE*. 2010(38).
95. Pomeranz B, Stux G, Berman B. *Basics of acupuncture*: Springer; 2003.
96. Wang F, Tian DR, Han JS. Electroacupuncture in the treatment of obesity. *Neurochemical research*. 2008;33(10):2023-7.
97. (AACP) AAoCP. *Safe Practice Guidelines for acupuncture physiotherapists*. 2017.
98. Sallam HS, Song J, Chen JZ. Electroacupuncture via Chronically Implanted Electrodes: Potential Treatment for Chemotherapy-Induced Delayed Emesis. *Neuromodulation : journal of the International Neuromodulation Society*. 2015;18(6):494-8; discussion 8.
99. Dundee JW, McMillan C. Positive evidence for P6 acupuncture antiemesis. *Postgraduate medical journal*. 1991;67(787):417-22.
100. Frey UH, Scharmann P, Lohlein C, Peters J. P6 acustimulation effectively decreases postoperative nausea and vomiting in high-risk patients. *Br J Anaesth*. 2009;102(5):620-5.
101. Alizadeh R, Esmaeili S, Shoar S, Bagheri-Hariri S, Shoar N. Acupuncture in preventing postoperative nausea and vomiting: efficacy of two acupuncture points versus a single one. *Journal of acupuncture and meridian studies*. 2014;7(2):71-5.
102. Özmert S, Salman N, Sever F, Akın M, Saydam S, Keskin G, et al. Acupuncture as an Antiemetic in Children who Underwent Adenoidectomy and/or Tonsillectomy. *Turkish journal of anaesthesiology and reanimation*. 2016;44(1):7-12.
103. Dundee JW, Sourial FB, Ghaly RG, Bell PF. P6 acupressure reduces morning sickness. *Journal of the Royal Society of Medicine*. 1988;81(8):456-7.
104. Han G, Leem J, Lee H, Lee J. Electroacupuncture to treat gastroesophageal reflux disease: study protocol for a randomized controlled trial. *Trials*. 2016;17(1):246.
105. Cheung B, Hofer K. Lack of gender difference in motion sickness induced by vestibular Coriolis cross-coupling. *J Vestib Res*. 2002;12(4):191-200.
106. Kousoulis P, Pantas A, Alevetsovitis G, Fydanaki O. Psychometric Properties of the Greek Version of the Gianaros Motion Sickness Assessment Questionnaire. *Aerospace medicine and human performance*. 2016;87(11):954-7.
107. Golding JF, Kerguelen M. A comparison of the nauseogenic potential of low-frequency vertical versus horizontal linear oscillation. *Aviat Space Environ Med*. 1992;63(6):491-7.
108. Tjen ALSC, Li P, Longhurst JC. Medullary substrate and differential cardiovascular responses during stimulation of specific acupoints. *American journal of physiology Regulatory, integrative and comparative physiology*. 2004;287(4):R852-62.
109. Yang ZK, Wu ML, Xin JJ, He W, Su YS, Shi H, et al. Manual acupuncture and laser acupuncture for autonomic regulations in rats: observation on heart rate variability and gastric motility. *Evidence-based complementary and alternative medicine : eCAM*. 2013;2013:276320.
110. Hideaki W, Tatsuya H, Shogo M, Naruto Y, Hideaki T, Yoichi M, et al. Effect of 100 Hz electroacupuncture on salivary immunoglobulin A and the autonomic nervous system. *Acupuncture in medicine : journal of the British Medical Acupuncture Society*. 2015;33(6):451-6.
111. Muth ER, Elkins AN. High dose ondansetron for reducing motion sickness in highly susceptible subjects. *Aviat Space Environ Med*. 2007;78(7):686-92.

112. Fydanaki O, Kousoulis P, Dardiotis E, Bizakis I, Hajiioannou I. Electroacupuncture Could Reduce Motion Sickness Susceptibility in Healthy Male Adults: A Double-Blinded Study. *Medical acupuncture*. 2017;29(6):377-82.

---