Treatment and Recovery Monitoring of Post Traumatic Brain Injury (TBI) Symptoms

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Proposal: Treatment and Recovery Monitoring of Post Traumatic Brain Injury (TBI) Symptoms (Linked to REB# B2011:116 and REB# B2012:076)

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Protocol

Proposal Summary

This proposal aims to investigate the effect of a promising treatment for persistent post Traumatic Brain Injury (TBI) symptoms, and to monitor TBI patient's recovery by an objective technique along with standard clinical assessments. The treatment tool is the application of repetitive Transcranial Magnetic Stimulation (rTMS) [1] to the dorsolateral prefrontal cortex (DLPFC) of the brain. The treatment efficacy and monitoring TBI patients' recovery will be objectively assessed using Electrovestibulography (EVestG^{TM}) [2]; this will be in parallel with clinical and standard assessments. This proposal is built upon our encouraging pilot studies *(REB# B2011:116 and REB# B2012:076)*

TBI is a significant health problem mainly because of its plausible prolonged sequelae and lack of objective measures for recovery. The conventional treatment after a TBI is physical rehabilitation that helps with motor functional recovery. However, there are usually some disabling persistent post-TBI symptoms (mostly neurological) that do not respond to the current clinical and physical rehabilitation. rTMS, on the other hand, is a promising, well-tolerated, non-invasive brain neuromodulation technique that has emerged as a therapeutic tool for a variety of neurological conditions. Thus, we aim to investigate the effect of rTMS treatment on post-TBI symptoms in patients identified by our medical collaborators (Drs. Mansouri and Salter). Equally important is to have an objective measure of treatment efficacy and patient's symptoms recovery. EVestG^{TM} [2] is a noninvasive technique to record neural activity from the vestibular apparatus and vestibular nuclei in the external ear. After a head injury, people commonly experience balance (vestibular) problems and dizziness, as well as confused thinking. Considering the well-known bidirectional anatomical links of the vestibular system, following an impact TBI, EVestG signals are expected to change, and our pilot studies show a great potential of EVestG to monitor the impact of TBI. Thus, we aim to use EVestG as an objective measure to monitor the recovery path during and after the rTMS treatment in parallel to clinical and neuro-psychological assessments.

The proposed research has the potential to lead to a treatment and objective monitoring protocol that would provide a much faster, more economical and more efficient treatment method than the current techniques. The outcomes of this proposal will provide a reliable means for quick and accurate diagnosis and treatment of TBI as well as monitoring its progress towards recovery.

Introduction

a. Rationale

Traumatic brain Injury (TBI) occurs when a sudden trauma causes either transient or permanent brain damage. In some literature, the term "concussion" is used to refer to the most common (mild) type of TBI. It is defined as an immediate and transient impairment of neural functions, such as the alteration of consciousness, balance and/or visual disturbances, due to a direct blow to the head or after a blow elsewhere that is transmitted to the head. In other literature, mostly neurological journals (and in this proposal), mild TBI (mTBI) and concussion are used interchangeably[1].

Every three minutes, there is a TBI case in Canada [3], and 50,000 Canadians sustain brain injuries each year [4]. Motor vehicle crashes and traffic-related incidents are major causes of TBI; 40% of TBI cases in Manitoba are due to car accidents [5]. Transport Canada reports that the road accident rate of the province of Manitoba is greater than the national average [6]. According to MPI's 2011/12 annual report, there was an 89% increase in brain injury claims from 146 in 2010/11 to 276 in 2011/12 [5].

The majority of patients with mTBI recover in the first 2-4 weeks; the recovery time is much longer (a few years) for those with severe TBI. In general, the fastest improvement occurs in the first six months after injury and the patient may continue to get better over a period of up to two years. However, many survivors of severe TBI and mTBI continue to experience disabling persistent post-TBI symptoms including somatic and emotional symptoms (sleep disturbances, fatigue, headache and emotional changeability) [7], as well as cognitive [8,9], visual [10-15], and vestibular abnormalities [16,17]. Any of these adverse consequences of TBI impact the individual's quality of life and functionality for years after the injury. In fact, half of the hospitalized TBI patients develop TBI-related long-term or permanent disability [18], and over 70% of people diagnosed with severe TBI require long-lasting care and support [19]. In addition, TBI is strongly associated with subsequent disabling neurological disorders including Alzheimer's and Parkinson's diseases [20].

TBI also imposes a heavy cost on the healthcare systems. The direct medical cost per TBI patient in need of rehabilitation in Canada is estimated to be as high as $93,340 per year (in 2007 CAD) [21]. In Australia, which has a similar economy and healthcare system to Canada, an average lifetime cost of severe TBI is AU$4.8 million per patient [22]. The estimated annual total medical cost of TBI cases for the United States is $79.1 billion (in 2013 USD) [23].

Given that TBI imposes substantial medical and socio-economic burden on patients, the healthcare system and the society in Canada and worldwide [18,24], there is an urgent need to develop effective assessment and treatment interventions for TBI and objective quantitative techniques for monitoring the recovery of patients. The two main technologies (rTMS and EVestG) proposed to be used in this study have already shown the potential to be used as

[1] The rates of concussion usually include the minor to moderate head injuries. Therefore one has to be cautious in deriving a general figure of the rate of brain injury.

treatment and monitoring tools. The description of each technology and the protocol for their use are detailed below.

b. Background

This project proposes to use two novel technologies for treatment and the monitoring of therapy efficacy: rTMS and EVestG.

Transcranial Magnetic Stimulation (TMS) – TMS is a relatively new, but popular and well-tolerated, neuromodulation method that is emerging as a therapeutic tool for a variety of neurological conditions [1]. TMS is a noninvasive procedure based on the principles of electromagnetic induction, whereby a magnetic field pulse (generated by the coil place on the scalp) produces electrical currents in underlying neural tissue of the brain. The repetitive application of TMS (rTMS) pulses can modulate cortical excitability, either increasing or decreasing it, even well beyond the duration of stimulation. This has shown to have therapeutic potentials for several neurodegenerative diseases, i.e. Parkinson, stroke and psychiatric disorders such as depression [25-26].

rTMS has been increasingly used and found to be a promising noninvasive treatment for an array of brain disorders such as depression (FDA approval in 2008), migraine (FDA approval for prophylaxis in 2008), post-traumatic stress disorder, obsessive-compulsive disorder, stroke, Parkinson's disease, Alzheimer's disease, and epilepsy, as well as tinnitus and a variety of pain syndromes [27-29]. There are several reports of case studies that show beneficial effects of rTMS treatment on patients with severe TBI [30-33]. Four clinical trials are currently in progress to examine the efficacy and safety of rTMS in the treatment of TBI [34]. It is proposed that potential targets of rTMS therapeutic application in TBI patients could be TBI-related symptoms and functional sequences [35]. A number of studies demonstrate that rTMS treatment improves cognitive functions (i.e. attention/concentration, memory, executive functions/working memory, learning, psychomotor speed, language, emotional processing, and global cognitive functioning) [36,37], gait [38], balance [39], symptoms of depression [40] and anxiety [41], tinnitus and auditory processing [42], visual acuity [43], sleep quality [44], motor function of upper and lower limb(s) [45,46], spasticity [47], and reduces fatigue [48]. The same pattern is likely to be translated to patients with above-named symptoms due to TBI.

The fundamental rationale for therapeutic use of rTMS is based on compelling evidence that rTMS is able to modulate long-term neural plasticity at the network level [39,49,50]. These lasting neuroplastic changes induced by rTMS would likely help promote the recovery of brain function and decrease the burden of disabling sequelae of TBI, based on the evidence that it helps slowing cognitive decline in Alzheimer's patients.

We are currently applying high-frequency (20 Hz) rTMS bilaterally over the dorsolateral prefrontal cortex (DLPFC) as treatment for Alzheimer's [51]. We envision using a similar protocol and same location of the brain for TBI treatment with rTMS, as four case studies [30-33] that applied rTMS to TBI patients, also applied it to DLPFC brain regions at the either 10 or 20 Hz frequency. The DLPFC plays an important role in cognitive (executive, attention, memory) function of the brain due to its interconnectedness with other brain regions. The DLPFC

coordinates function with the rest of the brain and also helps to shift between tasks, and therefore has a role in working memory [50].

In general, rTMS is considered to be a safe, non-invasive, painless and harmless procedure. Review papers on rTMS tolerability and safety when applied to populations with depression (and on pregnant women with depression), Parkinson's disease, Huntington's disease, epilepsy, and anxiety have reported mild discomforts including mild tension headache (due to stimulation of the peripheral muscles in the scalp) after the session that diminishes within a couple of hours and some mild annoyance during the stimulation. The induction of migraine by rTMS is rare, and indeed rTMS to the left DLPFC has been used to reduce migraine headache. rTMS at high frequencies increases the risk of seizure induction. Although the risk of seizure at frequencies lower than 30 Hz is very low, in our study, we exclude people with a history of seizure as well as those with large ischemic scars (as that also increases the risk of seizure induction).

ElectroVestibuolography (EVestG) – EVestG [1] is a noninvasive technique to record neural activity from the vestibular apparatus and vestibular nuclei. EVestG signals are recorded from the external ear in response to a vestibular stimulus. They are the brain signals modulated by the vestibular response. The recorded signal is comprised of a series of acoustic and vestibular random and driven generated small field potentials from which the vestibular response can be separated. The vestibular response can be separated by taking measures when the vestibular system is at rest and when perturbed by passive whole body tilt [52]. EVestG signal analysis has shown great promise for diagnosis and separation of patients with depression [53], Parkinson's disease [54], schizophrenia [55], Meniere's disease [56], Attention Deficit Hyperactivity Disorder [57] from healthy controls. Pilot studies have shown EVestG to have sensitivities and specificities above 85% for a population of between 40 and 50 years of age.

TBI is commonly associated with vestibular dysfunction, and many survivors often experience persistent dizziness, imbalance, vertigo [16, 17]. Considering the well-known bidirectional anatomical links of the vestibular system (i.e., the vestibular nucleus is linked to the pre-frontal cortex path), EVestG signals are expected to change following TBI, and should be indicative of an injury. A recent pilot study conducted by our group has demonstrated that evaluation of vestibular performance using EVestG might be a useful measure of the physiological recovery state following mTBI (see Figure 1) [58]. Hence, physiological EVestG assessment may offer a great promise in evaluating treatment efficacy and monitoring of recovery after TBI.

Objectives

The objectives of this proposal are sorted in three key themes as follows.

<u>Theme 1: Applying rTMS treatment and its evaluation by neuropsychological and clinical assessments</u>

1. Recruit people (from Riverview Health Center and also from Dr. Mansouri's referrals), who have had a head injury within the past two to 12 months, have a clear diagnosis of TBI, and have persistent post-TBI symptoms. Collect standard neuropsychological assessment data at baseline.

2. Enroll the study participants into a "Sham Group" and a "Treatment Group" with a three-week protocol, and apply the treatment.

3. Record spatio-temporal assessments before and after treatment sessions, and examine the efficacy of rTMS treatment on the post-TBI symptoms by standard clinical and neuropsychological assessments by statistical analysis.

Theme 2: Monitoring treatment efficacy by objective measures, EVestG and spatio-temporal assessments

4. Record EVestG data with all its seven current stimuli at baseline (before the treatment) and immediately after treatment and also four and eight weeks after the last treatment.

5. Analyze EVestG data for extracting the optimum measures (biofeatures) showing the changes due to rTMS treatment.

6. Optimize (reduce the number of stimuli if possible) the EVestG recording protocol upon the results of Objective 5.

7. Examine the statistical correlation of the EVestG biofeatures representing the TBI recovery with data from the clinical and neuropsychological assessments as well as spatio-temporal assessments (derived in Objective 3).

Theme 3: Evaluating the objective measures of EVestG and spatio-temporal assessments in Control group

8. Recruit 20 age-and-gender-matched individuals with no history of head injury and record their EVestG data four times with a similar schedule to that of TBI patients, and investigate the consistency of the EVestG data between the sessions and compare with those of people with TBI during treatment.

9. Run the spatio-temporal assessments at the same sessions of EVestG recording in the Control Group and examine the effect of learning on the performance in these assessments.

Research Plan and Methods

The study will be performed as a pilot prospective, randomized, controlled, double blind, two parallel groups clinical trial (examining sham versus active treatment). At the end of the study, the active treatment will be offered to the Sham Group if the treatment is shown to be effective.

Study Protocol

Study Population/Participants

A total of 20 individuals with a clear diagnosis of TBI within the last 12 months (as confirmed by their treating Neurologist, Psychiatrist or Medical Rehab Physiatrist, who are the co-investigators in this study) prior to the commencement of this study will be recruited from Riverview Health Center patient and Dr. Mansouri's clinic patient population. Ten patients will be randomly assigned to **Treatment Group** and 10 others to **Sham Group.** Neither the patients, nor the clinical assessors will know the sham versus real treatment group assignment. In addition, as one of the objectives of this study is to evaluate the EVestG assessment as a

diagnostic and monitoring tool, 20 age-and-gender-matched cognitively healthy volunteers will be recruited as controls for the EVestG assessment. The healthy **Control Group**'s participants must not have any history of TBI and also meet other exclusion criteria for patients group listed below.

Inclusion Criteria for Patients

Participants must be of age 18-70 years, and have had TBI in the last 12 months prior to inclusion and presence of persistent TBI symptoms at the time of inclusion as confirmed by the co-investigator physicians.

Exclusion Criteria for all Participants

1) Use of neuro- or psycho-active medications as published in recommendations [26]
2) Active use of illicit drugs
3) History of epilepsy
4) History of any other brain lesions including tumors, infectious, vascular, or metabolic lesions
5) Severe or recent heart diseases
6) Alcoholism
7) Pregnancy
8) The presence of metallic objects in the body; dental implants are fine but people with pacemakers are to be excluded; anything that is unsafe under MRI would be considered unsafe for TMS [26].
9) Lack of ability to adequately communicate (understand, read, speak) in English and understand the experimental protocol.
10) Pending litigation (i.e., patients with pending actions regarding disability reports, litigation, or other kinds of financial compensation).

Participants will receive the details of the study, and be asked to sign a written consent form prior to experiments. Upon meeting the eligibility criteria and providing informed consent, each patient participant will be randomly assigned to either treatment or sham groups; this assignment will not be revealed to the patients until the end of study. *The Sham Group's participants will be offered a course of treatment after the study is finished if the results show improvement beyond the placebo for the participants in Treatment Group.* Patients will be thoroughly assessed by the medical collaborators for their symptoms, and localization of the damage to the brain. The cognitively healthy Control Group will not receive any rTMS treatment. All participants will complete a series of cognitive and mental assessments, and EVestG assessments. The Control Group will go through a lesser number of questionnaires as there is no need for run concussion severity assessment on control group. The details of the study procedure are described below, and Table 1 summarizes the study protocol.

rTMS Treatment Procedure

The treatments will be administered daily (five days/week) for two weeks, followed by three days on the third week (total of 13 treatments). Patients of both real and sham treatment groups will undergo rTMS treatment of 1.5-second duration trains of pulses at 20 Hz for a total of 25 trains with intertrain interval of 10 seconds applied to DLPFC bilaterally. Thus, there will

be a total of 1500 pulses per two sides of the brain per day, which is well within the safety limit of the rTMS application.

During the intertrain intervals, the patients will be presented a series of objects and actions and asking to name them. The images will be projected on the wall in front of patient with duration of three seconds for each image. The aim is to keep the brain active while we stimulate it with rTMS. Prior to each treatment session, the patient's resting motor threshold (RMT) will be measured using a single pulse of TMS, noting the intensity necessary to cause a small twitch in the thumb finger in three consecutive pulses. Then, the 70 mm cooled figure-8-coil will be placed on the head at a location for optimal stimulation of the DLPFC at the intensity of 100% of the RMT. Each rTMS treatment session will take approximately 20 minutes.

The same protocol will also be used while using sham stimulation. For the sham stimulation we will attach a 2-cm-thick piece of wood with the same size and shape as the coil, under the coil; the wood is an insulator and dissipates all the energy of the pulses, while the sensations and the sounds do transmit through the wooden piece. This is currently used for our rTMS treatment of Alzheimer's patients.

EVestG Measurement

All study participants (in all three groups) will go through four sessions of EVestG assessments: 1) before rTMS treatment, 2) after 12 sessions of rTMS treatment, 3) four weeks after the last rTMS treatment, and 4) eight weeks after the last rTMS treatment.

The subjects sit in a hydraulic chair with their eyes closed and head rested on the chair headrest; they receive a series of orthogonal passive whole body movement stimuli: up/down translation and a horizontal rotation to the right and return to center (RTC) in both sitting upright and supine positions, and side tilts to the right and left.

Each tilt and the rotation are about 40 degrees, while up/down movement are about eight inches; the movements are designed to be smooth with a constant acceleration/deceleration over 3s. The recordings are made in an acoustically attenuated (>30dB) and electromagnetically shielded chamber at the EVestG Lab, Riverview Health Center. The active gelled recording electrodes are TM-EcochGtrode (Bio-logic, France), and placed in both ears proximal to the eardrum. Reference electrodes (Biopac EL254S for earlobe and EL258S for forehead) are placed on the ipsilateral earlobes and a common ground electrode is placed on the forehead.

The left and right ears' signals are recorded using Spike2 software via a CED-1902 amplifier (60Hz notch filter, 10k gain, 1Hz high pass filter) and digitized using CED1401 ADC board at sampling rate of 41,666Hz. Each recording's duration was 60s for each stimulus: 20s stationary at the center position, 3s motion to a position (up or rotated), 17s stationary in that position, 3s return to the center, and another 17s of stationary recording in the center position.

The chair's position is also recorded simultaneously with the ear signals; it is used to extract the segments of interest for analysis. The particular segments of interest, shown in Figure 2, are: 1.5s immediately prior to the movement (BGi), 1.5s acceleration (onAA) and 1.5s deceleration (onBB) as well as the 1.5s segments from the return to the center: RTC BGi, RTC onAA and RTC

onBB. The acceleration/deceleration segments are selected as they give the largest differences compared to background. Each EVestG recording may take up to one hour.

Standard Neuropsychological and Screening Measures

The neuropsychological assessments include: Rivermead Post Concussion Symptoms Questionnaire (RPQ) [7,59], Montreal Cognitive Assessment (MoCA) [60], Montgomery Asberg Depression Rating Scale (MADRS) [61] and Stroop tasks [62]. Patients with TBI will go through all above mentioned assessments four times, similar to EVestG assessments. The healthy Control Group will go through only MoCA and MADRS assessments at the beginning of the study and at the last assessment session.

Custom Designed Visuo-Spatial and Spatio-Temporal Assessments

Our custom designed visuo-spatial and spatiotemporal assessments include our virtual reality navigational orientation assessment [63].

Data analysis

EVestG Biofeature Extraction – The NEER algorithm [52] will be used to locate and extract vestibular neural events. The interval histograms of the neural events are also used to extract the basic statistical properties of the neural firings such as probability density function (pdf), mean and variance, as well as fractal dimension, kurtosis and skewness of the signal. The features extracted from all tilts will be investigated to determine biofeatures specific to a concussion. The extracted biofeatures, e.g. fractal dimension, kurtosis and skewness of the potentials' distribution, from the recorded signal will be compared between Sham and Treatment Groups.

Statistical Analysis, Clustering, Decision Making and Validation – After data collection, the multivariate Analysis of Variance (MANOVA) statistical test will be run to determine the significant differences of any of the extracted biofeature measures between the sessions and the Control Group and the Treatment and Sham Groups. In all instances, a p-value less than 0.05 is considered significant. Cross correlation analysis will also be used to find the correlation between these measures and the neuropsychological assessments scores. Once the statistically significant features among the groups are found, the classic approach of discriminant analysis with leave-one-out routine (for robust results in small size data) will be run to investigate whether concussion cases can be identified. An important issue to address is the membership assignment of the subjects. Since there may not be confirmed and solid clinical and neuropsychological assessments for the recovery from the TBI post-symptoms, we will also run unsupervised (blind) clustering of the objective measures followed by our recently developed diagnostic decision making algorithm to identify TBI recovery. The diagnostic and monitoring algorithms will be checked with the updated diagnoses of the clinical symptoms (by the referring physician) and the neuropsychological evaluations.

Table 1: Treatment and Assessment Schedule

Study Groups	Week	# of Treatments	Assessments
Treatment and Sham Groups	0 (Baseline)	None	EVestG, MoCA,, MADRS, RPQ, Stroop, and spatiotemporal
	1	5 – Monday to Friday	None
	2	5 – Monday to Friday	None
	3	2 – Mon/Wed or Tue/Thu	None
	4		EVestG, MoCA,, MADRS, RPQ, Stroop and spatiotemporal
	8		EVestG, MoCA,, MADRS, RPQ, Stroop, and spatiotemporal
	12		EVestG, MoCA,, MADRS, RPQ, Stroop, and spatiotemporal
Healthy Control Group	0		EVestG, MoCA, MADRS
	1		
	2		
	3		
	4		EVestG
	8		EVestG
	12		EVestG, MoCA, MADRS

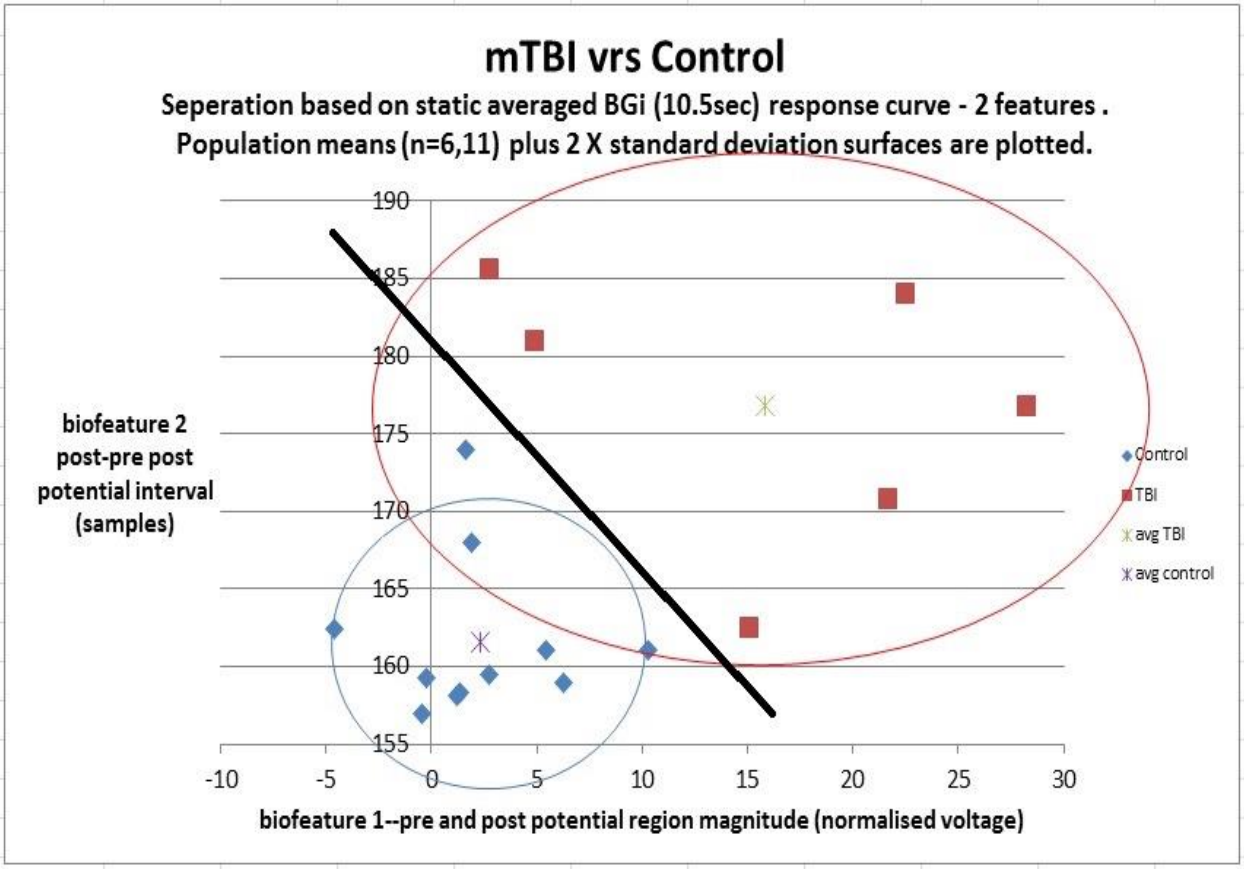

Figure 1. Separation of mTBI and control subjects using two post potential features.

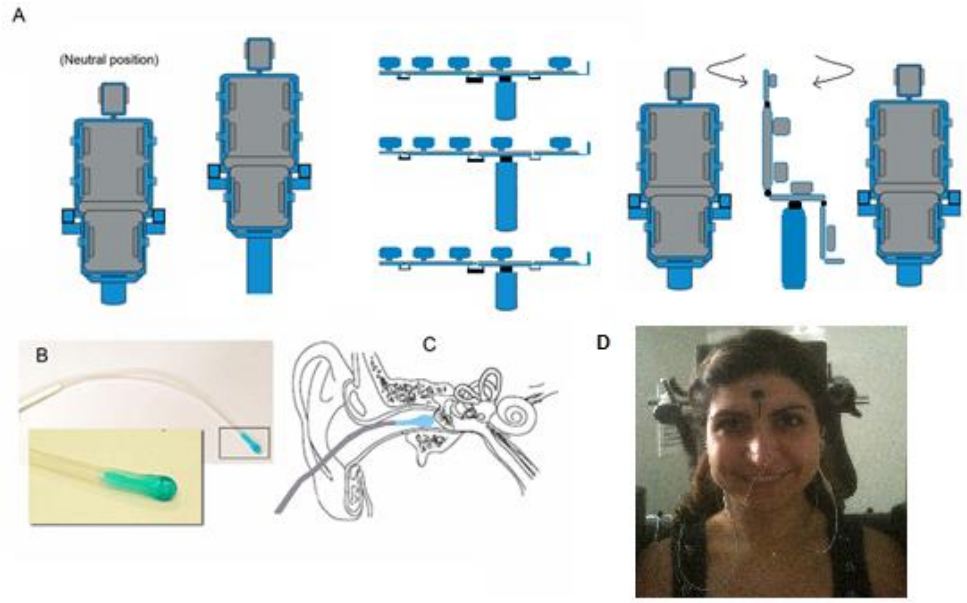

Figure 2. A) Sitting up/down movement, supine up/down movement, sitting horizontal rotation. B) Ear Electrode; C) Electrode placement; D) Subject connections.

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