New Method for Performing Vibratory Stimulation and Detection of Early Cortical Response

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Abstract: Deep sense capability is one of very important indicators of numerous pathologies in medicine, and one of the indicators of deep sense is the sense of vibration. One of the methods for testing the sense of vibration is vibratory evoked potentials, which present the response of the nervous system to vibratory stimulus. Currently used vibratory stimulation has a small clinical value because obtained results do not incorporate quantifiable information about the entire afferent activity of vibratory sensory pathway (VSP), and response appears around 50 ms, providing no information about early cortical activity.

The aim of this research was to develop a method of vibratory stimulation that would provide information about the functional integrity of the whole VSP.

The impossibility of monitoring the function of the whole VSP is related to changes in stimulation parameters between successive stimuli and because of that the basic premise of evoked potentials (equal parameters for every stimulus) is disrupted. A vibratory stimulator with controllable pressure of vibratory applicator was constructed in order to provide equal parameters for every stimulus to obtain quantifiable information about the entire VSP. Optimum parameters of stimulation were chosen (stimulus frequency of 120 Hz, stimulus duration of 50 ms, and wrist as the site of stimulation).

Keywords: deep sense, vibratory sensory pathway, vibratory stimulation, evoked potentials, vibratory stimulator

Introduction

Deep sense capability is one of very important indicators of numerous pathologies in medicine, and because of that it is of great bearing on the determination of exact quantitative parameters related to deep sense. One of the indicators of deep sense is the sense of vibration. It occurs as a response of the nervous system to the vibration stimulus. Major receptors responsible for the sense of vibration are mechanoreceptors (Merkel's receptors, Meissner and Pacinian corpuscles) and each type of mechanoreceptors is most sensitive to a particular frequency range (Guyton, 1999). Merkel's corpuscles are the most sensitive to low range frequencies, Meissner's corpuscles to medium range frequencies and Pacinian corpuscles to high range frequencies (Bensmaïa, 2005, Gilman, 2002). The most appropriate frequency range for vibratory stimulation is around 100 Hz, because in this range both Meissner and Pacinian corpuscles are most sensitive.

Evoked potentials are the neurophysiological method that has been in use for many years and it provides information about the functionality of specific parts of the nervous system. This technique registers electrical activity of the brain that occurs as a response to specific stimuli [9]. Vibratory stimulation activates vibratory receptors and elicited electrical response could be registered along vibratory sensory pathways and on the sensory cortex.

The currently used vibratory stimulation has a small clinical value because the obtained results do not incorporate quantifiable information about the entire afferent activity of vibratory sensory pathways, from receptors in the skin to the sensory cortex. Elicited responses appear around 50 ms and they are the reflection of late cortical integration, but with little diagnostic relevance.

As opposed to that, the electrical stimulation of the somatosensory pathways, anatomically and physiologically almost identical to the VSP, obtains complete information on the functionality of the pathway and provides information about the response of pre cortical structures and also cortical response, so it could be assumed that the problem with the stimulation of the vibratory sensory pathways lies in an inadequate stimulation of the vibratory sensory receptors.

Therefore, there is a need to establish a method that could provide quantified information about the functionality of vibratory sensory pathways. The aim of our study was to develop a method of vibratory stimulation that would provide quantified information and facilitate the implementation of an improved method in daily clinical routine.

The most commonly used method for testing the sense of vibration is an examination with a vibratory fork. In this method, a vibratory fork is reclined to a patient's body, usually at the wrist, and the patient expresses his/her subjective sense of vi-

brations. The disadvantage of this method is a lack of objectivity and dependence on the patient's subjective perception and cooperation. The use of this method is impossible with patients in a coma, patients that are unable to communicate or with small children (Krbot, 2011).

In addition to classical tuning fork that vibrates with a single frequency, there is also a quantitative tuning fork, Rydel-Seiffer tuning fork, which has the ability to change the frequency from 64 Hz to 128 Hz (Lai S, 2014, Martina, 1998, Pestronk, 2004). Both types of tuning forks only provide information about subjective ability to sense the vibration, which is insufficient for quantified diagnostics. The quantitative tuning fork has advantages over classic ones in the objectivity of the information gathered, but this method is still subject to the subjective impact of the single person and does not provide quantified information.

Sense of vibration could also be examined with quantitative sensory testing (QST). The method is based on the examination of the sense of heat and vibration on skin, but usually it provides only information about participants' threshold. It is dependent on participants' cooperation and the interpretation of results differs between research groups (Chong, 2004, Siao, 2003, Zaslansky, 1998).

Also, devices like Vibratron (Physitemp Instruments, Clifton, NY) are used for examination of vibratory threshold. Device consists of one control unit and two vibratory units that produce vibration of different frequencies.

All described methods do not have standardized parameters, and standardized parameters are important for longitudinal follow up of disease progression and for comparison of results achieved between different research groups (Burns, 2002). Any of these methods do not provide quantified and comparable information about the functional integrity of vibratory sensory pathways.

In order to provide proper information about vibratory sensory pathways, neurophysiological methods with quantified vibratory stimulation (vibratory stimulator) were used (Goldber, 1979). Constant voltage was used for stimuli with constant amplitude, and in this setup, there was control about the amount of energy delivered to receptors. The amount of energy delivered to receptors is not an appropriate measurement, because there is no control over the energy received by them.

Experiments conducted in this area used different parameters of stimulation (duration, frequency, place of stimulation), but they did not achieve early evoked response (Hämäläinen, 1990, Münte, 1996, Snyder, 1992, Tobimatsu, 1999, Tobimatsu, 2000). Münte and his group stimulated extensor carpi radialis on both hands with different frequencies of stimulation (40 Hz, 80 Hz, 160 Hz), and the first registered neurophysiological component was P50 (positive component that appeared 50 ms after the stimulus) (Münte, 16). Similar results were achieved by Hämäläin-

en who stimulated the middle finger of the hand with a low frequency (24 Hz) and high frequency (240 Hz) stimulus, but the earliest registered component appeared 45 ms after the stimulus over the contralateral primary sensory cortex (Hämäläinen, 1990). No early cortical activity was detected.

Evoked potentials

Evoked potentials provide insight into the function of different parts of the nervous system and the brain. The application of the evoked potentials method is widely accepted, from different fields of medicine (clinical neurophysiology, intraoperative neurosurgical and surgical monitoring) to neuroscience, with particular emphasis on the field of cognitive neuroscience.

The method is completely non-invasive and it has excellent temporal resolution (around 1 ms), and because of that it is suitable for testing the functional state of a particular sensory or motor pathway.

The advantage of evoked potentials is the complete independence of the cultural and educational influence (Lai CL, 2010), which is of great importance for cognitive testing where the objective assessment of skills is necessary. Also, participants could not affect the results of evoked potentials, because in specific situations it is possible to obtain an electrophysiological response even when the participant does not pay attention to the presented stimulus (Luck, 2005).

The method is based on the electrical activity that occurs as a response of the nervous system and the brain to specific stimuli. Participants are exposed to different stimuli and the response of the nervous system to specific stimuli is registered, and further processed through averaging an adequate number of responses to the identical stimulus (Išgum, 2009). Identical stimuli would provide an identical response of the nervous system, and the average of the specific numbers of successive responses would be identical to a single response only if all the successive stimuli have identical characteristics.

The results of the evoked potentials method are presented in the form of specific components. The latency (time of appearance) and the amplitude of the component provide information about the characteristics of the evoked response

Theoretical background for construction of vibratory stimulator

The currently used vibratory stimulation technique in the evoked potentials method has a small clinical value because it does not provide quantitative information

about the whole vibratory sensory pathway, which is reflected in the absence of the early components of the evoked response.

The aim of this research was to establish an objective method for the examination of functional integrity of the whole vibratory sensory pathways, from receptors in the skin to primary sensory cortex in the brain.

The electrical stimulation of somatosensory pathways activates all neuronal fibres in a stimulated nerve and provides complete information about the functional integrity of these pathways, from the earliest response to the results of the late cortical integration. Neuronal fibres that transmit information from the vibratory receptors have the identical anatomical path as the somatosensory pathways, but their evoked response consists only of late cortical components. That leads to the assumption that, due to the anatomically preserved transmission path, the problem with the activation of vibratory sensory pathways with vibratory stimulation is related to an inadequate stimulation of vibratory receptors.

In the evoked potentials method stimuli should be identical in order to generate identical and repeatable responses. According to literature, vibratory receptors generate action potentials synchronized to vibratory stimulation, and it is questionable why evoked activity could not be detectable through the entire vibratory sensory pathway (Rugiero, 2010). Vibratory sensitive mechanoreceptors respond to vibratory stimulation in correlation to stimulation parameters and because of that identical stimulus should evoke identical response of the nervous system (Loewenstein, 1996, Rugiero, 2010). It can be concluded that the problem with the registration of evoked activity through the entire vibratory sensory pathways is caused by the fact that successive stimuli do not have identical parameters and because of that action potentials with different characteristics are generated. Inadequate activation of mechanoreceptors causes asynchronous propagation of action potentials through the pathways and disables registration of peripheral components and early components of cortical response. The results of previous studies with vibratory stimulation showed late components as a manifestation of late cortical integration of asynchronous input to primary sensory cortex (Hämäläinen, 1990, Münte, 1996).

Currently used vibratory stimulators have constant displacement of vibratory applied part, which generates identical amplitude of for every stimulus. It means that constant amount of energy is transferred to tissue (Goldber, 1979), but it does not define the amount of energy received by tissue because the geometrical relationship between the vibratory applicator and the tissue is variant. Therefore, although the amount of energy transferred to tissue is always the same; the delivered amount of energy depends on the mutual relationship between the tissue and the applicator.

There is no stable geometrical relationship between vibratory applicator and stimulation site because of inevitable macro and micro movements of the vibratory stimulator relative to the participant (movements of participants, breathing, etc.), and because of that constant amplitude generates vibratory stimuli with different parameters. This means that successive stimuli are not quantitative repeatable and have different parameters, and without an identical stimulus there is no possibility of evoking identical repeatable response, which is necessary for averaging and noise suppression applied in the evoked potentials method.

Pacinian corpuscle is a mechanoreceptor sensitive to changes at the beginning and end of stimulus, which is specific for vibratory stimulus (Guyton, 1999). It generates an action potential dependent on stimulus characteristics and it is necessary that characteristics of pressure applied to corpuscle are identical for every stimulus. In order to achieve this, it was necessary to construct vibratory stimulator that would generate successive vibratory stimulus with identical pressure of vibratory applicator.

According to these conclusions, a specially designed vibratory stimulator was constructed. It has the ability to retain constant pressure of vibratory stimulus instead of constant amplitude, and because of that, it generates identical stimuli with well-defined parameters necessary to monitor the functional integrity of the whole vibratory sensory pathways.

The working principle of vibratory stimulator is shown in Fig. 1. The initial signal for vibratory stimulator consists of two components: the initial pressure of vibratory applicator and the amplitude of vibratory stimuli. The pressure sensor is in con-

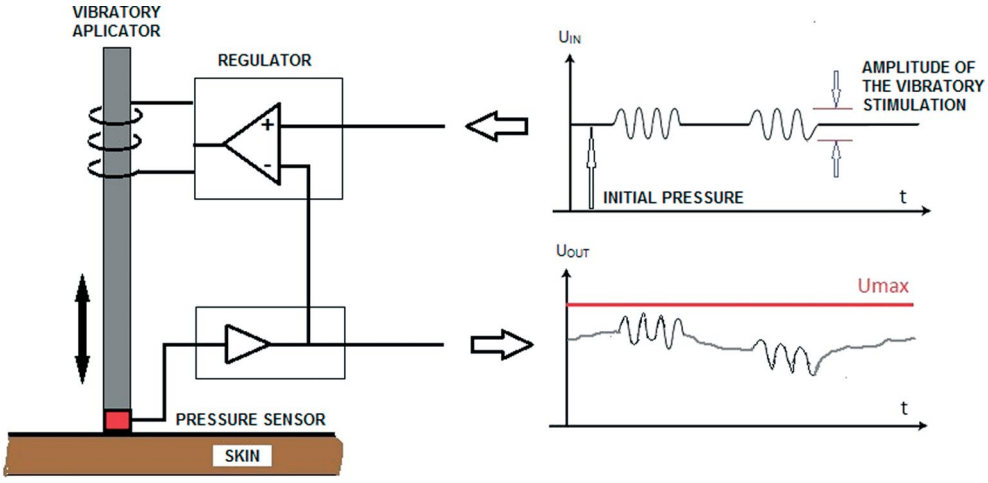

Fig. 1 – The working principle of the vibratory stimulator

tact with the skin and sends feedback about the vibratory applicator pressure in the controller. If there is a change in the pressure, then negative feedback regulates the displacement of the vibratory applicator in order to achieve controllable pressure through the entire stimulation.

The constructed vibratory stimulator has well defined parameters of stimulation. Two control waveforms can be selected (sine and triangle), stimulation frequency is adjustable in the range from 30 to 300 Hz, stimulus duration from 10 to 500 ms, and interstimulus interval from 100 to 2000 ms. Also, different intensities of the pressure can be chosen. There are separate controls over intensity of initial constant pressure and superimposed variable pressure. Stimulation frequency is chosen according to physical characteristics of vibratory receptors and according to relevant literature, target frequency is around 100 Hz (Fattorini, 2006). Stimulus duration also has a significant impact on evoked neurophysiological response, and because of that, the aim of this research is to find suitable parameters of stimulation in order to achieve repeatable and reliable responses.

Materials and methods

In this study 38 participants were included, 15 females, mean age 39.8 years (18-72 years). Measurements were performed in the Laboratory for Cognitive and Experimental Neurophysiology, Department of Neurology, University Hospital Center Zagreb. The Ethical Committee of the University Hospital Center Zagreb approved the study. Before starting, the experiment was explained in detail to every participant. All participants signed an informed consent.

During the experiment participants were placed in a sound insulated chamber. They sat in a comfortable armchair and were instructed to relax and minimize blinking in order to reduce artifacts. Vertical oculogram was recorded with bipolar channel, one electrode situated below the right eye and referred to reference electrode at Cz position in order to detect vertical ocular movements for a more precise treatment of ocular artifacts.

32 electrodes were used for recordings and the main goal was to examine parameters of stimulation necessary to achieve repeatable evoked response (stimulation frequency, duration, interstimulus interval, and place of stimulation). A specially designed cap (actiCap) with 32 electrodes positioned according to International 10-20 system was used [BrainProducts GmbH, Germany]. The cap is made of active electrodes, based on high-quality Ag/AgCl sensors with integrated noise subtraction circuits for lower noise levels. Activity was recorded with monopolar channels

referred to average value of voltage for all electrodes. Before the measurement, areas under each electrode were cleaned with abrasive paste in order to reduce impedance, and conductive paste was applied to each area in order to achieve adequate conductivity for recording very small signals (order of magnitude ~μV).

For the known comparison, somatosensory evoked potentials (SSEP) with current stimulation were recorded for every participant. SSEP is a well-established diagnostic method used in daily clinical routine. For the current stimulation, constant current stimulator [Twister, Germany] was used. The registration of evoked responses was performed with the same electrodes as for vibratory stimulation. Monopolar square wave electrical pulses, duration of 200 μs and stimulation rate of 5 pps were used for electrical stimulation. Stimulation intensity was dependent of the threshold of the direct muscle response for every participant.

Based on many years of experience working with various modalities of vibratory stimulation, for all measurements in this study the constant pressure presented over the measuring system as the effect of the weight of 270 grams was selected.

Each of the measurement conditions was tested by 200 stimuli, which was sufficient to achieve repeatable and reliable response.

Recordings were performed with BrainAmp amplifier and recording software Brain Vision Recorder [BrainProducts GmbH, Germany]. Recorded signals were filtered with band pass filter from 0.5 Hz to 250 Hz. The sampling frequency was 5000 Hz. Data analysis was performed with Brain Vision Analyzer Software [BrainProducts GmbH, Germany].

Results and discussion

The examination was performed with four different frequencies of stimulation (30 Hz, 120 Hz, 200 Hz, and 300 Hz). The main components are N1 and P1, as shown in Fig. 2. N1 component appears around 20 ms and P1 component appears around 30 ms.

The neurophysiological response evoked with a frequency of 120 Hz provides results most comparable with the activity evoked with current stimulation, somatosensory evoked potentials (SSEP). A frequency of 120 Hz is in concordance with the data from the relevant literature (Fattorini, 2006, Gilman, 2002). Meissner and Pacinian corpuscles, mechanoreceptors sensitive to vibratory stimulation, overlap their area of sensitivity around the frequency of 100 Hz. Stimulation with a fre-

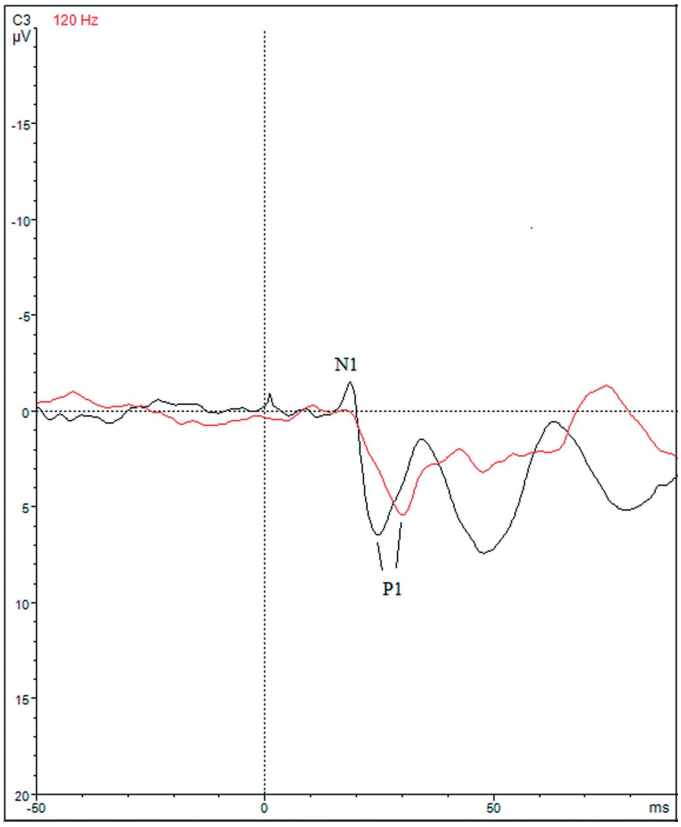

Fig. 2 – Evoked response – stimulation frequency 120 Hz, comparison of SSEP response (black) and vibratory stimulation response (red)

quency around 120 Hz is appropriate for vibratory stimulation because it activates a larger number of mechanoreceptors and this is why the frequency of 120 Hz was chosen as a stimulation frequency for further measurements.

The registered components (N1 and P1) present early cortical response, which is in concordance with the results of SSEP. Also, the achieved components appeared around 20 ms, which is much earlier than the components observed in studies with other vibratory stimulator (around 50 ms) (Hämäläinen, 1990, Münte, 1996). Identical parameters of successive stimuli enable repeatable and identical evoked response, which allows the detection of early cortical response.

The second important parameter is stimulus duration. Measurements were performed with a stimulus duration of 10 ms and with 50 ms. The results obtained with both durations had the morphology of main components similar to the morphology of SSEP, and for both durations, the complete evoked response was obtained.

The spatiotemporal distribution of evoked response indicates that responses evoked with a duration of 50 ms have higher intensity. A longer duration of stimulation provides longer exposure of the primary sensory cortex to sense of vibration which ensures a stronger activation of the primary sensory cortex, and because of that the intensity of evoked activity is higher. The duration of 50 ms reached desired evoked response and because of the minimal required duration of the experiment longer durations of stimulation were not tested.

The third important information is information about the place of stimulation. According to the well know somatotopic organization in humans (homunculus), sensory cortex area for the hand has a wider surface then sensory areas for other body parts. It can be easily detected with non-invasive, surface electrodes, and it has clear lateralization (contralateral side of the cortex). Therefore, the hand was chosen as the stimulation position. Measurements were performed on three different positions: the finger (first distal joint of the middle finger), the wrist and the elbow. Responses evoked with stimulation of the wrist or the elbow were in concordance with the results evoked with SSEP, while stimulation of the finger evoked responses with recognizable morphology, but longer latency. This presentation of the results was expected, because latency of the response is related to the distance of the place of stimulation from the sensory cortical area (the length of the activated peripheral pathway). Pacinian corpuscles, mechanoreceptors sensitive to the sense of vibration, had small spatial density (Gilman, 2002) and because of that bigger surface should be stimulated in order to achieve better activation. Stimulation of the finger evokes lower quality response in comparison with responses evoked at wrist or elbow, due to the small surface available for stimulation. Stimulation of the elbow evokes response in only 50% of participants, while evoked response of wrist stimulation is recognizable and repeatable for every participant, due to the activation of a higher number of Pacinian corpuscles for wrist stimulation. According to the presented facts and results, the wrist was chosen for the place of stimulation.

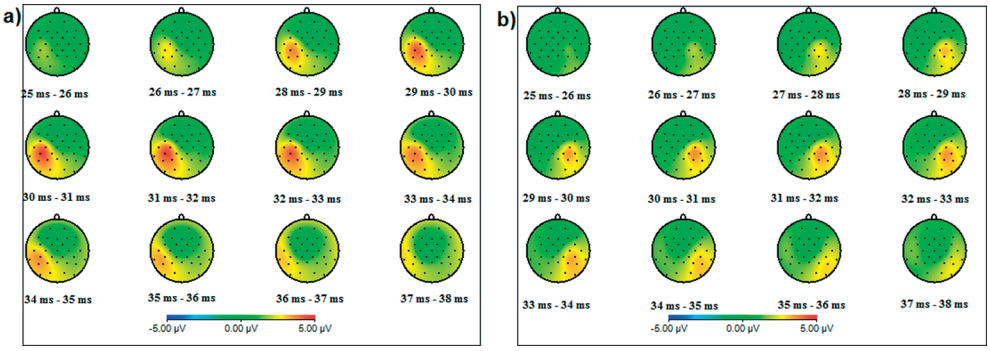

Fig. 3 – Vibratory evoked response: a) stimulation of the right hand; b) stimulation of the left hand

The evoked response achieved with vibratory stimulation meets expected anatomical requirements; stimulation of the right/left hand activates the adequate sensory cortical area on the contralateral hemisphere (as presented in Fig. 3).

The reproducibility of the evoked response was achieved for a single participant, but also for a group of participants, which provides evidence that evoked response is not created only by chance, it is a real neurophysiological response of vibratory sensory pathways to vibratory stimulation.

Conclusion

The results presented in this research provide information about the parameters necessary to achieve reliable and repeatable neurophysiological response to vibratory stimulation (frequency of stimulation, duration of stimulation, place of stimulation). Evoked response can be described with well-defined parameters (latency, amplitude and localization of the main components) which enable longitudinal monitoring of a single participant, but also a comparison of results between groups of participants. This is the main advantage of this method, because it allows the presentation of the functional state of vibratory sensory pathways in the form of quantified information. Also, the achieved results include early components which provide information about early cortical activity necessary for the functional examination of the entire vibratory sensory pathway. Further measurements on the population with different types of pathologies related to the vibratory sensory system are necessary in order to present the diagnostic value of the method.

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