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Original Article

Median nerve somatosensory evoked potentials in medical students: Normative data

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Abstract

Background: The median nerve N20 component constitutes the initial response of the primary somatosensory cortex to somatosensory stimulation of the upper extremity. Knowledge of the underlying generators is important for basic understanding of the initial sequence of cortical activation.

Materials and Methods: In the present study, normative data of cortical evoked potentials in particular of N20 wave onset and peak latencies by median nerve stimulation in a group of 100 medical students aged between 18 and 30 years were documented and the effect of physiological variables were studied. Descriptive statistics and Student *t*-test were used to analyze the healthy subjects and to compare N20 latencies for handedness, respectively. Regression analysis was used to show association between average N20 latencies and physiological variables from which regression formulae were calculated to predict normative values of these parameters.

Results: The results of the study indicated that N20 onset and peak latency values are significantly affected by limb length at 95% confidence level. Height is showing as a significant factor affecting N20 onset latencies but it is probably because of high correlation of height with limb length. Age though on linear regression showed some significant correlation with N20 onset and peak latency, multiple regressions showed that it does not affect N20 onset and peak latencies in the presence of other variables. Handedness did not affect both N20 onset and peak latency values.

Conclusion: Physiological variables do affect the N20 latencies and these should be standardized before usage for research in basic sciences at all age groups.

Key Words: Median nerve somatosensory evoked potentials, N20 latency, normative data, physiological variables

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INTRODUCTION

In the past half century, evoked potentials (EPs) have evolved from a challenging scientific tool to a commonly applied technique in clinical neurology.[1] EPs are the electrical signals generated by the nervous system in response to sensory stimuli. Auditory, visual, and somatosensory stimuli are used commonly for clinical EP studies.

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Somatosensory evoked potentials (SSEPs) evaluate conduction from Ia afferents in the peripheral nerves of upper (median, ulnar) and lower (tibial, peroneal) limbs through the dorsal column pathway of the spinal cord and medial leminiscus of the brainstem to the primary somatosensory cortex.[2] SSEPs consist of a series of waves that reflect the sequential activation of specific neural structures along the somatosensory pathways, which is also called the dorsal medial leminiscal system.[3]

In many ways EPs have become standard tools used in the care of patients with neurological problems, including patients cared for in the intensive care unit (ICU) and during surgical procedures. SSEPs provide objective measures of function along the somatosensory pathways. The importance of preparation of a normative data arises from the following:

- The major advantage of SSEPs lies in evaluating the relatively long sensory pathways from peripheral nerve to spinal cord and the cerebral cortex. The sensory pathways are vulnerable to a number of pathologies because of their length. There a number of technical modifications, because of which, the comparison of SSEP results among different laboratories is difficult. It is therefore necessary to pay attention to various technical details for reproducible results. Moreover, a standard protocol of SSEP by establishing a normative data would allow valid comparison among different laboratories.[1]
- Establishment of normative data is important because the evoked responses, which are described in terms of latencies and amplitudes, inter-peak latencies, Central Conduction Time CCT, latency differences between two sides or between upper and lower extremities can be compared with normative data and scored as either normal, impaired, or completely abolished.[4]

The SSEPs recorded from the scalp thus represents the integrity of the nerves from periphery to cortex, which comprises of:

- Components corresponding to the peripheral nerve action potentials- N5, N9
- Components generated in the brainstem- cervical component-N13
- Far field components- P14, N18
- Components generated at the cortex – N20 is the first component recorded from the cortex followed by later components.[5] The earliest localized major component of the scalp recorded median nerve SSEPs is the N20. It is recorded over the centroparietal region, contralateral to the stimulated nerve and it represents the first cortical response to the afferent somatosensory volley.[3]

In this study, short latency cortical SSEPs N20 – P22 have been recorded and in particular N20 onset and peak latencies have been documented and normalized. N20 latencies were then correlated with physiological variables like age and anthropometric variables like limb length, height, and handedness.

MATERIALS AND METHODS

Study was carried out on 100 healthy medical student volunteer subjects aged between 18 and 30 years. Informed consent was taken. They were briefed about the technical procedure. Relevant history and clinical examination was part of the selection process, which was based on inclusion and exclusion criteria. The study was conducted under auspices of Department of Physiology at Sri Devaraj Urs deemed university between April 2008 and March 2010.

Inclusion criteria

Healthy subjects aged less than 30 years.

Exclusion criteria

- Subjects aged >30 years, with peripheral neuropathies and other chronic medical illness (alcohol abuse, endocrine (e.g., diabetes mellitus), metabolic, and nutritional disorders)
- Subjects with metal implants, orthopedic (e.g., cervical spondylosis), congenital or acquired abnormalities of upper limb
- Those who were on medications like antiepileptic agents, Central Nervous System (CNS) depressants, antidepressants, which could alter the results, were excluded from the study.

Physiological parameters like age, height, upper limb length, and weight were measured using standard equipment. Arm length (tip of acromion to tip of middle finger) was recorded. Handedness of the subject was determined using Edinburgh Handedness Inventory by Oldfield.[1] Instrumentation, preparation, and recording, specific instrumentation for stimulation, signal acquisition, processing and storage and electrode placements was done according to International Federation of Clinical Neurophysiology (IFCN's) guidelines on standards of clinical practice.

Following technical adjustments were made with minor modifications of the IFCN guidelines. Amplification: Gain was adjustable in steps of not more than 2.5 to 1. The differential input impedance of the amplifier was 10 kΩ. The noise level of the amplifier did not exceed 2 μV. The recording electrode impedance was maintained at 5 kΩ by proper skin cleaning and grounding of the subject. Filter setting was between 20 Hz and 5 kHz to minimize the noise

without reducing the waveforms of interest. Digital recorders, which have easily understandable voltage and time scales, were utilized for recording and display of SSEPs on subjects.

The median nerve contralateral to the electrode placement on the scalp was stimulated with a minimal electrical intensity of 8 mA for 100 ms and the SSEPs were recorded using RMS EMG PK II machine manufactured by RMS recorders and medicare system Chandigarh.

The results were averaged, the end point being taken when the maximum waveform was discernable. Recording montage used was cephalic bipolar in which both the reference and the active electrode were placed on the scalp. A cephalic bipolar montage has the advantage of being relatively free from noise and is preferred for routine clinical use.[6] In this study montage consisting of a single channel has been used. Channel 1: Contralateral scalp (C3) – Scalp (Fz). There is no mandatory minimum number of channels required to record clinical SEP studies. A single channel upper extremity study can contain all the needed data, or serial studies of different levels or paradigms can be obtained from that data.[7]

Monophasic rectangular pulses (square waves) was delivered to the median nerve at the wrist by the stimulator placed at the wrist. The stimulus was of sufficient intensity to produce small visible twitch of the thumb. Right and left median nerves of the subjects were stimulated independently. Averaging of 1000 epochs was done to get a discernable waveform and to reduce the signal-to-noise ratio. Two separate runs were utilized to ensure reproducibility and repeatability.

The ethical clearance was obtained from the institutional ethical committee for Human's research as per Helsinki.

Statistical analysis

Descriptive statistics and Student *t*-test were used to analyze the healthy subjects and to compare N20 latencies for handedness, respectively. Regression analysis was used to show association between average N20 onset and peak latencies vs limb length and age and association with multiple variables. *Z*-test was used:

- To test significant difference of means between right hand latencies of right handed and left handed subjects and
- To test significant difference of means between left hand latencies of right handed and left handed subjects.

RESULTS

In this study 100 neurologically normal male subjects were subjected to median nerve SSEPs. Table 1 shows descriptive statistics of the subjects. Table 2 shows that the mean N20 onset latency of right hand and left hand were 15.72 and 15.82, respectively. Mean N20 peak latency of right and left hand were 18.7 and 18.83, respectively. Table 3 depicts correlation coefficient of N20 onset and peak latency with age were 0.54 and 0.63, respectively, correlation coefficient of N20 onset and peak latency with limb length were 0.81 and 0.62, respectively, similarly with handedness the values were 0.12 and 0.19, respectively. Table 4 shows regression of N20 onset and N20 peak latency with limb length $R^2 = 0.65$ and 0.66, respectively. Similarly with age R^2 value was 0.29 and 0.31, respectively. Table 4 also shows multiple regression of N20 onset and N20 peak latency versus age, limb length, height, weight with $R^2 = 0.69$ and 0.68, respectively. Table 5 shows the right hand N20 onset values of right handed and left handed subjects were 15.65 and 15.76, respectively, with *Z* value - 0.66. The left hand N20 onset values of right handed and left handed subjects were 15.72 and 15.90, respectively, with *Z* value - 1.24. The right hand N20 peak latencies of right handed and left handed subjects were 18.92 and 18.95, respectively, with *Z* being 0.069. The left hand N20 peak latencies of right handed and left handed subjects were 18.82 and 18.93, respectively, with $Z = 0.303$. Table 6 shows prediction equations for N20 onset and peak latencies with the variables.

DISCUSSION

Analysis of SSEP components must concern variables like limb length, height, age, handedness, sex etc.[8] The present study correlated SSEP's with certain variables. In this study it was found that there is no difference in the right hand and the left hand N20 latencies.

Table 1: Descriptive statistics of the sample considered

Parameter	Minimum	Maximum	Mean	Standard deviation
Age (years)	18	30	23.8	5.1
Limb length (cm)	72	87	80.6	3.06
Height (cm)	160	184	173.2	5.28
Weight (kg)	48	95	66.5	9.05

Table 2: Student *t*-test comparing the N20 latencies of right and left hand

Dependent variable	Mean (ms)	*t* Stat	*P* value (two tail)
N20 onset latency right hand	15.72	−26.89	0.0000*
N20 onset latency left hand	15.82		
N20 peak latency right hand	18.7	−6.516	0.0000*
N20 peak latency left hand	18.83		

ms:Milliseconds,*Highly significant

Table 3: Correlation coefficients depicting correlation between N20 onset and peak latencies and the physiological variables

Dependent variable	Age	Height	Weight	Limb length	Handedness
Average N20 onset latency	0.54	0.60	0.43	0.81	0.12
Average N20 peak latency	0.63	0.37	0.34	0.62	0.19

Table 4: The regression analysis and multiple regression analysis to show association between average N20 onset and peak latencies vs. limb length and age and with variables age, limb length, height, and weight

The regression analysis to show association between latencies vs. limb length and age				
Independent variable	**Dependent variable**	**R^2**	**Significance *F***	***P* value**
Limb length	N20 onset latency	0.65	0.00	0.00*
	N20 peak latency	0.663	0.00	0.00*
Age	N20 onset latency	0.29	0.00	0.00*
	N20 peak latency	0.31	0.00	0.00*
The multiple regression analysis to show association between latencies with variables				
Age	N20 onset latency	0.69	0.00	0.1795
Height				0.0478
Weight				0.0646
Limb length				0.0000*
Age	N20 peak latency	0.688	0.00	0.0827
Height				0.1351
Weight				0.5306
Limb length				0.0000*

*Highly significant. Note: Age, which showed significance to N20 onset and peak latencies on linear regression, does not show significance to N20 onset and peak latencies on multiple regressions when considered with other variables. Correlation of handedness with the N20 onset and N20 peak latency was very low (0.12 and 0.19, respectively) and hence handedness has been eliminated from the regression analysis. The equation for the multiple regression model is: Average N20 onset latency=5.73+0.09 (Limb length) + 0.01 (Height)

Table 5: *Z*-Test to determine significance of N20 onset and peak latencies with handedness

N20 onset latency	Right handed subjects	Left handed subjects	*Z* value
Right hand values	15.65	15.76	-0.66
Left hand values	15.72	15.90	-1.24
N20 peak latency			
Right hand values	18.92	18.95	0.069
Left hand values	18.82	18.93	0.303

Z value: -1.96 to+1.96

Table 2 indicates Student *t*-test, which was done to compare the means of N20 onset and peak latencies of right and left hand. The *P* value (0.0000) obtained for N20 onset and peak latencies shows high significance between the means implying that there is no difference in the right hand and the left hand N20 latencies and hence the average values of the recordings of N20 latencies from the left limb and right limb have been used for statistical evaluation. In a study similar findings has been quoted. Measures of responses to stimulation of right and left peripheral nerves should not be treated as independent observations; it should be lumped together, since a high positive correlation exists between such paired EP observations in normal subjects.[3]

In this study, it was found that limb length is the highest, which is 0.81 in N20 onset latency, and age is the highest, which is 0.62 in N20 peak latency [Table 3], while correlating all the physiological variables and this indicates the correlation between N20 onset and peak latency values with limb length and age. Correlation of handedness with latency values is very low (0.12).

In this study the significance of the variable, limb length on N20 onset latencies were tested by linear regression and it was found that limb length significantly affected N20 onset and peak latencies with a *P* value (0.00) [Table 4]. In a study by Huisman *et al.*, the impact of arm length on the peak latencies of the identified SEP components was investigated and observed that the arm length correlated with the N20, the primary cortical response.[9] Bercovici *et al.* in their study have stated that after 4 years of age, the N20 peak latency begins increasing until adulthood as the arm length dramatically increases with growth. Hence arm length should be taken into account while studying patients with neurological disorders.[8] While preparing normative data, the value obtained must be based on limb length or height. Failure to do so will result in taller individuals being labeled as having abnormal SSEPs.[10]

Age though showed significance with N20 onset and peak latencies ($P = 0.00$) in the linear regression output [Table 4] but age did not significantly affect the N20 onset ($P = 0.1795$) and peak values ($P = 0.0827$) in presence of other variables like height, limb length, handedness as shown in multiple regression output of N20 onset, and peak latencies [Table 4]. In a study conducted by Sonoo *et al.*, multiple regression analysis showed that the N20 latencies correlated with age.[11] The possible explanation for the discrepancy between the report by Sonoo *et al.* and the present results is that they studied rather smaller number (62 subjects) compared with the present study (100 subjects) in which there is lack of uniform distribution of subject ages. In study by Tanozaki *et al.*, the age group was between 20 and 78 years and in the present study the age group involved was between 18 and 30 years.[12] It has been well documented that age changes in

Table 6: Prediction equations for N20 onset and peak latencies with the variables

Dependent variables	R^2	Regression model	*P* value
Avg N20 onset latency			
Limb length	0.65	Avg N20 onset latency=6.32+(0.12×limb length)	0.0000*
Age	0.29	Avg N20 onset latency=14.67+(0.047×age)	0.0000*
Age	0.69	Avg N20 onset latency=5.73+(0.01×age)+(0.01×weight)+(0.01×height) +(0.09×limb length)	0.1795
Height			0.0478*
Weight			0.0646
Limb length			0.0000*
Avg N20 peak latency			
Limb length	0.66	Avg N20 peak latency=0.7434+(0.2237×limb length)	0.0000*
Age	0.31	Avg N20 peak latency=16.575+0.09 (age)	0.0000*
Age	0.68	Avg N20 peak latency=3.94+(0.03×age) +(0.003×weight)-(0.01×height) +0.21×(limb length)	0.087
Height			0.1351
Weight			0.5306
Limb length			0.0000*

Avg: Average, *Statistically significant

SSEP recordings appear after the age of 40 years. In a study on short latency SSEPs in children, it was established that the SSEP components decreased in latency until 4-5 years of age because of central nervous system maturation after which latencies increased until adulthood, on the basis of brain and body growth.[13]

To test whether any significant difference exists between right hand and left hand (N20 onset latencies) of left handed and right handed subjects, *Z* test was used [Table 5]. This test checks whether there is any significant difference between the means recorded for the corresponding latency values of right handed and left handed subjects. From Table 5, it can be seen that *Z* value computed for N20 onset and peak latencies fall within acceptable range of –1.96 to + 1.96 implying that there is no significant difference in the right hand values (N20 onset) in right handed and left handed people and left hand values (N20 onset) in right handed and left handed people. Brain asymmetry is a phenomenon well-known for handedness and language specialization and has also been studied in motor cortex. Less is known about hemispheric asymmetries in the somatosensory cortex. In a study by Jung *et al.*, found that across the subjects, there were no significant correlations between indices of N20 and handedness.[14]

Height shows some correlation (0.60) with N20 onset latency [Table 3] and on multiple regression [Table 4] showed a significance of 0.0478 ($P < 0.05$), which is secondary to highly significant correlation of N20 onset latency with limb length, since limb length and height are significantly correlated.[15]

Accurate interpretation of SSEP latencies require that normative standards must take into account the physiological variables.[16] SSEPs are different from Visual Evoked Potentials (VEPs) and Brainstem evoked response audiometry (BERA) in that peripheral conduction of somatosensory impulse constitutes a large portion of the total impulse propagation to the recording site. Hence in lower extremity SSEP recording height is an important determinant and in upper limb SSEP arm length becomes an important determinant for the SSEP components.[17]

Prediction equations for N20 onset and peak latencies with the variables [Table 6] were formatted by utilizing regression model and these will be of use for further research on SSEPs and clinical diagnosis of neurological disorders.

The data on SSEPs vary from laboratory to laboratory depending on the various technical factors as well as physiological factors of the subjects. Reliable identification of any abnormalities in the SSEPs, requires their statistical evaluation in neurologically normal subjects in relation to the physiological factors like age, limb length, height, sex, handedness, and so on. This normative data can then be used as a reference while making clinical assessment of the patients.

Limitations of study

- Components corresponding to the peripheral nerve action potentials, components generated in the brainstem-cervical component, and far field components – N5, N9, N13, P14, and N18 have not been considered in the study
- Only male subjects were considered because female subjects did not give consent.

Recommendations

- N5, N9, N13, P14, and N18 components should be considered and correlated.

CONCLUSIONS

- N20 onset and peak latency values are significantly affected by limb length at 95% confidence level.
- Even though height is showing as a significant factor affecting N20 onset and peak latencies, it is probably because of high correlation of height with limb length
- Age though on linear regression showed some significant correlation with N20 onset and peak latency, on multiple regression showed that it does not affect N20 onset and peak latencies in the presence of other variables
- Handedness does not affect N20 onset and peak latency values.

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