The Cortical and Sub-Cortical Network of Sensory Evoked Response in Healthy Subjects*

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Abstract— **The aim of this study was to find the cortical and sub-cortical network responsible for the sensory evoked coherence in healthy subjects during electrical stimulation of right median nerve at wrist. The multitaper method was used to estimate the power and coherence spectrum followed by the source analysis method dynamic imaging of coherent sources (DICS) to find the highest coherent source for the basic frequency 3Hz and the complete cortical and sub-cortical network responsible for the sensory evoked coherence in healthy subjects. The highest coherent source for the basic frequency was in the posterior parietal cortex for all the subjects. The cortical and sub-cortical network comprised of the primary sensory motor cortex (SI), secondary sensory motor cortex (SII), frontal cortex and medial pulvinar nucleus in the thalamus. The cortical and sub-cortical network responsible for the sensory evoked coherence was found successfully with a 64-channel EEG system. The sensory evoked coherence is involved with a thalamo-cortical network in healthy subjects.**

I. Introduction

In non-human primates there have been several studies on anatomical and microelectrode recordings stating that the somatosensory evoked inputs functions with a generalized network of cortical areas. These cortical areas are interconnected either through cortico-cortical connections or thalamo-cortical connections [1-3]. But in humans there have been limited number of studies were the complete network responsible for the sensory evoked potentials have been analyzed using dipole source analysis [4, 5]. The involvement of thalamus, brain stem and other cortical areas has been addressed in an MEG study using functional source separation [6]. The functional magnetic resonance imaging (FMRI) also revealed the same cortical areas in response to right median nerve stimulation [7, 8]. In certain studies the sensory evoked coherence were estimated for sensory stimulation and found coherence at the stimulated frequency and there harmonics [9, 10]. In this study, we used a 64-channel EEG system, coherence and a spatial filter technique [11, 12] in healthy subjects to find the complete network of sources responsible for the right median nerve stimulation, in particular, to determine whether the thalamus source could be identified as indicated from non-human primate studies and FMRI studies on humans.

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II. Methods

A. Data Acquisition

The median nerve of the right hand of 11 healthy subjects was stimulated, with pulses of a Gaussian distribution with the interpulse interval at a frequency range between [2-5 Hz]. Due to these pulses the abductor pollicis brevis muscle (APB) is activated in a frequency centered on 3Hz. Surface EMG was recorded from the APB muscle on the right hand with two silver-chloride electrodes positioned at the muscle and the proximal phalanx of the thumb. EEG was recorded in parallel with a standard 64 channel recording system (Neuroscan, Herndon, VA, USA) using a linked mastoid reference. A standard EEG cap was used with electrode positions according to the extended 10-20 system. EEG and EMG was band pass filtered (EMG 30-200 Hz; EEG 0.05-200 Hz) and digitized with a sampling rate of 1000 Hz. The digitized data were stored in a computer and analyzed off-line. EMG was full wave rectified, the combination of band pass filtering and rectification is the common demodulation procedure for oscillatory EMG [13]. The recording duration was 10 minutes. Each record was segmented into a number of 1s - long high quality epochs discarding all those data sections with visible artefacts. For each record, depending on the length of the recording and the quality of the data, between 400 and 540 segments of 1s were used for the analysis.

B. Coherence

The linear time-invariant relationship between two signals is estimated by coherence as follows:

$$\hat{C}(f) = \frac{\left|\hat{S}_{xy}(f)\right|^2}{\hat{S}_{xx}(f)\hat{S}_{yy}(f)} \qquad (1)$$

where S_{xy} is the cross spectrum and S_{xx}, S_{yy} are the individual power spectra; the overcap indicates the estimate

of that quantity [11]. The coherence is a linear measure between 0 and 1, where 0 indicates absolutely independent signals and 1 the opposite. The power spectrum and the coherence spectrum of a single healthy subject are shown in Fig.1. The statistical significance of the coherence is estimated by

$$1-(1-\chi)^{1/(M-1)} \tag{2}$$

where χ is set to 0.99, so that the confidence limit is given as

$$1-0.01^{1/(M-1)} \tag{3}$$

The coherence values above this confidence limit are considered to indicate correlation between the analyzed two time series; the values below this limit indicate there is no correlation.

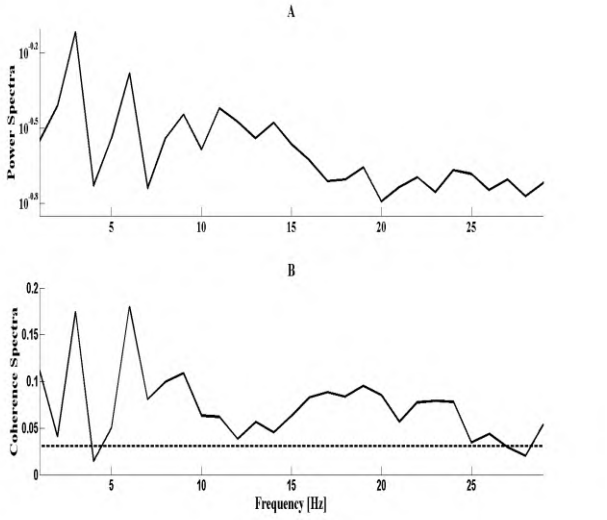

Figure 1. A. The power spectrum of the EMG (APB muscle) M1. B. The coherence spectrum between EEG channel C5 and muscle M1.

C. Source model and Spatial filter

In order to project the coherence calculated on the surface of the head to the cortex a volume conduction model was used with a boundary element method [14]. The well-known single sphere model was used. The head was modeled by giving in the radius and the position of the sphere with the electrode locations. The lead field matrix [15] was used for the mapping of electric sources within the cranium to the scalp recordings outside of the scalp.

The power and coherence at any given location in the brain can be computed using a linear transformation which in our case was the spatial filter. The spatial filter [12] relates the underlying neural activity to the electromagnetic field in the surface.

$$S(p_0) = (F^T(p_0) \cdot V^{-1}(x) \cdot F(p_0))^{-1} \cdot Y \tag{4}$$

$$Y = F^T(p_0) \cdot V^{-1}(x) \tag{5}$$

this is the LCMV spatial filter S as a function of the transfer function F and data covariance matrix V . The main aim of the LCMV method is to design a bank of spatial filters that attenuates signals from other locations and allows only signals generated from a particular location in the brain. The full description of the method is described elsewhere [16]. The brain source with strongest coherence to the EMG signal at the basic frequency 3Hz was identified. This source was defined as the reference region for further coherence analysis between brain areas. Since the coherence of a reference region with it is always 1, the reference region was projected out of the coherence matrix and further coherent areas were identified. As described previously [17], individual maps of strongest cerebro-muscular coherence were spatially normalized, averaged and displayed on a standard brain in SPM5.

D. New test for Statistical Significance of the sources

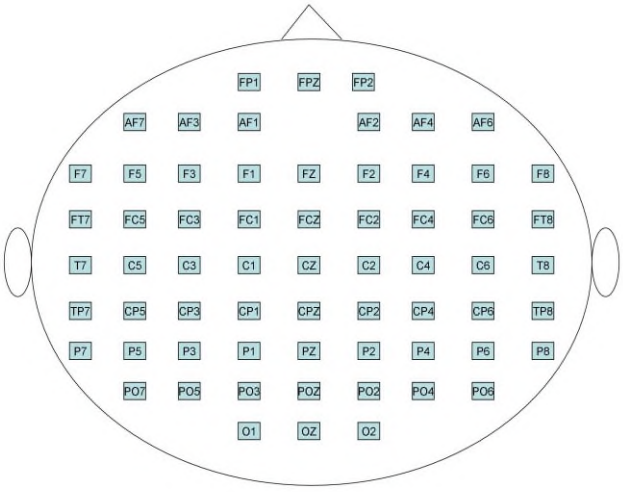

Figure 2. The actual configuration of the 64 channel layout of the EEG system.

The statisitcal significance of the sources were done by a surrogate analysis in this study. The electrodes in the scalp are randomly shuffled with the criteria that the distance between two neighbouring electrodes (For eg., C3 and C1) in the actual configuration as seen in Figure 2 after shuffling the C1 electrode should be in the place of C2 or C5 (column wise shuffling). In this way the spatial information is not any more valid which is essential for the source anaylsis. This is done 99 times and the source analysis is repeated to get the actual coherence values (For eg: the thalamus source). The highest surrogate value out of these 99 surrogates will be the significance threshold for the thalamus source in the real data. The real data coherene value is greater than the highest surrogate value then the identifed source is a significant source. In figure 3 all the surrogate values for the thlamus source signal with the EMG are shown. The significane

threshold value wase p=0.005 in this example subject. So, in this way for each subject the significance threshold is identified for each of the sources separately.

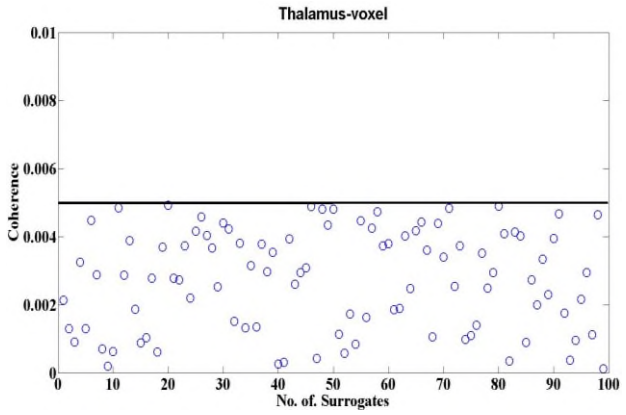

Figure 3. The source coherence values of the thalamus voxel witht the EMG signal for all the 99 surrogates. Define the threshold to be p=0.005.

III. RESULTS

A. Power and Coherence

The power spectrum of the EMG is shown in Figure 1.A. The power spectrum is from a single healthy subject where there was high power at the basic frequency 3Hz and followed by several harmonics. The coherence spectrum between the contralateral electrode C5 and the muscle M1 (APB muscle) are depicted in Figure 1.B which shows clear peaks at the basic and the several harmonics of the stimulation frequency from the same subject. The coherence was high at the basic frequency 3Hz and at its first harmonic 6Hz in all the subjects.

B. Source analysis

The DICS [18] was applied on this data, and sources for the basic frequency 3Hz were projected on a standard MRI. Indeed we saw the contralateral posterior parietal cortex as the first source for the basic frequency as shown in Figure 2 A. This result was reproducible in all 11 healthy subjects. The next step was to find the complete network which was coherent to the activation in the posterior parietal cortex for the basic frequency. Four additional sources were identified in all subjects. The sources located were the B. contralateral primary sensory cortex SI source, C. contralateral secondary sensory cortex SII source, D. frontal contralateral and the E. medial pulvinar nucleus in the thalamus as shown in Figure 2. The grand average of all the healthy subjects is shown in Figure 2 in single slice plots in all three directions of axial, coronal and sagittal.

The cortical sources were all contralateral to the right hand median nerve stimulation in all subjects. But the subcortical source in the thalamus was presented medial in 7 subjects and contralateral in 4 subjects. So, the grandaverage of all the subjects leads to a medial and contralateral thalamus as shown in Figure 2 E.

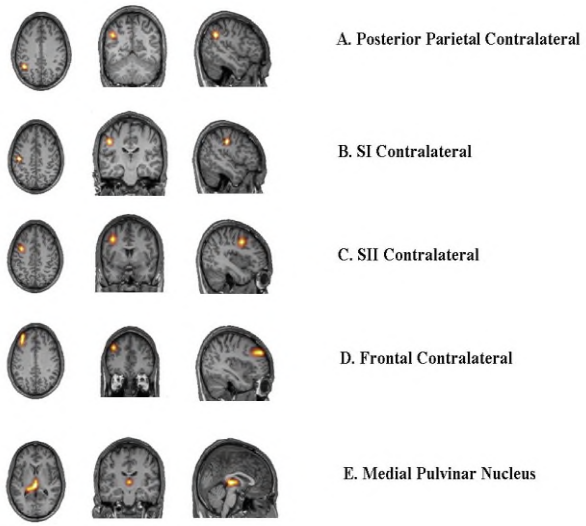

Figure 4. The grandaverage from all 11 healthy subjects. The first source is A. Posterior paretial contralateral source. The network comprises of B. Primary sensory cortex SI, C. Secondary sensory cortex SII, D. Frontal cortex, E. Medial pulvinar nucleus in the thalamus.

IV. DISCUSSION

In the present study, sensory evoked coherence due to right hand median nerve stimulation (MNS) on the wrist was analyzed in 11 healthy subjects. The main aim was to find the complete cortical and sub-cortical network which produced a thumb twitch in the right hand for the MNS stimulation. The earlier studies on anatomical and microelectrode recordings from monkeys have given us a good knowledge on the network involved in somatosensory inputs [1-3]. A part of the knowledge is from behavioral and electrophysiological studies in humans with lesions [19-21]. But, the lesions do not give information on the network involved in the somatosensory inputs. In the present study, this question is answered by providing information on the network involved for MNS in humans. The dipole source analysis [4, 5] and FMRI studies [7, 8] have concentrated on the sensory evoked potential of the median nerve stimulation. In our work, the sensory evoked coherence between the EEG and EMG is taken into account for the frequency domain source analysis (DICS). This method has the advantage of identifying the complete network responsible for a certain frequency in our case the stimulation frequency 3Hz.

V. NETWORK OF SENSORY EVOKED COHERENCE

The posterior parietal source contralateral to the stimulated hand is the first source found in this analysis this

could be due to the analysis of sensory evoked coherence and not the S1 which is usually found in most of the studies analyzing sensory evoked potentials [4, 22]. Both the SI and SII combined with the posterior parietal source have been previously reported to be the main contributors for the MNS in MEG [23, 24]. In some of the MEG studies of humans and monkeys [4, 25] the SII and frontal sources were located more parietal due to MEG which is insensitive to sources perpendicular to skull surface, but in our case of EEG these locations were identified correctly.

The unilateral median nerve stimulation have bilateral activation in the somatosensory areas around 100ms which is been reported in several studies on SEP [26, 27]. However, the bilateral activation is low as 3% in studies with larger population on SEP's [28] and 50% in smaller populations [8]. In our case there is no bilateral activation because the stimulation interval is 200ms to 450ms and this study is based on sensory evoked coherence and not on SEP components.

The pre-frontal and the thalamus have been discussed in studies on monkeys [1-3] and in humans [4, 5]. In an EEG study with functional source separation they were able to detect sub-cortical sources in the brain stem and thalamus [6]. In this study we were able to locate a contralateral pre-frontal source in 10 out of 11 subjects. The thalamus source was located in the medial pulvinar nucleus which is reported in monkeys [1]. We, suggest that the sensory evoked coherence with median nerve stimulation in healthy subjects is a thalamo-cortical phenomenon and not a cortical phenomenon.

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REFERENCES

[1] EG. Jones, TP. Powell., "An anatomical study of converging sensory pathways within the cerebral cortex of the monkey", Brain 93, pp. 793-820, 1970.

[2] MM. Mesulam, "A cortical network for directed attention and unilateral neglect" (review), Ann. Neurol. 10, pp. 309-325, 1981.

[3] C. Baleydier, F. Mauguiere, "Network organization of the connectivity between parietal area 7, posterior cingulated cortex and medial pulvinar nucleus: a double fluorescent study in monkey", Exp. Brain Res, 66, pp. 385-393, 1987.

[4] F. Mauguiere, et al., "Activation of a distributed somatosensory cortical network in the human brain. A dipole modelling study of magnetic fields evoked by median nerve stimulation. Part I: Location and activation and timing of SEF sources", Electroencephalogr. Clin. Neurophysiol 104, pp. 281-289, 1997.

[5] M. Scherg, P. Berg, "New concepts of brain source imaging and localization", Electroencephalogr. Clin. Neurophysiol. Suppl. 46, pp. 127-137, 1996.

[6] C. Porcaro, G. Barbati, F. Zappasodi, PM. Rossini, F. Tecchio, "Hand sensory-motor cortical network associated assessed by functional source separation", Hum Brain Mapp 29(1), pp.70-81, 2008.

[7] M. Boakye, SC. Huckins, NM. Szeverenyi, BJ. Taskey, CJ. Hodge, "Functional magnetic resonance imaging of somatosensory cortex activity produced by electrical stimulation of the median nerve or tactile stimulation of the index finger", J. Neurosurg 93, pp. 774-783, 2000.

[8] A. Korvenoja, et al., "Activation of ipsilateral primary sensorimotor cortex by median nerve stimulation", Neuro rep. 6, pp.2589-2593, 1995.

[9] AMFL. Miranda, LB. Felix, AFC. Infantosi, "A matrix-based algorithm for estimating multiple coherence of a periodical signal and ist application to the multi-channel EEG during sensory stimulation", IEEE T Bio.med 51, pp.1140-1146, 2004.

[10] AMFL. Miranda, AFC. Infantosi, DB. Melges, "A multiple coherence-based detector for evoked responses in the EEG during sensory stimulation", IEEE EMBS proceeding 1, pp. 3516:3519, 2008.

[11] DM. Halliday, JR. Rosenberg, AM. Amjad, P. Breeze, BA. Conway, SF. Farmer, "A frame work for the analysis of mixed time series /point process data-theory and application to study of physiological tremor, single motor unit discharges and electromyograms", Prog Biophys Mol Bio, 64, pp. 237-238, 1995.

[12] WV. Drongelen, M. Yuchtman , BD. Van Veen, AC. Van Huffelen, "A Spatial Filtering Technique to Detect and Localize Multiple Sources in the Brain", Brain Topography 9, pp. 39-49, 1996.

[13] HL. Journee, "Demodulation of amplitude modulated noise: a mathematical evaluation of a demodulator for pathological tremor EMG's", IEEE Trans Biomed Eng, 30(5), pp. 304-8, 1983.

[14] M. Fuchs, J. Kastner, M. Wagner, S. Hawes, JS. Ebersole, "A standardized boundary element method volume conductor model", Clin Neurophysiol 113, pp. 702-712, 2002.

[15] D. Weinstein, L. Zhukov, C. Johnson, "Lead-field Bases for Electroencephalography Source Imaging" , Annals of Biomedical Engineering 28, pp. 1059-1065, 2000.

[16] M. Muthuraman, J. Raethjen, H. Hellriegel, G. Deuschl, U. Heute, "Imaging coherent sources of tremor related EEG activity in patients with Parkinson's disease", IEEE EMBC (1), pp. 4716-4719, 2008.

[17] J. Gross, L. Timmermann, J. Kujala, M. Dirks, F. Schmitz, R. Salmelin, "The neural basis of intermittent motor control in humans", Proc Natl Acad Sci USA 99, pp. 2299-2302, 2002.

[18] Gross, J, Kujala, J, Hamalainen, M, Timmermann, L, Schnitzler A, Salmelin R, "Dynamic imaging of coherent sources: studying neural interactions in the human brain, Proc. Natl. Acad. Sci. USA, 98(2), pp. 694–699, 2001.

[19] S. Corkin, B. Milner, T. Rasmussen, "Somatosensory thresholds. Contrasting effects of postcentral gyrus and posterior parietal lobe excisions", Arch.Neurol. 23, pp. 41-58, 1970.

[20] RJ. Caselli, "Ventrolateral and dorsomedial somatosensory association cortex damage produces distinct somesthetic syndromes in humans", Neurology 43, pp. 762-771, 1993.

[21] F. Mauguiere, JE. Desmedt, J. Courjon, "Astereognosis and dissociated loss of frontal or parietal components of somatosensory evoked potentials in hemispheric lesions", Brain 106, pp. 271-311, 1983.

[22] N. Forss et al., "Activation of the human posterior parietal cortex by median nerve stimulation", Exp. Brain. Res 99, pp. 309-315, 1994.

[23] R. Hari et al., "Somatosensory evoked cereberal magnetic fields from SI and SII in man", Electroenceph. Clin. Neurophysiol 57, pp. 254-263, 1984.

[24] R. Hari et al., "Functional organization of the human first and second somatosensory cortices: a neuromagnetic study", Eur. J. Neurosci 5, pp. 724-734, 1993.

[25] L. Krubitzer, J. Clarey, R. Tweedale, G. Elston, M. Calford, "A redefinition of somatosensory areas in the lateral sulcus of macaque monkeys", J. Neurosci. 15, pp. 3821-3839, 1995.

[26] MT. Sutherland, AC. Tang, "Reliable detection of bilateral activation in human primary somatosensory cortex by unilateral median nerve stimulation", Neuroimage 33, pp. 1042-1054, 2006.

[27] K. Hoechstetter, HM. Meinck, P. Henningsen, M. Scherg, A. Rupp, "Psychogenic sensory loss: magnetic source imaging reveals normal tactile evoked activity of the human primary and secondary somatosensory cortex", Neurosci. Letters 323, pp. 137-140, 2002.

[28] A. Kanno, N. Nakasato, K. Hatanaka, T. Yoshimoto, "Ipsilateral area 3b responses to median nerve somatosensory stimulation", Neuro Image 18, pp. 169-177, 2002.