Neuroscience Letters 485 (2010) 157–161

Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

Study of the origin of short- and long-latency SSEP during recovery from brain ischemia in a rat model

Dan Wu[a], Bezerianos Anastassios[a,c], Wei Xiong[b], Jai Madhok[a], Xiaofeng Jia[a,d], Nitish V. Thakor[a,*]

[a] Department of Biomedical Engineering, Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA
[b] Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD 21287, USA
[c] Department of Medical Physics, School of Medicine, University of Patras, 26500 Patras, Greece
[d] Department of Physical Medicine and Rehabilitation, Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA

ARTICLE INFO

Article history:
Received 8 May 2010
Received in revised form 12 August 2010
Accepted 28 August 2010

Keywords:
Somatosensory evoked potential
Short/long-latency
Brain ischemia
Independent component analysis
Thalamocortical

ABSTRACT

Somatosensory evoked potentials (SSEPs) have been established as an electrophysiological tool for the prognostication of neurological outcome in patients with hypoxic–ischemic brain injury. The early and late responses in SSEPs reflect the sequential activation of neural structures along the somatosensory pathway. This study reports that the SSEP can be separated into early (short-latency, SL) and late (long-latency, LL) responses using independent component analysis (ICA), based on the assumption that these components are generated from different neural sources. Moreover, this source separation into the SL and LL components allows analysis of electrophysiological response to brain injury, even when the SSEPs are severely distorted and SL and LL components get mixed. With the help of ICA decomposition and corrected peak estimation, the latency of LL-SSEP is shown to be predictive of long-term neurological outcome. Further, it is shown that the recovery processes of SL- and LL-SSEPs follow different dynamics, with the SL-SSEP restored earlier than LL-SSEP. We predict that the SL- and LL-SSEPs reflect the timing of the progression of evoked response through the thalamocortical pathway and as such respond differently depending upon injury and recovery of the thalamic and cortical regions, respectively.

Somatosensory evoked potentials (SSEPs) consist of a series of waves generated from the sequential activation of neural structures along the somatosensory pathway. Yet there is no clear view about the mapping of SSEP peaks with their origins. The SSEP waveform is conventionally viewed as comprised of two components—the short-latency (SL) and the long-latency (LL) complexes. Researchers have looked into SL and LL complex in humans, and established the SL-peak N20 as an indicator of thalamocortical integrity and the LL-peak N70 as an indicator of cortical function [23], with a general understanding of SL-SSEP to be a thalamocortical response and LL-SSEP to be a corticocortical response [7]. There have been subjective definitions of short/middle/long-latencies [8,10,23], but the justifications for such definitions are unclear. Simple time-domain segmentation may lose its power when the signals are not standard and highly variable which is often the case when SSEPs are recorded from injured brain. Therefore, a more universal and justified segmentation approach is needed to assist the analysis of SSEPs.

In this paper we study the SL- and LL-SSEPs during recovery from brain ischemia in a rat model of asphyxial cardiac arrest (CA) [12]. In view of the association of SL and LL responses in SSEP with their thalamocortical origins, it is expected that the separation of SL- and LL-SSEP would shed insights into diagnosis and prognosis of different levels of brain injury. Here, we present an innovative way of separating SL- and LL-SSEPs using independent component analysis (ICA), based on the assumption that they are generated from different sources and can thus be considered statistically independent.

ICA has been a well-established method for blind source separation in various neural signals [24–26], for example, ICA components have been used in dipole source modeling to find the source underlying surface EEG recordings [21]. Therefore, we expect ICA to decompose the inputs of multichannel SSEP recordings into the SL and LL components of different sources. The remainder of this paper discusses the effectiveness of using ICA for SSEP segmentation, along with the advantages and limitations of this method.

Our experimental studies are motivated by the problem of assessing the neural electrophysiological changes as a result of global ischemia following cardiac arrest (CA). The experiment protocol was approved by the Johns Hopkins Animal Care and Use Committee. Sixteen male Wistar rats (350 ± 25 g) were subjected to either a 7 min ($n = 8$) or 9 min ($n = 8$) of asphyxia. Rats were mechanically ventilated with 1.5% isoflurane in a 50:50% N_2/O_2 gas mixture. The femoral artery and vein distal to the inguinal liga-

* Corresponding author. Tel.: +1 410 955 7093; fax: +1 410 502 9814.
E-mail address: nitish@jhu.edu (N.V. Thakor).

0304-3940/$ – see front matter © 2010 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.neulet.2010.08.086

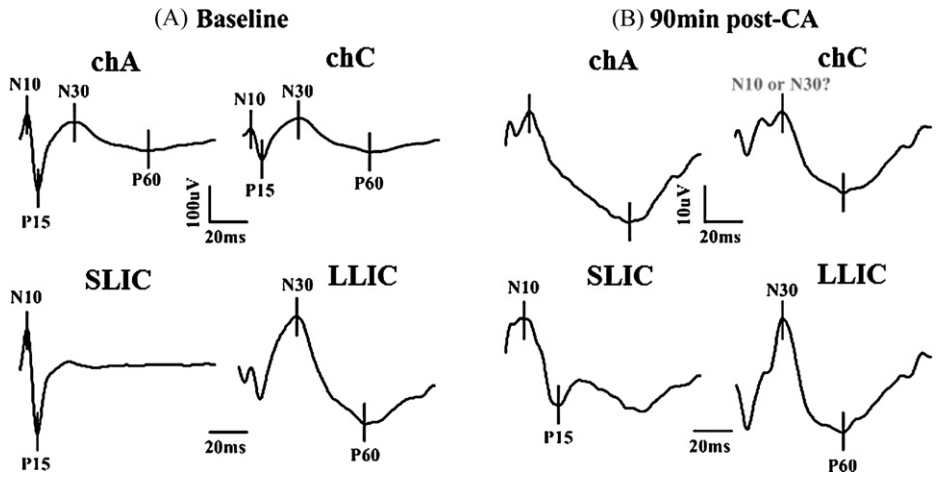

Fig. 1. ICA decomposition of SSEPs into short- and long-latency components at baseline (A) and after cardiac arrest (B) in a typical CA experiment. The upper two panels in (A) and (B) are two channels of SSEPs recordings, and the lower two panels are the ICA-decomposed independent components (ICs), corresponding to SL- and LL-SSEPs. The SSEPs are averaged over 20 sweeps to improve SNR. The ICA transformed signals are in arbitrary units. Notice that (1) the slow and flat LL complex N30/P60 is magnified in LLIC; (2) in (B), the injured SSEP, the P15 peak is missing from the raw data but shows up in SLIC; (3) the N10 and N30 peaks are ambiguous in the raw data, whereas after decomposition, the SL and LL components are distinct and peaks are easier to identify.

ment were cannulated in order to monitor mean arterial pressure (MAP), sample arterial blood gas (ABG) and administer drugs. Body temperature was maintained within normal values 36.5–37.5 °C throughout the experiment. After a 15 min baseline recording, the isoflurane was washed out for 5 min to eliminate the residual effect of anesthesia. 2 mg/kg of vecuronium was infused 2 min after washout and the gas mixture was switched to room air. CA was initiated with cessation of mechanical ventilation and lasted for 7 or 9 min, as predetermined. Cardiopulmonary resuscitation (CPR) was performed with external chest compressions, mechanical ventilation, and infusion of epinephrine and $NaHCO_3$ until return of spontaneous circulation (ROSC). Isoflurane was restarted at 0.5% after 45 min to maintain animal comfort during SSEP recording.

One week prior to CA, rats were implanted with 4 epidural screw electrodes (plastics one, roanoke, VA) on the left (chA, chC) and right (chB, chD) somatosensory cortex, along with a ground in the parasagittal right frontal lobe. Median nerve stimulation was given alternatively through needle electrodes in the right and left distal forelimbs with 200-μs long 0.6 mA pulses delivered at 0.5 Hz. The SSEPs were recorded using the TDT data acquisition system (Tucker Davis Technologies, Alachua, FL) at 6.1 kHz, and the first 150 ms signals post-stimulus were recorded and analyzed. Signals were recorded continuously for 1 h after onset of CA, intermittently for the next 3 h with 15 min rest periods, and for 15 min at 24 h, 48 h and 72 h after ROSC.

The neurological outcome after CA is determined by an extensive neurological examination using the neurological deficit score (NDS). The NDS, ranging from 80 (best) to 0 (worst) was previously developed and validated by us [11,12,15,16].

ICA is implemented to separate the SL and LL complexes of the SSEP. The ICA is a method for solving the blind source separation problem, which aims to find a linear coordinate system such that the constituent signals derived from a mixture are as statistically independent from each other as possible [20]. Assume that there are m independent source signals $\mathbf{s} = (s_1,\ldots,s_m)$, being observed in n channels $\mathbf{x} = (x_1,\ldots,x_n)$, then the ICA model is defined as [5] $\mathbf{x} = \mathbf{As}$ with a mixing matrix $\mathbf{A}$, and a demixing matrix $\mathbf{W}$ to estimate the underlying sources $\mathbf{u} = \mathbf{Wx}$. The adaptive algorithms for $\mathbf{W}$ have been derived from many criteria [14]. The particular model used in this study was proposed by Bell and Sejnowski [3] using information maximization (Infomax). We choose Infomax ICA because it is more robust to sources that are not strictly independent and also more tolerant to noise, than other ICA methods such as fastICA [13]. The Infomax ICA algorithm is essentially a feed-forward neural network designed with a non-linear transformation $y_i = g_i(u_i)$ after the linear transformation from $\mathbf{x}$ to $\mathbf{u}$. The goal of Infomax is to maximize the joint entropy $H(y_1,\ldots,y_n)$, and $\mathbf{W}$ is recursively adjusted [2] towards the maximization of $H(y)$.

Here, Infomax ICA is implemented by taking two channels of SSEPs on the same hemisphere (chA/C or chB/D) from the somatosensory cortex as input vector and giving outputs of two independent components (ICs)—the short-latency IC (SLIC) and long-latency IC (LLIC) component. The Infomax procedure is executed using EEGLAB Matlab toolbox [6].

For preprocessing, SSEP signals are low-pass filtered with a cutoff frequency of 150 Hz and then averaged over 20 sweeps to improve the signal-to-noise ratio (SNR). The use of epidural electrodes bypasses the cranial filtering, thereby records a less damped signal than clinically used scalp recordings. We consider an average over 20 sweeps to be sufficient to obtain a stable signal with a high SNR for analysis. After filtering and averaging, a typical SSEP waveform consists of N10/P15 and N30/P60 complexes in the SL and LL ranges, respectively

An illustration of ICA decomposition of baseline SSEP signals is shown in Fig. 1(A). It is self-explanatory that the ICs, transformed from chA and chC recordings, correspond to SL and LL components, respectively. In SLIC, the N10/P15 complex is emphasized with flattened late responses, whereas in LLIC, the N30/P60 complex became prominent with blurred early responses. This pattern of separation and grouping is consistently observed across subjects in the cohort of animals.

The separation of short and long latencies shows its importance during early recovery from brain ischemia induced by CA. The SSEP waveforms can be severely distorted due to the injury with some typical peaks missing and some unexpected peaks emerging. Some SSEP peaks are so small that they are over-ridden by the preceding or following peaks. The observed delay of these peaks makes the situation even worse—delayed SL-peaks can be mixed or overlapped with LL-peaks. Therefore, early peak detection is technically difficult with a high probability of false detection. ICA improves peak detection in three ways: (1) it highlights LL-SSEP which is subtle compared to SL-SSEP in raw recordings (Fig. 1(A)), (2) it retrieves small peaks which are missing from the raw observations, and (3) it minimizes the mutual interference between the SL and LL complex to obtain the true waveforms for SL and LL alone, as evidenced in Fig. 1(B). These improvements are not trivial but significant when