

A time-varying source connectivity approach to reveal human somatosensory information processing

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ABSTRACT

Exploration of neural sources and their effective connectivity based on transient changes in electrophysiological activities to external stimuli is important for understanding brain mechanisms of sensory information processing. However, such cortical mechanisms have not yet been well characterized in electrophysiological studies since (1) it is difficult to estimate the stimulus-activated neural sources and their activities and (2) it is difficult to identify transient effective connectivity between neural sources in the order of milliseconds. To address these issues, we developed a time-varying source connectivity approach to effectively capture fast-changing information flows between neural sources from high-density Electroencephalography (EEG) recordings. This time-varying source connectivity approach was applied to somatosensory evoked potentials (SEPs), which were elicited by electrical stimulation of right hand and recorded using 64 channels from 16 subjects, to reveal human somatosensory information processing. First, SEP sources and their activities were estimated, both at single-subject and group level, using equivalent current dipolar source modeling. Then, the functional integration among SEP sources was explored using a Kalman smoother based time-varying effective connectivity inference method. The results showed that SEPs were mainly generated from the contralateral primary somatosensory cortex (SI), bilateral secondary somatosensory cortex (SII), and cingulate cortex (CC). Importantly, we observed a serial processing of somatosensory information in human somatosensory cortices (from SI to SII) at earlier latencies (<150 ms) and a reciprocal processing between SII and CC at later latencies (>200 ms).

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Introduction

An external stimulus activates a complex brain network to draw attention, and to process subsequent cognitive and affective information (Downar et al., 2000, 2002; Mouraux and Iannetti, 2009; Mouraux et al., 2011), thus instructing to the execution of appropriate behaviors (e.g. coping with physical threat) (Yamashiro et al., 2008). The exploration of stimulus-activated neural sources and their effective connectivity provides an effective way for us to understand the basic mechanisms of sensory information processing within the complex brain network (Schoffelen and Gross, 2009).

In the somatosensory system, tactile sensation is transmitted by large myelinated fibers (A β) (Crucchi et al., 2008) in the peripheral nerve (Devlin et al., 2006) to the dorsal horn of the spinal cord, and then to the brain stem and thalamus through the dorsal column-

medial lemniscal system (Crucchi et al., 2008; Kandel et al., 2000; Treede, 2007). The first cortical regions elicited by tactile stimulation are the primary and secondary somatosensory cortices (SI and SII) (Blatow et al., 2007; Garcia-Larrea et al., 1995; Kakigi et al., 2000; Nguyen et al., 2005; Ruben et al., 2001). In addition, insula and cingulate cortex (CC) are frequently reported to be activated by tactile stimulation in both electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) studies (Downar et al., 2000, 2002; Mouraux and Iannetti, 2009).

Anatomical and electrophysiological evidences supported a hierarchical structure in the primary somatosensory cortex (Iwamura, 1998; Zhang et al., 2001b). However, the information flow among cortices involved in the somatosensory information processing is not well understood. While anatomical cortico-cortical connections between SI and SII suggested that the serial processing existed between SI and SII (Inui et al., 2004; Pons et al., 1992), the presence of direct thalamo-cortical projections from the thalamus to SII may imply a parallel processing between SI and SII (Blatow et al., 2007; Chakrabarti and Alloway, 2006; Zhang et al., 2001a). In addition, the relationship between the contralateral somatosensory cortices (both SI and SII) and ipsilateral SII is not clearly understood (Iwamura, 1998), even cortico-callosal connections

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were observed between contralateral SI/SII and ipsilateral SII (Blatow et al., 2007). When considering the process of higher-order affective and/or cognitive information, which highly involves the activation of CC (Allman et al., 2001; Bush et al., 2000), few studies have so far investigated the causal relationship between CC and the somatosensory cortices (SI and SII), even the cortical activation in CC was likely to be slower than those in SI and SII (Frot et al., 2008; Mouraux and Iannetti, 2009).

Among various non-invasive neuroimaging techniques, e.g. fMRI and EEG, EEG has extremely high time resolution in the order of milliseconds, which makes it a suitable technique for investigating the fast-changing brain activities elicited by external stimuli. Adopting the EEG technique, numerous scientific findings and clinical applications concerning the brain regions activated by external stimuli (e.g., visual, auditory, somatosensory, laser, etc.) have been achieved (Garcia-Larrea et al., 2003; Michel et al., 2004; Pascual-Marqui et al., 1994), but most of these studies do not directly deliver any information on how these activated brain regions communicate with each other. The absence of such information in previous studies is mainly caused by two difficulties in the analysis of EEG signals: (1) it is difficult to estimate the stimulus-activated neural sources and the source activities; and (2) it is difficult to identify transient effective connectivity between neural sources in the order of milliseconds. In several electrophysiological studies, information flow between cortices was inferred based on the temporal order of activations (Frot et al., 2008; Inui et al., 2004; Ploner et al., 2009). However, this temporal order cannot directly determine causal relationships between neural activations (Ploner et al., 2009). Indeed, during the last decade, a number of advanced methods to identify the connectivity on the source level were proposed, such as the structural equation modeling (SEM) (McIntosh and Gonzalez-Lima, 1994) and the dynamical causal modeling (DCM) (Friston et al., 2003). However, their dependence on prior knowledge about structural model impedes their broad applications in various electrophysiological studies. Effective connectivity analysis based on the concept of Granger causality (Granger, 1969) have demonstrated a powerful capacity of evaluating the direction and strength of causality between neuronal activations (Astolfi et al., 2007a; Ploner et al., 2009; Sato et al., 2009; Schoffelen and Gross, 2009). Granger causality is generally tested by multivariate autoregressive (MVAR) modeling of time series data, and is often represented as frequency domain measures like partial directed coherence (PDC) (Baccala and Sameshima, 2001) and directed transfer function (DTF) (Kaminski and Blinowska, 1991). Nevertheless, the MVAR model assumes that the underlying cortical processing is stationary, so it cannot be used to reveal the temporally dynamic effective connectivity conveyed through transient and markedly non-stationary neurophysiologic signals (Pereda et al., 2005).

In this paper, we proposed a time-varying source connectivity approach to reveal the information processing within the human somatosensory system in response to tactile stimulation by identifying dynamic effective connectivity among SEP sources from high-density EEG recordings. This approach is comprised of two consecutive steps: source estimation and causality inference, described as follows.

- 1) Source estimation: the locations of SEP sources and their single-trial waveforms were estimated by modeling equivalent current dipoles from a spatiotemporal source model (Huizenga et al., 2002). This step is important to mitigate the intrinsic volume conduction (field spread) effect in EEG scalp recordings (Schoffelen and Gross, 2009), which will contribute to a high value of causality between scalp electrodes even if the underlying source activities are temporally uncorrelated (Ploner et al., 2009; Schoffelen and Gross, 2009).
- 2) Causality inference: the time-varying effective connectivity among SEP sources was explored using a Kalman smoother based method. To assess the time-varying effective connectivity,

a time-varying MVAR (tvMVAR) model is used to describe the evolution of single-trial response variations of the estimated dipoles, where the averaged time courses were removed from all single-trial SEPs (Ding et al., 2000), and a Kalman smoother is used to identify the tvMVAR model. The advantage of Kalman smoother over Kalman filter (Milde et al., 2010) to estimate the tvMVAR model was proved using a simulation study. The effective connectivity patterns among SEP sources were calculated from the Kalman smoother-based tvMVAR coefficient estimates and presented as time-varying PDC in the time-frequency domain. The significance of effective connectivity patterns were finally assessed by a bootstrapping technique.

Materials and methods

Somatosensory evoked potentials

Subjects

EEG data were collected from 16 right-handed healthy volunteers (eight females and eight males) aged from 22 to 28 years (24.4 ± 1.8 , mean $\pm$ SD). None of the subjects had a history of neurological or psychiatric disease. All participants gave written informed consent, and the local ethics committee approved the procedures.

Stimulation and experimental paradigm

Bipolar transcutaneous electrical stimuli, consisting of monophasic square-wave electrical pulse of 0.1 ms duration, were applied to the median nerve of the right hand (Cruccu et al., 2008). To attenuate stimulus artifacts, a ground electrode was placed on the right arm, midway between the wrist and the elbow. The intensity of the electrical stimulus was adjusted at 2 times the subject's sensory threshold and was never reported as painful. The scalp electrode/skin impedances were kept below 5 k Ω . For each subject, an auditory warning signal was given 2–5 s before the onset of each electrical stimulus. Sixty electrical stimuli were delivered with an inter-stimulus interval ranging between 10 and 15 s (rectangular distribution). Participants were seated in a comfortable chair. They were asked to focus their attention on the stimuli, relax their muscles, and to keep their eyes open and their gaze slightly downward.

EEG recording

The EEG data were recorded using a 64-channel NeuroScan system (pass band: 0.05–100 Hz, sampling rate: 1000 Hz) with scalp electrodes placed according to the international 10–20 system. The nose was used as a reference channel. To monitor ocular movements and eye blinks, electro-oculographic (EOG) signals were simultaneously recorded from four surface electrodes, one pair placed over the higher and lower eyelid, the other pair placed 1 cm lateral to the outer corner of the left and right orbit.

EEG data preprocessing

EEG data were imported and processed using EEGLAB (Delorme and Makeig, 2004), an open source toolbox running in the MATLAB environment. Continuous EEG data were band-pass filtered between 1 and 30 Hz. EEG epochs were extracted using a window analysis time of 1500 ms (500 ms pre-stimulus and 1000 ms post-stimulus) and baseline corrected using the pre-stimulus time interval. Trials contaminated by eye-blinks and movements were corrected using an independent component analysis (ICA) algorithm (Delorme and Makeig, 2004; Jung et al., 2001; Makeig et al., 1997). In all datasets, individual eye movements, showing a large EOG channel contribution and a frontal scalp distribution, were clearly observed in the removed independent components. After artifact rejection and baseline correction, SEP trials were re-referenced to a common average reference. For each subject, average waveforms were computed, and time-locked to the onset of the stimulus. Single-subject average waveforms

were then averaged to obtain group-level average waveforms. For each waveform, the latency and baseline-to-peak amplitude of N60 were measured at C3, and the successive peaks (N120 and P240) were measured at Cz. Group-level scalp topographies at the latencies of the N60, N120, and P240 were computed by spline interpolation (Delorme and Makeig, 2004).

Source analysis

Sources of SEP waveforms were modeled as equivalent current dipoles from a spatiotemporal source model (Huizenga et al., 2002), where each dipole is specified by its location, orientation, and strength. Single-trial SEP source waveforms were then calculated within the estimated equivalent current dipolar model (Stenbacka et al., 2002).

Dipolar source estimation

Averaged SEP data were imported into Brain Electrical Source Analysis software (BESA 5.3, Scherg, 1992; Scherg and Berg, 1996), and the dipolar configuration was calculated within a realistic head model (provided by BESA 5.3) and estimated according to the best correspondence between the recorded and estimated scalp distribution. Once the estimated dipoles are obtained, the corresponding model undergoes empirical evaluation of its ability to explain satisfactorily the recorded scalp topography. Such an evaluation is carried out by calculating the residual variance (RV) of the signal, i.e., the percentage of data that cannot be explained by the fitted dipoles.

For average SEP responses both at group level and at single-subject level, the locations of the N60, N120, and P240 sources were obtained by fitting one free dipole, two symmetrical dipoles, and one free dipole in their 20 ms peak intervals (peak latency ± 10 ms) respectively. The choice of this four-dipole model was based on previous reports of dipole source analysis of ERP waveforms elicited by somatosensory stimuli (Schlereth et al., 2003; Shimojo et al., 2000; Tarkka and Treede, 1993; Tsuji et al., 2006). If the four dipole model resulted to less than 20% of RV (for the time interval from 0 ms to 400 ms), the obtained dipole configurations were accepted for the following analysis. For each dipole, its location, orientation, and time course (i.e., its strength at every time point) were extracted. Finally, the source locations were transformed to normalized Talairach space.

Single-trial source waveform extraction

Single-trial SEP data were also imported into BESA software (Scherg, 1992; Scherg and Berg, 1996). Using the dipolar configuration (the location and orientation of each dipole) calculated in the above step (Dipolar source estimation), the single-trial waveforms of each dipolar source were calculated within a realistic head model (provided by BESA 5.3) by minimizing the sum of squared errors between measured and calculated spatiotemporal signals for each subject.

Effective connectivity analysis

Time-varying multivariate autoregressive model

Denote the single-trial SEP time courses, which were obtained through the source analysis and the subtraction of the averaged SEP waveforms, of M sources and with N time points as $y(n) = [y_1(n), y_2(n), \dots, y_M(n)]^T \in R^{M \times 1}$ ($n = 1, 2, \dots, N$). The variations of these single-trial source waveforms can be described by a P -order tvMVAR model (Milde et al., 2010; Moller et al., 2001; Weiss et al., 2008) as:

$$y(n) = \sum_{p=1}^P A_p(n)y(n-p) + e(n) = X(n)a(n) + e(n) \quad (1)$$

where $A_p(n) \in R^{M \times M}$ ($p = 1, 2, \dots, P$) is the tvMVAR coefficient matrix, $a(n) = \{\text{vec}[A_1^T(n)], \dots, \text{vec}[A_P^T(n)]\}^T \in R^{MMP \times 1}$ is the concatenation of vectorized $A_p(n)$, $X(n) = [I_M \otimes y^T(n-1), \dots, I_M \otimes y^T(n-P)] \in R^{M \times MMP}$ ($\otimes$ denotes the Kronecker product, and I_M is an $M \times M$ identity matrix) is the concatenated matrix of past measurements $y(n-p)$, and $e(n) \in R^{M \times 1}$ is a residual vector, which is assumed to constitute a zero-mean multivariate Gaussian process with a covariance matrix $\Sigma(n)$. From Eq. (1), the tvMVAR model is actually a multiple linear regression accounting for a time-varying linear relationship between current measurements and past measurements. The tvMVAR model order P can be selected by minimizing the Akaike information criterion (AIC) value (Lütkepohl, 2005; Wei, 2006):

$$AIC(P) = \ln[\det(\Sigma)] + 2M^2P/N. \quad (2)$$

When considering multiple trials of source waveforms belonging to the same experimental condition, the tvMVAR coefficients can be obtained by two different ways: (1) calculating the mean coefficients of all single-trial tvMVAR coefficients, and (2) calculating the tvMVAR coefficients of the data concatenated from all single-trial source waveforms. The second way is often considered to be more effective and accurate (Arnold et al., 1998; Milde et al., 2010; Moller et al., 2001), which is also validated in our simulation model.

The tvMVAR model describing K trials of M source waveforms $y(n; k) \in R^{M \times 1}$, $k = 1, \dots, K$, can be rephrased as a standard multiple linear regression form:

$$\bar{y}(n) = \bar{X}(n)a(n) + \bar{e}(n) \quad (3)$$

where $\bar{y}(n) = [y^T(n; 1), \dots, y^T(n; K)]^T \in R^{KM \times 1}$, $\bar{X}(n) = [X^T(n; 1), \dots, X^T(n; K)]^T \in R^{KM \times MMP}$, $a(n) = \{\text{vec}[A_1^T(n)], \dots, \text{vec}[A_P^T(n)]\}^T \in R^{MMP \times 1}$, and $\bar{e}(n) = [e^T(n; 1), \dots, e^T(n; K)]^T \in R^{KM \times 1}$.

Identification of tvMVAR model by Kalman smoother

Previously, the identification of the tvMVAR model (i.e., the estimation of tvMVAR coefficients $a(n)$) from multiple trials of source waveforms was achieved by the recursive least-squares (Arnold et al., 1998; Ding et al., 2000; Milde et al., 2010; Moller et al., 2001) or Kalman filtering (Kaminski et al., 2001; Milde et al., 2010; Weiss et al., 2008). In the present study, we employed a Kalman smoother method to obtain a more accurate tvMVAR model estimation for estimating the tvMVAR coefficients from Eq. (3).

In the framework of the Kalman filter/smoothing, the tvMVAR coefficient vector $a(n)$ is the system state, and its variation is described by a stochastic model as:

$$a(n) = F(n)a(n-1) + \delta(n) \quad (4)$$

where $F(n) \in R^{MMP \times MMP}$ is the state transition matrix and $\delta(n)$ is the state noise vector, which is generally assumed to be a zero mean multivariate Gaussian process with a covariance matrix $\Delta(n)$. In practice, the state transition matrix $F(n)$ is usually chosen as an identity matrix, resulting in a random-walk model to describe the dynamics of $a(n)$. The random-walk model is the most popular model to describe the state variations when such prior information is unavailable (Arnold et al., 1998; Milde et al., 2010; Tarvainen et al., 2004; Zhang et al., 2010). The random-walk model of Eq. (4) and the multiple regression model of Eq. (3) constitute a linear state-space model as follows:

$$\begin{cases} a(n) = a(n-1) + \delta(n) \\ \bar{y}(n) = \bar{X}(n)a(n) + \bar{e}(n) \end{cases} \quad (5)$$

The optimal state estimator in the minimum mean square error criterion for the state-space model can be computed by the following

standard Kalman filter recursions:

$$\hat{a}(n|n-1) = \hat{a}(n-1|n-1) \quad (6-a)$$

$$P(n|n-1) = P(n-1|n-1) + \Delta(n) \quad (6-b)$$

$$\varepsilon(n) = \bar{y}(n) - \bar{X}(n)\hat{a}(n|n-1) \quad (6-c)$$

$$K(n) = P(n|n-1)\bar{y}^T(n) \cdot \left[\bar{y}(n)P(n|n-1)\bar{y}^T(n) + \Sigma(n) \right]^{-1} \quad (6-d)$$

$$\hat{a}(n|n) = \hat{a}(n|n-1) + K(n)\varepsilon(n) \quad (6-e)$$

$$P(n|n) = [I - K(n)\bar{y}^T(n)] \cdot P(n|n-1) \quad (6-f)$$

where $\hat{a}(n|\tau)$ ($\tau = n-1$ or n) represents the estimator of $a(n)$ given the measurements up to time τ , $P(n|\tau)$ is the auto-covariance matrix of $\hat{a}(n|\tau)$, the state estimate at time n is $\hat{a}(n) = \hat{a}(n|n)$, and $K(n)$ is the Kalman gain. Although the covariance matrices $\Delta(n)$ and $\Sigma(n)$ have a substantial and direct influence on the estimated results, they are usually unknown in real-world applications. In this study, the covariance matrices $\Delta(n)$ and $\Sigma(n)$ are recursively estimated as a weighted sum of the previous covariance estimate and the outer product of the current residual vector (Arnold et al., 1998; Ding et al., 2000; Milde et al., 2010; Moller et al., 2001):

$$\Delta(n) = \lambda\Delta(n-1) + (1-\lambda)K(n)\varepsilon(n)\varepsilon^T(n)K^T(n) \quad (7)$$

$$\Sigma(n) = \lambda\Sigma(n-1) + (1-\lambda)\varepsilon(n)\varepsilon^T(n) \quad (8)$$

where $0 < \lambda < 1$ is a forgetting factor to control the adaptation speed, and it is generally set to be close to and smaller than 1, say 0.99. This type of random-walk Kalman filter coupled with an adaptive covariance estimation is a commonly-used simplification of the standard Kalman filter for practical implementations, where the true parameters of the state-space model are unknown (Arnold et al., 1998; Tarvainen et al., 2004; Zhang et al., 2010). For a Bayesian inference point of view, such a covariance estimation actually uses the posterior probability at a previous time-point as the prior for current time-point.

As the Kalman filter finds the optimal estimator for the tvMVAR coefficients only based on past measurements, it would result in an undesired tracking lag, which would bias the estimation of the precise temporal order of cortical connectivity (Tarvainen et al., 2004). In addition, because the covariance matrices $\Delta(n)$ and $\Sigma(n)$, which strongly and directly influence the estimation results, may not be accurately estimated from single-trial source waveforms, the Kalman filter may exhibit large estimation variance and result in artificial connectivity patterns. Fortunately, the tracking lag and the large estimation variance can be eliminated and alleviated by employing a fixed-interval Kalman smoother method (Tarvainen et al., 2004). The Kalman smoother obtains the optimal estimator by making use of the whole period of single-trial source waveforms and smoothing the results of the Kalman filter, $\hat{a}(n)$, backwards:

$$\tilde{a}(n) = \tilde{a}(n+1) - \Delta(n)P^{-1}(n+1|n)[\tilde{a}(n+1) - \hat{a}(n)] \quad (9)$$

where $\tilde{a}(n)$ is the Kalman smoother estimate at time n and the initialization is $\tilde{a}(N) = \hat{a}(N)$.

To validate the superiority of the Kalman smoother over Kalman filter for estimating the tvMVAR model, we adopted a simulated model. In this simulated model, waveforms from three sources ($M=3$, $N=256$, data length = 1 s and sampling frequency = 256 Hz) were generated (Fig. 1). While most of the simulated tvMVAR coefficients were constant ($A_1[1,1]=0.6$; $A_2[1,1]=-0.1$; $A_1[2,1]=0.4$; $A_1[3,2]=-0.3$; others except $A_2[3,1]$ are zero), the tvMVAR coefficient from source 1 to source 3 with a lag of 2 exhibited a sudden change at

0.5 s (for $t=[0 \ 0.5]$ s, $A_2[3,1]=0.2$; for $t=[0.5 \ 1]$ s, $A_2[3,1]=0.5$) (Fig. 1, top panel). Using this simulated model, the performance of an estimator in both static and fast-varying conditions can be evaluated. Following, two types of noises were added in the model to simulate more realistic noise scenarios: Type 1 noise was uncorrelated white Gaussian processes and was used as the innovative noise of MVAR processes; Type 2 noise was correlated non-Gaussian processes simulated from spontaneous EEG and was used as additive noise. Type 1 noise (random Gaussian noise with zero mean and unit variance) was first added as the innovative noise of the MVAR processes to generate 60 trials ($K=60$) of the process (Fig. 1, middle panel). Next, spontaneous EEG data (collected before the SEP data recording using the same experimental setting) from 3 randomly selected channels were added to the simulated data with Type 1 noise as additive Type 2 noise, which was correlated across sources and non-Gaussian distributed (Fig. 1, bottom panel). Note that this procedure was repeatedly performed for each Monte-Carlo realization, and such Type 2 correlated non-Gaussian noise was randomly selected from different scalp channels across different Monte-Carlo realizations. This random selection of channels across realizations can (1) help generate more realistic Type 2 noise, which was systematically correlated in each realization, and (2) take into account possibly diversified spatial correlations of source noise in different realizations (different subjects in real case). The variance of Type 2 noise was adjusted to achieve a SNR of 5 dB, where the “signal” was the simulated trials without Type 2 noise (but with Type 1 noise) and the “noise” was the Type 2 noise simulated from spontaneous EEG trials. Such a noise scenario was used to generate a more realistic noise in this simulation study.

To simulate another real situation where source noise of all subjects shares similar spatial correlations, spontaneous EEG data from 3 fixed channels (F3, Fz, and F4) were also added to the simulated data as Type 2 noise to test the performances of different methods (Supplementary Fig. 1). Such Type 2 correlated non-Gaussian noise was selected from the same scalp channels in all 60 single trials and all 100 realizations.

The generated noise-contaminated source waveforms (both with and without Type 2 noise) were adopted to test the accuracy of the following four methods that were used to identify tvMVAR model:

- 1) Calculating tvMVAR coefficients of every single-trial source waveforms using the Kalman filter and averaging these estimated tvMVAR coefficients across all single trials (abbreviated to AVG-KF, hereafter);
- 2) Calculating tvMVAR coefficients of every single-trial source waveforms using the Kalman smoother and averaging these estimated tvMVAR coefficients across all single trials (abbreviated to AVG-KS, hereafter);
- 3) Estimating tvMVAR coefficients of concatenated source waveforms from all single trials using the Kalman filter (abbreviated to CON-KF, hereafter);
- 4) Estimating tvMVAR coefficients of concatenated source waveforms from all single trials using the Kalman smoother (abbreviated to CON-KS, hereafter).

To quantitatively assess the performance of different methods, the mean squared deviation (MSD) between the estimated vectorized coefficients $\hat{a}(n)$ and the true vectorized coefficients $a(n)$ was calculated as:

$$MSD(n) = 10 \log_{10} \left\{ \| a(n) - \hat{a}(n) \|_2^2 \right\} \quad (10)$$

Time-varying partial directed coherence

As measures of Granger causality, both PDC (Baccala and Sameshima, 2001) and DTF (Kaminski and Blinowska, 1991) are

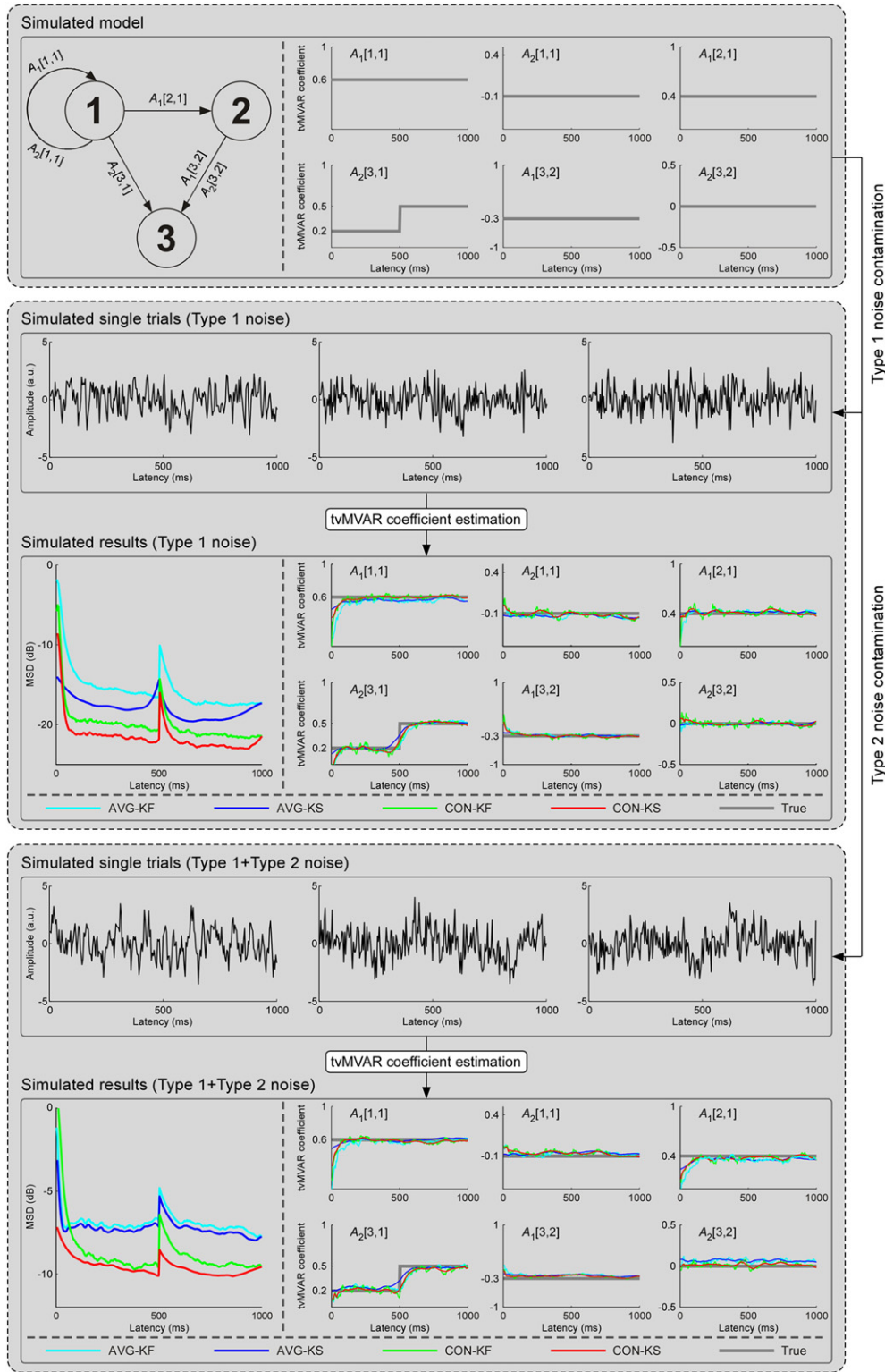


Fig. 1. Connectivity patterns in the simulated model and the performances of estimating tvMVAR coefficients across four methods (AVG-KF, AVG-KS, CON-KF, and CON-KS). *Top panel:* graphic representation and the simulated tvMVAR coefficients of the simulated model are displayed in the left and right part of this panel respectively. Note that $A_p[m_i, m_j]$ is the (m_i, m_j) -th entry of the tvMVAR coefficient matrix $A_p(n)$, and it denotes the causal influence of m_j on m_i with a time lag of p sample (ms). *Middle panel:* an example of single-trial waveforms of the sources in the simulated model, where only Type 1 noise (random Gaussian noise with zero mean) is added, is displayed in the top part of this panel. The performances to identify tvMVAR model using four methods (AVG-KF, AVG-KS, CON-KF, and CON-KS) in one realization are shown in the bottom right part of this panel along with the true tvMVAR coefficients. The averaged MSD curves of the four methods (AVG-KF, AVG-KS, CON-KF, and CON-KS) from 100 independent Monte-Carlo realizations are displayed in the bottom left part of this panel. *Bottom panel:* an example of single-trial waveforms of the sources in the simulated model, where both Type 1 noise (uncorrelated Gaussian noise) and Type 2 noise (correlated non-Gaussian noise simulated from spontaneous EEG) are added, is displayed in the top part of this panel. The performances to identify tvMVAR model using four methods (AVG-KF, AVG-KS, CON-KF, and CON-KS) in one realization are shown in the bottom right part of this panel along with the true tvMVAR coefficients. The averaged MSD curves of the four methods (AVG-KF, AVG-KS, CON-KF, and CON-KS) from 100 independent Monte-Carlo realizations are displayed in the bottom left part of this panel. Note that the performances when estimating tvMVAR coefficients using CON-KF and CON-KS methods were markedly better than that using AVG-KF and AVG-KS methods in both noise scenarios (with and without Type 2 noise). In addition, the CON-KS method demonstrated a more accurate estimation of the tvMVAR coefficients than the CON-KF method especially when the coefficients are static.

frequently used as effective connectivity indexes in the frequency domain. Compared to DTF, PDC does not explore indirect causality and has a reduced computational complexity (Astolfi et al., 2008; Baccala and Sameshima, 2001). For this reason, time-varying PDC (tvPDC) is adopted in this study to describe the temporal and spectral characteristics of the causal influences between sources. The tvPDC is calculated as:

$$tvPDC_{\kappa,\nu}(n,f) = \frac{|A_{\kappa,\nu}(n,f)|}{\sqrt{\sum_{m=1}^M |A_{m,\nu}(n,f)|^2}}, \quad \kappa = 1, \dots, M, \quad \nu = 1, \dots, M, \quad (11)$$

where $A_{\kappa,\nu}(n,f)$ is the (κ,ν) -th entry of the matrix $A(n,f) = \sum_{p=0}^P a_p(n) e^{-j2\pi p f / Fs}$ with the sampling rate Fs . The tvPDC provides a representation of the effective connectivity in the time-frequency domain, and its values are distributed between 0 and 1. To assess the changes of effective connectivity relative to the pre-stimulus period, the estimated tvPDC values were baseline-corrected by subtracting the average tvPDC values in a pre-stimulus time interval at each estimated frequency. Therefore, a higher positive value of $tvPDC_{\kappa,\nu}(n,f)$ denotes a stronger increased effective connectivity (compared to the pre-stimulus time interval) from the ν -th source to the κ -th source at the latency n and the frequency f .

Statistical analysis

To test whether the tvPDC values within the post-stimulus time interval were significantly different from those within the pre-stimulus time interval, a bootstrapping method (Delorme and Makeig, 2004; Durka et al., 2004), was adopted. The procedure of the bootstrapping method is summarized as follows:

1. At each time-frequency point (n,f) , two populations are extracted for comparison: the investigated population Ψ_I , which is the collection of $tvPDC_{\kappa,\nu}(n,f)$ from 16 subjects, and the reference population Ψ_R , which is a collection of $tvPDC_{\kappa,\nu}(\tau,f) \in \text{reference time interval}$ from 16 subjects. The null hypothesis is that there is no difference in means between the two populations Ψ_I and Ψ_R .
2. The pseudo- t statistic of two populations is calculated as $t_p = (\bar{\Psi}_I - \bar{\Psi}_R) / V_{pooled}$, where $\bar{\Psi}_I$ and $\bar{\Psi}_R$ are respectively the mean of two populations and V_{pooled} is the pooled variance of the two populations. The pseudo- t statistic is a better measure than the difference of mean because it takes into account the different variances of two populations.
3. The probability distribution of the pseudo- t statistic was estimated by drawing with replacement two populations of the same sizes as Ψ_I and Ψ_R from the reference population and calculating t_p from the two populations. The permutation was executed 5000 times and the distribution of the pseudo- t statistics from the reference population, $\mathcal{P}_R(t_p)$, can be generated.
4. The investigated pseudo- t statistic t_p is located in the distribution $\mathcal{P}_R(t_p)$, yielding the bootstrap P value for the null hypothesis.

The bootstrap method can detect the time-frequency regions, where the tvPDC values are significantly different compared to those values in the reference interval. To address the problem of multiple comparisons, the significance level (P value) was corrected using a false discovery rate (FDR) procedure (Durka et al., 2004). In addition, small time-frequency regions (less than 10 time-frequency points) were discarded in further analysis.

tvPDC estimation of SEP data

The CON-KS method, which provided the best performance in identifying the tvMVAR model in our simulation study, was used for analyzing real SEP data. The averaged SEP source waveforms were then removed from all single-trial SEP source responses. The SEP source variations were down-sampled to 200 Hz, and the tvPDC values were evaluated from 1 to 30 Hz at a frequency step of 0.5 Hz.

The tvPDC values were further baseline-corrected by subtracting the average tvPDC values enclosed within the pre-stimulus reference interval (from -350 to -50 ms) at each estimated frequency to avoid edge effects around the stimulus onset (Ploner et al., 2009).

Results

SEP waveforms and topographies

Fig. 2 shows the grand average SEP waveforms in all channels, with the scalp distribution at the latencies of several typical SEP peaks (N60, N120, and P240). The group average SEP waveform, measured at Cz, consisted of a clear negative deflection (N120) peaking at 121 ms (-2.2 mV) followed by a positive deflection (P240) peaking at 246 ms (2.6 mV). In addition, a preceding negative deflection (N60), peaking at 70 ms (-3.1 mV), was measured at C3. As previously described in (Mouraux and Iannetti, 2009), the scalp distribution of the N120 extended bilaterally towards temporal regions with maximum at both the contralateral temporal region and the central region, the scalp topography of the P240 was centrally distributed with a clear maximum at the fronto-central region (Fig. 2). The scalp topography of N60 was restricted to the hemisphere contralateral to the stimulated site, and displayed a clear maximum close to C5.

Dipolar source analysis

Fig. 3 shows the time courses and locations of the estimated dipolar sources of the SEPs, and Supplementary Fig. 2 shows ten randomly-selected single-trial source waveforms. Locations of fitted dipoles are summarized in Table 1, and peak latency and strength of each dipole are summarized in Table 2. Note that the adopted four dipolar model explained the scalp distribution of SEPs with a RV of 6.8% and of $11.4 \pm 3.4\%$ within the time interval from 0 ms to 400 ms at group level and single-subject level respectively.

At both group level and single-subject level, source analysis results indicated that (1) the source explaining the time window of the N60 wave was located in the contralateral SI, (2) the sources explaining the time window of the N120 wave were located in the contralateral and ipsilateral SII, and (3) the source explaining the time window of the P240 was located in the CC (Table 1). It should be noted that the peak latencies of all four sources were significantly different ($F = 169.5$, $P < 0.001$, one-way ANOVA). Post hoc comparisons by Fisher's least significant difference (LSD) test revealed that (1) the peak latencies of SI were significantly shorter than the peak latencies of all other sources ($P < 0.001$ in all comparisons), (2) the peak latencies of SIIc were significantly shorter than the peak latencies of both SIIi ($P = 0.019$) and CC ($P < 0.001$), and (3) the peak latencies of SIIi were significantly shorter than the peak latencies of CC ($P < 0.001$).

Kalman smoother vs. Kalman filter to estimate tvMVAR model

A simulated model was used to compare the performances of different Kalman filter/smoothing-based methods (AVG-KF, AVG-KS, CON-KF, and CON-KS) for estimating the tvMVAR model. The tvMVAR coefficients estimated using the four methods and the true coefficients were displayed in the middle and bottom panels of Fig. 1 and Supplementary Fig. 1 (right parts). The performance of identifying the tvMVAR model was similar for both CON-KF and CON-KS approaches, and they both markedly outperformed AVG-KF and AVG-KS, with and without Type 2 noise. In the middle and bottom panels of Fig. 1 and Supplementary Fig. 1 (left parts), we displayed the average MSD curves of the four methods (AVG-KF, AVG-KS, CON-KF, and CON-KS) using 100 independent Monte-Carlo realizations (in each realization, 60 trials were simulated). The performance of the CON-

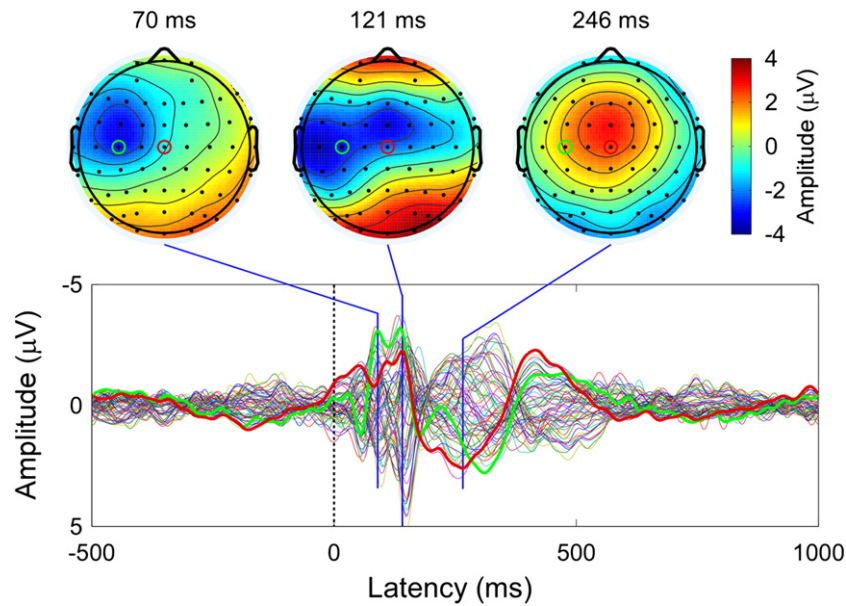


Fig. 2. Group average waveforms and scalp topographies at N60, N120, and P240 peak latencies of SEPs. SEPs were recorded from 64 electrodes. Group average waveforms from each electrode are plotted in different colors and superimposed. Scalp topographies are displayed at 70 ms, 121 ms, and 246 ms. Noteworthy is that the scalp topography at N60 peak latency was restricted to the hemisphere contralateral to the stimulated site and maximally expressed close to C5 electrode, the scalp distribution at N120 peak latency was extended bilaterally towards temporal regions with maximum at both the contralateral temporal region and the central region, and the scalp topography at P240 peak latency was centrally distributed with a clear maximum at the central region.

KF and CON-KS methods was markedly better compared to the AVG-KF and AVG-KS methods, with and without Type 2 noise, which is consistent with several previous studies (Arnold et al., 1998; Ding et al., 2000; Milde et al., 2010; Moller et al., 2001). When estimating the tvMVAR coefficient, the CON-KS method was more accurate than the CON-KF method everywhere, except two short time periods: (1) when sudden coefficient changes occurred (around 0.5 s in this

simulated model), and (2) when backward smoothing just began (around 1 s in this simulated model). Taken together, with and without Type 2 noise and no matter whether Type 2 noise was generated from 3 randomly selected channels or 3 fixed channels (e.g. F3, Fz, F4), the CON-KS method exhibited the best performance (the most accurate estimation of tvMVAR coefficients) among the four tested methods (AVG-KF, AVG-KS, CON-KF, and CON-KS).

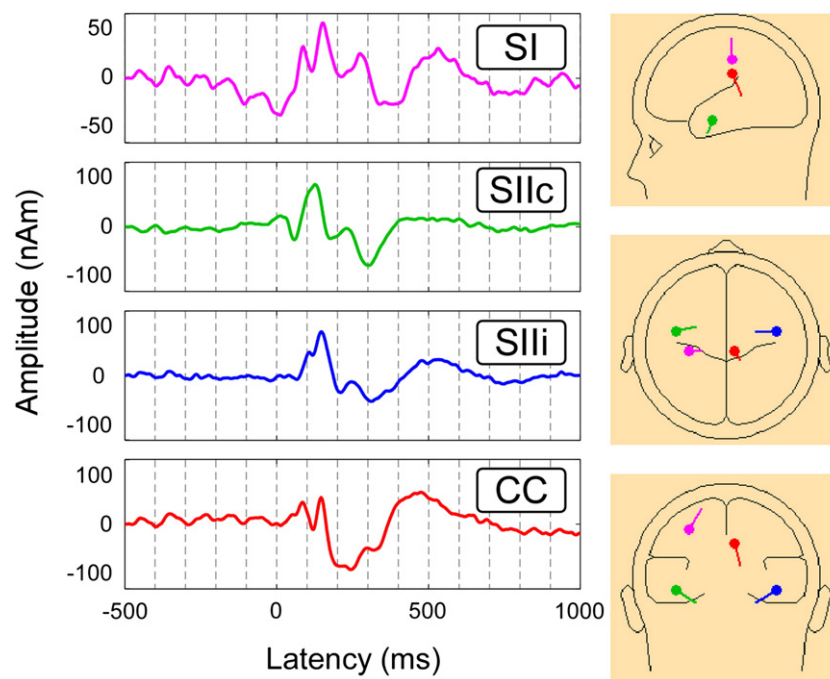


Fig. 3. Dipolar locations and their corresponding time courses of group average SEPs. The time courses of dipolar sources are displayed in the left panel, and the locations and orientations of dipolar sources are displayed using three head views in the right panel. The N60 activity is mainly generated from contralateral SI (represented in purple color); the N120 responses are mainly generated from bilateral SII (represented in green and blue color for contralateral and ipsilateral SII respectively); and the P240 responses are mainly generated from CC (represented in red color).

Table 1
Locations of dipolar sources of SEPs.

	Dipole 1 (SI)			Dipole 2 (SIIc)			Dipole 3 (SIIi)			Dipole 4 (CC)		
	Location(mm)			Location(mm)			Location(mm)			Location(mm)		
	x	y	z	x	y	z	x	y	z	x	y	z
Group level	−32	−27	45	−44	1	−10	44	1	−10	7	−25	31
Individual level (mean ± SD)	−33 ± 7	−29 ± 14	43 ± 6	−41 ± 10	−7 ± 18	−6 ± 16	41 ± 10	−7 ± 18	−6 ± 16	−0.6 ± 6	−15 ± 16	26 ± 8

SI: primary somatosensory cortex; SIIc: contralateral secondary somatosensory cortex; SIIi: ipsilateral secondary somatosensory cortex; CC: cingulate cortex.

tvPDC estimation of SEP data

Single-trial variations of four SEP source waveforms (SI, SIIc, SIIi, and CC; $M = 4$), each having 60 trials ($K = 60$), obtained from dipolar source analysis and the subtraction of the averaged SEPs, were used in the tvPDC estimation to assess the relationship among SEP sources. The tvMVAR orders, selected using AIC, ranged from 12 to 19 (15.3 ± 1.6 , mean $\pm$ SD), and the average of MVAR coefficients across all subjects were displayed in Supplementary Fig. 3 (note that since the MVAR model order was different across subjects, the average of MVAR coefficients across subjects was plotted by manually setting an MVAR order of 15 for all subjects). Time-frequency regions exhibiting significantly increased tvPDC values were displayed in Fig. 4 (the results without baseline correction were displayed in Supplementary Fig. 4), and their detailed time-frequency characteristics were summarized in Table 3. Since no significant changes were observed in the post-stimulus interval from 500 ms to 1000 ms, only the tvPDC values in the post-stimulus interval from 0 to 500 ms are shown in Fig. 4. In addition, to show the time-vary total connectivity pattern summed over all regions, we displayed the total outflow connectivity $\sqrt{\sum_{m=1}^M |\Lambda_{m,v}(n,f)|^2}$, and total inflow connectivity $\sqrt{\sum_{m=1}^M |\Lambda_{k,m}(n,f)|^2}$, and their differences of each neural source in Supplementary Fig. 5.

Time-varying effective connectivity patterns among SEP sources, represented as time-frequency regions that have significantly increased tvPDC values ($P < 0.01$, FDR corrected, bootstrap analysis) (Fig. 4), were summarized into three temporally distinct groups (Fig. 5).

1. In the early-latency interval (post-stimulus interval: around 50–150 ms), significant increases in effective connectivity were observed from SI to both SIIc (A: 60–160 ms, 1–5 Hz; centered at 111.8 ms and 2.1 Hz) and SIIi (B: 65–145 ms, 7–12 Hz; centered at 99.0 ms and 9.7 Hz), and from SIIc to SIIi (C: 80–170 ms, 1–10 Hz; centered at 126.4 ms and 5.5 Hz) (Fig. 5, left panel).
2. In the middle-latency interval (post-stimulus interval: around 150–300 ms), significant increases of effective connectivity from SIIi to CC (D: 155–330 ms, 1–14 Hz; centered at 236.1 ms and 8.0 Hz), and from CC to both SIIc (E: 190–245 ms, 1–4 Hz; centered at 220.2 ms and 1.8 Hz) were observed (Fig. 5, middle panel). No

Table 2
Latencies and strength of SEP dipolar activities.

		Dipole 1 (SI)	Dipole 2 (SIIc)	Dipole 3 (SIIi)	Dipole 4 (CC)
Group level	Latency (ms)	67	107	127	224
	Strength (nAm)	24.4	65.3	67.5	−70.2
Individual level (mean ± SD)	Latency (ms)	63 ± 14	107 ± 17	125 ± 19	227 ± 31
	Strength (nAm)	34.4 ± 20.6	82.9 ± 43.9	84.3 ± 40.7	−96.2 ± 44.0

ms: millisecond; nAm: nanoAmpere $\times$ meter.

significant increase of effective connectivity from SIIc to CC was detected.

3. In the late-latency interval (post-stimulus interval: around 250–400 ms), significant increases of effective connectivity from CC to SIIi (G: 340–430 ms, 2–8 Hz; centered at 387.9 ms and 5.3 Hz), from SI to SIIc (F: 255–390 ms, 1–6 Hz; centered at 322.9 ms and 2.6 Hz), and from SIIc to SIIi (H: 300–380 ms, 1–4 Hz; centered at 342.5 ms and 2.1 Hz) were observed (Fig. 5, right panel).

To sum up, our results indicated the following two findings.

1. The somatosensory information at early latencies (< 150 ms) was processed in serial among somatosensory cortices. Somatosensory information was firstly observed in SI, and then transmitted from SI to SIIc (A), from SI to SIIi (B, approximately 5 ms later than A), and from SIIc to SIIi (C, approximately 15 ms later than B).
2. The somatosensory information at middle and late latencies (> 150 ms) was processed in reciprocal from SIIi to CC (D), from CC to SIIc (E, approximately 35 ms later than D), and from CC to SIIi (G, approximately 150 ms later than E).

Discussion

In this study, we developed a two-step approach integrating dipolar source analysis and a Kalman smoother based causality inference to assess the time-varying effective connectivity among stimulus-elicited neural sources. A simulation study showed the superiority of Kalman smoother over Kalman filter (Milde et al., 2010) when estimating tvMVAR coefficients, thus providing a more accurate estimation of time-varying effective connectivity. When applying this approach to SEP data, we observed that SEP sources were mainly located at contralateral SI, bilateral SII, and CC after right hand electrical stimulation, which is in line with several previous studies (Shimojo et al., 2000; Tarkka and Treede, 1993). In addition, time-varying effective connectivity revealed that the cortical processing of somatosensory input (1) at early latencies was processed in serial (from SI to SIIc, from SI to SIIi, and from SIIc to SIIi) and (2) at middle and late latencies was processed in reciprocal (from SIIi to CC, and then from CC to bilateral SII).

Methodological considerations

In this study, we performed a dipolar source analysis using a model with four equivalent current dipoles, and found that N60, N120, and P240 in SEPs (Fig. 2) were mainly generated from the contralateral SI, bilateral SII, and CC respectively (Fig. 3, Tables 1 and 2). It should be noted that the accuracy of the obtained dipolar sources could be confirmed by three aspects. First, a similar four dipolar model, which can provide an approximate and robust estimation of neural generators in response to sensory stimuli, has been successfully adopted by several research groups (Schlereth et al., 2003; Shimojo et al., 2000; Tarkka and Treede, 1993; Tsuji et al., 2006). Second, the four fitted dipoles explained the scalp distribution of SEPs with RV of 6.8% and $11.4 \pm 3.4\%$ in the group level and single-subject level

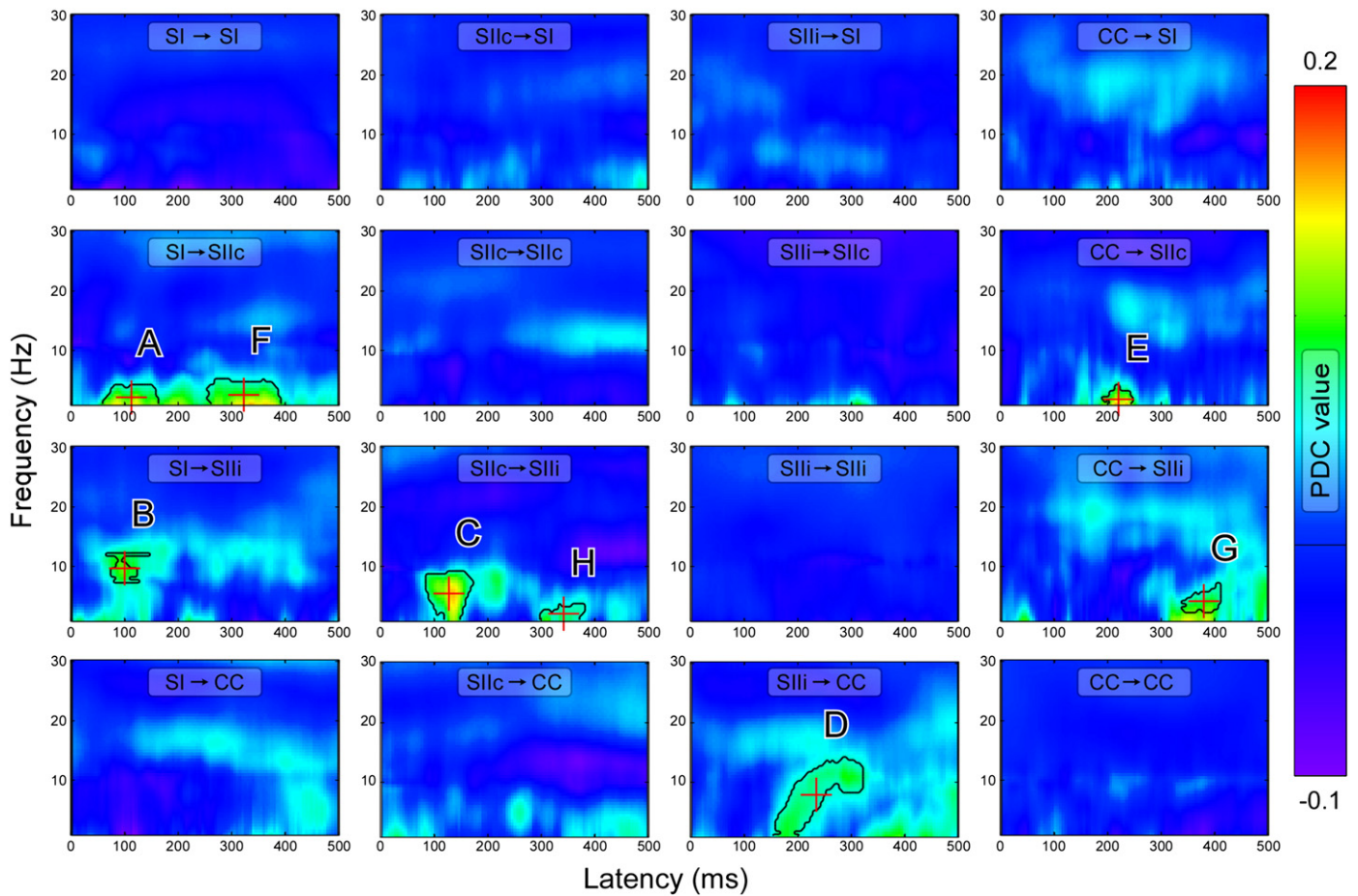


Fig. 4. Time-frequency representations of time-varying PDC as a measure of causal influences within the neural network comprising SI, SIlc, SIIi, and CC averaged across subjects. The regions circled by black lines had significantly larger PDC values than those in the reference interval from -350 to -50 ms ($p < 0.01$, FDR corrected). These identified time-frequency regions were labeled as A–H according to the temporal sequence of their center latencies. The centroid of each significant time-frequency region was marked using the red cross sign. It should be noted that the center latency and center frequency of each identified time-frequency region were respectively calculated using $\frac{1}{L} \sum_{l=1}^L t(l)$ and $\frac{1}{L} \sum_{l=1}^L f(l)$, where $t(l)$ and $f(l)$ are the latency and frequency of l -th ($l = 1, 2, \dots, L$) time-frequency point and L is the total number of time-frequency points in the identified time-frequency region.

respectively. Third, the obtained source results, i.e., that the neural sources of N60, N120, and P240 in SEPs were mainly located at the contralateral SI, bilateral SII, and CC respectively, were consistent with a large number of previous studies (Blatow et al., 2007; Kany and Treede, 1997; Mouraux and Iannetti, 2009; Shimojo et al., 2000).

As the neural activity of any source would be expected to be widely spread at the scalp electrodes because of volume conduction in EEG

(Nunez and Srinivasan, 2006), it would be difficult to accurately estimate effective connectivity between neural sources using pairs of electrodes. The accurate estimation of cortical sources and their neural activities helps mitigate the degree of volume conduction, thus providing a more accurate estimation of effective connectivity among stimulus-elicited neural sources. In addition, performing effective connectivity analysis on the source level provides a more direct assessment of the anatomical location of interacting brain regions (Schoffelen and Gross, 2009).

There are several approaches, including SEM (McIntosh and Gonzalez-Lima, 1994) and DCM (Friston et al., 2003), that can be also used to assess effective connectivity among brain regions. Compared with these approaches, the Granger causality-based effective connectivity approach used in this study has two important advantages: (1) it does not rely on prior knowledge about structural connectivity (Rowe, 2010; Sato et al., 2009); (2) it provides a frequency-domain connectivity pattern, which is of particular interest in EEG/MEG studies because electrophysiological information has been reported to be transferred in the brain via oscillatory activities (Buzsaki and Draguhn, 2004; Pfurtscheller et al., 1996; Schnitzler and Gross, 2005; Varela et al., 2001).

Several Granger causality-based measures, like PDC and DTF, can be calculated from the tvMVAR coefficients to estimate the effective connectivity. There is evidence that these measures are capable of providing similar connectivity patterns in the spectral domain

Table 3

Time-frequency characteristics of identified time-frequency regions having significantly increased tvPDC connectivity patterns (Fig. 4).

	Time-frequency regions							
	A	B	C	D	E	F	G	H
Center latency (ms)	111.8	99.0	126.4	236.1	220.2	322.9	387.9	342.5
Center frequency (Hz)	2.1	9.7	5.5	8.0	1.8	2.6	5.3	2.1
Onset latency (ms)	60	65	80	155	190	255	340	300
Offset latency (ms)	160	145	170	330	245	390	430	380
Minimal frequency (Hz)	1	7	1	1	1	1	2	1
Maximal frequency (Hz)	5	12	10	14	4	6	8	4

Note that center latency and center frequency of each identified time-frequency region are respectively calculated as $\frac{1}{L} \sum_{l=1}^L t(l)$ and $\frac{1}{L} \sum_{l=1}^L f(l)$, where $t(l)$ and $f(l)$ are the latency and frequency of l -th ($l = 1, 2, \dots, L$) time-frequency point and L is the total number of time-frequency points in the corresponding region.

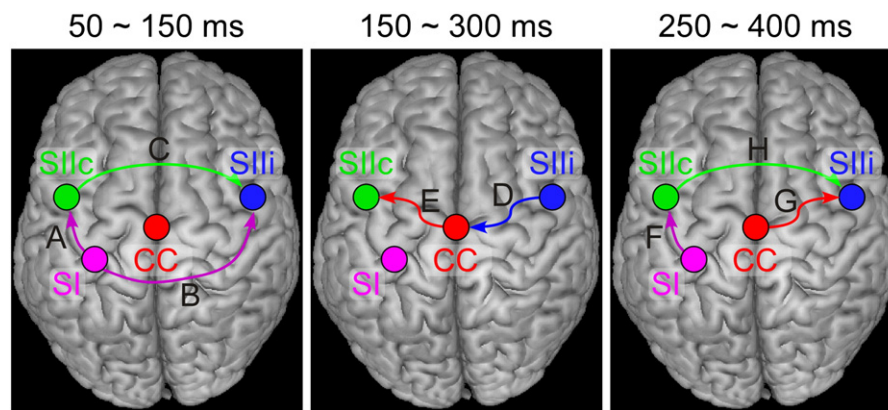


Fig. 5. Graphic representations of the information flows among SEP sources at different time intervals. *Left panel:* in the early-latency interval (about 50–150 ms), the cortical information was transmitted from SI to SIIc (A), and then to SIIi (B, about 5 ms later than A). Following, evident information flow was observed from SIIc to SIIi (C, about 15 ms later than B). *Middle panel:* in the middle-latency interval (about 150–300 ms), significant connectivity patterns were observed from SIIi to CC (D) and then from CC to SIIc (E). *Right panel:* in the late-latency interval (about 250–400 ms), the cortical information was transmitted from CC to SIIi (G), from SI to SIIc (F), and from SIIc to SIIi (H).

(Astolfi et al., 2007b; Ploner et al., 2009). In the present study, we employed the PDC measure because it does not interfere with indirect causality and has a low computational complexity (Astolfi et al., 2008; Baccala and Sameshima, 2001).

Some tracking methods (Arnold et al., 1998; Ding et al., 2000; Kaminski et al., 2001; Milde et al., 2010; Moller et al., 2001; Weiss et al., 2008), e.g. recursive least-squares and Kalman filtering, have been applied to estimate the tvMVAR coefficients in effective connectivity studies. However, these tracking methods attempted to find the optimal estimator for the tvMVAR coefficients only based on past measurements, thus unavoidably having some problems caused by the tracking lag (Tarvainen et al., 2004). In contrast, the Kalman smoother can effectively avoid the tracking lag, thus providing a more accurate estimation of the effective connectivity patterns.

It is important to note that the Kalman smoother could be applied to single-trial waveforms from a large number of sources or electrodes as well, even though it was used for waveforms from only four sources in this study. However, a large number of sources leads to a dramatic increase of the number of unknown tvMVAR coefficients, and causes a series of problems like, heavy computational complexity, large memory requirements, algorithmic instability, underdetermination, and so on. Therefore, the Kalman smoother method must be extended and improved to handle these problems. The high-dimensionality problem can be addressed by incorporating some specific assumptions to simplify the structure of covariance matrices of state and measurement noise, which is similar to the general linear Kalman filter proposed by Milde et al. (2010). Alternatively, sparsity-enhancing regularization techniques could be incorporated into the Kalman smoother to distinguish and estimate a few non-zero coefficients from a large number of zero coefficients (Valdes-Sosa et al., 2005).

It is not trivial to mention that, a tvMVAR model can only be used to describe a zero mean stochastic process (Ding et al., 2000; Truccolo et al., 2002), while the averaged SEPs at the source levels are deterministic processes, which could not be correctly described by such a tvMVAR model. To better model deterministic + stochastic signals (e.g. single-trial SEPs), we could either adopt a non-zero-mean innovation noise to describe the evolution of SEP trials or remove the averaged time courses from all single trials before using tvMVAR model to describe these trials (Ding et al., 2000).

Interestingly, we observed a reciprocal information flow between bilateral SII and CC, which occurred at distinct frequencies (1–14 Hz from ipsilateral SII to CC; 1–4 Hz and 2–8 Hz from CC to contralateral

and ipsilateral SII respectively) and at overlapped time intervals (155–330 ms from ipsilateral SII to CC; 190–245 ms and 340–430 ms from CC to contralateral and ipsilateral SII respectively) (Fig. 4, Table 3). This kind of feedback process (distinct in frequency and overlapped in latency) can be optimally identified using the time-varying source connectivity approach (i.e. Kalman smoother based time-varying effective connectivity) adopted in this study.

Effective connectivity in the somatosensory system

In this study, we found that (1) contralateral SI was the earliest source activated by somatosensory stimuli (peaking at 63 ± 14 ms, Fig. 3, Table 2) and (2) the information flow from contralateral SI to SIIc was the earliest effective connectivity (onset at 60 ms in latency and centered at 2.1 Hz in frequency, Fig. 4, Table 3). Therefore, we believe that contralateral SI is the earliest area of the cerebral cortex that responds to somatosensory input in the human somatosensory system (Baumgartner et al., 1998; Inui et al., 2004; Iwamura, 1998; van de Wassenberg et al., 2008a,b), which is also supported by the well-documented thalamo-cortical connections from the thalamus to SI (Iwamura, 1998; Jones and Peters, 1986; Kandel et al., 2000). Contralateral SII was activated (peaking at 107 ± 17 ms, Fig. 3, Table 2) after receiving somatosensory information from SI in the same hemisphere, indicating that contralateral SI and SII were consecutively activated in a serial hierarchical processing of gradually more complex sensory features (Blatow et al., 2007; Iwamura, 1998). This cortico-cortical connection (from SI to SII in the same hemisphere) has been consistently reported in a large number of studies, both in human and higher non-human primates (Allison et al., 1989a,b; Hari et al., 1993; Pons et al., 1992).

Importantly, our results demonstrated that ipsilateral SII was activated (peaking at 125 ± 19 ms, Fig. 3, Table 2) after receiving somatosensory information from both contralateral SI (onset at 65 ms in latency and centered at 9.7 Hz in frequency, Fig. 4, Table 3) and contralateral SII (onset at 80 ms in latency and centered at 5.5 Hz in frequency, Fig. 4, Table 3) via cortico-callosal connections (Blatow et al., 2007). This finding is in accord with the notion that ipsilateral SII activation reflects the summation of cortico-callosal inputs from both contralateral SI and SII (Blatow et al., 2007; Shuler et al., 2001).

Taken together, when considering the cortical information processing in the somatosensory system, our results strongly indicated that somatosensory input was processed in serial, from thalamus to

contralateral SI, then from contralateral SI to bilateral SII, and finally from contralateral SII to ipsilateral SII (Figs. 4 and 5).

Effective connectivity between somatosensory system and cingulate cortex

Our results revealed that CC was activated (peaking at 227 ± 31 ms, Fig. 3, Table 2) after receiving somatosensory information from ipsilateral SII (onset at 155 ms in latency and centered at 8.0 Hz in frequency, Fig. 4, Table 3), and that information in the cingulate cortex was further projected to both contralateral SII (onset at 190 ms in latency and centered at 1.8 Hz in frequency, Fig. 4, Table 3) and ipsilateral SII (onset at 340 ms in latency and centered at 5.3 Hz in frequency, Fig. 4, Table 3). It should be noted that CC has been reported to receive sensory inputs from multiple cortical sources (e.g. insula, somatosensory cortex, and motor and premotor cortices) and send back projections to most of them (Baleydier and Mauguire, 1980; Frot et al., 2008; Morecraft and Van Hoesen, 1992; Morecraft et al., 2000, 2004). In addition, by assessing the effective connectivity of cortical responses to laser stimuli between pairs of scalp EEG electrodes, Weiss et al. (2008) reported an “unexpected” effective connectivity from CC to the SII/insula of each hemisphere. The effective connectivity from CC to the SII/insula is in accord with the strong tvPDC from CC to bilateral SII observed in this study (E and G, Fig. 4). However, the effective connectivity from ipsilateral SII to CC was not reported in their study (Weiss et al., 2008), which may be caused by the relatively weaker effective connectivity strength (smaller tvPDC values in this study) (D, Fig. 4).

Overall, our results supported the view that somatosensory information was reciprocally processed between SII and CC (Fig. 5). This reciprocal processing may be particularly relevant in the processing of novel/salient sensory information (please refer to the experimental design), which would elicit the involvement of sensory, affective, and emotional processes that must be integrated to generate a coherent percept of sensory information. While the SII is believed to perform higher-order functions including sensorimotor integration, integration of information from the two halves of the body, attention, learning and memory (Chen et al., 2008; Dijkerman and de Haan, 2007; Garcia-Larrea et al., 1995), CC is thought to serve as a central station for processing top-down and bottom-up tasks, assigning appropriate control to other areas in the brain, and/or assessing the salience of emotion and motivational information (Allman et al., 2001; Bush et al., 2000). The combined activation of these brain regions in a reciprocal manner could contribute to particular functions of higher-order cognitive processes, such as the construction of an integrated, sensory perceptual environment, the directing of attention to salient features of that environment, and the selection of those features for entry into awareness (Knudsen, 2007; Mesulam, 1998).

Conclusions

Combining dipolar source analysis and a Kalman smoother has been demonstrated to provide an accurate estimation of time-varying effective connectivity among neural sources in the order of milliseconds from the multi-channel scalp electrophysiological recordings. When applied to SEP data, we showed that neural sources that responded to somatosensory stimuli were mainly located at contralateral SI, bilateral SII, and cingulate cortex. Further, our results confirmed the serial processing of somatosensory information in human somatosensory cortices, and, importantly, revealed the reciprocal processing of somatosensory information between somatosensory cortices and cingulate cortex, which may contribute to higher-order cognitive processing and provide an integrated framework of cortical processing related to novel/salient stimuli.

Notably, this approach can be easily applied to various types of evoked potentials, e.g. visual-evoked potentials, auditory-evoked potentials, and laser-evoked potentials, to estimate the information flow

among brain regions that are activated by these stimuli. Importantly, such time-varying source connectivity measures, which could provide new insights into the functional significance of the brain processes underlying neural responses to sensory stimuli, may provide a more subtle indicator of abnormality in disease states (Tracey, 2005), thus potentially serving as important parameters in the use of evoked potentials as a diagnostic tool in clinical studies.

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Appendix A. Supplementary materials

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.neuroimage.2012.03.094>.

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