Evidence-Based Source Modeling of Nociceptive Cortical Responses: A Direct Comparison of Scalp and Intracranial Activity in Humans

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Abstract: *Background:* Source modeling of EEG traditionally relies on interplay between physiological hypotheses and mathematical estimates. We propose to optimize the process by using evidence gathered from brain imaging and intracortical recordings. *Methods:* We recorded laser-evoked potentials in 18 healthy participants, using high-density EEG. Brain sources were modeled during the first second poststimulus, constraining their initial position to regions where nociceptive-related activity has been ascertained by intracranial EEG. These comprised the two posterior operculo-insular regions, primary sensorimotor, posterior parietal, anterior cingulate/supplementary motor (ACC/SMA), bilateral frontal/anterior insular, and posterior cingulate (PCC) cortices. *Results:* The model yielded an average goodness of fit of 91% for individual and 95.8% for grand-average data. When compared with intracranial recordings from 27 human subjects, no significant difference in peak latencies was observed between modeled and intracranial data for 5 of the 6 assessable regions. Morphological match was excellent for operculo-insular, frontal, ACC/SMA and PCC regions (cross-correlation > 0.7) and fair for sensori-motor and posterior parietal cortex (c-c ~ 0.5). *Conclusions:* Multiple overlapping activities evoked by nociceptive input can be disentangled from high-density scalp EEG guided by intracranial data. Modeled sources accurately described the timing and morphology of most activities recorded with intracranial electrodes, including those coinciding with the emergence of stimulus awareness. *Hum Brain Mapp* 38:6083–6095, 2017. © 2017 Wiley Periodicals, Inc.

Key words: laser-evoked potentials; pain; source modeling; sEEG; insula

INTRODUCTION

Starting in the early 1950s [Brazier, 1949; Henderson et al., 1975], efforts to disclose the brain sources underlying

electroencephalographic (EEG) activity have resulted in a variety of source modeling algorithms that are still evolving to this day (for a review, see Michel and Murray [2012]). Despite theoretical and practical limitations, source

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modeling has been surprisingly successful in predicting the location of epileptic foci (e.g., Koessler et al., 2010; Yang et al., 2011) even with limited electrode sampling [Merlet et al., 1998; Wennberg and Cheyne, 2014]. Epileptic signals, however, may be up to 10–20 times larger than spontaneous EEG activity or physiological sensory brain events, resulting in enhanced signal-to-noise ratios which render modeling attempts substantially easier. Furthermore, epileptic foci are often associated with anatomo-functional alterations, thus offering some validation criteria via the comparison of source modeling with anatomical studies, neuroimaging results of the same ictal event, or neurosurgical brain resection (e.g., Merlet et al., 1996; Koessler et al., 2010; reviewed in Plummer et al., 2008).

As these approaches are difficult or impossible to implement when dealing with physiological activity in a normal brain, the quality of EEG modeling solutions is most often estimated via a combination of mathematical approaches (goodness of fit between source-derived and scalp-recorded signals) and physiological plausibility (Nunez and Srinivasan, 2006; Michel et al., 2009). Multiple “physiologically plausible” solutions with equivalent goodness of fit are however common, and small differences in parameters estimates such as skull conductivity can lead to important localization errors (Akalin Acar et al., 2016). Functional imaging (fMRI) using the same experimental conditions can helpfully complement these data by providing spatial information, but the time course of the fMRI responses integrates 10–20 s of activity, and is unable to reflect the rapid neural changes underlying subjective experiences that are tagged with EEG. Indeed, the progression from sensory activity to conscious perception, memory encoding, and the integration of external input with self-awareness develops in <1 s, and can hardly be disentangled from functional imaging data. Intracranial EEG (iEEG) recordings, on the other hand, allow detecting the time activation of the structures where electrodes are implanted with millisecond-precision, and can therefore provide a unique straightforward validation of source modeling results. This approach has been successfully applied in the past to ascertain the existence of sources, essentially in sensory or motor cortices, at locations

predicted by source modeling (Allison et al., 1992; Lenz et al., 1998a,b; Garcia-Larrea et al., 2003; Frot et al., 2008, 2013). However, the limited spatial sampling of intracranial recordings, commonly restricted to a small number of sites, often gives only a very partial image of the actual spatio-temporal processing and does not allow a comprehensive comparison of scalp, intracranial, and source-reconstructed signals.

To overcome this problem, we recently investigated the responses to nociceptive stimuli from over 300 intracranial electrode contacts exploring sensory, motor, associative, paralimbic, and limbic cortical areas, which allowed us to reconstruct a spatio-temporal picture of brain network activity during the first second following a nociceptive stimulus (Bastuji et al., 2016). In this study, we used the result of such intracranial analysis as a *spatial constraint* to source modeling of scalp signals recorded in response to the exact same stimuli. Thus, putative sources of high-density scalp EEG were initially located within brain regions where activity was known to occur, and we investigated to what extent the time course and morphological features of such modeled sources coincided with that of actual signals obtained with intracranial EEG. Such spatial constraint of source modeling was complemented with meta-analyses of fMRI and intracortical data to nociceptive stimuli (Neurosynth database, Yarkoni et al., 2011). The results show that source modeling of high-density EEG, when adequately oriented, is able to capture in a noninvasive way a considerable portion of the nociceptive temporal dynamics documented in intracranial recordings.

SUBJECTS AND METHODS

Participants

Twenty healthy adults (mean age: 28; 6 women) gave written informed consent and received compensation for participation in this experiment, which was approved by the local ethics committee (Léon Bérard-Lyon; 2008-A01437-48) and part of a larger dataset collection (Bradley et al., 2016). All participants were right handed, without history of neurologic or psychiatric illnesses or under medication. Two participants were excluded because their recordings were not fit for modeling (systematic artefacts in one, no reliable potentials in the other).

Nociceptive Laser Stimuli

Specific activation of the spino-thalamic pathway was achieved using infrared laser pulses (Nd:YAP laser; 1.34 μm wavelength; El.En-Florence, Italy) (Plaghki and Mouraux, 2003). Laser stimuli consisted of 5 ms pulses, delivered on a 4-mm-diameter spot on the dorsum of the right hand. Intensity was set to individual nociceptive threshold, using a staircase procedure, to elicit a subjective sensation similar to the burn-and-sting of a droplet of

Abbreviations

ACC	anterior cingulate cortex
c-c	cross-correlation
iEEG	intracranial electroencephalography
L.Frontal	left frontal cortex
L.PIMO	left posterior insula-medial operculum
L.PPC	left posterior parietal cortex
L.S1/M1	left somatosensory-motor cortex
LEPs	laser-evoked potentials
PCC	posterior cingulate cortex
R. Frontal	right frontal cortex
R. PIMO	right posterior insula-medial operculum
SMA	supplementary motor area

boiling water. This sensation was attributed an intensity rating of 4–5 on a numeric verbal scale, where 1 corresponds to perception, 4 to nociceptive threshold and 10 to the worst possible pain. Mean laser intensity was $102 \pm 22 \text{ mJ/mm}^2$.

Experimental Design

Subjects were comfortably seated in a quiet semi-darkened room; they wore protective goggles and earphones playing white noise. They were asked to relax and restrain from blinking after the stimulation. After determining individual pain threshold, LEPs were recorded to laser stimulation of the right-hand dorsum at that level. Pairs of stimuli were delivered at an intertrial interval of $\sim 1 \text{ s}$; only the response to the first stimulus is analyzed here. An intertrial interval of 10–15 s between trials allowed participants to rate pain intensity for each stimulus and to signal detection by contralateral index movement. Participants underwent 2 recording sessions, 1 month apart, each of which consisted of 80 laser stimuli divided in 4 runs of 20 stimuli each.

Laser-Evoked Potentials

Recording

LEPs were recorded with a 128-channel EEG cap (WaveguardTM, ANTNeuro) in accordance with the 10–10 extended international system. All electrodes were referred to the nose and impedance was kept below 10 k Ω . Recordings were made using ASATM software and asalabTM amplifiers (ANTNeuro) with 512 Hz sampling rate and bandpass filter 0.263–256 Hz.

Time-domain analysis

The continuous EEG was processed off-line in BrainVisionAnalyzer2.0 (BrainProducts[®]). A digital bandpass filter was applied (Butterworth zero-phase, 0.5–30 Hz, 12 dB/oct; plus 50 Hz notch) before segmenting into 1000 ms epochs (100 ms prestimulus period), detrending and baseline correcting. Epochs were rejected if voltage variations exceeded $\pm 100 \mu\text{V}$ or if muscle, head, or eye movement artefacts were visible. Under these strict conditions, an average of 17% of epochs was rejected. Activity from accepted epochs was averaged in each subject, and a grand-average data set was created from the pooled activity of all participants.

LEP Source Modeling

Source reconstruction of laser-evoked potentials was performed using dipolar modeling in BESA Research 6.0[®] (Germany). BESA iteratively correlates the scalp potential distributions generated by theoretical dipoles within the brain with the actual scalp distribution obtained

experimentally. It outputs an estimate of source position, orientation, and activity over time (the model) which then has to be judged according to the amount of recorded data it explains (as estimated by goodness of fit or GoF¹) but also to current anatomical and functional knowledge. In this study, previous knowledge regarding location of brain nociceptive responses, derived from intracranial EEG recordings and functional MRI studies, was exploited to constrain initial source positions. Nonmoving equivalent current dipoles were placed within a standardized FEM (finite-element method) head model in BESA Research 6.0 (created from an average of 50 individual MRIs in Talairach space, comprising three compartments: brain/cerebrospinal fluid, skull, and scalp), with standard conductivity values (anisotropic skull conductivity with tangential = $3 \times$ radial conductivity; radial skull conductivity to brain conductivity ratio = 80), overlaid on the standard average anatomical MRI.

An eight-dipole model was constructed based on intracranial EEG data (Frot et al., 2013; Bastuji et al., 2016). Of the regions identified in these two studies, not all regions could be modeled by an individual dipole: some regions are known to lead to closed electrical fields (amygdala and hippocampus), others have inconsistent and rare responses in intracranial recordings (S1 3b, dPCC, and ACC), and some were in locations challenging to source modeling (perigenual ACC and orbito-frontal cortex: close to the eyes and orbits). Finally, some regions are anatomically too close or superimposed to be disentangled from scalp EEG, even with 128 electrodes, and had to be considered together (e.g., S1 and M1, posterior insula and operculum, anterior insula and frontal operculum, ACC and SMA, precuneus, and vPCC). Consequently, dipoles were placed in bilateral posterior operculo-insular (PIMO) cortex (Lenz et al., 1998a; Frot et al., 1999, 2007; Ohara et al., 2004; Garcia-Larrea, 2012; Bastuji et al., 2016), mid-cingulate and supplementary motor areas ACC/SMA (Lenz et al., 1998b, Ohara et al., 2004; Frot et al., 2008; Bastuji et al., 2016), contralateral sensori-motor (Frot et al., 2013), contralateral posterior parietal cortex (Bastuji et al., 2016), bilateral prefrontal (Bastuji et al., 2016; Frot et al., 2014), and posterior cingulate cortices (Stancák et al., 2010, 2013; Bastuji et al., 2016). Initial positions of putative dipolar sources were directly taken from intracortical recording mean coordinates (Frot et al., 2013; Bastuji et al., 2016; see Supporting Information, Table S1) and kept fixed, while orientation was allowed to adjust to the best-fitting orientation and strength was allowed to vary over the entire interval.

To mitigate the unavoidably arbitrary nature of using sEEG coordinates to seed dipoles, the model was further refined by allowing local adjustments within a “bounding

¹Goodness of Fit (GoF) is defined as $1 - \text{RV}$, where RV (residual variance) is defined as the sum over channels and time-points of the squared difference of data and model values, divided by the sum over channels and time-points of the squared data values.

box,” defined for each dipole from a functional MRI meta-analysis (Neurosynth database [Yarkoni et al., 2011]; feature keyword “nociceptive,” unthresholded forward inference maps; <http://neurosynth.org/>, last accessed on the 15th of June 2017) to encompass the entire local meta-analysis activation. For two dipoles (inferior PPC and PCC), no meta-analysis activation was present; the bounding box was therefore defined on each axis as the maximum spread of intracranial electrode coordinates (Supporting Information, Table S2). Dipoles were allowed to change position in 1 mm steps within this bounding box until they reached a local best position (Table I), allowing the grand-average model to attain a goodness-of-fit of 95.8% (Supporting Information, Fig. S2).

The model was then applied to individual data, allowing changes only in orientation and strength of the source (not position). Depending on both dipole and individual participant, several peaks may be considered to reflect the initial and/or main activity of the source. Here, the main (largest) peak in the data was considered. Automatic maximum (peak) and preceding minimum (onset) detection was performed over the entire interval; all automatic measurements were validated by visual inspection and corrected if necessary. If any ambiguity (e.g., two equivalent neighboring peaks) occurred, the peak with latency closest to the main (largest) peak in the grand-average data was chosen.

Intracortical Recordings

Intracortical recordings in response to laser stimuli identical to those used here were obtained in 27 epileptic patients undergoing stereotactic electrode implantation for diagnosis of their refractory epilepsy (SEEG recordings). Acquisition and data analysis were similar to scalp evoked potential analysis, except data were screened for abnormal epileptic activity. Responses from a wide range of cortical regions were analyzed, each including a variable number of subjects (numbers given in Results). Unless stated otherwise, bipolar recordings from adjacent contacts (2-mm-long contacts, separated from each other by 1.5 mm) were computed to allow local activity recording (please see Frot et al. [2013] and Bastuji et al. [2016] for a complete description of the procedure).

Statistical Analysis

In GraphPad-Prism5, after assessing normality of distributions, onset and peak latency measures were entered in a repeated-measures one-way analysis of variance (RM-ANOVA), with “source location” (L.PIMO, R.PIMO, L.Frontal, R.Frontal, L.S1/M1, L.PPC, ACC/SMA, PCC) as “within” factor. Tukey’s test was used to investigate significant post-hoc effects. Goodness of fit values at baseline and during the interval that encompasses the classically described scalp N1/P1, N2 and P2 activities were compared

TABLE I. MNI coordinates of the eight dipoles

Dipole	MNI coordinates		
	x	y	z
L.PIMO	−49	−11	10
L.S1/M1	−30	−30	60
L.PPC	−47	−49	40
L.Frontal	−27	39	13
R.Frontal	31	44	13
R.PIMO	49	−11	10
ACC	0	6	38
PCC	−2	−52	25

Abbreviations: L.PIMO, left posterior insula-medial operculum; L.S1/M1, left somatosensory-motor cortex; L.PPC, left posterior parietal cortex; L.Frontal, left frontal cortex; R.Frontal, right frontal cortex; R.PIMO, right posterior insula-medial operculum; ACC, anterior cingulate cortex; PCC, posterior cingulate cortex.

using two-sided paired *t* tests. To compare modeled activity with intracranial recordings, onset and peak latencies obtained through both methods were tested against each other for each brain structure, using two-sided unpaired *t* tests with Welch’s correction when variances were unequal. Significance level was set to $P = 0.05$ (two-sided). To further compare activity over the entire interval, average waveforms were Z-score normalized in Matlab (Mathworks®), and cross-correlation was computed across all pairs (i.e., each dipolar waveform was compared to all intracranial waveforms). As we were interested in evaluating whether or not activity from intracranial sources and modeled sources has a similar time-course, under the assumption that there is no electrical conductance delay between intracranial sources and scalp sensors, only a single (zero) time-lag was considered. Results are expressed in the text as mean $\pm$ SD. When referring to sources in what follows, the terms “contralateral” and “ipsilateral” will be used relative to the stimulation (right) side.

RESULTS

Source Reconstruction

An 8-dipole model (Fig. 1) yielded a goodness of fit (GoF) of $\sim 95.8\%$ for the grand-averaged data over the first second following nociceptive laser stimuli, while application of the model to single subjects resulted in an average GoF of $91\% \pm 3\%$ [range: 82–95%]. Goodness of fit was significantly higher ($t(17) = 7.7$, $P < 0.0001$) in the time-window which encompasses the classically described scalp N1/P1, N2 and P2 activities (135–495 ms, GoF = $92.4\% \pm 3\%$) than during the baseline (−100 to 0 ms, GoF = $72.5\% \pm 10\%$). Amplitude and orientation of sources can be found in Supporting Information, Tables S3 and S4 and Figure S1.

There was a significant effect of source location on onset latencies ($F(7,17) = 49.3$, $P < 0.0001$). Posterior cingulate cortex (PCC) had a significantly later onset than all other

Figure 1.

LEP source model. (A) Eight dipoles were seeded in distinct brain regions guided by data from intracranial recordings and functional imaging meta-analyses; their position on the standard MRI in BESA is shown as the intersection of the red lines on three planes (sagittal, coronal, and axial, respectively). Left sources are contralateral to stimulation delivered to the right hand. Abbreviations: L. PIMO, left posterior insula-medial operculum; R. PIMO, right posterior insula-medial operculum; L. S1/M1, left somatosensory-motor cortex; L.PPC, left posterior parietal cortex; ACC, caudal anterior cingulate cortex; L. Frontal, left frontal cortex; R. Frontal, right frontal cortex; PCC, posterior

cingulate cortex. (B) Average time-courses of each dipole are represented as mean (thick black line) and standard error of the mean (SEM, shaded grey area) across individual models ($N = 18$), when applied to a 900 ms epoch of high-density EEG data following a nociceptive laser stimulus. (C) Three “key” LEP topographies, corresponding to the classically described N1, N2, and P2 laser-evoked potentials are illustrated as original recordings (top, shown with an average reference) and reconstructed model (bottom). [Color figure can be viewed at wileyonlinelibrary.com]

sources ($P < 0.001$). The anterior cingulate cortex and supplementary motor area (ACC/SMA) source onset was significantly later than for all other sources ($P < 0.01$), except L.Frontal (left frontal cortex) (Fig. 2A, black symbols; Table II). Other onset latencies did not differ significantly.

Dipolar sources also peaked at significantly different latencies ($F(7,17) = 98.97$, $P < 0.0001$) (Fig. 2B, black symbols; Table II). The PCC source, maximally active around 400 ms, peaked significantly later than all other sources ($P < 0.001$). The source in the posterior insula ipsilateral to stimulation (R.PIMO) peaked also later than its contralateral counterpart (L.PIMO), and the R.Frontal, L.S1/M1 and L.PPC sources ($P < 0.05$), whose peak latencies did not differ between themselves. Finally, medial cingulate source (ACC/SMA) peaked later than L.PIMO and L.PPC ($P < 0.05$).

Comparison to Intracortical Recordings

Next, we compared dipolar source activity to intracortical data recorded from locations surrounding the modeled dipole position (Fig. 3A,B). Specifically, dipolar source activity from PIMO, frontal regions, S1/M1, PPC, ACC/SMA, and PCC (number of participants: $N_{\text{model}} = 18$ for all sources) were compared with intracranial data from posterior operculo-insular cortex ($N = 25$), frontal Brodmann's area (BA) 46 ($N = 13$), pericentral areas BA1/2 ($N = 4$; referential grand-average data only), postero-inferior parietal cortex BA 40 ($N = 9$), caudal anterior cingulate (BA24) ($N = 8$), and internal supplementary motor area (BA6) ($N = 7$), and ventral posterior cingulate cortex (BA23–29) ($N = 5$), respectively. Very few intracranial responses were recorded ipsilateral to laser stimulation; hence no comparison between intracranial and modeled data was made for ipsilateral (right) operculo-insular and frontal sources (R.PIMO and R.Frontal).

The timing of intracranial recorded data and modeled dipolar sources, as estimated by their respective onset and peak latencies, was in general concordant (Fig. 2). No significant latency difference was observed between actual and modeled operculo-insular, primary somatosensory (peak L.S1 B² in Frot et al., 2013), and posterior cingulate cortex activities. Anterior cingulate cortex and left frontal cortex activities had respectively significantly earlier and later onsets in intracranial than in modeled scalp recordings (ACC: $t(24) = 3.5$, $P = 0.002$; L.Frontal: $t(29) = 4.3$, $P = 0.0002$), but presented no peak latency differences. Finally, L.PPC had significantly earlier onset and peak latencies in modeled than in intracranial recordings (onset: $t(25) = 6.7$, $P < 0.0001$; peak: $t(25) = 6.8$, $P < 0.0001$).

²If peaks L.S1 A or C (in Frot et al. [2013]) were considered as onset in intracranial data, modeled activity had a respectively later ($t(20) = 3.1$, $P = 0.006$) or earlier ($t(20) = 4.6$, $P = 0.0002$) onset in the modeled S1/M1 source as compared to intracranial recordings.

Figure 2.

Onset (A) and peak (B) latencies of the first major activity of each source, for the modeled sources (black symbols) and the intracranial recordings (grey symbols). Error bars are standard error of the mean. Statistically significant differences between modeled and intracranial recordings are denoted by ** ($P < 0.01$) and *** ($P < 0.001$); statistically significant differences within modeled source activity latencies are not explicitly marked here (please refer to Results). The absence of intracranial data for ipsilateral (right) operculo-insular and frontal sources (R.PIMO, R.Frontal) is due to the scarcity of such information in intracranial recordings; hence, no comparison to modeled data was made. See previous caption for dipole abbreviations.

Interestingly, modeled anterior cingulate cortex activity seemed to find a better match with referential (i.e., recording from a larger area of cortex) rather than bipolar intracortical recordings from ACC, and with SMA (internal BA6) referential recordings (Fig. 4); the pooled activity from these two areas was therefore considered for further analysis.

To allow further comparison of the waveforms shape across the entire interval, cross-correlation at zero time-lag was computed for all pairs of waveforms, cross-correlation being a measure of morphological similitude between two signals. As shown in Figure 5, cross-correlation (c-c) values

TABLE II. Onset and peak latencies for the first major dipolar activity (in ms)

		L.PIMO	L.S1/M1	L.PPC	L.Frontal	R.Frontal	R.PIMO	ACC/SMA	PCC
Onset (ms)	Mean	116	120	114	118	117	119	136	164
	SD	13	11	10	18	11	12	10	15
Peak (ms)	Mean	211	205	202	215	208	236	228	372
	SD	20	20	27	29	24	34	19	50

Abbreviations: L.PIMO, left posterior insula-medial operculum; L.S1/M1, left somatosensory-motor cortex; L.PPC, left posterior parietal cortex; L.Frontal, left frontal cortex; R.Frontal, right frontal cortex; R.PIMO, right posterior insula-medial operculum; ACC, anterior cingulate cortex; PCC, posterior cingulate cortex.

between modeled sources and their intracranial counterparts were good to excellent (0.73–0.94) for the operculo-insular, frontal, and posterior cingulate areas and pooled referential ACC/SMA (against $c-c = 0.4$ for comparison with bipolar recordings). Cross-correlation values were medium (0.49 and 0.57, respectively) for the PPC and S1/M1 sources, owing to the presence of multiple peaks of activity within these regions in the model, but not in intracranial data.

DISCUSSION

Nociceptive laser-evoked potentials (LEPs) are an important tool both in basic research and in the clinics, where they play a major role in neuropathic pain diagnosis (reviews in Cruccu et al. [2008] and Garcia-Larrea [2012]), and possibly prediction (Vartiainen et al., 2016). This study proposes a source model of LEPs using a resolutely different approach to previous work, by seeding sources of high-density EEG at locations gathered from other neuroimaging data. It also provides for the first time a direct comparison between reconstructed source activities and invasive intracortical recordings. Seeding putative sources on the basis of intracranial recordings to the same stimuli is intuitive, and yielded excellent results: not only the goodness of fit of the model was excellent at both group and individual level, but the *time course and overall morphology* of the calculated source waveforms were strikingly similar to those of their intracranially recorded counterparts.

Similarities and Discrepancies of Modeled and Intracranial Activities: Sources are Regional in Nature

Comparison of modeled and intracortical recordings revealed strikingly similar time-courses for responses in regions receiving major spino-thalamic input (Dum et al., 2009); thus, operculo-insular activities recorded intracranially were barely distinguishable from their modeled counterparts, and their onset and peak latencies were statistically not different (Fig. 3, top). Arguably, it would have been interesting to further differentiate between inner parietal operculum and posterior insula activities (Frot et al., 2007). However, these two regions receive virtually

simultaneous spinothalamic input (Dum et al., 2009; Bastuji et al., 2016); their respective spatial projections to the scalp are highly superimposed in time and space and it may not be possible to differentiate between them from scalp EEG data alone—at least with the electrode density used in this study. The use of a regional source instead of a dipole, allowing orthogonally oriented activities to express themselves (e.g., Scherg, 1992), combined with magnetic MEG recordings would possibly help disentangle these activities.

The above example points to a recurring theme: the number of modeled sources is less than that of actual areas recorded with iEEG, which means that modeled sources are likely to group together activity from closely spaced generators. In our case, “PIMO” sources lumped activity from the suprasylvian operculum and the posterior insula; “frontal” sources most likely associated activities from the infero frontal cortex and anterior insula, and the “ACC/SMA” dipole combined mid-anterior cingulate cortex with supplementary motor area activity. Indeed, intracranially recorded LEPs from closely located regions, often display high similarity in both time-course and morphology (see, e.g., figure 2 in Bastuji et al. [2016]); therefore, it should be kept in mind when interpreting dipolar sources that, despite being graphically “point-like,” they reflect activity from extended areas and are “regional” in nature. This is particularly evident in the ACC/SMA source, which not only reflected pooled regional activity including ACC and SMA, but was also much better correlated in shape and timing with the intracranial response recorded in *referential* mode, relative to *bipolar* mode. The referential intracranial EEG response gathers activity from a larger volume than the bipolar response, including from neighboring areas MCC and SMA, probably explaining its close similitude with the modeled source.

A similar point might be argued for the sensori-motor cortex (S1/M1 source) where early activity showed good correspondence, but a late “rebound” peak was present in modeled but not intracranial data, and for the posterior parietal cortex source, which displayed two peaks (one early, one late) in the model against only one peak (less defined and later) in the intracranial recordings. These two sources displayed the lowest cross-correlation values, and L.PPC presented significant latency differences with

Figure 3.

Comparison of modeled and intracortical recorded laser-evoked activities. (A) Normalized (Z-score transformed) mean activities of modeled sources (full line) were superimposed to intracortical bipolar activities (dashed line), for contralateral posterior operculo-insular, somatosensory (BA1: referential), posterior parietal (BA40) and frontal (BA46) cortices, and middle and posterior cingulate cortex. (B) For each structure, position of the seeded dipole (full black dot) was compared to that of the intracortical recording contacts (black circles) in MNI space, overlaid on an individual 3-D MRI (overlay and slicing in MRICroGL). The absence of intracranial data for ipsilateral (right) operculo-insular and frontal sources (R.PIMO, R.Frontal) is due to the scarcity of such information in intracranial recordings; hence no comparison to modeled data was made and only 6 (contralateral) comparisons are presented.

intracranial recordings, suggesting that activity in the parietal region is not fully accounted for in this model. Several factors may have interacted to contribute to this situation: a) LEP-related activity in S1 is less consistently reported than for other regions (e.g., operculo-insular cortex) and may be more dependent on experimental design, b) the superior parietal region is rarely explored in sEEG and measurement numbers were consequently few ($N = 4$ for BA 1/2), and c) other close cortical regions are likely to have contributed to the modeled data, that could not be explored by sEEG here, such as area 3a and 3b (Baumgärtner et al., 2011), or area 5 and 7 (superior parietal cortex). When area 7 was explored in sEEG (unpublished data), relatively sharp, early responses to LEPs were seen, more consistent with the first peak of activity of the PPC dipole. Inclusion of such a source could possibly resolve some of the discrepancies seen here, but would likely necessitate a larger number of electrodes (please see Limitations for further discussion).

Onset and Peak Latencies: Multiple Sources are Active Concomitantly

While the peak latencies of sources reported here are consistent with those measured in intracranial data (e.g., Lenz et al., 1998a,b; Frot et al., 2008; Ohara et al., 2004; Bastuji et al., 2016), it may seem strange that the onset of ACC and S1 sources was relatively late with respect to PIMO. Some investigators have indeed described S1 and ACC responses to noxious laser as being later (Ohara et al., 2004 for ACC/SMA), or earlier (e.g., Valentini et al., 2012 for S1) than operculo-insular potentials; however, other data suggest very similar, virtually simultaneous onset latencies for PIMO, S1, and ACC (Ploner et al., 1999; Frot et al., 2008, 2014). One likely explanation of S1 and ACC latency delays in the present work is that their onset latencies were considered relative to the *main peak* in each source. However, as shown in Figure 1, both S1 and ACC main sources were preceded by a small but well-defined activity of opposite polarity, which is likely to represent the actual onset of activity in this region. Had we taken this point as onset, it would have been virtually identical to that of the contralateral operculo-insular source. Indeed, intracranial recordings from the ACC–MCC area often show a double-peaked response, in which the early component is simultaneous to PIMO responses (e.g., fig. 3 in Frot et al. [2008]).

One striking feature of the source model developed here is that none of the scalp-recorded LEP classical “peaks” (N1, N2, or P2) appeared to reflect activity from single sources. While this has long been acknowledged by a number of authors, results from early models of LEPs that included a smaller number of sources (Tarkka and Treede, 1993; Bromm and Chen, 1995; Valeriani et al., 1996, 2000; Schlereth et al., 2003; Wang et al., 2007) have remained for many authors a “gold standard,” and it is commonplace in literature, especially clinical, to find N1 peak equated with operculo-insular and/or primary somatosensory

Figure 4.

Comparison of modeled and referential intracortical laser-evoked activities in caudal anterior cingulate cortex. (A) Normalized (Z-score transformed) mean activities of modeled ACC source (full line) and intracortical referential activities (dashed line), for ACC, neighboring BA6 (SMA), and the combination of both ACC and SMA activities. (B) For each structure, position of the seeded dipole (full black dot) is compared to that of the

intracortical recording contacts (black circles) in MNI space. A striking improvement in timing and shape similitude becomes evident when intracranial recordings from caudal ACC proper and its neighboring SMA (BA6) are considered referentially rather than in bipolar mode (Fig. 3), indicating that the modeled source most likely accounts for activity from both areas, and could not discriminate between them.

activity and scalp N2–P2 with cingulate cortex activity (Garcia-Larrea et al., 2003; Kakigi et al., 2005). This study reinforces the idea that these scalp-recorded peaks reflect the combined, almost concomitant activity from many sources. In light of the present results, a useful schema for interpretation would be to consider three broad periods of scalp EEG activity: (i) one very short initial activity in opercular and posterior insular regions, manifested in surface recordings by bilateral negative fields over the temporal scalp (“N1”) often reversed in polarity at anterior frontal electrodes and accompanied by sensori-motor and posterior parietal activity; (ii) a broad negative/positive vertex complex (“N2–P2”) reflecting the combined activity in bilateral frontal, antero-insular, and ACC/SMA areas;

and (iii) finally, a broader and late (>400 ms) positive wave of centro-parietal scalp distribution (P2b or “P400,” Legrain et al., 2002), enhanced in conditions involving cognitive processing, and which, when present, would include posterior cingulate source activation.

Late Posterior Cingulate Source: Experimental Context and Self-Awareness

The current work comes in the wake of more than two decades of attempts at modeling the sources of laser-evoked potentials (LEPs), and most of this past work ignored the possible activation of a posterior cingulate

Figure 5.

Cross-correlation matrix. Zero-lag cross-correlation value (numerical and color-coded) of the comparison between each normalized intracortical activity (vertically distributed) and normalized modeled activity (horizontally distributed). Values close to 1 (toward red) indicate high similarity of the waveforms, while values closer to -1 (toward blue) indicate anticorrelation. [Color figure can be viewed at wileyonlinelibrary.com]

source (e.g., reviews in Garcia-Larrea et al., 2003; Kakigi et al., 2005; see also Perchet et al., 2008). A small number of studies—often in very few participants—suggested the activation of a late posterior cingulate source, but differed widely in the consistency of its location or latency (Bromm and Lorenz, 1998; Bentley et al., 2002, 2003). More recently, posterior cingulate activity estimated from scalp LEPs has been reported, mainly in experiments using higher electrode densities and involving cognitive or emotional contexts, for example, during pain anticipation (Brown and Jones, 2008), C-fiber stimulation (Stancak et al., 2011), or modulation by emotional sounds or pictures (Stancák and Fallon, 2013a, 2013; Fallon et al., 2015).

In the present work, explanation of activity after 300 ms poststimulus clearly required the addition of a source located in posterior cingulate cortex (PCC), the activity of which was very much in line with intracranial responses (see their superposition in Fig. 3, bottom). Both in intracranial EEG and in the source model, PCC activity occurred late, and the source explains a substantial portion of data variance in a time-window where other sources are abating, peaking around ~400 ms. In the remainder of this paragraph, we speculate on the possible functional significance of such an activation. Activity in this region,

implicating retrosplenial cortex (Brodmann's areas BA29 and BA30, neighboring the splenium of the corpus callosum), and the more dorsal posterior cingulate areas BA23 and BA31 (Vogt, 2005; Vann et al., 2009), has been consistently linked to a number of high-order activities including episodic memory and spatial processing, possibly supporting coordinate transformations between allocentric and egocentric frames (e.g., Lin et al., 2015; Bicanski and Burgess, 2016; for a review, see Vann et al., 2009). More specifically, the PCC seems to play a crucial role in integrating stimuli with aspects of self-consciousness, such as the sense of self-location (in space) and of body ownership (Guterstam et al., 2015) and may be more generally involved in a network for reflective self-awareness (e.g., Kjaer et al., 2002; Northoff and Bermpohl 2004; for reviews, see Brewer et al., 2013; Demertzi et al., 2013). The PCC activity observed here developed concomitantly, and peaked *after* the conscious detection of nociceptive stimuli by participants (i.e., later than their motor responses), and this was also the case in intracranial EEG studies (Bastuji et al., 2016), which is consistent with a possible contribution to stimulus awareness, or to its modulation and further cognitive processing such as memory encoding. Concordant with this view, subjective reports of

touch in the absence of actual somatosensory stimulation were shown to result in activation of a network comprising the posterior cingulate and precuneus together with medial frontal cortex (Lloyd et al., 2011), while subliminal, imperceptible somatosensory stimulation resulted in decreased functional connectivity between somatosensory and PCC cortices as compared to rest (Nierhaus et al., 2015). However, PCC activation is absent from many neuroimaging studies of pain, and PCC *deactivations* (i.e., a decrease in BOLD signal) have been reported, for example, in response to painful punctate stimuli, in the context of hyperalgesia (Iannetti et al., 2005), or in the development of wind-up pain (Perrotta et al., 2016). While these deactivations have often been interpreted in terms of reallocation of resources away from the default mode network (DMN, of which PCC is a key node), their physiological and functional significances are still poorly understood and are by no means incompatible with electrophysiological findings operating on a different spatial and temporal scale.

Limitations and Perspectives

While the sensor distribution used here (128 electrodes) was one of the highest reported in LEP literature, the mean interelectrode distance of 2.5 cm did not allow discriminating between closely activated areas such as, for instance, the anterior insula and the inferior prefrontal cortex, which had to be grouped together in a single dipole. Higher electrode densities (256 electrodes), digitization of electrode positions and use of individual magnetic resonance images should help make that distinction in the future. Beyond such technical improvements, the current model could have benefited from the addition of dipoles describing activities that have been recorded intracranially but are missing here. Perigenual cingulate cortex responses (Bastuji et al., 2016) are an example of such an activity; they are however potentially more labile and thought to be linked to the “suffering” aspects of the pain experience, which typically need much higher intensities than those used herein and are minimal in the response to phasic, moderate experimental pain. This, together with the technical problems of modeling sources in areas close to skull “holes” such as the orbits, determined our choice not to include an equivalent dipole.

Another serious limitation is the lack of description of “deep” sources, known to be active in the studied time-window. Indeed, it has been shown that the amygdala is activated as early as the posterior insula, probably via the disynaptic spino-parabrachial pathway triggered in parallel to the spinothalamic tract (Bastuji et al., 2016; review in Veinante et al., 2013). However, the amenability of this activity to source modeling is challenged by a number of considerations: (i) the amygdala’s configuration is thought to result in a relatively closed field (LaBar and Warren, 2009), unlikely to produce scalp-recordable potentials; (ii) it is located deep within the brain, leading to strong decay

of activity amplitude with distance, and to spatial blurring; (iii) any resulting activity may be obscured by the other—numerous—sources active at the same time, and located more externally, with an optimal configuration. A similar point may be made for the hippocampal formation.

Finally, this work carries limitations that are inherent to intracranial recordings: electrode implantation is determined by the patient’s symptoms and clinical hypotheses, resulting in an uneven exploration of brain-space, with a bias toward the temporal, parietal, and frontal lobes. Occipital cortex was rarely explored but is not expected to have a major contribution to LEPs, especially given the participants were not looking at the stimulated hand. Another consequence of implantation methods is that some regions are more perpendicular (e.g., ACC) than parallel (e.g., operculo-insular) to the axis of the implanted electrode, resulting in an ambiguity concerning the amplitude of activity recorded at that location (minimized for a perpendicular source, maximized for a parallel source). Hence we did not compare amplitude relationship between sources at the intracranial and modeled level. Last, in the corpus of intracranial recordings that was accessible, few responses were recorded ipsilateral to laser stimulation; hence no comparison between intracranial and modeled data was made for ipsilateral (right) operculo-insular and frontal sources. Our current findings, however, suggested a 25 ms lag between contralateral and ipsilateral operculo-insular responses, which is well in consistency with previous sEEG literature (Frot and Mauguère, 2003). To the best of our knowledge, this information is not available for the frontal cortex sources.

CONCLUSION

The model of LEP sources proposed here is, to the best of our knowledge, the most comprehensive description of early nociceptive activity based on scalp responses reported so far. Even though it remains incomplete (e.g., lacks activity from deep structures such as the amygdala/hippocampus) and should be furthered by the use of higher electrode densities, its strong congruence with direct intracranial recordings in humans confirms its validity, and illustrates that multiple concomitant activities evoked by nociceptive input can be disentangled using high-density EEG scalp recordings. This opens the door to studies investigating the specific contribution of these different brain structures to the cortical processing of nociceptive stimuli and their modulation, all the way from unconscious nociceptive processing to conscious awareness of these salient stimuli.

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CONFLICTS OF INTEREST

None to declare.

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