Point-Process Deconvolution of fMRI BOLD Signal Reveals Effective Connectivity Alterations in Chronic Pain Patients

Guo-Rong Wu · Daniele Marinazzo

Abstract It is now recognized that important information can be extracted from the brain spontaneous activity, as exposed by recent analysis using a repertoire of computational methods. In this context a novel method, based on a blind deconvolution technique, is used to analyze potential changes due to chronic pain in the brain pain matrix’s effective connectivity. The approach is able to deconvolve the hemodynamic response function from spontaneous neural events, i.e., in the absence of explicit onset timings, and to evaluate information transfer between two regions as a joint probability of the occurrence of such spontaneous events. The method revealed that the chronic pain patients exhibit important changes in the insula’s effective connectivity which can be relevant to understand the overall impact of chronic pain on brain function.

Keywords Point process · BOLD deconvolution · Effective connectivity · Granger causality · Chronic pain

Introduction

Recent results have shown that chronic pain is a condition that, beyond the feeling of acute pain, affects normal brain function and structure, causing cognitive impairments, including depression, sleeping disturbances and decision-making abnormalities (Apkarian et al. 2004, 2005; Baliki et al. 2008).

Disruptions and modifications in cortical dynamics due to chronic pain have been demonstrated using functional magnetic resonance imaging (fMRI), both studying activation in response to external stimulation (Derbyshire 1999; Peyron et al. 2000) as well as using seed based correlation analysis during the execution of simple attention demanding tasks (Baliki et al. 2008). In particular, the latter study showed for the first time that the dynamics of the default mode network (DMN) is disrupted in chronic pain.

A recent study (Baliki et al. 2012) reported that it is even possible to identify a temporal profile of brain parameters which changes during pain chronification in patients suffering sub-acute back pain. These changes involve medial prefrontal regions of the cortex, notably the insula as well as the nucleus acumbens. The insular cortex is often activated bilaterally during noxious somatosensory stimulation and has been suggested to play an important role in pain processing (Coghill et al. 1994, 1999). At the same time, the extensive connectivity of the insula suggests a multifaceted role in the dynamic of pain perception, and the need to develop new methods to unravel its complexity.

The present study uses a novel approach to detect neural events in BOLD signals to investigate the network of directed dynamical influences between brain regions involved in pain processing, in particular the insula sub-regions. The approach is able to deconvolve the hemodynamic response function (HRF) to spontaneous neural events, i.e., in the absence of explicit onset timings, and to evaluate information transfer between any two regions as a joint probability of the occurrence of such spontaneous events.
The paper is organized as follows: the next section describes the brain imaging data as well as the numerical methods for deconvolution and Granger causality mapping. In Sect. 3 the main findings are presented indicating important changes in the insula’s effective connectivity in chronic pain patients. The paper closes in Sect. 4 with a brief discussion on the method’s novelty as well as on the physiological relevance of the results.

Materials and Methods

fMRI Data Acquisition and Preprocessing

The data analyzed here correspond to 12 chronic back pain patients (CBP) (age: 29–67 years, mean/SD=51.2/11.1; Beck depression index: 7.25 ± 1.3; Beck anxiety index: 9.12 ± 17; pain duration: 6.3 ± 0.98 years [mean ± SD]) and 20 healthy controls (HC) (age: 21–60 years, mean/SD=38.4/3.43; Beck depression index: 8.96 ± 1.3; Beck anxiety index: 7.46 ± 1.98). All subjects were right-handed and all gave informed consent to procedures approved by Northwestern University (Chicago) IRB committee (Tagliazucchi et al. 2010). There is no significant difference in depression indices between the groups. The patients participated in an earlier study, and their clinical and demographic data, as well as pain-related parameters, have been described in (Tagliazucchi et al. 2010; Baliki et al. 2008).

Participants were asked to lay still in the scanner and to keep their mind blank, eyes closed and avoid falling asleep (Fox et al. 2005). Functional magnetic resonance data was acquired using a 3T Siemens Trio whole-body scanner with echo-planar imaging capability using the standard radio-frequency head coil. Scanner parameters were similar to those used in an earlier study (Baliki et al. 2008). For each subject, a total of 300 images (spaced by 2.5 s, TR) were obtained, in which the blood oxygenation level dependent (BOLD) signal was recorded for each one of the 64 × 64 × 49 sites (voxels of dimension 3.4375 × 3.4375 × 3 mm).

Preprocessing of BOLD signal was performed using FMRIB Expert Analysis Tool (Jezzard et al. 2003). Data preprocessing included motion correction using MCFLIRT, slice-timing correction using Fourier-space time-series phase-shifting, non-brain removal using BET, spatial smoothing using a Gaussian kernel of full-width-half-maximum 5 mm. Brain images were normalized to standard space using the MNI 152 template using FLIRT and data was resampled to 4 × 4 × 4 mm resolution. A zero lag finite impulse response filter was applied to band pass filter (0.01–0.1 Hz) the functional data (the lower frequency was chosen to avoid noise related to scanner drift and the higher frequency was chosen to eliminate high frequency artifacts related with physiological noise and head motion) (Cordes et al. 2000, 2001). An independent component analysis (ICA) de-noising procedure (Beckmann and Smith 2004) consisting of edge removal and high frequency artifacts by linear regression was performed using Melodic.

A predefined pain matrix mask (described in Table II of Cifre et al. 2012) was employed in the present study, and is visualized in Fig. 1 and as contours in Figs. 2 and 3. As a control, a region with no expected pain effects, the primary visual cortex (BA 17) was used for comparison.

Spontaneous Point Event Detection and HRF Deconvolution

Previous studies have shown that the hemodynamic processes are inhomogeneous across the whole brain (Handwerker et al. 2012). These inhomogeneities acting over the hemodynamic response can limit the inferences of temporal precedence (Valdes-Sosa et al. 2011) which are central for establishing effective connectivity between regions. To overcome this limitation, a novel blind deconvolution technique (see Fig. 1) was developed recently for resting-state BOLD-fMRI signals (Wu et al. 2013). The approach relies on the idea that the resting-state BOLD spikes can be seen as the response to spontaneous neuronal events, something supported by the increasing evidence of non-random patterns governing the dynamics of the brain at rest (Tagliazucchi and Chialvo 2011; Petridou et al. 2013).

These spontaneous events can be detected by point process analysis (PPA), picking up BOLD fluctuations of relatively large amplitude (Tagliazucchi et al. 2010, 2011, 2012). After detecting these resting-state BOLD transients, the BOLD event onsets are stored for further reconstruction of the HRF. The voxel-specific HRF is obtained by fitting raw BOLD signal with triggered averages and shifted BOLD event onsets, in order to finally recover signals at the neural level by Wiener deconvolution (Glover 1999).

To characterize the HRF elicited by spontaneous point events, two easily interpretable parameters of the HRF which estimate the potential changes in neuronal activity (Lindquist and Wager 2007) were calculated: the response height and the time to peak.

Granger Causality Mapping

To explore the large scale directional interactions between insula and neuronal assemblies in other cortical regions of pain matrix, Granger causality (GC) analysis is applied on the deconvolved BOLD-fMRI data. Here we provide a brief introduction to GC. Given \( k \) covariance-stationary variables \( \{x_i(t)\}_{i=1,…,k} \), the state vectors are denoted \( X_k(t) = (x_2(t-m), \cdots, x_k(t-1)) \), \( m \) being the model order. Let \( e(x_k|Y) \) be the mean squared error prediction of
The Granger causality index from $b_{2}^{RN}/C2$ to $a_{2}^{RN}/C2$ is defined as follows:

$$c(b \rightarrow a) = \log \frac{\epsilon(x_{b}|X_{a})}{\epsilon(x_{a}|X_{a} \cup X_{b})}$$

in addition, for further statistical analysis, GC value $c$ is transformed into $c' = \sqrt{n \cdot c - (m - 1)/3}$, which is
considered to be approximately normal (where $n = N - m$. If $c = 0$, $n \cdot c \sim \chi^2(m)$) (Geweke 1982).

The model order used in this study is $m = 1$, evaluated by leave-one-out cross-validation, and common in fMRI GC studies (Roebroeck et al. 2005). Regression models were estimated by the ordinary least squares algorithm.

Finally, pairwise causal interaction was investigated by mapping the influence between the seed ROI of bilateral insula and the deconvolved BOLD time series of the individual voxels belonging to the entire pain matrix (see above).

**Statistical Analysis**

To compute the group differences (i.e., patient vs. control groups) on pain matrix at voxelwise level, a two-sample $T$ test was implemented in SPM8, independently for HRF parameters and seed based GC mapping. Statistical significance was estimated via a Monte Carlo simulation (Alphasim). A cluster-wise threshold of $p<0.05$ by combining a $p<0.04$ individual voxel threshold and different minimum cluster size of $k$ contiguous voxels, corrected for multiple comparisons (implemented in the REST toolbox, www.restfmri.net). Gaussian filter width was estimated from each SPM T-map, and $k$ varied with Gaussian filter width; cluster connection radius 5 mm, and 1,000 iterations).

**Results**

**Spontaneous Hemodynamic Response**

Figure 2 summarizes the main findings concerning the parameters of spontaneous BOLD activity. It is seen that in terms of the HRF’s time to peak (compared to the control subjects) patients response function was characterized by longer time to peak latency in precentral and postcentral gyrus, but shorter time to peak latency in anterior cingulate, posterior cingulate, medial frontal gyrus, dorsal anterior cingulate cortex (dACC), orbitofrontal cortex (OFC), precuneus (PCUN) and retrosplenial cingulate cortex (RSC) (see bottom panel of Fig. 2).

Concerning the other parameter, the HRF response height, the major modifications were found predominately in the insula. Other regions included putamen, superior temporal gyrus, parahippocampal gyrus, caudate and amygdala (AMG) (see top panel of Fig. 2). As a control we looked at the same quantities in the primary visual cortex V1, a region not involved in pain processing, finding no significant difference between groups.

**Seed-Based Granger Causality Mapping**

To compute the effective connectivity mapping of the insula, we selected seeds ROIs based on the two sample $t$-test results of the hemodynamic responses. They were centered at the two peaks $T$-values (response height) inside the bilateral insular regions (MNI coordinates: left ventral posterior insula (l-vPI), $[-40 -4 -4]$; right dorsal anterior insula (r-dAI), $[32 20 8]$; with sphere 8mm diameter). GC mapping was then independently implemented for these two subregions of the insula.

The GC mapping between left vPI and the following regions exhibited lower information transfer, both incoming and outgoing, for patients: medial frontal gyrus, precentral gyrus, postcentral gyrus, premotor cortex (BA6), supplementary motor area (SMA), paracentral lobule (PCL), primary motor cortex (BA4), primary somatosensory cortex (BA3,1 and 2).

For the case of the right dAI it was found that there is significantly less information transfer for voxels located in: premotor cortex, superior frontal gyrus, supplementary motor area, medial frontal gyrus, paracentral lobule, precentral gyrus, postcentral gyrus. No significant difference in the effective connectivity was reported from the pain matrix to right dAI.

The results are presented in Fig. 3 and summarized in Table 1.

**Joint Probabilities of Neural Events**

To further characterize the causal effects from and to the insula, and to demonstrate how instantaneous neural events detected in the BOLD signal can be not only helpful for deconvolution, but can even reveal themselves this causal effects, we investigated the relative timing of the onset of the neural events in the paracentral right lobule (see Table 1) with respect to those occurring in the left vPI.

Every time that an event was detected in the time series of a voxel belonging to the paracentral right lobule, we searched for other events occurring in the left vPI centered at the onset, where $L = 3$ TR. These co-occurring events were accumulated in time for each spatial location, defining in this way the joint distribution probability reported in Fig. 4. Thus this distribution describes how events in the left vPI trigger events in the paracentral right lobule (positive lags) or vice-versa (negative lags). The distributions in the patient and control groups are compared with randomized cases in which the timing of the onsets in the Insula were randomized (on 500 trials), preserving the original values of the inter-events times (Fig. 4). These distributions confirm the decreased influence in both direction found by GC analysis.
Discussion

The present study proposes a novel data-driven approach to map the altered patterns on effective connectivity of insular subregions in chronic back pain patients. The results demonstrate a dissociation in the pain information integration profiles of posterior and anterior insula, which has not been emphasized in the prior literature. The joint probabilities of neural events method allow us to identify precise time lag distribution of causal interactions between the source and target regions.

The insular cortex is a functionally and cytoarchitectonically diverse region, exhibiting extensive anatomical connectivity to sensory regions, as well as to higher cognitive brain areas. Plenty of neuroimaging studies have explicitly investigated functional differences across subregions of the insula. Posterior insula (PI) was found to be functionally connected to primary and secondary motor and somatosensory cortices; additionally it conveys pain information and is a critical site for interoception (Craig 2002). Accumulated evidences also suggests that dorsal anterior insula (AI) is functionally connected to the cognitive control network, might play a general role in negative affect processes, and correlate to empathy for pain (Bernhardt et al. 2013; Deen et al. 2011). In the current study, we evaluated the parameters of the hemodynamic response at rest to detect pain sensitive subregion of the insula: l-vPI and r-dAI, then explored the pain processing pathway of information transmission in the insula, such as somatosensory/interoceptive information from PI or affective information from vAI influence pain perception and pain-related behavior.

Reduced information transfer to and from the insula in chronic back pain is thus an indicator of how this region loses part of its potential as a hub for information processing. The prominence of this effect to and from somatosensory and motor areas suggests that long term pain itself could modify motor behavior, (i.e. patients exercise less and differently from healthy subjects), and consequently the dynamics of these regions, as afferents and efferents.

Table 1 Significant results of HRF parameters/Granger causality mapping resulting from the comparison between the patient and the control groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Brain region</th>
<th>BA</th>
<th>C. size</th>
<th>peak MNI (x,y,z)</th>
<th>peak T value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resp. height</td>
<td>Temporal sup L</td>
<td>–</td>
<td>116</td>
<td>–44</td>
<td>–4</td>
</tr>
<tr>
<td></td>
<td>Hippocampus R</td>
<td>–</td>
<td>124</td>
<td>20</td>
<td>–8</td>
</tr>
<tr>
<td>Time to peak</td>
<td>postcentral L</td>
<td>–</td>
<td>62</td>
<td>–32</td>
<td>–28</td>
</tr>
<tr>
<td></td>
<td>rectus L</td>
<td>11</td>
<td>78</td>
<td>–4</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td>vermis 4</td>
<td>–</td>
<td>52</td>
<td>4</td>
<td>–48</td>
</tr>
<tr>
<td>In, l-vPI</td>
<td>SMA R</td>
<td>–</td>
<td>215</td>
<td>12</td>
<td>–8</td>
</tr>
<tr>
<td>Out, l-vPI</td>
<td>PCL R</td>
<td>–</td>
<td>445</td>
<td>8</td>
<td>–28</td>
</tr>
<tr>
<td>Out, r-dAI</td>
<td>PCL R</td>
<td>–</td>
<td>166</td>
<td>8</td>
<td>–28</td>
</tr>
</tbody>
</table>

C. size cluster size, res. height response Height, time to peak time to peak response, in, l-vPI incoming network, left vPI, out, l-vPI outgoing network, left vPI, Out, r-dAI outgoing network, right dAI

Fig. 4 Distribution of the relative timing of events occurring in the paracentral right lobule with respect to events in the left vPI. The blue dots represent the relative number of large BOLD activations occurring in voxels belonging to the paracentral right lobule each time that a large event is detected in the left vPI, against the distribution of randomized events for each lag (in orange), for patients (left) and control subjects (right) (Color figure online)
The present results add to a large body of evidence indicating that chronic pain involves dynamical changes that affects normal brain function which in turn can impair cognitive function, including depression, sleeping disturbances and decision-making abnormalities (Apkarian et al. 2004, 2005; Baliki et al. 2008).

The approach used here is derived from two lines of work that together allows for a novel view of the changes in brain dynamical connectivity. On one side it adds strength to the previous suggestions (Tagliazucchi et al. 2010, 2011, 2012; Wu et al. 2013) that a few (relatively large) BOLD events can contain substantial information to describe functional connectivity. On the other side, the seed based Granger causality mapping allows the precise description of the effective connectivity at a fine scale.

The changes in the effective connectivity described in the results section are fully consistent with the current data (Apkarian et al. 2009) validating the novel methodology and encouraging a more detailed analysis of other regions of interest described recently (Baliki et al. 2012) as involved in the transition from acute to chronic pain.

It should be pointed out that the long TRs may affect the precision and robustness in the evaluation of HRF and Granger causality mapping. Consequently, further studies with more convenient imaging parameters would be necessary in order to investigate more closely the distinct and hemispherical patterns of large-scale effective connectivity of all insular subregions, and the link with pain magnitude. Effects of age on metabolism and consequently on HRF are controversial and encouraging a more detailed analysis of other regions of interest described recently (Baliki et al. 2012) as involved in the transition from acute to chronic pain.

In summary, we have shown that by deconvolving the HRF to spontaneous neural events it can be demonstrated via Granger causality that chronic pain patients display important changes in effective connectivity to and from subregions of the insula, mainly involving sensorimotor areas; these changes are flanked by modification to the shape of the HRF in the pain matrix.

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