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Camille Fauchon, H el ene Bastuji, Roland Peyron, Luis Garcia-Larrea

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Chapter 32

Fractal Similarity of Pain Brain Networks

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Camille Fauchon, H el ene Bastuji, Roland Peyron, and Luis Garcia-Larrea

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Abstract The conscious perception of pain is the result of dynamic interactions of neural activities from local brain regions to distributed brain networks. Mapping out the networks of functional connections between brain regions that form and disperse when an experimental participant received nociceptive stimulations allow to characterize the pattern of network connections related to the pain experience.

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Although the pattern of intra- and inter-areal connections across the brain are incredibly complex, they appear also largely scale free, with “fractal” connectivity properties reproducing at short and long-time scales. Our results combining intracranial recordings and functional imaging in humans during pain indicate striking similarities in the activity and topological representation of networks at different orders of temporality, with reproduction of patterns of activation from the millisecond to the multisecond range. The connectivity analyzed using graph theory on fMRI data was organized in four sets of brain regions matching those identified through iEEG (i.e., sensorimotor, default mode, central executive, and amygdalo-hippocampal).

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Here, we discuss similarities in brain network organization at different scales or “orders,” in participants as they feel pain. Description of this fractal-like organization may provide clues about how our brain regions work together to create

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C. Fauchon (✉) · H. Bastuji

Centre de Recherche en Neurosciences de Lyon – NeuroPain – INSERM U1028 – CNRS UMR5292 – UCBL, UJM Saint-Etienne, Saint-Etienne, Bron, France
e-mail: camille.fauchon@univ-st-etienne.fr

R. Peyron

Centre de Recherche en Neurosciences de Lyon – NeuroPain – INSERM U1028 – CNRS UMR5292 – UCBL, UJM Saint-Etienne, Saint-Etienne, Bron, France

Centre hospitalier universitaire – Centre de la douleur de Saint-Etienne, Saint Etienne, France

L. Garcia-Larrea

Centre de Recherche en Neurosciences de Lyon – NeuroPain – INSERM U1028 – CNRS UMR5292 – UCBL, UJM Saint-Etienne, Saint-Etienne, Bron, France

Centre d’ valuation et de traitement de la douleur, H pital Neurologique, Lyon, France

the perception of pain and how pain becomes chronic when its organization is altered. 23
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Keywords Pain · Multiscale brain organization · Functional MRI · Intracranial EEG · Chronic pain · Graph theory 25
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32.1 Brain Dynamics of Pain Perception 27

Pain is a complex sensory experience that transforms simple noxious stimuli into conscious perceptive events. The process of building a subjective perception of pain intensity engages multiple levels of the central nervous system [15]. Noxious stimulus information is first transduced by afferent peripheral nociceptors from discrete body region and their inputs are integrated over multiple spinal levels and differing time frames. This pre-processed information is transmitted to the thalamus and cortex (supraspinal structures) where an individually unique experience of pain magnitude is elaborated. This involves the processing of sensory-discriminative features of the pain stimulus, but also its affective-motivational features [73], with descending modulation pathways (i.e., top-down controls) that act to modulate incoming nociceptive activity [38, 63]. 28
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Human brain imaging has revealed that the multidimensional integration of pain is possible thanks to the coordinated activation of multiple and widespread brain regions interacting dynamically, commonly described as “the dynamic pain connectome (DPC)” [45]. The notion that pain perception needs joint cortico-subcortical interaction has been abundantly documented [3, 34]. This is not a fixed arrangement of structures but rather a system composed of several interacting brain networks, hierarchically organized [33]. 39
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Human brain electrophysiological approaches have also revealed the importance of brain dynamics and that brain regions are engaged successively during the pain experience [8]. The first brain activations associated with pain stimulation mainly involved the posterior operculo-insular cortex (pIns and parietal operculum: S2), mid-cingulate cortex (MCC), and the parietal sensory areas. This set of brain regions (or modules) that process raw nociceptive inputs reflect the smallest scale (first order) of interaction, but alone are not sufficient to sustain the conscious perception of pain [7, 42]. The involvement of a higher-order set of regions belonging to cerebral networks outside this “nociceptive matrix” is crucial for nociception to become pain [33, 34]. Second-order interactions link this raw sensory information with stimulus salience and motor control (including the anterior insula (aIns) and anterior cingulate regions). The largest-scale interactions (third order) link these sensorimotor and salience networks with brain structures that support high-level cognition and control (including pain re-evaluation in prefrontal and posterior parietal regions; see Fig. 32.1). The organization of these brain segregations (both temporally and topologically) forms a continuum going from pre-conscious cortical 46
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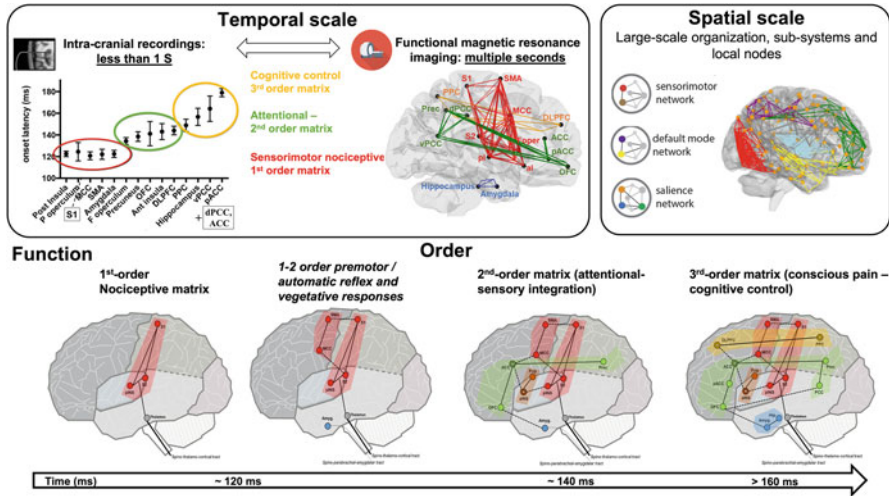


Fig. 32.1 Self-similarity of brain patterns in pain at different spatial and temporal resolutions from pre-conscious cortical nociception to conscious pain. The smallest scale (first-order) interactions occurred in brain regions that process raw nociceptive inputs (red network). Second-order interactions link this encoding of raw sensory information to stimulus salience and motor control (green network). The largest-scale interactions (third-order) link the sensorimotor and salience networks with brain structures that support high-level cognition and control (including re-evaluation; yellow network). The repeating network patterns at different scales might allow our brains to weave a high-level understanding of what is happening from the fabric of our raw sensory experiences (see [24]). *pINS* and *aINS* posterior and anterior insula, S1 and S2: primary and secondary somatosensory cortex, *SMA* supplementary motor area, *pACC*, *ACC*, *MCC*, and *PCC* perigenual, anterior, middle, and posterior cingulate cortex, *OFC* orbito-frontal cortex, *Prec* Precuneus, *Fop* frontal operculum, *DLPFC* dorsolateral prefrontal cortex, *PPC* posterior parietal cortex, *Amyg* amygdala, *Hip* hippocampus

nociception to autonomic control, to attentional, to emotional, to full-on conscious pain [8, 24, 34].

Therefore, from a simple noxious event activating few brain recipients of the spinothalamic tract (i.e., a first-order nociceptive matrix), it becomes a very complex process involving large and interconnected part of the cortex (i.e., second- and third-order high-level cognitive-pain networks), found in several temporal scales, which is the basis for the description of fractal in nature.

Fractal objects are made of subunits (and sub-sub-units, etc.) that look like the structure of the overall object and can be quantified by computing the fractal dimension (FD). FD is a measure of complexity derived from nonlinear dynamical systems theory [69], capturing nonstationary changes in the signal, and sometimes described as the “roughness” of the signal. FD is based on the self-similar behavior of time series [1, 39], which refers to the fact that the fractal dimension of a signal is the same, regardless of the scale at which that signal is observed – “scale-free” [22]. The fractal concept can be applied to complex time-varying processes that lack a

single scale of time such as heart rate variability [40] or cortical neural activity [48] 77
with many clinical applications. 78

This is a suitable approach to describe the irregular and nonperiodic patterns 79
recorded by neuroimaging techniques, no matter what the properties (stationary, 80
nonstationary, deterministic, or stochastic) of the analyzed signal. In other words, 81
FD analysis could be a useful tool for deriving features of brain states related to a 82
nonlinear phenomenon such as spontaneous pain, which is commonly observed in 83
individuals with chronic pain. The fluctuations of spontaneous pain ratings do not 84
possess a stable mean or variance (because the source of evoking stimulus is often 85
unknown) and therefore resemble fractal time series [29]. Brain patterns during pain 86
also appear largely scale-free, with “fractal” activity and connectivity properties 87
reproducing at short- and long-time scales [24]. 88

Several computational techniques (e.g., Higuchi’s fractal dimension (HFD), 89
Hausdorff dimension, Grassberger-Procaccia correlation dimension (GP), Entropy, 90
etc.; see Chaps. 1, 2, 3, 4 and 5 for more details) can be used to assess FD. However, 91
while this type of nonlinear approach is no longer an issue, to the best of our 92
knowledge, there are very few applications for the analysis of micro [2, 70, 74] 93
and macro [29, 65] neuroimaging data related to chronic pain and none on acute 94
pain in healthy individuals. 95

In the following sections of this chapter, we illustrate the self-similarity of 96
patterns (subunits) of pain processing at different spatial and temporal resolutions – 97
i.e., multiscale characterization: from iEEG local recording to whole brain fMRI 98
recording during pain stimulations. 99

32.2 Organization of Pain Brain Networks 100

When two brain structures appear to change their responses in similar ways and 101
with the same dynamic, this is called a “functional connection” because it suggests 102
that the phenomena that are driving the two structures synchronize them in some 103
way. Functional magnetic resonance imaging (fMRI) and graph theory of the brain 104
connectome are used to extract functional networks connecting correlated human 105
brain regions. Analysis of the resulting networks in tasks [24, 55] or at rest [13, 106
14, 26] shows that the distribution of functional connections and the probability 107
of finding a link are both scale-free [21, 28]. The patterns of intra- and interareal 108
connections across the brain are incredibly complex, they form a scale-free network 109
with small world properties, assortative mixing, and “fractal” connectivity proper- 110
ties reproducing at short- and long-time scales [66, 85]. Decomposing brain activity 111
into functional modules of regions to investigate their interactions is a well-suited 112
approach to study pain – an experience that requires the spatiotemporal coordination 113
of different brain regional subsets [54]. 114

In recent studies, we assessed how large-scale topological organization 115
(macroscale brain function) obtained from fMRI shapes neural function and 116
processing hierarchy provided by intracerebral stereo-electroencephalography 117

during noxious pain stimulation. Findings indicate striking similarities in the activity and topological representation of networks at different orders of temporality, with reproduction of patterns of activation from the millisecond to the multi-second range. The brain connectivity analyzed using graph theory (modular detection) during pain was organized into four modules matching those identified through iEEG (i.e., sensorimotor, default mode, central executive, and amygdalo-hippocampal). Such topological aspects at a long-time scale appear relevant to reflect local neurobiological features of iEEG responses to noxious stimulation (Fig. 32.1). Their similarities across the different orders of the pain process are discussed in what follows.

32.3 First-Level Nociceptive Processing

32.3.1 *How Does the Brain Encode Noxious Events?*

The understanding of the physiological mechanism of pain has moved from a concept associating pain with somatosensory processes to a framework involving more directly the insular cortices. Pain was assumed to involve primarily S1, S2 cortices, and thalamus, but only half of the neuroimaging studies confirmed this prediction, except for S2, which was found at different temporal scales to be almost consistently involved when nociceptive stimulation is applied.

Functional imaging reviews [34, 59, 60, 68, 79] and intracerebral recordings [33, 52] have shown that the posterior opercular-insular cortices are the regions the most consistently activated in response to a nociceptive stimulation and that they are capable of encoding pain intensity. These cortices receive most of the spinothalamic tract projections [20]. In addition, the operculo-insular cortex is the only brain region where a direct electrical stimulation can produce a pain sensation [50–52]. Direct focal electrical stimulations at minimal intensities in the other regions of the pain circuit (i.e., more than 4000 stimulations) are not able to elicit pain. Insular epilepsy (or propagation of discharges to the insular cortex) is the only focal epilepsy to be possibly associated with painful symptoms [53]. Finally, small lesions restricted to the parietal operculum/S2/posterior insula remove the ability of the brain to produce a pain sensation, and patients do not perceive nociceptive stimuli anymore. For example, they did not perceive the needle of venous punctures, they also did not perceive thermal pain with a 50 °C stimulation and their brain were unable to create a laser-evoked potentials [32, 35, 37]. Thus, the operculo-insular cortex can be presented as the only area in the brain to respond to the features of a first-order nociceptive matrix.

32.3.2 *An Insular Pattern*

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Intracranial EEG (iEEG) recordings have helped to characterize the activation dynamics of brain regions of the pain connectome. This information illustrates that three successive and overlapping waves of activation sustain the transition from unconscious nociception to conscious pain in less than 1 s. The brain regions activated with the shortest latencies following a noxious stimulus include the posterior insula and S2, but also the MCC, SMA, and amygdala (see Fig. 32.2). Brain network organization at longer time periods such as those explored in fMRI-based imaging is segregated in four modules (i.e., group of regions with high inter-connectivity) during pain which is consistent with the spatiotemporal organization of nociceptive-related activation at short time-scale (Fig. 32.1; [24]). A sensory-motor module encompassed the first activated brain regions but also included the anterior insula, which is not a direct spinothalamic recipient but marks the transition from the first to the second-order matrix [81].

The posterior and anterior subdivisions of the operculo-insular cortex have not the same function relative to pain, and this can be found at several fractal temporal resolutions. The posterior areas are specific to the discriminative processes related to painful conditions, whereas the antero-insular components appear as nonpain-specific contributions that can be recruited by any “salient” sensory input from various modalities such as auditory or visual [47]. Listening to baby cries in pain, seeing pictures or videos showing somatic pain, all the empathic experiments recruit large parts of the pain network, including the anterior insular cortex, with the noticeable exception of the SII-posterior operculo-insular region. In fMRI using high temporal resolution recording of the insular cortex by step of 641 ms and by delivering stimulations through a YAP-laser at a fixed intensity above the pain threshold, we were able to examine the latencies of activation along the postero-anterior axis of the insular cortex (see Fig. 32.3; [64]). Stimulations were mostly perceived as painful, but in a minority of situations, it was perceived as nonpainful. As expected, in the parietal operculum (S2) and posterior insula, the BOLD response was significantly more intense as the perception of the stimulation was painful suggesting that this portion of the operculo-insular cortex truly encode for the physical intensity of stimuli. This encoding will determine the ensuing perception. Conversely, the intensity of the response was no more discriminant in the mid and anterior insular cortices with a delayed response as compared to the first one. An interesting finding suggesting different sequential treatments (in time) was that the latency of the anterior insular response was shorter when the sensation was painful as compared to the nonpainful sensation. Fast processing as compared to slower ones may indicate (in the second order processes), a priority organization as the stimulation is considered as harmful or threatening. An independent study performed in our laboratory with intra-cerebral recordings replicated these findings [31]. They demonstrated that after a laser stimulation, responses were sequential in time with early and high amplitude of response in the posterior insula and a later response when the recording was anterior. Functional coherence levels

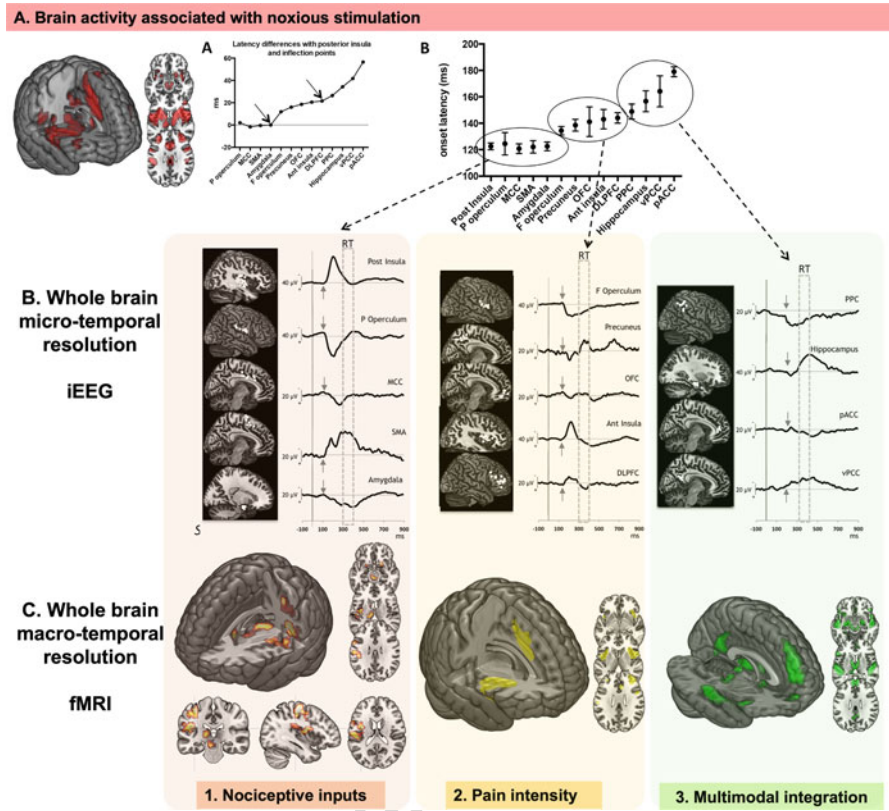


Fig. 32.2 Deconstructing brain processing of pain, from large-scale brain activity to local modules in 3 steps. (a) Top: brain activation pattern associated with pain stimulations in functional magnetic resonance imaging (fMRI) and onset latencies of nociceptive responses recorded with intracranial electrophysiology (iEEG). (b) Middle: micro-temporal dynamic of 14 brain regions recorded in iEEG, the onset latencies of the nociceptive responses are illustrated (Reproduced and edited by permission from Ref. [8]). Latency differences clearly distinguish 3 groups relative to that of the posterior insula (i.e., 110–130 ms; 130–150 ms, and 150–180 ms onset latency). The small arrows point to the mean onset of the responses and the areas delineated with dotted lines correspond to time windows during which motor reaction occurred (RT). (c) Bottom: macro-temporal dynamic in fMRI of brain activity related to pain stimulus, the first brain recipients of noxious inputs to high order and multimodal fronto-parietal brain regions are illustrated (see for details [23]). Split the BOLD activity related to the pain experience in three acts allow to illustrate that almost the same set of regions shape the three successive waves of activations measure in iEEG

with the posterior insula increased with time in a large majority of other cortical 196
 areas and irrespective of time window, the largest spectral coherence values with 197
 the posterior insula were observed in the anterior insula, parietal operculum, and 198
 perigenual anterior cingulate cortex [8]. This pattern was suggestive of an early 199
 treatment of sensory information (input) in the parietal operculum-S2-posterior 200
 insula and secondary order processes within the anterior insular subdivisions. The 201

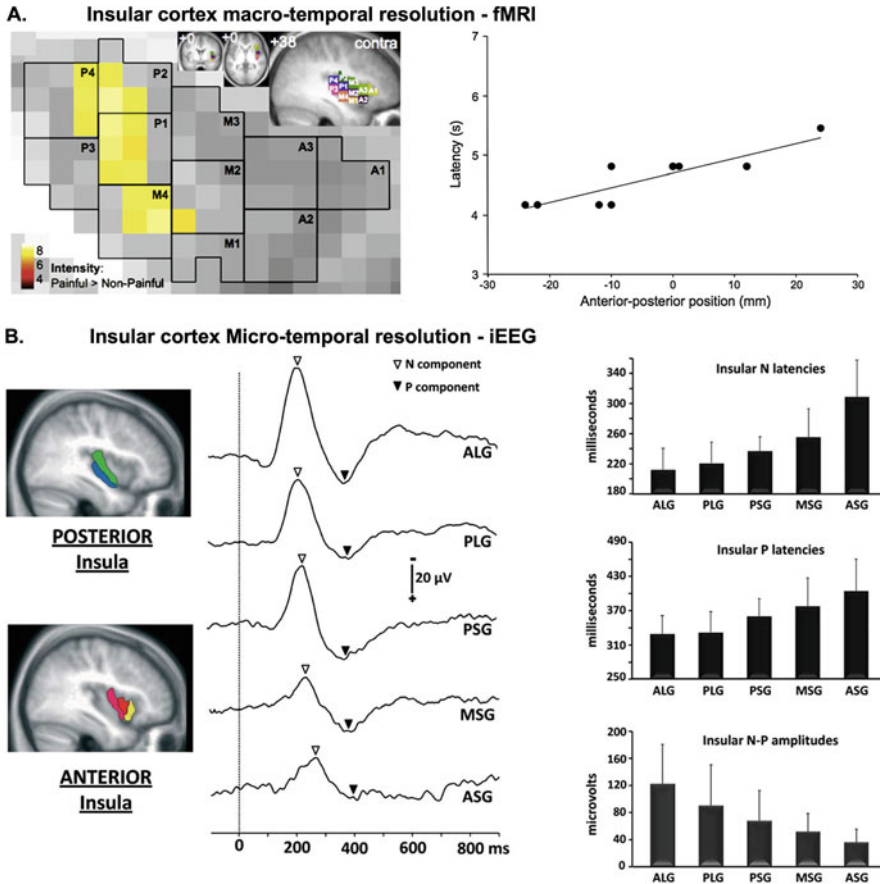


Fig. 32.3 Posterior to anterior insular cortex responses to noxious laser stimulations, as recorded with (Top) high-resolution fMRI (Reproduced and edited by permission from Ref. [64]) or with (Bottom) deep electrodes implanted into the brain (Reproduced and edited by permission from Ref. [31]). (a) Responses with shorter latency are in the posterior insular cortex and that its amplitude predicts painful perception. Correlation between latencies and anterior–posterior position shows that the haemodynamic response to painful stimuli peaks earlier in the posterior insula on the side contralateral to laser stimulation. In the anterior insular subdivisions, latencies of the response are shorter for stimulations that will be interpreted as painful while latencies are significantly delayed for responses that will be interpreted as innocuous. (b) Direct recordings show that insular responses have the shortest latency in the posterior subdivisions, while the anterior subdivisions have longer latencies. These two independent studies provide similar conclusions with a posterior to anterior gradient of response latencies and emphasize the fractal similarity of brain responses to pain in this cortex

“neurological pain signature” predicting physical acute pain, described by Wager et al. [79], largely overlaps with this brain activity pattern. 202

Functional networks are scale free that implies that there is always a small but finite number of brain regions having broad access to most other brain regions. The 204
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anterior insula is a crucial hub in the pain connectome and may participate to inform higher-order networks (i.e., fronto-parietal) on the physical-somatic nature of the stimulus [9]. The high “centrality” of the anterior insula, reflecting its control over passing information, is consistent with a role in orchestrating potentially necessary changes in the perception of pain intensity and the concomitant behavioral responses [12].

32.4 Second-Level Attentional Control and Cross-Modality Sensory Integration

The anterior mid-cingulate cortex (aMCC) is also consistently activated as stimulations reach a nociceptive level with an activity range that may be proportional to the intensity of perceived pain. As the anterior insula, the aMCC is a multimodal structure that may be activated in a similar manner as a volunteer is in pain or is doing a cognitive task requiring attention. Since the more you have pain, the more you load attention to this stimulation, the functional significance of aMCC activations has moved from a strictly nociceptive one to a confound involving associated processes such as oriented attention [61, 62]. Interestingly, the same pattern of information flow could also be demonstrated in the aMCC where high temporal resolution fMRI showed earlier responses when the stimulus is perceived as painful compared to a nonpainful one. This pattern of response suggests that after identification of what happens in the parietal operculum-posterior-insula, second-order processes may occur in the anterior insula and aMCC with a priority transmission linked to time as a function of emergency or threatening. fMRI and iEEG findings add a new temporal dimension to the nociceptive responses. By merging information obtained by both techniques, it is possible to demonstrate that a faithful decoding of noxious laser stimulation can be implemented and transformed into pain sensation by changes in functional connectivity between affective areas such as the amygdala and the anterior insula [36].

Nociceptive inputs reach the amygdala through a low-speed tract (the spino-parabrachial-amygdalar pathways [11] leading to responses with a different temporal shape than other cortical regions (see Fig. 32.2 in [33]). At long-time scale in fMRI, this led to an isolated limbic module, made up of the amygdala-hippocampus couple (see Fig. 32.1). This module has low connectivity with other brain regions of the dynamic pain connectome, and similarly, this functional independence was also detected in iEEG data, which showed no significant spectral coherence between the amygdala and regions of the ascending pain pathway [9]. Activity within the limbic brain matrix is engaged early and is believed to be involved in the encoding and retrieval of emotionally charged memories associated with pain perception, while communications with other networks are dedicated to multimodal brain hubs such the anterior insula [24].

32.5 Third-Level Conscious Pain and Cognitive Control 245

Conscious experiences are not confined to sensory areas but rather represented over 246
 large, interconnected portions of the cortex (Aru et al. 2012; Michel et al. 2019). The 247
 second and third modules involved brain regions of higher order in the hierarchy 248
 of noxious stimulus processing, i.e., associative, and multimodal areas with longer 249
 response latencies than the regions described above (Figs. 32.1 and 32.2). 250

These include the central executive network anchored in the dorsolateral 251
 prefrontal cortex (DLPFC) and posterior parietal cortex. This network contributes 252
 to many neurocognitive functions including decision-making and working 253
 memory [17]. The default mode network is also recruited and comprises the 254
 precuneus/posterior cingulate cortex and the ventro-medial prefrontal cortex. 255
 It is involved in the experience of mind-wandering (attentional level) and self- 256
 consciousness [30]. Activity in these networks participates to a third-order matrix, 257
 which may to some degree reflect pain awareness and cognitive control, which 258
 could be associated with the engagement of descending pain modulatory systems to 259
 dampen or inhibit pain [18]. 260

In iEEG recordings, activity in this module persists after the stimulus has 261
 produced an overt motor or verbal response [8], suggesting a role in both the 262
 consolidation of immediate perceptions and the control of adequate behavioral reac- 263
 tions. Communication between the different subsystems is supported by “network 264
 connector hubs” detected in the graph model and located in the anterior insula, 265
 DLPFC, and PPC. Such connectors play a key role in network organization by virtue 266
 of their control over information passing between other brain regions [41], but are 267
 also, logically, loci of vulnerability in brain disorders [76]. The results in the pain 268
 field are therefore consistent with a general framework which, whatever the sensory 269
 modality considered, links the conscious availability of sensory information with 270
 the enhancement of the functional coupling between sensory areas and high-order 271
 fronto-parietal networks. 272

32.6 Pre-stimulus Brain State Influence How Pain Is Perceived 273

Pain neurosciences studies are mainly focused on the brain activity associated with 275
 the noxious stimuli, but it is important to also consider how ongoing activity in 276
 the prestimulus state may influence subsequent pain perception [46]. Spontaneous 277
 brain activity is behaviorally relevant, as it contains predictive features about how 278
 brain networks will respond to a wide range of sensory and cognitive events [72]. 279
 Recording of local field potentials and discharges of single neurons by electrophys- 280
 iological techniques have revealed that the variability of stimulus-evoked responses 281
 is influenced by the preceding spontaneous brain activity [5]. 282

There is also growing evidence that a wide range of ongoing neural activity in the micro-time (milliseconds) or macro-time (seconds) scales leading up to sensory stimulation strongly influences whether acute pain stimulus will be perceived or the degree of pain intensity perceived [46, 49]. Trial-to-trial brain response variability in the pain network and the magnitude of pain ratings may be dependent upon pre-stimulus: (i) BOLD signal within third-order networks including sensorimotor and default mode networks, (ii) the spectral power of the ongoing EEG alpha and gamma oscillations [49, 75], and (iii) functional connectivity between the anterior insular cortex and regions of descending pain control pathway [36, 63, 80]. These pre-stimulus neural fluctuations are reproduced at different spatial and temporal scales, but their impacts on conscious pain processes are still unclear. Bastuji et al., [10] show that the probability for a phasic noxious stimulus to entail an arousal is modulated by the prestimulus interareal phase coherence between sensory and higher level cortical areas. Fluctuations in interareal communication immediately before the noxious stimulus may determine the responsiveness to incoming input by facilitating or preventing the transfer of noxious information from sensory to multiple higher-level cortical networks [10]. Ongoing activity must play an important role in cortical function and cannot be ignored when investigating cognitive processes influencing pain experience.

32.7 Large-Scale Characterization of Brain Activity Can Predict Evoked Pain Intensity

Information about pain intensity is coded in the brain at multiple anatomical scales: locally, distributed across regions and networks, and globally (Lee and Tracey 2013; [45]). There is a localization of specific function in a single region, but also a distributed character for multidimensional processing [34].

As described above, neuroanatomy and direct electrical stimulation of a single neuronal unit have pointed out the dorsal posterior insula as subserving a fundamental role in human pain [52, 53, 68], whereas the distributed models of pain in the brain are supported by neuroimaging studies and the concepts named ‘pain brain networks’[24], ‘neurosignature of pain’[79], or the ‘dynamic pain connectome’[45].

What is the gain of looking at the entire brain rather than 1 region? Using multi-study analysis and multivariate predictive model applied on BOLD fMRI data, Petre et al. [58] show that all spatial scales conveyed information about pain intensity. Individual regions have a lot of useful information: 80% of them. It makes sense that some regions seem important, and many predict well, but distributed, multisystem models predicted pain 20% more accurately than any individual region or network and are more generalizable to multimodal pain (thermal, visceral, and mechanical) and more specific to pain. However, these findings demonstrated that most of the information conveyed by a single brain region is also embedded in large-scale brain

networks, illustrating the fractal features of the spatiotemporal organization of the brain during pain.

32.8 Disruption of Brain Fractal Patterns in Chronic Pain

Chronic pain is the most prevalent disease worldwide, leading to substantial disability and enormous societal costs [16]. Evidence supporting structural and functional central nervous system changes in patients with chronic pain is mounting and supported by systematic reviews [4, 19, 34, 44, 59] and meta-analyses [71, 84].

One of the aspects of the chronic pain brain most explored with fMRI is functional activity at rest so-called resting-state networks (RSNs). It can capture the macroscopic spatial dynamics of the blood oxygenation level dependent (BOLD) signal of the brain, and its synchronization (functional connectivity) between different brain regions is the basis for forming networks [30]. Several neuroimaging studies have detected alterations in the activity and connectivity of RSNs in chronic pain patients compared to healthy controls [6, 19, 25]. Moreover, technologies that can examine brain activity at millisecond resolution (i.e., electroencephalography and magnetoencephalography (MEG)) have reported that people with chronic pain exhibit altered neuronal oscillations including an altered resting-state alpha-band [25, 83]. Specifically, brain activity dysfunctions at rest (spatially, spectrally, and temporally) can be more pronounced in several chronic pain conditions that have a neuropathic pain component. Because scale-free complex networks are known to show resistance to failure, facility synchronization, and fast signal processing, it would be important to see whether brain networks scaling properties are altered under various chronic pain conditions. To identify nonperiodic irregularities in the functional activity of RSNs associated with chronic neuropathic pain conditions, few studies have computed fractal dimension measures.

In an original work, Foss et al. [29] were able to differentiate between different types of chronic pain conditions using FD values to characterize the variability of spontaneous pain ratings and brain activity recorded in fMRI. They showed a correspondence between FD for ratings and for brain signal and found FD to be lowest for thermal pain and greatest for chronic pain [29]. In the same vein, Porcaro et al. [65] illustrated that FD values within frontal networks (dorsal attention system and anterior part of the default mode network) were higher, and lower within the posterior part of the default-mode network in patients with chronic migraine compared with healthy controls [65]. In electrophysiology, Tran et al. [74] studied nonoscillatory EEG markers for neuropathic pain and the effects of virtual reality interventions using fractal dimension. Using Higuchi's FD, they found significant increases in FD for the central and parietal regions during the virtual reality task [74]. These changes in neural signals have been interpreted as a normalization of the affected subcortical-cortical system following intervention. A previous work of Anderson et al. [2] found that spinal cord injury participants with neuropathic pain to have lower fractal dimension of EEG signals compared to healthy individuals and

may be used to classify patients [2]. In sum, these studies illustrated that the fractal dimension of EEG signals is of a lower value for people suffering from chronic pain compared to healthy individuals.

Higher FD values generally correspond to higher signal complexity, and a reduction in FD may indicate a loss of neural efficiency, as previously found in people suffering from brain disorders compared to healthy people [43, 67]. This loss of complexity in brain activity may lead to the brain networks becoming less flexible and efficient [2, 87] in processing and controlling sensory information. These findings illustrate the importance of nonlinear nonoscillatory brain features, specifically Higuchi FD, which may be used as new prognostic neuromarkers to analyse the brain activity of people with chronic pain. It may help to characterize the microstructure complexity of brain pain networks and potentially differentiate between chronic pain conditions, and thus may have mechanistic and clinical utility.

32.8.1 Fractal Dimension of Temporally Recurrent Brain Microstates

Recognition that brain time series contains “hidden information” that might be captured by nonlinear methods such as fractal analysis provides crucial and, so far, overlooked neurophysiological information in pathological conditions such as chronic pain. Hidden Markov Model (HMM) is similar to fractal analysis since it is a measure of complexity based on the fact that a simple process that is repeated endlessly becomes a very complex process, which is the basis for the description of fractals in nature. The HMM approach is used to reduce cortical activity at rest into sequences of transient, intermittently reoccurring events, known as brain microstates [77, 78]. The brain signal is considered as brief bouts of activity that are repeated intermittently (i.e., nonrhythmic; see Fig. 32.4A).

This approach applied to neuroimaging data was successfully used to characterize profiles of time-varying connectivity associated with opioid analgesia [57]. Using MEG data, this method provided a fine probabilistic estimation of when the different brain states are active [82]. We recently applied it to MEG data from individuals with neuropathic pain to describe how their brain moves from one activity state to another [27]. Our main finding is that neuropathic pain impairs the dynamic coordination of neural network activity. Compared to healthy individuals, the neuropathic pain patients exhibited shorter time intervals between transitions to (i.e., visits of) the microstate characterized by activations of sensorimotor brain regions and their brains spent more active time in this state. Moreover, in the beta frequency band, patients had higher power and coherence in the sensorimotor state. Conversely, their brains showed lower coherence and spent less time in the frontal attentional state. We hypothesized that these findings illustrate an imbalance of temporal dynamics between sensorimotor and frontal microstates in neuropathic pain that may contribute to abnormal pain regulation in these patients. Reorganization

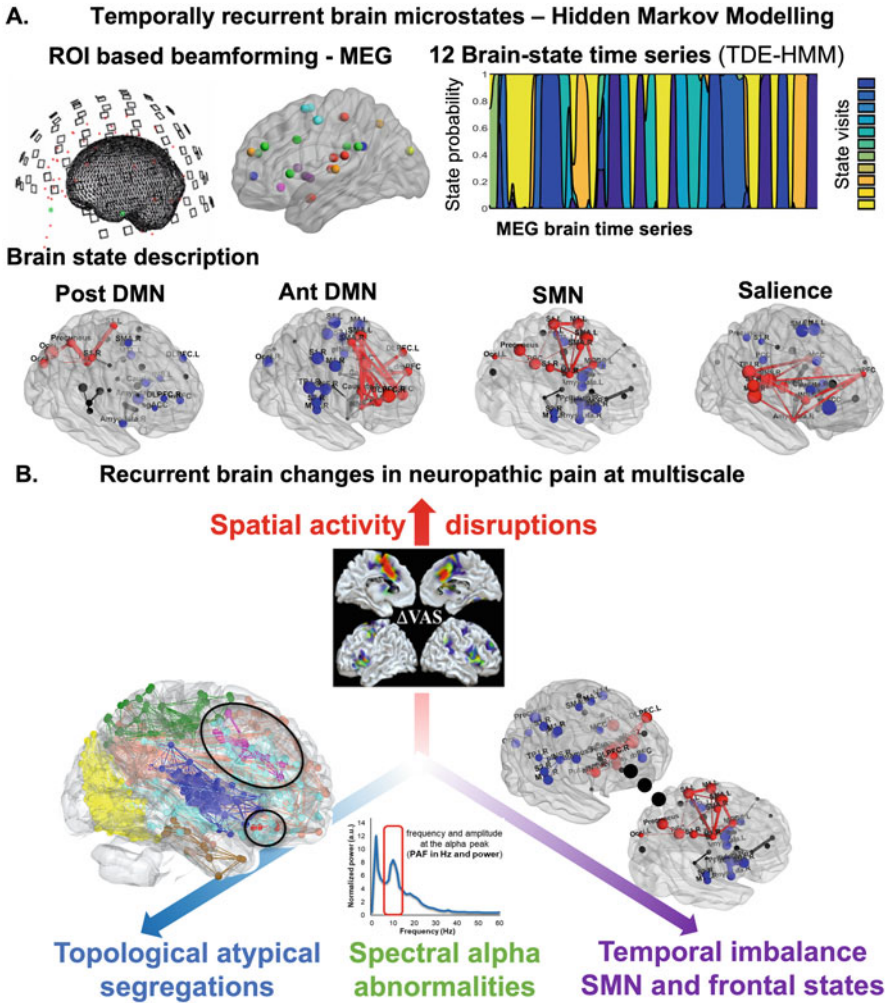


Fig. 32.4 Example of brain activity patterns repeated in time: fractal dynamics. (a) Illustration of TDE-Hidden Markov Model approach applied on MEG data. HMM inference is used to identify the state time courses (state probability). Each state is characterized as having its own distinct spatial, temporal, and spectral properties. Brain regions with significant power and phase coupling are represented across a wideband frequency range (1–30 Hz) for 4 estimated states. Node spectral power is relative to the temporal average (blue and red colors reflect power that is lower or higher than the average over states, respectively). Edges between nodes show functional connectivity. (b) Altogether recent findings illustrate that neuropathic pain alters neuronal activity repeatedly at several scales in the brain (see [27]). Locally in several brain regions (including the primary somatosensory cortex and the anterior insula); topologically in the network organization with higher segregation and cross-network connectivity; spectrally in the alpha band; and temporally by changing the temporal dynamic of brain microstates

of the sensorimotor subsystem (SMN) has been reported in numerous studies, such as abnormal activity and hyper-connectivity of the SMN and altered hub topology in chronic pain [26]. Abnormal SMN beta and alpha power activities were also found and could be due to cortical plasticity after a lengthy period of nociceptive input [86], or it could also serve as a compensatory mechanism to maintain sensory perception. Although the neurophysiological meaning behind these discrepancies is unclear, it illustrates that neuropathic pain has an impact on the overall dynamic orchestration of neural activity that is replicated at multiscale (spatial, topological, and temporal) in the brain (Fig. 32.4b).

32.9 Conclusion

Analysis of brain activity related to noxious stimuli over a scale of seconds or minutes reveals that pain fluctuates as a scale-free process. Using both large-scale brain imaging in healthy individuals and in those suffering from chronic pain, and direct neuronal measurements in a clinical population, allows to describe how the brain networks of pain are hierarchically organized in both space and time. Description of this fractal-like organization provides clues about how our brain regions work together to create the perception of pain and how pain becomes chronic when its organization is altered.

The modular organization reported in fMRI studies appears relevant to shape the dynamic patterns of responses to pain stimuli determined at short time scale using iEEG and are, therefore, consistent with the fractal properties of brain connectivity being reproduced at short and long time scales [56]. The results are consistent with a model of nociceptive integration whereby the conscious experience of pain emerges from the dynamic cooperation, segregation, and integration of multiple functional subsystems. It can help to ultimately understand how pain function is simultaneously constrained by both local and global features of cortical organization.

Findings using fractal analysis and brain microstates decomposition highlight the brain network reorganizations occurring in patients with chronic pain. At the individual level, studies also found a certain variability, showing that the neuropathological state differs among patients. This approach to brain dynamics in chronic pain can reveal novel information with potential mechanistic and clinical significance. It could serve as an individual blueprint to characterize the mechanisms through which local changes of neural function impact spatially distant sites, and therefore could contribute to the development of personalized treatment.

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