Neuroanatomical Signatures of Acute and Chronic Orofacial Pain

6

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Abstract

The more fully we understand chronic pain, the more adept we as providers will be able to deliver effective care to the patient with TMD. There have been significant advances in our current understanding of the neuroanatomical and neurochemical elements that underlie chronic pain, but the picture of how it is established and maintained is by no means complete. This chapter presents a short synopsis of our current appreciation of pain in general as well as a discussion of the research that contributes to the basis of our contemporary knowledge and theories that help us understand TMD-associated chronic pain.

6.1 Neuroanatomy of Pain: A General View

Wilder Penfield and colleagues lead the way to our current understanding regarding the principles of the cortical representation of somatosensory input. Their spectacular discoveries led to the famous somatosensory homunculus, a distorted scaled model of the human body neurally arranged at the postcentral gyrus [1, p. 1721]. Later on, cortical motor, sensory, and speech areas were discovered based on electrical stimulation of respective brain areas within the context of presurgical examination in epileptic patients [2]. Interestingly, those pioneering works revealed no distinct pain responses. Penfield and Jasper noted that some patients expressed feeling sensations best described as prickling or tingling and slightly unpleasant, but not painful at all [3].

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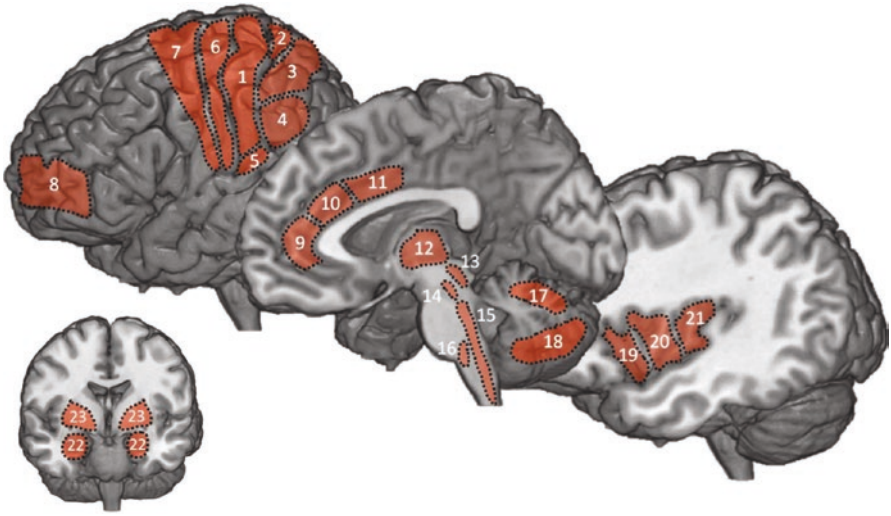

Fig. 6.1 Schematic illustration of cortical and subcortical areas found to be incorporated in the processing of experimental and chronic pain (see corresponding Table 6.1 for anatomical and functional description)

With the advent of noninvasive neuroimaging techniques, this spectacular initial work was extended and resulted in extensive knowledge incorporating the whole signaling cascades from peripheral somatosensory transduction mechanisms to their repository in different cortical and subcortical areas. Over the decades, profound explorations regarding neuroanatomical and functional aspects have led to the identification of a pain-associated neural network often denoted as a "pain matrix" [4, p. 883] or in more recent publications as a "neurologic signature of physical pain" [5, p. 1072]. This network can be summarized as a confluence across a huge amount of clinical and basic research with a main focus on pain. Fig. 6.1 and Table 6.1 provide a schematic according to brain areas observed to be involved in coding the whole experience of pain.

For quite some time, a rather deductive approach leads clinicians and scientists to believe that pain was primarily a nociceptive phenomenon and thus assignable to just a few distinct cortical areas across the pain matrix, with the primary somatosensory cortex playing the major role. This obvious simplification was on the one hand attributable to methodological constraints but also due to a primary "sensory-guided" view of pain processing. After all, sensory input is sensory by nature and thus should be processed within somatosensory areas. Thus, it logically followed that pain, as the strong(est) sensory sensation, must be localized and most pronounced within those sensory regions [6, p. 913, 7, p. 1145].

Since then, our knowledge regarding the underlying principles of brain-related pain processing have broadened substantially. In particular, the importance of a multifaceted perspective on the topic became evident. Today, even a simple definition of pain has become challenging. Currently, the International Association for the

Table 6.1 Corresponding anatomical and functional descriptions of areas within the "cortical functional pain circuit" delineated in Fig. 6.1

Nr	Anatomical description	Primary functions within a pain experience
1	Postcentral gyrus (S1)	Primary somatosensory "Somatosensory homunculus"
2	Superior-parietal area	Somatosensory association
3	Superior-parietal area	Somatosensory association
4	Supramarginal area	Somatosensory association
5	Subcentral area/parietal operculum	Somatosensory association, somatosensory awareness, intensity coding
6	Precentral gyrus (M1)	Motor reactions and planning "Motor homunculus"
7	Extend precentral areas	Supplementary motor reactions, motor anticipation
8	Prefrontal/frontopolar areas	Somatosensory/pain-related attention and evaluation Memory/meta-memory regarding pain and/or thread linked with pain Pain memory/reference Pain chronification
9	Pregenual anterior cingulate	Emotional integration/partly visceral integration Anticipation "Suffering component" of pain
10	Anterior mid-cingulate	Cognitive-evaluative processing linked with avoiding of potentially pain evoking situations Anticipation "Suffering component" of pain
11	Posterior mid-cingulate	Cognitive-evaluative processing linked with motor reactions
12	Thalamus	Relay station for all spino-cortical and corticospinal signaling cascades
13	Periaqueductal gray (PAG)	Modulating functions of somatosensory input, can be mitigating or amplifying
14	Nucleus cuneiformis (NCF)	Primary pain inhibitory function Recent work point to a more complex involvement/modulation of pain signals
15	Spinothalamic, spinoreticular, and spinomesencephalic paths with embedded nuclei	Stimulus conduction periphery-thalamus
16	Rostroventral medulla (RVM)	Primary pain inhibitory function Recent work point to a more complex involvement/modulation of pain signals
17	Anterior cerebellum	Stimulus sensory and cognitive processing Anticipation
18	Posterior cerebellum	Rather cognitive and emotional processing Anticipation
19	Anterior insula	Chiefly involvement in a variety of cognitive-evaluative aspects regarding pain processing Anticipation
20	Middle insula	Complex involvement in a variety of different pain-related processes, its subclassification not entirely clear
21	Posterior insula	Chiefly involved in a variety of direct sensory-related pain processes The only region pain can be induced by intracranial stimulation
22	Amygdala and hippocampus areas	Fear of pain, pain anxiety, pain memory Probably involved in several key mechanisms to chronify pain
23	Putamen and pallidum (basal ganglia)	Motor-and anticipation related pain processing

Study of Pain (IASP) suggests the following: *An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage* (http://www.iasp-pain.org/terminology). Of course, there are lots of additional contents listed, but the key element is evident by focusing on the term *experience*.

Indeed, pain has to be interpreted as a "global experience," being hardly definable by anyone single, distinct neural constituent. Current views and explanations regarding human pain take into account multiple, complexly intertwined systems including sensory, motor, attentional, and cognitive neural processes [8, p. 1874, 9, p. 887]. Further, there is little doubt that pain has a strong and unique attentional activation quality that channels feelings, emotions, and thoughts in a specific direction, preserving the negative thoughts related to the possible events and consequences surrounding a specific pain experience [10, p. 1820]. But despite pain being a mostly unpleasant experience, it is probably the most important aspect of somatosensation [11, p.1667, 12, p. 958]. We need pain in order to be protected from injury and tissue damage. Without an intact, functioning pain system, it's challenging for an individual to stay healthy and free from injury. Indeed, reports on people suffering from congenital insensitivity to pain quite remarkably demonstrate the consequences of this statement. Several cases describe affected individuals who learned to live with their handicap and long-term outcomes were worsened by severe orthopedic complications mostly as a result of untreated skeletal injuries sustained in childhood [7, p. 1145, 13, p. 2017, 14, p. 2018].

Based on the above reasoning, when one considers the areas delineated in Fig. 6.1/Table 6.1, it now makes sense why there are numerous brain regions that participate in the experience of pain. There is a complex interplay of sensory, vegetative, emotional, motor, and cognitive aspects of pain, and it is now evident that the brain as a whole is challenged to adequately deal with such a global experience.

6.2 Acute Versus Chronic Pain

A healthy somatosensory system is one that is optimally equipped to accurately process pain, meaning that temporally, the pain diminishes either simply through the passage of time or by administration of medication. But some people are less "lucky"; in some cases, the pain remains and turns into a disruptive chronic entity, sometimes accompanied by severe comorbidities that become very difficult to treat [15, p. 613, 16, p. 1803, 17, p. 2021]. There are several open questions regarding this maladaptive development, and the associated risk factors remain poorly understood [18, p. 2027]. The rather simplified assumption was that chronic pain results from either constant nociceptive activation or central/peripheral somatosensory system damage which was generally summarized as neuropathic pain [19, p. 2028]. Others suggested that the chronicity derives from structural reorganization within the spinal cord and associated brain regions due to either the stimulation of long-lasting intense pain or severe psychologically/environmentally coincident stress

experienced when the injury was sustained [20, p. 980, 21, p. 1091, 22, p. 1157]. More recent views suggest a complex intermingling of structural alterations in combination with disturbances of default mode networks (DMN) and connectivity patterns, which are probably interdependent on each other [23, p. 1820, 24, p. 1917]. Additionally, cortically localized "risk factors" have been theorized to exist in the form of deviant circuits incorrectly connecting relevant cerebral areas that could underlie a person's vulnerability to develop the manifestations of chronic pain. Additionally, brain regions not classically considered to be associated with pain processing, structures located within the corticolimbic system (dorsal medial prefrontal cortex-amygdala-nucleus accumbens, ventral medial prefrontal cortex-amygdala, orbitofrontal cortex-amygdala), have been hypothesized to be key regions involved in the development of an individuals increased risks or susceptibility to chronic pain [18, p. 2027].

6.2.1 Example

A very interesting investigation by Mutso et al. [25, p. 2019] took a look at the structural and functional mechanisms underlying the transition from acute to chronic back pain. Based on the results of previous animal research, they assumed that the hippocampus would be the locus where structural and connective deviations would lead to the generation of the maladaptive circuitry, which is ultimately responsible for the switch from subacute to chronic pain. Indeed, they observed a significant involvement of hippocampal and prefrontal areas during the transformation from subacute (1–4 months) to chronic back pain (>10 years). The most severe alterations were observed in the structural reorganization of the hippocampus itself in addition to unbalanced connectivity patterns between the hippocampus/amygdala and prefrontal areas. Strikingly, experimentally driven acute pain studies very rarely report the hippocampal area as being activated.

However, another hypothesis favors the existence of a dynamic pain connectome, which exists as a spatiotemporal neural signature involving a variety of brain networks that communicate in a distinct fashion to integrate all the aspects of the pain experience. This model seems to represent the most accurate view we have to date (adapted from [10, p. 1820]). Table 6.2 summarizes the suggested networks and assigned functions to the areas involved in this theory.

It is not entirely clear which underlying mechanisms drive the alterations in network connectivity and increases or decreases in neural center activity. There are indications of aberrant DMN (default mode network) characteristics in several chronic pain states, but caution is advised in terms of conclusive causal interpretations of the reported observations. Also, alterations in connectivity strengths between respective areas/networks are discussed in both directions (amplification or mitigation) again in several chronic pain states [25, p. 2019, 26, p. 266, 27, p. 135, 28, p. 2118]. The underlying basic systems—sensorimotor, default mode, salience, and nociceptive—can further be interpreted as being involved in other daily behavior regulation processes we only begin to understand in detail [29, p. 1472]. Thus,

Table 6.2 A possible dynamic connectome regarding cortical pain processing including suggested networks, supposed functions, and associated areas

Network/system	Function	Areas involved
Sensory-motor (SM)	Sensory and motor-related fundamental states in regard to pain events	Primary somatosensory area Primary motor area
Salience (SN)	Pain-related interoceptive and sustained attention	Anterior insula Dorsolateral prefrontal area Posterior insula Temporoparietal junction Orbitofrontal area
Default mode network (DMN)	Most likely suppressed when concentrating on pain or when ruminate toward pain	Posterior cingulate areas Medial dorso-/anterior prefrontal Medial temporal lobe
Antinociceptive system (AS)	Descending pain modulation, amplified under acute pain, mitigated under chronic pain	Medial prefrontal Thalamus Brainstem substructures PAG/NCF/RVM

despite the concept of a dynamic pain connectome representing an intelligible approach for explaining the proneness to pain chronification and its neural manifestations, it is still challenging to allocate the different facets of pain specifically to a single areas connectivity changes in resting state network architecture or structural changes in areas belonging to the neural signature of pain.

Thus, to summarize this short general sketch, based on what we know from brain studies, both human and animal, chronic pain seems rather maintained by cortical areas, networks, and circuits whose functions are assigned to all sensory, vegetative, as well as emotional and cognitive processes. This might be a result of a maladaptive learning and association process [30, p. 987] or the amplification within prevulnerable systems possibly manifested in aberrant fronto-limbic structures and related processing [18, p. 2027].

6.3 Neuroanatomy of TMJ-Related Pain

The neural arrangement of the temporomandibular joint is—from a non-nociceptive somatosensory perspective—quite unequivocal: the locus is within the face area of the primary somatosensory cortex, tightly adjoining the hand area. Aside from the hand/finger area, the face area is the largest representation in this part of the brain, correlated with the associated peripheral receptor densities reflected in the sensitivity of the tongue, teeth, lips, nose, eye, and the skin of the human face in general. Thus, this system constitutes the main afferent pathways for all somatosensory processing regarding these structures, including the mandibular joint as well as associated muscles and tendons. Considering the pain-related neural signature delineated in Fig. 6.1, it's important to note that trigeminally mediated nociceptive input is underrepresented compared to pain evoked at other body sites [31, p. 1506, 32, p. 1950]. This is quite astonishing as trigeminal pain and associated burden,

suffering, and costs would justify enormous effort toward examination of underlying brain processing. In principle, there are two options to pursue to unravel this paradox, either one can study chronic TMJ conditions or focus on studying healthy volunteers in experimental orofacial pain models.

6.3.1 Experimental Approaches

Investigating healthy human subjects in experimental orofacial pain models in a standardized setting represents an important branch of research aimed to elucidate fundamental mechanisms of associated cortical pain processing. In this vein, toothache can be utilized as an acute form of orofacial pain, thus providing the researcher with an ideal experimental orofacial pain paradigm to evaluate trigeminally mediated cortical activation and response patterns. Indeed, several reports have been published applying either painful or painless stimuli to a least one tooth, while concomitantly recording brain responses. The modalities range from tactile/vibrotactile, electric, and air stimuli. An overview is given in Table 6.3.

To summarize, brain response patterns in response to tooth stimulation strongly resemble those from experimental pain applied to extra-trigeminal sites, especially stimulation at painful levels. This means that the associated neurological signature encompasses the areas illustrated in Fig. 6.1, however, with a number of obvious peculiarities.

Focusing firstly on somatotopic cortical organization aspects, the study by Jantsch et al. [34, p. 683] demonstrated S1 activity contralateral to hand pain compared to bilateral activity during tooth pain. This bilateral activity pattern might be related to the fact that the stimulated left incisor tooth is close to the body midline, whereas the hand is clearly more distal. It is critical to be cautious about this result as ideally, both incisor teeth should be stimulated to conclusively prove this assumption. The work conducted by Brügger et al. [31, p. 1506] addresses this issue by stimulation of the left/right maxillary canines and central incisors. A direct comparison between central incisor and canine stimulation revealed a more prominent tendency toward contralateral S1 activity for canines compared to central incisors. This finding implies a certain cortical lateralization scheme related to the distance from the body midline. Both findings support the concept of somatotopic organization within S1 also for teeth, however, with the limitation that this somatotopic pattern was induced by pain and not by painless somatosensory stimulation.

Utilizing MEG (Magnetic Encephalography) as an alternative method, the work by Kubo et al. [36, p. 1074] compared painless stimulation of the right maxillary first premolar with the median nerve of the right wrist. The findings also revealed bilateral activity in a region the authors termed “parieto-temporal” area. But when looking at the sources of this activity, a contralateral main focus located in the central sulcus (S1) was observed for tooth and wrist stimulation with a slight posterior/superior shift of tooth stimulation. Further fMRI-based evidence investigating possible somatotopy of the intraoral area is further supported by results of Miyamoto et al. [35, p. 1075]; their protocol also involves applying painless stimuli to the right

Table 6.3 Studies combining tooth stimulation and neuroimaging

Authors	Imaging technology magnetic field strength	N subjects	Stimulus modality Pain/painless/both	Stimulated tooth/teeth
Ettlin et al. [33]	fMRI 3 T	5 (2 male)	Mechanical vibrotactile Painless	Central incisor/canine/second premolar and second molar of each jaw quadrant
Jantsch et al. [34]	fMRI 1.5 T	8 (4 male)	Electric Weak and strong pain	Left maxillary central incisor
Miyamoto et al. [35]	fMRI 3 T	14 (8 male)	Tactile, rubber tip Painless	Right central upper incisor (beside lower lip/tongue)
Kubo et al. [36]	MEG	7 (7 male)	Electric Painless	Right maxillary first premolar
Brügger et al. [37]	fMRI 3 T	14 (8 male)	Electric Graded from painless to painful	Left/right maxillary canine
Trulsson et al. [38]	fMRI 3 T	10 (10 male)	Mechanical vibrotactile Painless	Left central upper incisor
Weigelt et al. [39]	fMRI 1.5 T	13 (8 male)	Electric pain	Left mandibular and maxillary canine
Brügger et al. [31]	fMRI 3 T	21 (13 male)	Electric pain (150% of pain perception thresholds)	Left/right maxillary canine and central incisor
Gutzeit et al. [40]	fMRS 3 T	10 (10 male)	Electric pain (4–5 out of 10 on a VAS)	Right maxillary canine
Brügger et al. [41]	fMRI 3 T	13 (13 male)	Electric 5 graded stimulus strengths from painless to painful	Right maxillary canine
Meier et al. [42]	fMRI 3 T	10 (2 male)	Air puffs 5 graded stimulus strengths from painless to painful	Right and left maxillary canine and molars
Gutzeit et al. [43]	fMRS 3 T	16 (16 male)	Electric pain (4–5 out of 10 on a VAS)	Right maxillary canine
Meier et al. [44]	fMRI 3 T	14 (14 male)	Electric pain (5 out of 10 on a NRS) Modulated by the anesthetic articaine	Left mandibular canine
De Matos et al. [45]	fMRS 3 T	13 (13 male)	Electric pain (4–5 out of 10 on a VAS)	Right maxillary canine

VAS means Visual Analog Scale, NRS means Numeric Rating Scale

upper central incisor tooth, the lower lip, and the tongue. They used a rubber tip and administered the stimuli manually. Clearly overlapping S1 activity was observed with a lip-tooth-tongue gradient from superior to inferior in rostral S1 subareas of their activity cluster. Important to note only the contralateral S1 region was investigated; therefore it is not possible to compare their results with the Jantsch/Brügger/Kubo reports as they observed a general bilateral activation pattern but with lateralization tendencies. Importantly, the report by Brügger et al. [31, p. 1506] demonstrated a robust bilateral activation pattern with further contralateral tendencies in the thalamus, in the posterior insula, around the parietal operculum (BA 43), and surprisingly in the amygdala. The finding of increased contralateral activation of the amygdala has to be specifically brought to attention as it is the only experimental human pain report demonstrating such a pattern. For example, a review by Baas et al. [46, p. 1102], summarizing 54 studies with amygdala activity, revealed no clear lateralization effect and highlighted the main functional contribution of the amygdala in processing primarily negative affective states such as fear and anxiety but no somatosensory encoding properties. On the other hand, Neugebauer [47, p. 1104] and Neugebauer [48, p. 1103] found evidence in rats that this structure consists of a so-called nociceptive amygdala located in the latero-capsular division of the central nucleus which directly processes sensory input. Yet, in humans, this has yet to be clarified although the study by Brügger and colleagues opened the window toward the amygdala's possible direct involvement in decoding somatotopic information. A possible explanation of this finding might be that tooth pain induces higher levels of threat/anxiety than pain originating from other parts of the human body, requiring the aberrant recruitment of additional brain structures to somato-topically encode the afferent sensory signals. A recent report by Meier et al. [49, p. 1436] substantiated this presumption by demonstrating enhanced conditioned fear induced by a short tooth pain stimulus compared to pain administered to the tibia. However, it must not be forgotten that functional measurements of such small subareas require specific imaging strategies especially when the amygdala is targeted. Mainly, this is due to its central localization, the surrounding vasculature and bordering cerebrospinal fluid. Those facts are accompanied by strong phase-encoding susceptibility inferences leading to false positive and negative activation patterns unrelated to a specific stimulation or task [50, p. 1101, 51, p. 1578].

Besides the information of "where" does it hurt and the "how much" does it hurt is—at least—of comparable importance. There is one report addressing this question directly by applying five different stimulus strengths to a right maxillary canine, whereas two were painless, and the remaining three were painful [41, p. 84]. Also, the study of Jantsch et al. [34, p. 683] can be interpreted as intensity coding as they applied "weak" and "strong" pain, however, no painless stimuli were used. An alternative approach was used by Trulsson et al. [38, p. 1073] also focusing on "intensity coding" by applying tactile stimulation of different frequencies to the left maxillary incisor, but no painful stimulation specifically. Cortical correlates of somatosensory intensity coding have been demonstrated across the literature, most particularly in the subareas of the insular and cingulate cortices (i.e., [52, p. 916, 53, p. 1144, 54, p. 919]). Beginning with the study of Brügger et al. [41, p. 84] which applied the whole range of perception

from painless to painful, the anterior insula together with two cingulate cortex subareas, namely, the anterior mid- and pregenual anterior cingulate cortex, demonstrated a significant linear relation between applied stimulus strengths and activity levels. The observation that the insular cortex plays a crucial role in intensity coding was also demonstrated by the Jantsch study, however; the insula also showed a stronger activity pattern during the hand stimulation, which may be due to the varying modalities used in their paradigm (electrical for tooth and mechanic for the index finger). Interestingly, the Trulsson study revealed generally stronger activity when applying higher tactile stimulus frequencies (100 Hz) and additional insular-opercular subarea activity, but only contralateral to the stimulation site. The same pattern was observed in the right cerebellar cortex. Generally, these results fit well into known cortical response patterns to stimuli of extra-trigeminal origin. But recent elaborations of cortical systems coding specifically for different strengths of somatosensory input suggest a multisensory magnitude—instead of a specific pain-related assessment module, particularly within the insular cortex [21, p. 1091, 55, p. 417, 56, p. 920, 57, p. 1415, 58, p. 206]. In our opinion, this line of reasoning is understandable, as somatosensory stimulation of, for example, the human back induces a multitude of perceptions due to a variety of different receptor types transmitting the whole range of sensory modalities. On the other hand, teeth are unique "organs" consisting of hard mineralized material surrounding densely innervated and vascularized soft tissue located within the tooth pulp. The pulp itself is predominantly innervated by C and A-delta fibers, implying that neural inputs are (1) of mostly nociceptive characteristic and (2) of rather homogenous perceptive quality [31, p. 1506, 59, p. 897]. This physiological specificity makes the tooth an ideal stimulation target in order to investigate more thoroughly the "pure pain perception" and probably also the processing of the intensity level of pain. Two studies can be considered in this vein: [42, p. 46] and [44, p. 1504]. The first investigated patients suffering from dental hypersensitivity in response to an application of an air stimulus sufficiently strong to evoke pain. A sensitive as well as an insensitive tooth were stimulated and patients were required to focus selectively on their intensity perception. Surprisingly, intensity coding related activity was observed in a multitude of areas, including anterior insular and mid-cingulate subareas (see results section for details). Those two regions were also found to specifically code for the sensitive tooth with clearly stronger activity, providing the evidence that these areas seem to have pain specific functions beside the intensity coding properties. To substantiate this finding, a follow-up study by the same group addressed this issue with an elegant approach [44, p. 1504]. Using electric stimuli at a constant intensity applied to the left mandibular canine, they injected an anesthetic drug (articaine) to block afferent signaling transmission while the stimulation continued at the same intensity level. Over time a gradual pain decrease was perceived despite the ongoing painful stimulation. The specific brain response pattern in reaction to the articaine-induced dental pain relief was observed in a small portion of the left posterior insula, reiterating the critical role of this brain area in coding pain specificity and related intensity coding.

From a neurochemistry perspective, there is strong evidence subserving the idea of the insula is key structure within the cortical dental pain circuitry derived from two studies using fMRS (functional magnetic resonance spectroscopy) [40, p. 882, 43, p. 1152]. In the first attempt, the whole left insular cortex was measured during

continuous stimulation of the right maxillary canine. Significant increases were measureable in the levels of glutamine (Gln) and the glutamine-glutamate complex (Glx) together with a significant drop in myo-inositol (mI). The second report investigated the insular cortex bilaterally, and they subclassified the insula into an anterior and posterior portion using the same paradigm. Comparable to the first study, Glx, Gln, and also glutamate (Glu) showed a significant increase during the pain stimulation phase, whereas mI significantly dropped. This pattern was observed in all four subareas. An interesting effect was found in significant differences between left and right insular subareas irrespective of stimulation or rest. As the insular cortex is incorporated in a manifold of different cortical functions, this fundamental disparity might support the suggestion that there are inherent functional differences between the subareas as pointed out by several investigations [20, p. 980, 60, p. 976] or [54, p. 919]. Neurochemical alterations within subareas of the right insular cortex have been shown by applying heat pain to an inner left forearm area. However, they measured a dorsal-anterior area, thus a rather evaluative-cognitive region than sensory encoding. Regardless, they revealed partly comparable reaction patterns with respect to increased Glu levels. None of the other metabolites demonstrated a pattern related with the stimulation. The stimulus related measurement of neurochemistry (event-related MRS or functional MRS) is complementary to fMRI in brain imaging. To date, only four studies have applied experimental pain while measuring changes in neurochemical compositions, thus, a lot of ambiguity remains that has to be investigated in more details.

The group of De Matos et al. [45] attempted a closer investigation into the fundamental nociceptive processing within the CNS. Applying the paradigm used in other studies by this group, the brainstem trigeminal nuclear complex (BTNC) was targeted while administering painful electrical stimuli to the right maxillary canine and neurochemical alterations during pain vs baseline were assessed. The BTNC constitutes the first CNS relay along the peripheral-central signaling cascade and therefore enables the investigation of pain-related processing at a very initial level. As the main result, a significant decrease in NAA and GABA during experimental orofacial stimulation was found. To date, a conclusive summary regarding this neurochemical pattern is not advocated by the authors as the results need clarification by further investigations. While of particular interest regarding early nociceptive processing, the study demonstrated above all, the possibility to measure the human brainstem neurochemistry with high accuracy, thus paving the way to a better understanding of this important brain area in the context of acute pain processing as well as pain related chronification mechanisms.

6.4 Summary

Pain is a multidimensional experience incorporating sensory, motor, affective and cognitive components. This applies to pain in general, as well as to orofacial pain in particular. This chapter provided an overview of neural signatures based on experimental acute orofacial pain up to explanatory approaches possibly underlying chronification mechanisms and chronic pain.

Summarized, brain responses of acute orofacial pain are quite well characterized based on sophisticated experimental models combined with imaging methods such as fMRI, fMRS, MEG and EEG. This strategy is important as such experiments allow standardized and controlled application of pain stimuli. In this way it is possible to understand the fundamental neural processes of experiencing pain, which in turn is the prerequisite for understanding the much more complex chronic pain. Concluded, these experiments revealed that several brain areas, often termed "Pain Matrix" or "Neurological Signature of Pain", representing the neural framework regarding the multidimensional facets of an acute pain experience.

Still a challenge to understand are neural underpinnings of chronic pain and associated mechanisms that facilitates the transition from acute to subacute and finally chronic pain. Recent investigations suggest that chronic pain involves additional areas not known as classic pain areas (hippocampus) or propose a highly "Dynamic Pain Connectome" linking attention and pain related brain areas such as Salience-, Default Mode and Antinociceptive networks.

Recent years of intensive basic and clinical research has not yet brought the solution, but we are on good terms to comprehend the basic processes of pain chronification better and better. Including multimodal approaches that measure and quantify different facets of brain function, together with improved analytical methods (i.e. deep learning and big data management), a much better understanding of this highly significant global health problem is closer than ever before.

References

1. Penfield W, Boldrey E. Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation. London: Macmillan; 1937.
2. Penfield W. Engrams in the human brain: mechanisms of memory. Proc Roy Soc Med. 1968;61:831–40.
3. Penfield W, Jasper H. Epilepsy and the functional anatomy of the human brain. Boston: Brown L; 1954.
4. Peyron R, Laurent B, García-Larrea L. Functional imaging of brain responses to pain. A review and meta-analysis (2000). Neurophysiol Clin. 2000;30:263–88.
5. Wager TD, Atlas LY, Lindquist MA, Roy M, Woo C-W, Kross E. An fMRI-based neurologic signature of physical pain. N Engl J Med. 2013;368:1388–97.
6. Bushnell MC, Duncan GH, Hofbauer RK, Ha B, Chen JI, Carrier B. Pain perception: is there a role for primary somatosensory cortex? Proc Natl Acad Sci U S A. 1999;96:7705–9.
7. Denk F, McMahon SB, Tracey I. Pain vulnerability: a neurobiological perspective. Nat Neurosci. 2014;17:192–200.
8. Moayedi M, Davis KD. Theories of pain: from specificity to gate control. J Neurophysiol. 2013;109:5–12.
9. Tracey I, Mantyh PW. The cerebral signature for pain perception and its modulation. Neuron. 2007;55:377–91.
10. Kucyi A, Davis KD. The dynamic pain connectome. Trends Neurosci. 2015;38:86–95.
11. Haggard P, de Boer L. Oral somatosensory awareness. Neurosci Biobehav Rev. 2014;47:469–84.
12. Scholz J, Woolf CJ. Can we conquer pain? Nat Neurosci. 2002;5:1062–7.
13. Minde J, Svensson O, Holmberg M, Solders G, Toolanen G. Orthopedic aspects of familial insensitivity to pain due to a novel nerve growth factor beta mutation. Acta Orthop. 2006;77:198–202.
14. Losa M, Scheier H, Rohner P, Sailer H, Hayek J, Giedion A, Boltshauser E. Langzeitverlauf bei kongenitaler Analgesie. Schweiz Med Wochenschr. 1989;119:1303–8.

15. Baliki MN, Chialvo DR, Geha PY, Levy RM, Harden RN, Parrish TB, Apkarian AV. Chronic pain and the emotional brain: specific brain activity associated with spontaneous fluctuations of intensity of chronic back pain. J Neurosci. 2006;26:12165–73.
16. Brown RS, Arm RN, Epstein JB. Diagnosis and treatment of chronic orofacial pain, 2nd edn. In: Clinician's guide. Hamilton, ON: BC Decker; 2008.
17. Apkarian AV, Baliki MN, Geha PY. Towards a theory of chronic pain. Prog Neurobiol. 2009;87:81–97.
18. Vachon-Presseau E, Tetreault P, Petre B, Huang L, Berger SE, Torbey S, Baria AT, Mansour AR, Hashmi JA, Griffith JW, Comasco E, Schnitzer TJ, Baliki MN, Apkarian AV. Corticolimbic anatomical characteristics predetermine risk for chronic pain. Brain. 2016;139:1958–70.
19. Treede R-D, Jensen TS, Campbell JN, Cruccu G, Dostrovsky JO, Griffin JW, Hansson P, Hughes R, Nurmikko T, Serra J. Neuropathic pain—redefinition and a grading system for clinical and research purposes. Neurology. 2008;70:1630–5.
20. Craig ADB. How do you feel—now? The anterior insula and human awareness. Nat Rev Neurosci. 2009;10:59–70.
21. Legrain V, Iannetti GD, Plaghki L, Mouraux A. The pain matrix reloaded: a salience detection system for the body. Prog Neurobiol. 2011;93:111–24.
22. van Ryckeghem DML, Crombez G, Eccleston C, Legrain V, van Damme S. Keeping pain out of your mind: the role of attentional set in pain. Eur J Pain. 2013;17:402–11.
23. Kucyi A, Davis KD. The neural code for pain: from single-cell electrophysiology to the dynamic pain connectome. Neuroscientist. 2017;23(4):397–414.
24. Davis KD, Kucyi A, Moayedi M. The pain switch: an "ouch" detector. Pain. 2015;156:2164–6.
25. Mutso AA, Petre B, Huang L, Baliki MN, Torbey S, Herrmann KM, Schnitzer TJ, Apkarian AV. Reorganization of hippocampal functional connectivity with transition to chronic back pain. J Neurophysiol. 2014;111:1065–76.
26. Napadow V, LaCount L, Park K, As-Sanie S, Clauw DJ, Harris RE. Intrinsic brain connectivity in fibromyalgia is associated with chronic pain intensity. Arthritis Rheum. 2010;62:2545–55.
27. Baliki MN, Baria AT, Apkarian AV. The cortical rhythms of chronic back pain. J Neurosci. 2011;31:13981–90.
28. Kucyi A, Moayedi M, Weissman-Fogel I, Goldberg MB, Freeman BV, Tenenbaum HC, Davis KD. Enhanced medial prefrontal-default mode network functional connectivity in chronic pain and its association with pain rumination. J Neurosci. 2014;34:3969–75.
29. Hutchison RM, Womelsdorf T, Gati JS, Everling S, Menon RS. Resting-state networks show dynamic functional connectivity in awake humans and anesthetized macaques. Hum Brain Mapp. 2013;34:2154–77.
30. Farmer MA, Baliki MN, Apkarian AV. A dynamic network perspective of chronic pain. Neurosci Lett. 2012;520:197–203.
31. Brügger M, Ettlin DA, Meier M, Keller T, Luechinger R, Barlow A, Palla S, Jäncke L, Lutz K. Taking sides with pain—lateralization aspects related to cerebral processing of dental pain. Front Human Neurosci. 2011;5:12.
32. Lin C-S. Brain signature of chronic orofacial pain: a systematic review and meta-analysis on neuroimaging research of trigeminal neuropathic pain and temporomandibular joint disorders. PLoS One. 2014;9:e94300.
33. Ettlin DA, Zhang H, Lutz K, Järmann T, Meier D, Gallo LM, Jäncke L, Palla S. Cortical activation resulting from painless vibrotactile dental stimulation measured by functional magnetic resonance imaging (FMRI). J Dent Res. 2004;83(10):757–61.
34. Jantsch HHF, Kemppainen P, Ringler R, Handwerker HO, Forster C. Cortical representation of experimental tooth pain in humans. Pain. 2005;118:390–9.
35. Miyamoto JJ, Honda M, Saito DN, Okada T, Ono T, Ohyama K, Sadato N. The representation of the human oral area in the somatosensory cortex: a functional MRI study. Cereb Cortex. 2006;16:669–75.
36. Kubo K, Shibukawa Y, Shintani M, Suzuki T, Ichinohe T, Kaneko Y. Cortical representation area of human dental pulp. J Dent Res. 2008;87:358–62.
37. Brügger M, Ettlin DA, Keller T, Luechinger R, Jäncke L, Palla S, Barlow A, Gallo LM, Lutz K. Interindividual differences in the perception of dental stimulation and related brain activity. Eur J Oral Sci. 2009;117:27–33.

38. Trulsson M, Francis ST, Bowtell R, McGlone F. Brain activations in response to vibrotactile tooth stimulation: a psychophysical and fMRI study. J Neurophysiol. 2010;104:2257–65.
39. Weigelt A, Terekhin P, Kemppainen P, Dörfler A, Forster C. The representation of experimental tooth pain from upper and lower jaws in the human trigeminal pathway. Pain. 2010;149:529–38.
40. Gutzeit A, Meier D, Meier ML, von Weymarn C, Ettlin DA, Graf N, Froehlich JM, Binkert CA, Brügger M. Insula-specific responses induced by dental pain. A proton magnetic resonance spectroscopy study. Eur Radiol. 2011;21:807–15.
41. Brügger M, Lutz K, Brönnimann B, Meier ML, Luechinger R, Barlow A, Jäncke L, Ettlin DA. Tracing toothache intensity in the brain. J Dent Res. 2012;91:156–60.
42. Meier ML, Brügger M, Ettlin DA, Luechinger R, Barlow A, Jäncke L, Lutz K. Brain activation induced by dentine hypersensitivity pain—an fMRI study. J Clin Periodontol. 2012;39:441–7.
43. Gutzeit A, Meier D, Froehlich JM, Hergan K, Kos S, V Weymarn C, Lutz K, Ettlin D, Binkert CA, Mutschler J, Sartoretti-Schefer S, Brügger M. Differential NMR spectroscopy reactions of anterior/posterior and right/left insular subdivisions due to acute dental pain. Eur Radiol. 2013;23:450–60.
44. Meier ML, Widmayer S, Abazi J, Brügger M, Lukic N, Lüchinger R, Ettlin DA. The human brain response to dental pain relief. J Dent Res. 2015;94(5):690–6.
45. de Matos NMP, Hock A, Wyss M, Ettlin DA, Brügger M. Neurochemical dynamics of acute orofacial pain in the human trigeminal brainstem nuclear complex. Neuroimage. 2017;162:162–72.
46. Baas D, Aleman A, Kahn RS. Lateralization of amygdala activation: a systematic review of functional neuroimaging studies. Brain Res Rev. 2004;45:96–103.
47. Neugebauer V, Li W. Differential sensitization of amygdala neurons to afferent inputs in a model of arthritic pain. J Neurophysiol. 2003;89:716–27.
48. Neugebauer V, Li W, Bird GC, Han JS. The amygdala and persistent pain. Neuroscientist. 2004;10:221–34.
49. Meier ML, de Matos NMP, Brügger M, Ettlin DA, Lukic N, Cheetham M, Jäncke L, Lutz K. Equal pain-unequal fear response: enhanced susceptibility of tooth pain to fear conditioning. Front Hum Neurosci. 2014;8:526.
50. Mathiak KA, Zvyagintsev M, Ackermann H, Mathiak K. Lateralization of amygdala activation in fMRI may depend on phase-encoding polarity. Magma. 2012;25:177–82.
51. Boubela RN, Kalcher K, Huf W, Seidel E-M, Derntl B, Pezawas L, Našel C, Moser E. fMRI measurements of amygdala activation are confounded by stimulus correlated signal fluctuation in nearby veins draining distant brain regions. Sci Rep. 2015;5:10499.
52. Vogt BA. Pain and emotion interactions in subregions of the cingulate gyrus. Nat Rev Neurosci. 2005;6:533–44.
53. Nieuwenhuys R, Voogd J, van Huijzen C. The human central nervous system. 4th ed. Berlin: Springer; 2008.
54. Kurth F, Zilles K, Fox PT, Laird AR, Eickhoff SB. A link between the systems: functional differentiation and integration within the human insula revealed by meta-analysis. Brain Struct Funct. 2010;214:519–34.
55. Baliki MN, Geha PY, Apkarian AV. Parsing pain perception between nociceptive representation and magnitude estimation. J Neurophysiol. 2009;101:875–87.
56. Mazzola L, Isnard J, Peyron R, Mauguière F. Stimulation of the human cortex and the experience of pain: Wilder Penfield's observations revisited. Brain. 2012;135:631–40.
57. Pomares FB, Faillenot I, Barral FG, Peyron R. The 'where' and the 'when' of the BOLD response to pain in the insular cortex. Discussion on amplitudes and latencies. NeuroImage. 2013;64:466–75.
58. Mouraux A, Diukova A, Lee MC, Wise RG, Iannetti GD. A multisensory investigation of the functional significance of the "pain matrix". NeuroImage. 2011;54:2237–49.
59. Sessle BJ. Peripheral and central mechanisms of orofacial inflammatory pain. Int Rev Neurobiol. 2011;97:179–206.
60. Craig ADB. The sentient self. Brain Struct Funct. 2010;214:563–77.