J Clin Periodontol 2012; 39: 441–447 doi: 10.1111/j.1600-051X.2012.01863.x

Journal of Clinical Periodontology

Brain activation induced by dentine hypersensitivity pain–an fMRI study

Michael L. Meier[1], Michael Brügger[2,3], Dominik A. Ettlin[3], Roger Luechinger[2], Ashley Barlow[4], Lutz Jäncke[1] and Kai Lutz[1]

[1]Institute of Psychology, Department of Neuropsychology, University of Zurich, Zurich, Switzerland; [2]Institute of Biomedical Engineering, Swiss Federal Institute of Technology and the University of Zurich, Zurich, Switzerland; [3]Center of Dental Medicine, Clinic of Masticatory Disorders, Removable Prosthodontics, and Special Care Dentistry, University of Zurich, Zurich, Switzerland; [4]GlaxoSmithKline, Consumer Healthcare, Weybridge, Surrey, UK

Meier ML, Brügger M, Ettlin DA, Luechinger R, Barlow A, Jäncke L, Lutz K. Brain activation induced by dentine hypersensitivity pain–a fMRI study. J Clin Periodontol 2012; 39: 441–447. doi: 10.1111/j.1600-051X.2012.01863.x.

Abstract

Aim: Dentine hypersensitivity (DH) is characterized by a short, sharp pain arising from exposed dentin. Most published literature reports on peripheral neural aspects of this pain condition. The current investigation focused on differential cerebral activity elicited by stimulation of sensitive and insensitive teeth by means of natural air stimuli.

Materials and Methods: Five graded stimulus strengths were randomly applied by means of a multi-injector air jet delivery system, each followed by an individual rating of perceived stimulus intensity. Brain activity was analysed by functional magnetic resonance imaging (fMRI).

Results: Stimulation of sensitive teeth induced significant activation in the thalamus, somatosensory cortices (SI & SII), anterior, middle and posterior insular cortices, anterior mid cingulate cortex, perigenual anterior cingulate cortex and frontal regions (BA10 and BA46). Differential responses to DH and painless perceptions were observed in the anterior insula and anterior midcingulate cortex.

Conclusion: For the first time, this fMRI study demonstrates the feasibility of investigating cerebral processes related to DH evoked by natural (air) stimuli. Our neuroimaging data additionally provide evidence that differential activity in the anterior Insula (aIC) and anterior midcingulate cortex (aMCC) may represent clinically relevant pain experienced by DH patients.

View the pubcast on this paper at http://www.scivee.tv/node/40036

Key words: anterior insula; anterior midcingulate cortex; dentine hypersensitivity; fMRI; pain

Accepted for publication 27 January 2012

Dentine hypersensitivity (DH) is a common clinical problem related to dental surface alterations caused by factors including e.g. abrasion, erosion, corrosion, gingival recession and periodontal treatment (Dowell & Addy 1983, Rees & Addy 2002, Que et al. 2010). The global prevalence is in the range of 10–30%, depending on study population, setting and design (Rees & Addy 2004). By comparison, patients with periodontal diseases have been reported to be at particularly high risk (up to 76%) for experiencing it (Chabanski et al. 1996, Tammaro et al. 2000, Troil et al. 2002). Multiple DH interventions have been tested over the years, but a lack of standardization of pain measurement has been identified as a major handicap for assessing the efficacy of agents applied (Poulsen 2011). A potential solution to this problem might be provided by modern neuroscientific techniques, including functional magnetic resonance imaging (fMRI). Neuroimaging methods revealed that a group of specific brain areas, known as the pain or nociceptive matrix, form a modular network that is preferentially activated when painful stimuli are applied to spinal nerve territories. However, numerous differences

Conflict of interest and source of funding statement

This study was funded by GlaxoSmithKline, Consumer Healthcare, Weybride, UK. The author A. Barlow is an employee of the sponsor, GSK. All other authors declare that they have no other link to this company and thus no conflicts of interests.

between the trigeminal and spinal sensory systems have been described, which justify focused dental pain investigations (Sessle 2007). Studies investigating the brain's reaction to painless and painful electric tooth stimuli revealed variable neural activation in the primary (SI) and secondary (SII) somatosensory cortices, subdivisions of the cingulate cortex, the insular cortex, thalamus, cerebellum and frontal regions by showing altered neural activity (Ettlin et al. 2004, 2009, Habre-Hallage et al. 2010, Weigelt et al. 2010, Brügger et al. 2011, 2012). Although toothache induction by electric current has merits as an experimental model, air blast application to sensitive teeth better mimics the clinical pain experienced by DH patients (Ide et al. 2001, Yilmaz et al. 2011). The current report aimed at identifying cortical regions that show a differential response between sensitive and insensitive teeth stimulations. This is the first report using fMRI for investigating DH.

Materials and Methods

Recruitment and sensitive tooth assessment

Seventy-one potential subjects read a web announcement and answered an online questionnaire; 26 of them were invited for a screening visit. This selection was primarily based on the self-report whether subjects experienced unpleasant and/or painful sensations when pulling air through the mouth/teeth. During the first visit, the sensitive tooth and the contralateral healthy insensitive tooth were clinically and radiographically evaluated by a dentist. After the medical history was reviewed and an oral soft tissue examination was performed, the sensitive tooth was required to show signs of facial/cervical erosion, abrasion and/or gingival recession and no facial restoration. Exclusion criteria for test teeth were: caries, defective restorations, full crowns, orthodontic bands, bleeding on probing and periodontal pockets deeper than 3 mm. Subjects with gross periodontal disease or treatment of periodontal disease in the past 12 months were excluded. Only incisors, canines and premolars were evaluated as molars were unsuitable for installation of the air delivery tubes (Fig. 1). Sensitivity to air was tested by a triple air syringe commonly used in dentistry. The evaporative stimuli consisted of 1 s blasts of air directed to the buccal area of the recession, at approximately 1 cm distance from the affected tooth surface. Subjects were instructed to report stimulus perceptions by means of a horizontal 0–10 numerical rating scale with 0 labelled as "no pain" and 10 as "worst imaginable pain". For each tooth, a rating of at least 5 was required to be classified as sensitive. Analogue insensitive contralateral teeth were tested for air blast insensitivity. Sixteen subjects did not fulfil the inclusion requirements: 13 of them had no insensitive tooth on the opposite side and 3 subjects experienced sensitivity in molar teeth only. The final DH study group consisted of 10 subjects (age 21–55, mean 29.7, eight women). The sensitive tooth was located in the maxillary jaw in 9 of 10 subjects. In five subjects, the sensitive tooth was located on the right side.

The study was approved by the local ethics committee of the University of Zurich and conducted according to the guidelines of the Declaration of Helsinki for treatment of experimental human subjects. Subjects were financially compensated.

Experimental material

Blu-Mousse (Thixotropic Vinyl Polysiloxane; Edgewood, MD, USA) impressions were taken from the subject's dentition; 6 mm diameter holes were drilled at the labial gingival margin of test teeth. Two clear polyurethane tubes (Festo AG, Dietikon, Switzerland) of 4 mm inner diameter for air stimulation were permanently mounted into the holes of the impression with blu-mousse. For outward flow of the applied air, little grooves were drilled beside the tube holding holes (Fig. 1).

A modified portable version of the air puff delivery system previously described (Megias-Alguacil et al. 2008) was used for tooth stimulation (Fig. 1). This system is capable of operating in a magnetic resonance imaging environment and enables application of graded air streams with flow rates starting at 1 l/min. (barely noticeable) to 20 l/min. The air temperature matched the room temperature, which in the MR scanner room was controlled at 19.5 ± 1°C.

Psychophysical examination

Between one and 2 weeks prior to the MR experiment, subjects received extensive training during a psychophysical test session, which served to familiarize subjects with the stimulation paradigm. For determination of stimulus perception threshold, subjects were seated upright in a dental chair and comfortable fit of the stimulation tube holding impression was checked. In particular, care was taken that the soft splint did not evoke any pain or discomfort. Air blast stimuli of 1 s duration were applied at randomized inter-stimulus intervals (ISI) between 7.5 and 12.5 s. Using a staircase method, the sensory detection threshold (SDT = defined as the lowest flow rate at which the volunteer sensed an air puff) was determined, starting at a flow rate of 1 l/min. (system inherent lower limit), with subsequent 1 l/min. increments.

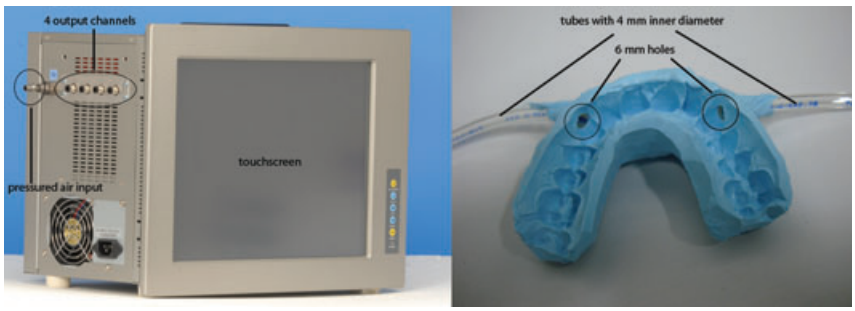

Fig. 1. Stimulation material. Left: MRI compatible multi-injector gas jet delivery system with touch screen. Right: Individual dental polysiloxane impression.

Pain detection threshold (PDT = the lowest flow rate that was perceived as just painful) and pain tolerance threshold (PTT = the maximum air flow rate that the subject would freely tolerate) were determined by further stepwise increases of flow rates. The threshold detection procedure was repeated three times with 5 min. breaks between each series. SDT, PDT and PTT were calculated as the mean of three repetitive measurements. All stimuli were controlled by a computer and neither the test persons nor the investigator viewed the computer screen to reduce bias in the psychophysical assessment procedure. The five stimulus strengths for the fMRI protocol were calculated as follows: PDT-40%, PDT-10%, PDT + 20%, PDT + 40% and PDT + 60% (Fig. 2). The same stimulus strengths were also applied to the insensitive tooth.

Once thresholds were determined, a psychophysical testing session was performed in order to familiarize subjects with the fMRI test protocol. The scanner environment was simulated by dimming room light and subjects were placed in supine position. They were given a headset playing an fMRI-EPI-sequence audiofile and were asked to wear video goggles displaying a computerized visual rating scale (coVRS) with 12 marks. The left anchor (first mark) was labelled "no sensation", the 4th mark "pain threshold" and the right anchor (12th mark) "worst imaginable pain" (Fig. 2). This approach enabled subjects to rate the perceived intensity of painless and painful stimuli using the same scale. Subjects were instructed to concentrate explicitly on the intensity of the perceived stimulus. The coVRS appeared one-second after stimulus onset and was shown for six-seconds during which subjects moved the lever of a MR compatible potentiometer. The position of this lever was linearly transformed into the position of a mark on the rating scale. The stimulation protocol consisted of 50 stimuli (10 stimuli/strength) applied in random order with a randomized ISI between 7.5 and 12.5 seconds to minimize anticipation and to optimize peri-stimulus fMRI sampling times (Fig. 2). After disappearance of the rating scale, a fixation cross was displayed until the next rating scale appeared.

FMRI data acquisition

Within 2 weeks after psychophysical testing, subjects underwent the fMRI protocol in a Philips 3-Tesla Achieva System (Philips Medical System, Best, the Netherlands). The protocol started by retesting individual thresholds (SPT, PDT). If either SDT or PDT deviated more than 20% from the value assessed during the previous psychophysical test session, subjects were excluded from further participation. As several investigations indicate a diurnal variation of pain perception (Fillingim & Ness 2000, Koch & Raschka 2004), this investigation took place at the same daytime as the psychophysical examination. Subjects underwent the same stimulation protocol as performed during psychophysical examination, except that headphones were replaced by earplugs and real fMRI scans were acquired.

For functional scanning, a blood oxygen level dependent (BOLD) sensitive single-shot gradient echo planar imaging sequence was used to acquire 33 axial slices, covering the entire cerebrum and cerebellum, using an 8 channel receive-only head coil. Parameters: echo time = 30 ms, flip angle = 75°, repetition time = 2500 ms, slice thickness = 4 mm, inter-slice gap = 0 mm, field of view = 230 mm and matrix size in plane = 128 × 128, resulting in a voxel size of 1.72 × 1.72 = 4 mm^3. Three dummy scans were first acquired and discarded to reach steady state magnetization. In addition, 180 high-resolution T1 weighted axial slices (spoiled gradient echo) were acquired with TR = 20 ms, flip angle = 20°, voxel size = 0.98 × 0.98 × 1.02 mm^3, FOV = 22 cm, matrix = 224 × 187, which were used as an underlay for individual functional maps and for obvious neurological disorders.

After the experimental protocol, participants were asked whether they had perceived the stimulation in the test tooth only or also in adjacent tissue.

Data analysis

For the current report, we focused on the stimulus strengths 3–5 of the sensitive tooth (painful) and insensitive tooth (painless) to investigate specific cortical underpinnings of the painful perceptions of DH in comparison with the painless perceptions elicited on the insensitive tooth with identical stimuli. Psychophysical data, i.e. the relationship between the physical stimulus strength and the subjective intensity rating, as well as region of interest (ROI) data, i.e. the relationship between the physical stimulus strength and corresponding signal change in each ROI, have been

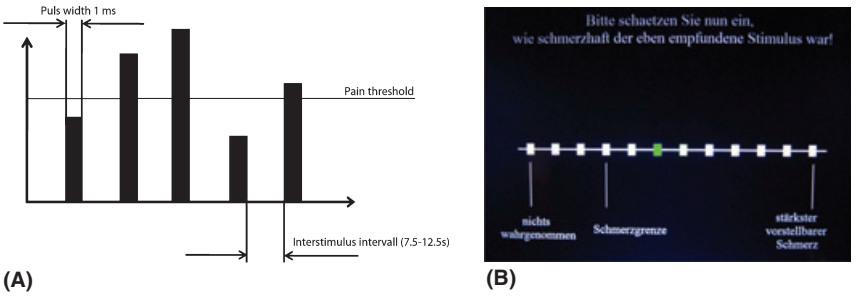

Fig. 2. Paradigm and rating. (A) Schematic of the fMRI paradigm. Stimulus duration was set to 1 s, interstimulus intervals were kept between 7.5 and 12.5 s. Strengths of the stimuli were PPT-40%, PPT-10%, PPT + 20%, PPT + 40% and PPT + 60%. The different strengths have then been applied randomly and subjects were required to rate every stimulus with respect to their perceived intensity by means of a MR compatible rating scale. (B) Illustrates the computerized visual rating scale (coVRS) the way it had been projected after every stimulus for 6 s. Green colour indicates the rectangle moved by the subject. Left; no perception (nichts wahrgenommen), the fourth rectangle; pain threshold (Schmerzgrenze), right; worst imaginable pain (stärkster vorstellbarer Schmerz). Important to note: subjects were trained prior to the fMRI experiment to handle correctly the coVRS and questions/uncertainties were answered. However, all subjects quickly understood the use of the scale.

analysed using SPSS 17 (SPSS Inc, Chicago, IL, USA).

SPM5 (http://www.fil.ion.ucl.ac.uk/spm) software package running on MATLAB R2008b (Mathworks, Natick, MA, USA) was used for functional voxel-by-voxel analysis. In a first step, spatial realignment to the first image in the series as reference was performed and it was assured that detected movement did not exceed 1.5 mm (translational) or 1° (rotational) in relation to the first image. For studying group effects, data were normalized to the MNI template brain (Evans et al. 1992) followed by smoothing with a Gaussian kernel of 6 mm (FWHM).

Image analysis to reveal significant changes in cortical activity due to the three painful stimulus strengths of the sensitive tooth and the three non-painful strengths of the insensitive tooth (conditions) was performed on each subject's data by means of individual (1st level) general linear models using the haemodynamic response function implemented in SPM5. Statistical parametric maps were then calculated, yielding beta estimates of the model fit for each subject and condition. To avoid any influence of lateralization effects, we flipped the parametric maps of the subjects who had their sensitive tooth on the left side.

We defined a ROI mask in the voxel-by-voxel analysis, comprising several brain regions involved in pain processing (Apkarian et al. 2005). As DH is classified as a true pain condition, we expected mainly activity among these regions. The primary and secondary somatosensory cortex (SI & SII), insular cortex, anterior cingulate cortex (ACC), thalamus and prefrontal cortex (PFC) were taken from the SPM tool "WFU-Pickatlas" (Lancaster et al. 1997, 2000) and the "SPM Anatomy Toolbox" (Eickhoff et al. 2005): In the voxel-by-voxel analysis, the ROI mask was applied as an explicit mask, which limits the investigated voxel space masking region. Average group statistical map was then calculated (second level) in a random effects model, using one-sample t-tests, testing the BOLD response to each painful stimulus strength against the null hypothesis of no related signal change. Resulting voxel T-values were colour-coded and superimposed onto the MNI single-subject-T1 brain (Fig. 4).

For more detailed investigation of the trigeminal nociceptive system, we calculated the mean activation in predefined anatomical regions of interest (ROI). For this purpose, the insula regions were divided into three parts, namely in an anterior (aIC), middle (mIC) and posterior (pIC) part, according to several reports, which suggest a complex anatomical (Varnavas & Grand 1999) and functional (Brooks et al. 2002, 2005) fragmentation within this particular brain area. The investigated cingulate cortex regions consisted of a subgenual part (sACC), a perigenual part (pgACC) and more posterior part, namely the anterior mid cingulate cortex (aMCC), after the classification of Vogt (2005). The secondary somatosensory cortex (SII) was delineated into four subregions OP1–OP4 based on Eickhoff et al. (2006). Finally, frontopolar (BA10) and frontomedial (BA46) areas constituted the prefrontal cortex.

The mean activation within each ROI, determined by the individual mean beta values, was calculated for each of the three stimulus strengths across both teeth. A repeated measures ANOVA was then calculated for all ROIs with tooth (sensitive/insensitive) as within-subject factor. For the ROI analysis, a significance threshold of $p < 0.05$ was used.

Results

Psychophysics

Due to the brief after-scanning interview, we were able to assure that all subjects felt the sensation at the stimulated tooth only. In all subjects, the highest applied stimulus strength was below PTT. Subjects reported no unpleasant or otherwise disturbing perceptions due to the inserted splint. In addition, they felt no lingering sensation after the stimulation, indicating that no tissue sensitization had been induced due to the experimental setup. Furthermore, no subjects had to be excluded due to excessive deviations from SDT, PDT and PTT values of the psychophysical examination.

Subjective mean ratings of the respective stimulus strengths during the scanning session showed clearly that the two lowest stimulus strengths applied on the sensitive tooth were rated as non-painful, whereas stimulus strengths 3–5 were rated as painful. As expected, stimulations of the insensitive tooth were always rated as non-painful (Fig. 3).

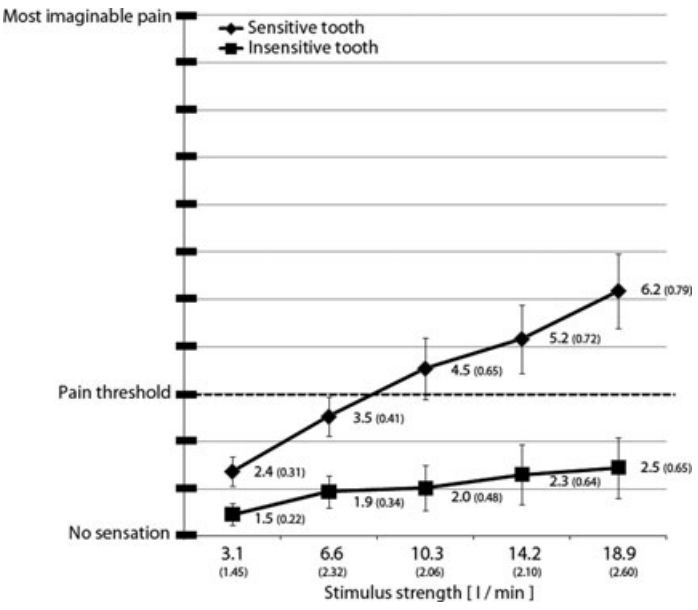

Fig. 3. coVRS ratings. Group mean stimulus strength in l/min. and corresponding mean coVRS ratings (with standard errors of the mean in brackets and graphically shown as T-bars) during the fMRI stimulation experiment. The pain threshold is illustrated by the dashed line.

Brain activation patterns

As hypothesized, painful stimulation of the sensitive tooth induced significant activation in regions of the pain matrix (Fig. 4), namely somatosensory cortices (SI & SII), anterior, middle and posterior insular cortices, pgACC and aMCC, thalamus as well as frontal regions (BA10 and BA46). See Table 1 for respective T- and *p*-values.

Region of interest analysis

We found a significant main effect of tooth, ipsi- and contralateral to the affected side, in the aIC ($F = 7.45$, $p = 0.02$/$F = 7.92$, $p = 0.02$) as well as in the aMCC ($F = 8.84$, $p = 0.02$/$F = 9.33$, $p = 0.01$). No further significant main effects of tooth were observed in any other investigated region (Fig. 5, Table 2).

Discussion

Patients with periodontal disease commonly suffer from DH, yet our knowledge of central mechanisms associated with DH is very limited. The key finding of this study is that air blast stimuli of graded flow applied to sensitive and insensitive teeth evoked significant BOLD signal changes in several areas of the human brain. Compared with baseline neural activity, painful stimulations of sensitive teeth resulted in significant activations of somatosensory cortices SI and SII, insular and cingulate cortices, thalamus and frontal regions (Fig. 4, Table 1). Activation of a similar modular network was previously reported in response to painful electric tooth stimulation (Ettlin et al. 2009, Weigelt et al. 2010, Brügger et al. 2011). Of particular interest was the head-to-head comparison between sensitive and insensitive teeth. Significant activation differences between sensitive and insensitive teeth for DH-pain *versus* painless air stimuli were observed in anterior portions of the insular (aIC) and anterior midcingulate cortex (aMCC) (Fig. 5). These structures might therefore play specific roles in processing DH pain. In the following section, we discuss these two regions and their potential relationship with DH pain in more detail.

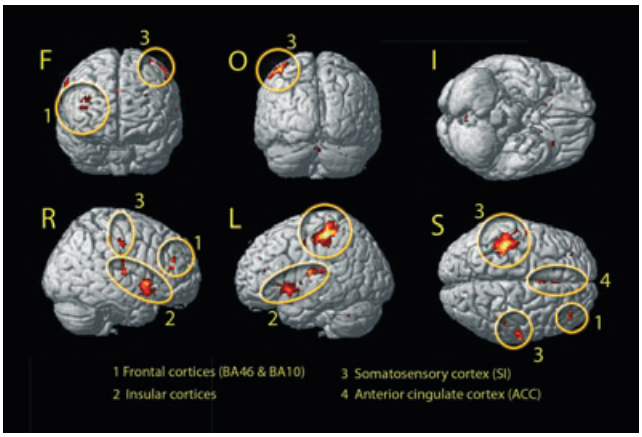

Fig. 4. Brain imaging data. fMRI activation projected on the rendered MNI single subject T1 template. Illustrated is the brain activity in response to the pooled painful stimulus strengths of the sensitive tooth revealed via one-sample *t*-tests. A conservative statistical threshold (FWE-corrected with $p < 0.05$) has been chosen. F = frontal, O = occipital, R = right, L = left, I = inferior and S = superior.

Table 1. Peak activations of sensitive tooth stimulation

Brain region (contralateral | ipsilateral)	Local maxima (MNI coordinates)	Local maxima (*p*-values)	Local maxima (T-values)
SI | contralateral	−54 −32 54	0.000	10.77
SI | ipsilateral	60 −16 44	0.000	8.29
SII | contralateral	−56 −26 14	0.000	7.99
SII | ipsilateral	62 −14 10	0.000	10.63
aIC | contralateral	−30 22 −2	0.000	9.43
aIC | ipsilateral	34 26 −2	0.000	11.63
mIC | contralateral	−44 10 −8	0.000	8.60
mIC | ipsilateral	44 10 −2	0.000	11.59
pIC | contralateral	−42 −12 2	0.003	4.75
pIC | ipsilateral	–	–	–
Thalamus | contralateral	−14 −20 2	0.000	8.72
Thalamus | ipsilateral	12 −12 2	0.000	6.21
pgACC | contralateral	−8 32 18	0.000	6.66
pgACC | ipsilateral	4 32 34	0.000	6.49
aMCC | contralateral	−2 30 32	0.000	8.21
aMCC | ipsilateral	6 26 38	0.000	10.58
BA 10 | contralateral	−30 44 30	0.000	6.81
BA 10 | ipsilateral	38 40 22	0.000	7.94
BA 46 | contralateral	−40 34 20	0.000	6.59
BA 46 | ipsilateral	44 38 20	0.000	8.48

Peak activations of brain areas during painful stimulation of the sensitive tooth *versus* baseline ipsi- and contralateral to the affected side.

Insular cortex

Despite several interpretations and discussions about its functional specificity, the insular cortex is generally considered to play an important role within the nociceptive functional integration circuitry. Posterior portions seem more related to sensory aspects of pain, while anterior parts are associated with emotional, cognitive and memory-related aspects of pain perception (Apkarian et al. 2005). Craig (2009) even postulates a posterior-to-mid-to-anterior pattern of integration of interoceptive sensory information in the insula. In a PET study, they demonstrated a distinct stimulus processing pattern: objective sensory information processing in the posterior part was followed by integration of the information in the middle part and was finally re-represented more subjectively in the anterior part (Craig et al. 2000). In other words, the incoming sensory stimulus receives its subjective signature in the aIC. The aIC thus seems to be involved in the very subjective decision whether a stimulus is painful or not,

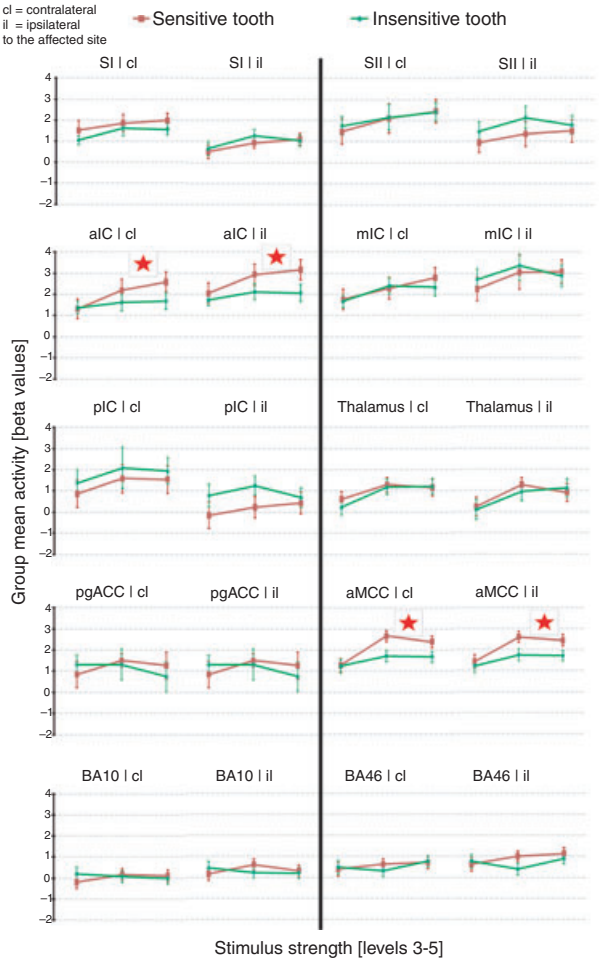

Fig. 5. Results of the ROI analysis. Illustrated is the relationship between brain activity (*y*-axis, mean beta values) and the respective stimulus strengths (*x*-axis, levels 3–5). Red lines indicate the sensitive, green lines the insensitive tooth. Stars indicate a significant main effect of tooth. T-Bars indicate standard errors of the mean.

Table 2. DH pain-related regions

Brain region (contralateral | ipsilateral)	*p*-Value	F-value
SI | contralateral	0.35	0.96
SI | ipsilateral	0.31	1.14
SII | contralateral	0.75	0.10
SII | ipsilateral	0.40	0.65
aIC | contralateral	0.02	7.45
aIC | ipsilateral	0.02	7.92
mIC | contralateral	0.84	0.04
mIC | ipsilateral	0.83	0.05
pIC | contralateral	0.12	2.95
pIC | ipsilateral	0.18	2.08
Thalamus | contralateral	0.19	1.93
Thalamus | ipsilateral	0.26	1.45
pgACC | contralateral	0.98	0.00
pgACC | ipsilateral	0.37	0.87
aMCC | contralateral	0.02	8.84
aMCC | ipsilateral	0.01	9.33
BA 10 | contralateral	0.97	0.00
BA 10 | ipsilateral	0.27	1.40
BA 46 | contralateral	0.46	0.58
BA 46 | ipsilateral	0.20	1.96

Results of the ROI analysis. Reported is the main effect "Tooth" of the repeated measures ANOVA with respective *p*- and F-values in ipsi- and contralateral regions to the affected side.

while posterior and middle portions of the insula most likely process and integrate objective information of incoming stimuli. This distinct posterior-to-anterior processing pattern is also depicted in our results. Objectively, the sensitive and the insensitive teeth received the same stimulus strengths, which could be the reason for the non-significant differences between both teeth in the posterior portion of the insula. Furthermore, it is reasonable to assume that sensations from sensitive teeth inform the brain about a greater potential for damage. Hence, activity differences within the aIC probably reflect the subjective interpretation whether the stimulation was painful or painless and whether a sensitive or insensitive tooth was stimulated, respectively.

Cingulate cortex

As in the aIC, we observed a similar tooth specific activation pattern in the aMCC. Approximately 87% of pain imaging studies report activation of the anterior cingulate cortex (Apkarian et al. 2005). However, none of the cingulate cortex subdivisions is attributed a specific role for nociception. They are rather thought to serve as integrative processing domains related to several cognitive and emotional aspects of pain experiences. A recent expert report proposed a "cingulate premotor pain model" in which pain stimuli lead to autonomic and behavioural motor responses (Sikes et al. 2008). It has also been known from animal studies that cingulate cortex lesions produce a decrease in pain sensitivity and avoidance behaviour (Devinsky et al. 1995). Considering our results, the aMCC activity levels showed differential activity in response to stimulation of sensitive teeth (DH pain) and insensitive teeth (painless). This could be a consequence of higher arousal and stronger response to potentially harmful states as, from a patient perspective, the painful air blasts may have had high negative valence. The stronger activation levels of sensitive teeth in the aMCC may indicate an initiation of avoidance behaviour and motor preparation in response to DH pain.

Conclusion

In the present study, we demonstrate that application of "natural" air stimuli to sensitive teeth induced cerebral activity patterns that share commonalities with the often-described "pain matrix", a modularly organized brain network mainly activated by nociceptive inputs (Peyron et al. 2000). Our neuroimaging data additionally provide evidence that differential activity in the aIC and aMCC may represent clinically relevant pain experienced by DH

patients. Therefore, response patterns in these two brain regions may potentially serve as supplemental (objective) outcome measure for assessing the efficacy of DH pain interventions in the future.

References

Apkarian, A. V., Bushnell, M. C., Treede, R. & Zubieta, J. (2005) Human brain mechanisms of pain perception and regulation in health and disease. *European Journal of Pain* **9**, 463–484.

Brooks, J. C., Nurmikko, T. J., Bimson, W. E., Singh, K. D. & Roberts, N. (2002) fMRI of thermal pain: effects of stimulus laterality and attention. *Neuroimage* **15**, 293–301.

Brooks, J. C., Zambreanu, L., Godinez, A., Craig, A. D. & Tracey, I. (2005) Somatotopic organisation of the human insula to painful heat studied with high resolution functional imaging. *Neuroimage* **27**, 201–209.

Brügger, M., Ettlin, D. A., Meier, M., Keller, T., Luechinger, R., Barlow, A., Palla, S., Jäncke, L. & Lutz, K. (2011) Taking sides with pain. Lateralization aspects related to cerebral processing of dental pain. *Frontiers in Human Neuroscience* **5**, 12. doi: 10.3389/fnhum.2011.00012.

Brügger, M., Lutz, K., Brönnimann, B., Luechinger, R., Barlow, A., Jäncke, L. & Ettlin, D. A. (2012) Tracing toothache intensity in the brain. *Journal of Dental Research* **91**, 156–160.

Chabanski, M. B., Gillam, D. G., Bulman, J. S. & Newman, H. N. (1996) Prevalence of cervical dentine sensitivity in a population of patients referred to a specialist periodontology department. *Journal of Clinical Periodontology* **23**, 989–992.

Craig, A. D. (2009) How do you feel–now? The anterior insula and human awareness. *Nature Reviews Neuroscience* **10**, 59–70.

Craig, A. D., Chen, K., Bandy, D. & Reiman, E. M. (2000) Thermosensory activation of insular cortex. *Nature Neuroscience* **3**, 184–190.

Devinsky, O., Morrell, M. J. & Vogt, B. A. (1995) Contributions of anterior cingulate cortex to behaviour. *Brain* **118**, 279–306.

Dowell, P. & Addy, M. (1983) Dentine hypersensitivity - a review. Aetiology, symptoms and theories of pain production. *Journal of Clinical Periodontology* **10**, 341–350.

Eickhoff, S. B., Schleicher, A., Zilles, K. & Amunts, K. (2006) The human parietal operculum. I. Cytoarchitectonic mapping of subdivisions. *Cerebral Cortex* **16**, 254–267.

Eickhoff, S. B., Stephan, K. E., Mohlberg, H., Grefkes, C., Fink, G. R. & Amunts, K. (2005) A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. *Neuroimage* **25**, 1325–1335.

Ettlin, D. A., Brügger, M., Keller, T., Luechinger, R., Jäncke, L., Palla, S., Barlow, A., Gallo, L. M. & Lutz, K. (2009) Interindividual differences in the perception of dental stimulation and related brain activity. *European Journal of Oral Sciences* **117**, 27–33.

Ettlin, D. A., Zhang, H., Lutz, K., Järmann, T., Meier, D., Gallo, L. M., Jäncke, L. & Palla, S. (2004) Cortical activation resulting from painless vibrotactile dental stimulation measured by functional magnetic resonance imaging (FMRI). *Journal of Dental Research* **83**, 757–761.

Evans, A. C., Marrett, S., Neelin, P., Collins, L., Worsley, K. & Dai, W. (1992) Anatomical mapping of functional activation in stereotactic coordinate space. *Neuroimage* **1**, 43–53.

Fillingim, R. B. & Ness, T. J. (2000) Sex-related hormonal influences on pain and analgesic responses. *Neuroscience Biobehavioral Reviews* **24**, 485–501.

Habre-Hallage, P., Hermoye, L., Gradkowski, W., Jacobs, R., Reychler, H. & Grandin, C. B. (2010) A manually controlled new device for punctuate mechanical stimulation of teeth during functional magnetic resonance imaging studies. *Journal of Clinical Periodontology* **37**, 863–872.

Ide, M., Wilson, R. F. & Ashley, F. P. (2001) The reproducibility of methods of assessment for cervical dentine hypersensitivity. *Journal of Clinical Periodontology* **28**, 16–22.

Koch, H. J. & Raschka, C. (2004) Diurnal variation of pain perception in young volunteers using the tourniquet pain model. *Chronobiology International* **21**, 171–173.

Lancaster, J. L., Rainey, L. H., Summerlin, J. L., Freitas, C. S., Fox, P. T. & Evans, A. C. (1997) Automated labeling of the human brain: a preliminary report on the development and evaluation of a forward-transform method. *Human Brain Mapping* **5**, 238–242.

Lancaster, J. L., Woldorff, M. G., Parsons, L. M., Liotti, M., Freitas, C. S. & Rainey, L. (2000) Automated Talairach atlas labels for functional brain mapping. *Human Brain Mapping* **10**, 120–131.

Megias-Alguacil, D., Keller, T., Lutz, K., Barlow, A. P. & Ettlin, D. A. (2008) Design and construction of a magnetic resonance compatible multi-injector gas jet delivery system. *Review of Scientific Instruments* **79**, 14301.

Peyron, R., Laurent, B. & García-Larrea, L. (2000) Functional imaging of brain responses to pain. A review and meta-analysis (2000). *Clinical Neurophysiology* **30**, 263–288.

Poulsen, S. (2011) Available evidence does not support use of oxalates for dentine hypersensitivity. *Evidence-Based Dentistry* **12**, 47–47.

Que, K., Ruan, J., Fan, X., Liang, X. & Hu, D. (2010) A multi-centre and cross-sectional study of dentine hypersensitivity in China. *Journal of Clinical Periodontology* **37**, 631–637.

Rees, J. S. & Addy, M. (2002) A cross-sectional study of dentine hypersensitivity. *Journal of Clinical Periodontology* **29**, 997–1003.

Rees, J. S. & Addy, M. (2004) A cross-sectional study of buccal cervical sensitivity in UK general dental practice and a summary review of prevalence studies. *International Journal of Dental Hygiene* **2**, 64–69.

Sessle, B. J. (2007) Pathophysiology of orofacial pain. In: Türp, J. C., Sommer, C. & Hugger, A. (eds). *The Puzzle of Orofacial Pain. Integrating Research into Clinical Management*, Vol. 15, pp. 56–74. Basel: Karger. ISBN 978-3-8055-8270-4.

Sikes, R. W., Vogt, L. J. & Vogt, B. A. (2008) Distribution and properties of visceral nociceptive neurons in rabbit cingulate cortex. *Pain* **135**, 160–174.

Tammaro, S., Wennstrom, J. L. & Bergenholtz, G. (2000) Root-dentin sensitivity following non-surgical periodontal treatment. *Journal of Clinical Periodontology* **27**, 690–697.

Troil, B., Needleman, I. & Sanz, M. (2002) A systematic review of the prevalence of root sensitivity following periodontal therapy. *Journal of Clinical Periodontology* **29**, 173–177.

Varnavas, G. G. & Grand, W. (1999) The insular cortex: morphological and vascular anatomic characteristics. *Neurosurgery* **44**, 127–136.

Vogt, B. A. (2005) Pain and emotion interactions in subregions of the cingulate gyrus. *Nature Reviews Neuroscience* **6**, 533–544.

Weigelt, A., Terekhin, P., Kemppainen, P., Dörfler, A. & Forster, C. (2010) The representation of experimental tooth pain from upper and lower jaws in the human trigeminal pathway. *Pain* **149**, 529–538.

Yilmaz, H. G., Cengiz, E., Kurtulmus-Yilmaz, S. & Leblebicioglu, B. (2011) Effectiveness of Er, Cr:YSGG laser on dentine hypersensitivity: a controlled clinical trial. *Journal of Clinical Periodontology* **38**, 341–346.

Address:
Michael L. Meier
Institute of Psychology
Department of Neuropsychology
University of Zurich
Binzmühlestrasse 14/25
8050 Zürich
Switzerland
E-mail: michael.meier@uzh.ch

Clinical Relevance

Scientific rationale for the study: DH can considerably impact quality of life. Pain research revealed that besides brain areas coding somatosensory information, regions for emotional and cognitive-behavioural signal processing are additionally activated during nociception. Brain activation in response to "natural" DH provoking stimuli was never investigated and was therefore this study's aim.
Principal findings: The present feasibility study provides the first functional neuroimaging data on human brain activity in response to graded air stimuli applied to sensitive and insensitive teeth.
Practical implications: Our new experimental approach is likely to improve our understanding of the neurobiology underlying DH beyond peripheral processes. We further investigate the neuronal activation patterns underlying painless and painful tooth stimulations, which can serve as an additional objective measure and validation of DH pain respectively.