Expertise modulates the student’s perception of pain from a self-perspective

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Abstract

Background

FMRI studies show that medical doctors suppress the pain matrix when they view painful actions executed on others. But how do doctors perceive pain from a self-perspective?

Objective

We hypothesize that virtual dental treatment from a self-perspective may induce brain activity in pain related areas in controls while this is less the case for dental students. We expect that dental students learn to control the motoric aspects of pain during their education because it is a prerequisite for manual treatment.

Methods

In this fMRI study, neural correlates of pain perception from a self-perspective in a sample of 20 dental students and 20 age matched controls were investigated through classic general linear model analysis and in house classification methods. All subjects viewed video clips presenting a dental treatment from the first-person perspective. Dental students and naïve controls exhibited similar anxiety levels for invasive stimuli.

Results

Invasive dentistry scenes evoked less affective component of pain in dental students compared to naïve controls. Reduced affective pain perception went along with suppressed brain activity in pain matrix areas including insula, anterior cingulate cortex and basal ganglia. Furthermore, a substantial reduction of brain activity was observed in motor related areas in particular the supplementary motor area, premotor cortex and basal ganglia (p<0.001, k=156). Within this context a classifier analysis based on neural activity in the
nucleus lentiformis ($p < 0.0005$ with $k = 125$) could identify dental students and controls on the individual subject level in 85 percent of the cases (sensitivity = 90.0%; specificity = 80.0%).

Conclusions

We speculate that dentistry students learn to control motoric aspects of pain during their education because it is a prerequisite for professional manual treatment of patients. We discuss that a specific set of learning mechanism might affect perceived self-efficacy of dental students, which in turn might reduce their affective component of pain perception.
Introduction

Dental pain is a variegated feeling and has a multidimensional nature with sensory-discriminative, affective-motivational, motoric and cognitive components [1-5]. Currently, neural correlates of orofacial pain are investigated through functional magnetic resonance imaging [fMRI] [6;7]. The affective component of pain is a subjective feeling that is often measured with standardized psychological scales that report the unpleasantness of stimuli. It is not only perceived when subjects are treated with physically painful stimuli, but also when individuals are confronted with psychological painful images or videos. However the ability to perceive the affective component of pain is modulated by the professional training of a subject. Viewing hurting scenes induces affective component of pain in controls while this is less the case for medical doctors [8;9]. The latter two studies also investigated the empathic abilities of doctors and controls. Interestingly enough, doctors did not differ from controls in their empathic abilities [8;9]. Even though no differences in empathic ability were reported on a between group level, individual differences in empathic ability between doctors may exist [10].

FMRI studies show that medical doctors suppress the pain matrix when they view painful actions executed on others while this is not the case for controls [8]. The pain matrix includes thalamus, SI and SII, insula as well as anterior cingulate cortex [11-13]. In addition cortical and subcortical motor areas including the basal ganglia are directly responsive to noxious stimuli [12;14]. Some of these [sub]cortical motor regions show a nociceptive somatotopic organization [15].

Further, EEG studies suggest that early and late signal components show dissimilar behavior when controls view painful scenes while this is not the case for doctors [9].
As discussed previous imaging studies showed that doctors and controls exhibit similar empathy, emotional contagion and interpersonal reactivity scores [8;9].

Statically valid differences between the two groups are exclusively found for scales that measure affective and sensory aspects of pain. From these neuroimaging studies we have to conclude that affective and sensory aspects of pain for others may be modulated by education while empathy for others as measured with several accepted scales is not. This leads to the somewhat counterintuitive conclusion that doctors maintain empathy for others while suppressing neural correlates of pain for others [8-10]. We do not think that more research in the field of empathy is needed simply because previous empathy measurers failed to show differences between doctors and controls. However observed differences in affective pain perception for others might be linked to the way how doctors perceive pain from a self-perspective. Furthermore one might speculate that differences in pain perception originate from medical training and occur in medical school.

We hypothesize that watching dentistry scenes from a self-perspective may induce brain activity in (affective and motoric aspects) pain related areas in controls while this is less the case for dentistry students (DS). We expect that DS learn to control the motoric aspects of pain during their education because it is a prerequisite for manual treatment.

We choose to investigate this hypothesis trough classic general linear model analysis and in house classification methods. Classification methods may have some advantages over classic analysis. Firstly one can specifically test whether hypothetical brain areas identified in other studies may in fact contribute to the identification of different neuro psychological states. Within this context we focused on previously reported coordinates that were related to different components of pain perception [12]. Secondly, while classic fMRI methods only
focus on univariate measures of brain activity, classification methods can identify the multivariate interplay between brain areas. These multivariate aspects of brain activity may be better predictors of a certain neuro psychological state as univariate measures. Finally, classification methods may isolate brain regions that are essential for a specific function.

**Methods**

**Participants**

Forty healthy (20 Dental students (DS), 20 controls), right-handed male volunteers (average age 28±9 years) participated in this fMRI-study.

All subjects had been dentally treated in the recent past and had participated in former fMRI-experiments. Controls were selected in the course of dental routine check-ups in the Department of Conservative Dentistry (RWTH Aachen University). DS were selected one year before graduating. All volunteers gave their approval to the experimental conditions in written form.

Procedures were approved by the local ethic committee of University Hospital of Aachen (UKA), all volunteers agreed to the WMA Declaration of Helsinki (1964) and subsequent amendments [http://www.wma.net].

**Stimuli used for fMRI experiment**

Participants viewed and listened to drilling and toothbrush movies (Figure 1). The subjects were instructed to imagine the dental treatment from the perspective of a patient (first-person-perspective). The sound level for drilling and toothbrush was the same. The total duration of this procedure was 9 minutes.
Anxiety questionnaire

The Hierarchical Anxiety Questionnaire was used to access the intensity of dental anxiety [18]. On the basis of an overall score ranging from 11 to 55, participants can be categorized into low anxious (<30), moderately anxious (31-38) and highly anxious (>38) groups.

Pain Perception Questionnaire

The pain perception scale is a common standard instrument for the Study of Pain allowing standardized and multifaceted quantification of pain experience. By default, it contains 19 sensory and 14 affective descriptions of pain. All subjects were assigned to rank each description for drilling and toothbrush on a four-point scale immediately after the fMRI-session [19].

fMRI data acquisition and analysis

Scanning was performed by a Philips 3Tesla MRI 'Model Achieva' (Philips medical Systems, www.medical.philips.com). Axial slices were oriented towards the anterior-posterior commissure. A T2*-weighted echo planar imaging sequence was obtained for functional images: echo time (TE) 30 ms, repetition time (TR) 2800 ms, thirty-two interleaved slices (3.5 mm thick), flip angle of 90 degrees, field of view of 220 mm, voxel size of 3.75x3.75x3.5 mm and 64x64 matrix. Functional data were imported into the SPM toolbox and coregistrated with the high resolution anatomical scan of the subject that was obtained in the same session. Preprocessing steps included: realignment, normalization to MNI space, spatial smoothing (8 mm) and high pass filtering (128 sec.). First level beta weights were obtained by modeling the canonical hemodynamic response function within a GLM approach. Beta weights were used to contrast experimental conditions and experimental groups on a second
level using a two sample t-test. Three contrasts are reported. First we wanted to know if controls exhibit higher brain activity for the toothbrush. Second, if controls exhibit higher brain activity compared to DS when the toothbrush was subtracted from the drilling \((\text{drill}_c - \text{toothbrush}_c) - (\text{drill}_\text{DS} - \text{toothbrush}_\text{DS})\). The latter contrast was liberally masked with \((\text{drill}_c - \text{toothbrush}_c)\) to avoid spurious activations. Finally we wanted know if DS exhibit higher brain activity compared to controls when toothbrush was subtracted from drilling. The latter contrast was masked with the toothbrush from DS. We thresholded all contrasts at \(p<0.001\). Subsequently we performed a monte-carlo based cluster threshold estimation procedure to correct for multiple testing. Next, beta contrast weights \((\text{drill}-\text{toothbrush})\) were extracted from 40 pain relevant (sub) cortical systems reported in a meta-analysis [12]. Extracted beta weights were subjected to a Support Vector Machine Analysis.

**Classifier analysis**

As information-based procedure to determine differences in brain activity between both groups on the individual subject level, we conducted a classifier analysis. Therefore, a modified support vector machine algorithm with a leave-one-out cross-validation was applied [17]:

1) **Region of interest definition and feature generation**

Beta contrast weights \([\text{drilling}-\text{toothbrush}]\) were extracted from pain relevant brain regions reported in a meta-analysis [12]. For this purpose, structural scans were segmented into grey and white matter using the standard tools as available in the SPM software package. Regions of interest were defined, centering 4 mm diameter spheres on MNI coordinates of 40 pain relevant brain regions reported in the above-mentioned meta-analysis. Beta weights were extracted only from those voxels within the sphere which were found within the grey matter.
This method avoids the extraction of spurious beta weights. Next we averaged the beta weights per region. We subtracted beta weights of the toothbrush conditions from drill conditions for every region and subject. Functional masking of the beta weights was not needed because beta contrast weights of the drilling were positive and larger than the respective beta weights of the toothbrush conditions in all regions in all subjects.

2) Feature selection

In order to consider only the most discriminating features for the classifier analysis, an information-based feature selection was applied. The discriminative power of a feature was defined as the absolute value of the Kendall tau correlation coefficient [20] which measured the correlation between a feature and the group indicator (-1 for controls, +1 for DS). Thus, a positive correlation coefficient indicates that the feature (i.e. the regional brain activity) increases in DS compared to controls whereas a negative correlation coefficient indicates that the feature decreases in the DS compared to controls.

In each fold of the leave-one-out cross-validation, the features obtained from the remaining 40-1 subjects were ranked according to their absolute value of the Kendall-Tau rank correlation coefficient and the feature, which exhibited highest relation to the group indicator, was selected.

3) Classifiers

The selected features were subjected to the classifier analysis applying support vector machines with a linear kernel [21]. Therefore, the support vector machine yielded a maximal-margin hyperplane in the feature space, which separated the groups in the respective training data set. Classification was tested in the left-out sample. The limited number of
subjects lent to the leave-one-out cross-validation method to investigate the generalizability of the classification results. Importantly, this cross-validation encompassed the feature selection as well as the classifier. Accuracy (percentage of all participants detected correctly), sensitivity (percentage of DS detected correctly), and specificity (percentage of controls detected correctly) quantified classification performance.
Results

After the fMRI session, all controls and DS declared that they could imagine being treated by a dental drill from a first-person-perspective.

Hierarchical Anxiety Questionnaire

From the 40 individuals under study 12 controls and 10 DS were categorized as low anxious, 8 controls and 8 DS were categorized as moderately anxious and 2 DS were categorized as highly anxious (average controls 29; average DS 30).

SES scales

We choose to analyze data with a very conservative approach. For every condition 33 t-tests were executed according to the number of items in the questionnaire. Next the critical Bonferroni threshold was 0.05/33 was estimated. Summary statistic based on 2 sample t-tests is visualized (Figure 2). No significant differences between DS and controls were observed for toothbrush but large differences were observed for drilling. For drilling significant differences between DS and controls were observed for affective pain scales but not for sensory pain scales.

DS showed significantly lower pain than controls for 4 affective items, namely agonizing, dreadful, horrible and enervating (P<0.001, Bonferroni).

Neural aspects of pain perception were not higher in controls compared to DS when toothbrush was shown. Moreover neural aspects of pain perception were not higher in DS compared to controls when drilling was compared to toothbrush (empty contrast). By contrast, neural aspects of pain perception were higher in controls than in DS when drilling was compared to toothbrush (Figure 3&4, Table 1).
Table 1. This table reports the relevant statistic for a given brain coordinate as reported by SPM12 for the contrast (drillC-toothbrushC)-(drillDS-toothbrushDS). The latter contrast was liberally masked with (drillC-toothbrushC). C=controls, DS=Dentistry students.

<table>
<thead>
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Table shows 3 local maxima more than 8.0mm apart

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Height threshold: T = 3.32, p = 0.001 (0.985)
Extent threshold: k = 159 voxels, p = 0.041 (0.158)
Expected voxels per cluster, <k> = 37.050
Expected number of clusters, <c> = 0.17
FWEp: 5.209, FDRp: Inf, FWEc: 1107, FDRc: 1107
FWHM = 15.5 15.1 12.9 mm mm mm; 7.8 7.5 6.5 {voxels}
Results (p<0.001 using a conservative cluster threshold of k=159; Figure 3) revealed that brain activations were organized around sensory-motor and limbic-affective systems. The sensory motor system included larger parts of the supplementary motor area as well as SII. Furthermore, limbic-affective structures included thalamus, basal ganglia as well as larger parts of the posterior and frontal insula and anterior cingulate cortex (ACC). It is clear that some structures can be part of more systems. For instance, the basal ganglia are part of the motor loop. We used the standard SPM preprocessing pipeline that employs rather crude smoothing kernels (8mm) and rough brain alignment methods. This may lead to spurious activations even when conservative cluster thresholds are used. In a next step we decided to threshold our image at 0.0005 in combination with a less conservative cluster threshold (k=125). Some of the previously discussed activations disappeared. Unfortunately, the SPM brain rendering does not fully inform about subcortical and insular activations. For this reason a ventral view of the activation is presented in Figure 4 using brain voyager software.

In DS, brain activity in a web of brain areas known as pain matrix was suppressed. Remarkably enough, difference between DS and controls were not found in areas that are of core importance for the processing of the sensorial aspects of pain such as SI. But, DS showed a marked suppression of brain activity in areas related to the affective aspects of pain including bilateral insula und bilateral ACC. In addition, motor related aspects of pain perception were reduced in DS. The latter included the pre motor cortex as well as nuclei of the basal ganglia and caudate nucleus (Figure 3&4).
**Classifier analysis**

In the classifier analysis, we were able to classify 85.0% all participants on the basis of neural activity found in the most discriminative region in each fold of the cross-validation (sensitivity = 90.0%; specificity = 80.0%). It turned out that in each fold of the leave-one-out cross-validation the neural activity in the right nucleus lentiformis (dark blue region in Figure 4) was selected as the most discriminative feature. Adding more regions to the classifier did not result into better classification performance.

**Discussion:**

We hypothesized that DS may suppress pain linked brain activity that is presented from a self-perspective.

In this study, affective items of SES clearly indicated a difference between controls and DS. Controls perceived drilling as more unpleasant when compared to DS. By contrast no affective pain perception differences were observed for the toothbrush. In addition both groups showed similar scores with regard to sensory aspects of pain regardless of the condition type under study. This indicates that DS experience less affective component of pain than controls when viewing invasive dentistry scenes. Reduced pain perception of DS went along with reduced brain activity of pain matrix areas. The latter included regions related to the somato-sensory system as well as regions that have been related to affective aspects of pain perception including parts of the insula [22] and anterior cingulate cortex (ACC) [11;23]. We also observed reduced activity of DS in (sub) cortical motor areas including precentral gyrus [BA6] and the basal ganglia in particular the lentiform nucleus. The observed differences in motor areas suggest that DS suppress motoric components of pain...
when confronted with invasive stimuli. In short most of our hypotheses were confirmed.

A difference between previous studies and our study is that we assessed affective pain perception from a self-perspective whereas Cheng and Decety investigated affective pain from another perspective. Despite the obvious difference in perspective we reproduce some important finding of Chen et al. In both studies controls exhibited increased activity in ACC/SMA when confronted with invasive stimuli [24]. However, Cheng observed that experts activate a frontal parietal system when confronted with invasive stimuli. They speculated that these increases in brain activation were linked to emotion regulation and theory of mind. We did not observe increased brain activity in DS. It may be possible that observed differences between the two studies is due to self-versus other perspective. But one should be careful with these kind speculations. In fact the study of Cheng lacked a control condition from a self-perspective while this study lacks a control condition from the other perspective.

Our study also shows the benefits of classification approaches. We expected that a larger number of areas was needed to obtain sufficient classification rates [16;17]. But in fact only one region namely the lentiform nucleus was needed to classify controls and DS on the basis of brain activity. This suggests that the latter region is of core importance in pain perception. While conventional GLM analysis may be used to trace differences between groups it is maybe not the ideal method to isolate brain areas that are of core importance for a specific function. Hence classification methods may be a useful compliment to conventional GLM methods.

Our findings suggest that affective and motoric component of pain suppression of DS might possibly originate from dental school training. Recently, it has been suggested that distinct learning mechanisms affect pain expectancy that in turn affect pain perception [25]. According to Peerdeman pain perception can be affected by cognitive instructions,
observational learning and operant conditioning. The three learning mechanisms mentioned may modulate pain expectancy in medical students. Pain expectancy has been linked to activity in the insula [26] and basal ganglia [27]. Our results suggest that missing activity in insula and basal ganglia in DS reflects lower anticipation of pain. Furthermore, Peerdeman argues that the aforementioned learning mechanisms may affect self-efficacy expectancy. This is defined as the extent to which people can voluntary control aspects of pain. Neural correlates of self-efficacy have been linked to the nucleus lentiformis [28]. As demonstrated in this study brain activity of this region predicts whether an individual belongs to the DS or controls. As mentioned above, we speculate that maintaining motor control in the face of pain is an important ingredient of medical education. In particular, for medical specializations that rely on manual treatment.

As limitation, the sample size of this study is 40 subjects. While this is perfectly normal for an fMRI study one might argue that the power to detect effects is not very large. We would like to argue that we replicate important findings of our colleges.

There are some limitations in our experimental design. First it might be better to study effect of hurtful scenes from a self and another perspective. Second it might be better to study DS at the end and beginning of their studies using a within subject design. Finally, one might investigate if individual differences in pain perception of DS are linked to their clinical performance [10]. In previous studies subjects viewed hurtful actions inflicted on others while in this study subjects viewed hurtful actions inflicted on the subject itself [8;9]. It is indeed possible that expertise obtained during medical school leads to a suppression of pain from a self-perspective that in turn might affect pain perception from another perspective. However in principle an opposite mechanism is possible namely: reduced pain perception for
others leads to reduced pain perception for one self. Unfortunately, it is not possible to identify the exact causal relation in this study.

Conclusion:

We conclude that DS suppress affective and motor related aspects of pain. The cognitive mechanisms that modulate pain expectancy and pain perception are poorly understood and deserve further investigation. A candidate mechanism is self-efficacy that may be linked to brain activity in nucleus lentiformis.

Conflicts of Interest: none
Drilling movies presented a medical glove-wearing hand with a dental handpiece drilling a tooth in the right lower jaw. Toothbrush movies displayed the same gloved-hand using an electric toothbrush. Every single movie was presented 12 times in counterbalanced order for 30 seconds and separated by 12 resting baseline conditions that lasted 15 seconds. Both movies were presented in a randomized fashion to the volunteers.

Figure 2. Pain perception Questionnaire - Comparison controls vs. Dental students (mean ± standard error of the mean, each group n = 20). (1. not appropriate, 2. somewhat appropriate, 3. largely appropriate, 4. fully appropriate) Asterisks (*) indicate significant differences between the ratings for DS and controls for the drilling movies (* P<0.05, ** P<0.01; *** P<0.001; t-test). Red Asterisks: Bonferroni threshold.

Figure 3. Controls exhibit higher brain activity compared to Dental students when the toothbrush conditions was subtracted from the drilling conditions (drill_c-toothbrush_c)-(drill_DS-toothbrush_DS). The latter contrast was liberally masked with (drill_c-toothbrush_c). Contrasts were thresholded at p<0.001 with k=156. C=controls, DS=Dental students.

Figure 4. Controls exhibit higher brain activity compared to Dental students when the toothbrush conditions was subtracted from the drilling conditions (drill_c-toothbrush_c)-(drill_DS-toothbrush_DS). The latter contrast was liberally masked with (drill_c-toothbrush_c). Contrasts were thresholded at p<0.0005 with k=125. In addition we visualize the region of interest (roi) that lead to best classification results.


Geissner E. [The Pain Perception Scale--a differentiated and change-sensitive scale for assessing chronic and acute pain]. Rehabilitation (Stuttg) 1995 Nov;34(4):XXXV-XLIII.


