

Abstract

Hypnotic hypoalgesia can suppress cortical activity

Hypnosis modulates pain perception, but the associated brain mechanisms in chronic pain conditions are poorly understood. Brain activity evoked by painful repetitive pin-prick stimulation of the left mental nerve region was investigated with use of functional magnetic resonance imaging in 19 patients with painful temporomandibular disorders (TMD) during hypnotic hypoalgesia and hyperalgesia and a control condition. Pain intensity and unpleasantness of the painful stimulation was scored on a 0-10 Numerical Rating Scale (NRS). NRS pain and unpleasantness scores during hypnotic hypoalgesia were significantly lower than in the control condition and significantly higher in the hypnotic hyperalgesia condition. In the control condition, painful stimulation caused significant activation of right posterior insula, primary somatosensory cortex (S1), BA21, and BA6, and left BA40 and BA4. Painful stimulation during hypnotic hyperalgesia was associated with increased activity in right posterior insula and BA6 and left BA40 whereas hypnotic hypoalgesia only was associated with activity in right posterior insula. Unexpectedly, direct contrasts between control and hypnotic hyperalgesia conditions revealed significant decreases in S1 during hyperalgesia. Direct contrasts between control and hypnotic hypoalgesia conditions demonstrated significant decreases in right posterior insula and BA21, as well as left BA40 during hypoalgesia. These findings are the first to describe hypnotic modulation of brain activity associated with nociceptive processing in chronic TMD pain patients and demonstrate that hypnotic hypoalgesia is associated with a pronounced suppression of cortical activity and a disconnection between patient-based scores and cortical activity in S1 during hypnotic hyperalgesia.

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Emneord:
Hypnosis;
pain
measurement;
brain mapping;
temporomandi-
bular disorder

Effect of hypnotic pain modulation on brain activity in patients with temporomandibular disorder pain

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Pain is a multi-dimensional experience including sensory-discriminative, affective-emotional, cognitive and behavioral components (1). Hypnosis can shape the individual's perception and report of pain and influence both the sensory and affective components of pain. For example, hypnotic hypoalgesia has been shown to reduce the unpleasantness and intensity of experimental pain in healthy individuals and is associated with different brain activation patterns in response to painful stimulation (2-4). Hypnosis may also relieve clinical pain, e.g., during and after surgical procedures (5-8), and in some chronic pain conditions (9-13). In experimental pain studies with healthy participants, hypnotic hypoalgesia is associated with changes in pain thresholds and physiological pain correlates including brain activity (14-17), somatosensory event-related potentials (SERPs) (18), and spinal reflexes (19-21). Highly hypnotic susceptible individuals generally display larger reductions in perceived pain, reflex responses, and amplitudes of SERPs to painful stimuli when compared to individuals with low hypnotic susceptibility (16,18,21).

The functional brain network associated with the experience of pain, commonly referred to as the »pain matrix«, involves the brainstem, thalamus, insula, anterior cingulate (ACC), primary (S1) and secondary somatosensory (S2) cortex (22,23). Brain imaging studies have shown that hypnotic hypoalgesia may produce changes in the responses in a number of brain regions, including the midcingulate cortex, insula, perigenual cortex, pre-supplementary motor cortex, brainstem, and thalamus (2,14,15,17,24). In particular, hypnotic suggestions of increased unpleasantness have been associated with increased ACC responses but without effects on S1 activity (3,4) whereas hypnotic suggestions of increased pain intensity are related to changes in S1 but without effects on ACC activity (2). However, most studies have been performed in healthy individuals and only relatively few studies have been conducted in chronic pain patients (25-27). To our knowledge there have so far been no studies of hypnotic modulation of nociceptive processing in chronic orofacial pain patients.

The aim of the present functional magnetic resonance imaging (fMRI) study was to explore whether patients with a common chronic orofacial pain condition, temporomandibular disorder (TMD), are able to modulate their pain experience and the associated brain responses by hypnotically induced hypoalgesia or hyperalgesia. We expected a decreased activity in the »pain matrix« during hypnotic hypoalgesia and an increased activity during hypnotically induced hyperalgesia compared with the control condition. We further explored whether individual variations in hypnotic susceptibility, changes of perceived pain intensity and unpleasantness would correlate with brain responses during hypnotic hypoalgesia or hyperalgesia.

Materials and methods

Patients

A total of 19 patients, one man and 18 women (mean age \pm standard error of the mean (SEM) 40.7 ± 2.3 years) referred to School of Dentistry in Aarhus, Denmark was included. The inclusion criteria were myofascial TMD pain according to the Research Diagnostic Criteria (RDC/TMD) type Iab (28) with a duration of 6 months or longer. Somatization, obsessive compulsive disorder, depression and anxiety were assessed with Symptom Check List (SCL) (28) and the present pain intensity was assessed on a 0-10 Numerical Rating Scale (NRS) with 0 corresponding to »no pain« and 10 to »the worst pain imaginable« (29). The study protocol was conducted in accordance with the Declaration of Helsinki and had been approved by the local ethics committee. All patients signed an informed consent form.

Experimental design

The patients were scanned using fMRI in three different experimental conditions: hypnotic hypoalgesia, hypnotic hyperalgesia, and a control condition with the patients in their normal alert state without any relaxation or imagery. The control condition

was always first followed by the two hypnotic conditions in randomized order. This design was necessitated to avoid carry-over effects of the hypnotic intervention and in accordance with previous brain imaging studies on hypnosis (2,3). Repetitive pin-prick stimuli with identical intensity were used as the painful stimulus in all three conditions. The perceived pain intensity and unpleasantness of the pin-prick stimuli were scored on a 0-10 NRS following each condition.

In each condition trains of identical painful pin-prick stimuli were applied to the skin overlying the left mental nerve (a total of 65 stimuli) during 30 s, alternating with 30 s rest (no stimulation). One condition included 5 cycles of stimulation followed by rest. The number of stimuli per cycle was determined by software restraints and with an onset synchronized to image acquisition. This frequency is close to 2 Hz stimulation used previously in repetitive stimulation protocols (30). The tip of the pinprick device was constructed as a von Frey hair with a 1 mm radius. The amplitude of the pin-prick device was adjusted at the onset of the experiment to give a painful stimulus corresponding to a self-reported level of pain around 5 on the NRS.

Hypnosis

A Danish version of Harvard Group Scale of Hypnotic Susceptibility, Form A (HGSHS:A) was used to determine hypnotic susceptibility on a scale from 0-12 (31,32). Patients were trained in the use of hypnosis in a one-hour session before the experiment. The training included induction with relaxation and guided imagery of an autobiographical pleasant place (for further details see Appendix 1). Glove anesthesia (33) and autobiographical memories of analgesia were used. During scanning, posthypnotic cues from the training session were used to induce the hypnotic trance as well as hypnotic hypoalgesia in the area of the left mental nerve. In the control condition there was no relaxation or imagery.

Image acquisition and analysis

The functional images were acquired on a 3.0 T GE Signa HDx Scanner (General Electric, Milwaukee, USA) with a 16-channel RF head coil (Nova Medical, USA). T2*-weighted echo planar imaging (EPI) with 39 axial slices of 3.5 mm thickness per volume were acquired with the following parameters: repetition time (TR) = 3 s, echo time (TE) = 30 ms, flip angle = 90°, field of view (FOV) = 240 mm² and in-plane resolution 1.875 x 1.875 mm. 100 volumes were acquired per session preceded by 5 dummy scans in order to remove initial T1-effects.

fMRI data analysis was performed in SPM8 (<http://www.fil.ion.ucl.ac.uk/spm/>). The functional images from each patient were motion corrected and realigned (34), unwarped (35), slice-time corrected, spatially normalized to MNI space using the SPM EPI template (36) and smoothed with a Gaussian kernel with a full-width at half maximum (FWHM) of 10 mm.

Statistical analysis was performed using a general linear mo-

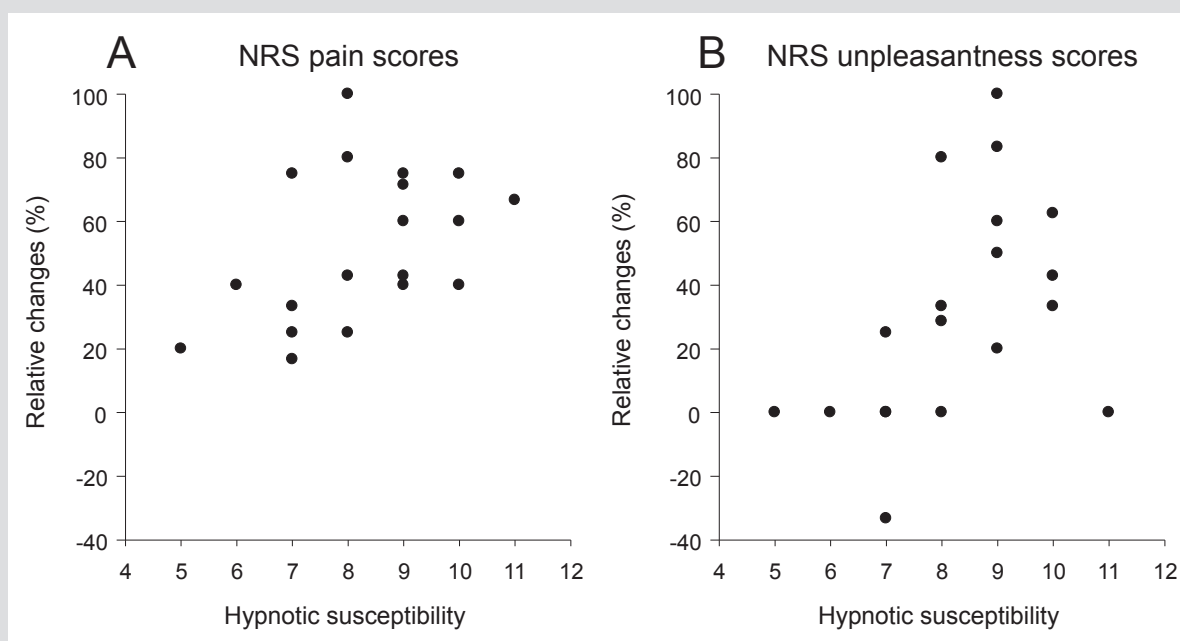


Fig. 1. Hypnotic susceptibility scores (0-12) and changes in NRS (numerical rating scale) pain (A) and unpleasantness (B) scores. Significant correlation between hypnotic susceptibility and NRS unpleasantness scores (Pearson correlation $R = 0.561$; $P < 0.047$) and a similar trend for NRS pain scores ($R = 0.394$; $P = 0.155$).

Fig. 1. Sammenhæng mellem hypnotiserbarhed (0-12), ændringer i selv-rapporteret NRS (numerical rating scale) smerteintensitet (A) og ubehag (B). Signifikant korrelation mellem hypnotiserbarhed og NRS ubehag (Pearson korrelationskoefficient $R = 0,561$, $P < 0,047$) og en lignende tendens for NRS smertescore ($R = 0,394$, $P = 0,155$).

del (37). For each patient a first-level model was constructed modeling cycles of 30 s stimulation followed by 30 s rest as an on-off boxcar convolved with a canonical hemodynamic response function. The time-series in each voxel was high-pass filtered with a 128 s cut-off to remove low-frequency drift and serial correlations were accounted for using an autoregressive AR(1) model.

A t -contrast was created for each patient testing for greater activation during stimulation relative to rest within each experimental condition. In order to assess the mean level of BOLD activation across all subjects and make inferences to the wider population of TMD patients, a second-level random-effects analysis (38) was performed using a one-sample t -test.

In order to assess changes in BOLD activation at the group level between a) the control condition and hypnotic hypoalgesia, and vice versa and b) the control condition and hypnotic hyperalgesia, and vice versa, the pattern of brain activation during the control condition was used as a reference. This was done by creating a mask that included all voxels exceeding a family-wise error (FWE) threshold of $P < 0.05$ in an F -contrast of this condition effect. The mask was then applied to the direct contrasts between the experimental conditions using a paired t -test.

Finally, to model the effects of individual differences between subjects a third model was created that included differences in hypnotic susceptibility, perceived pain intensity and unpleasantness entered as general linear model covariates.

A conservative statistical analysis of the fMRI data was applied. All contrasts were thresholded at $P < 0.05$, FWE corrected for multiple comparisons and an extent threshold of > 10 voxels was applied to the excursion set to report only clusters larger than this size. Anatomical regions and corresponding Brodmann areas (BA) were localized using the Wake Forest University Pickatlas (39,40) and automated anatomical labeling for SPM (41).

Statistics

The NRS pain and unpleasantness scores of the pin-prick stimuli during the three experimental conditions are presented as mean values \pm SEM and compared with the use of analysis of variance (ANOVA). The relative changes in NRS pain and unpleasantness scores from the control condition were calculated for the hypnotic analgesic and hyperalgesic conditions. The Tukey HSD test was used for post-hoc analyses. Pearson's correlation coefficients were used to test for linear associations among NRS pain and

unpleasantness scores of pin-prick stimuli, hypnotic susceptibility and NRS present pain intensity. $P < 0.05$ was considered to be statistically significant.

Results

Clinical characteristics

All patients had a long history of myofascial TMD pain (12.4 ± 2.1 years) and reported moderate levels of clinical pain in the cranio-facial region including the masseter muscles (mean NRS scores: 4.8 ± 2.1). The majority of TMD patients also had concomitant health and other pain problems (14/19). SCL scores for somatization, obsessive compulsive disorder, depression and anxiety were 0.8 ± 0.5 , 0.9 ± 0.6 , 0.8 ± 0.5 and 0.6 ± 0.6 , respectively. The mean hypnotic susceptibility score of the TMD patients was 8.3 ± 0.4 (range 5-11). The effect of hypnosis on clinical TMD pain has previously been reported (10).

KLINISK RELEVANS

Hypnose kan formodentlig anvendes til smertelindring af patienter med kroniske myofasciale, temporomandibulære smerter (TMD). Ved hjælp af hypnotisk hypoalgesi er TMD-patienterne i stand til at reducere smerteoplevelsen signifikant i forhold til den normale tilstand. Smertereduktionen er forbundet med en markant undertrykkelse af den kortikale aktivitet. Studiet brugte funktionel magnetisk resonans billeddiagnostik for få information om hjernens centrale procesmekanismer under hypnose hos TMD-patienter. Hjerneaktiviteten blev målt, mens patienterne var udsat for samme eksperimentel smerte i regio mentalis i henholdsvis normal tilstand (baseline), under hypnotisk hypoalgesi (smerten formindskes) og hypnotisk hyperalgesi (smerten forstærkes).

Pin-prick stimulation

	Left		Right	
	Coordinates x / y / z	Max Z score	Coordinates x / y / z	Max Z score
Control condition				
Posterior insula			40 / -20 / -2 (1866)	6.10
Supramarginal gyrus (BA40)	-62 / -24 / 20 (690)	5.62		
Posterior middle temporal gyrus (BA21)			52 / -58 / 2 (67)	5.38
SI (BA2)			28 / -40 / 62 (130)	5.37
Precentral gyrus (BA4)	-44 / -12 / 56 (16)	5.09		
Middle frontal gyrus (BA6)			50 / 2 / 48 (13)	4.67
Hypnotic hyperalgesic condition				
Posterior insula			46 / -18 / 20 (176)	5.30
Inferior parietal lobule (BA40)	-42 / -40 / 26 (161)	5.20		
Precentral gyrus (BA6)			58 / -8 / 46 (16)	4.97
Hypnotic hypoalgesic condition				
Posterior insula			42 / -32 / 22 (35)	4.69

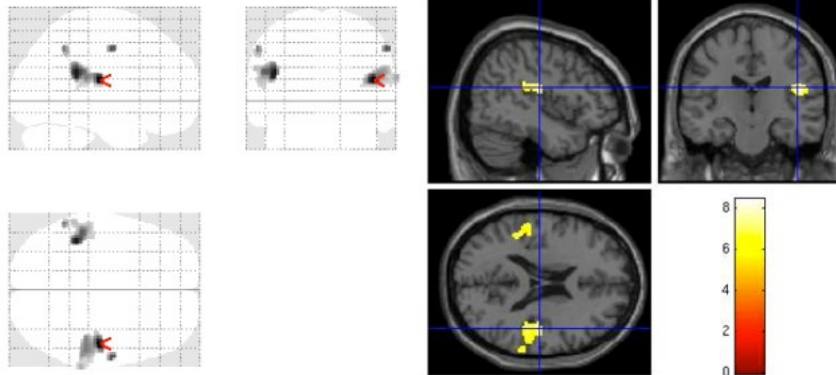
MNI coordinates (x / y / z), corrected Z values and cluster size in parentheses (height threshold $T = 6.406$; $P < 0.05$, FWE corrected; spatial extent threshold >10 voxels).

Table 1. Effects of painful pin-prick stimulation (stimulation minus no stimulation) in three experimental conditions.

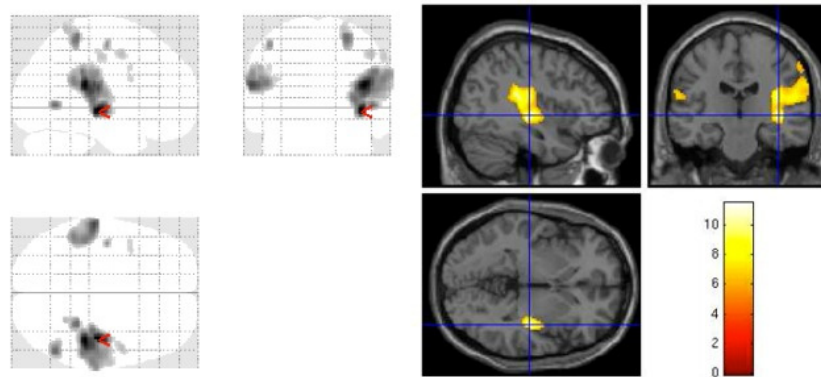
Tabel 1. Opsummering af hjerneområder med størst aktivitet under smertestimulation i de 3 eksperimentelle tilstande.



A. Hypnotic hyperalgesia condition



B. Control condition



C. Hypnotic hypoalgesia condition

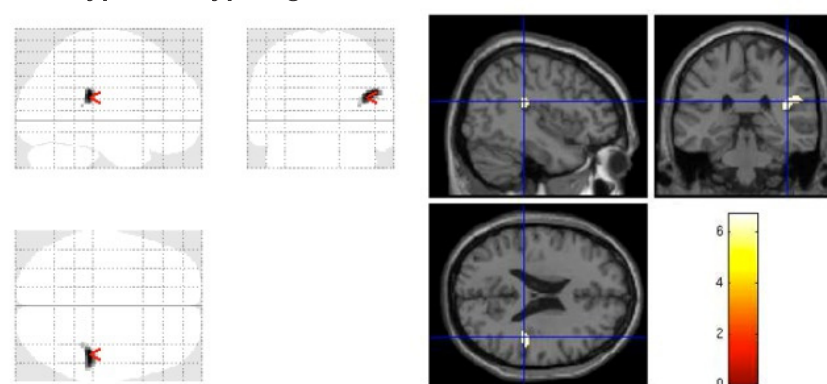


Fig. 2. Significant effects on brain activity evoked by painful pin-prick stimulation (stimulation minus no stimulation) in three experimental conditions: Top panel A: Hypnotic hyperalgesia, Middle panel B: Control, Bottom panel C: Hypnotic hypoalgesia. Three glass brain and T1-weighted MRI sections of the brain represent a sagittal, coronal, and horizontal view, respectively. Note the striking contrast between the control and hypnotic hypoalgesia conditions. Color-coded bars represent the Z-scores. All contrasts are thresholded at $P < 0.05$, family-wise error (FWE) corrected for multiple comparisons with an extent threshold of > 10 voxels.

Fig. 2. Hjernens aktivitet under smertestimulation (stimulation minus ingen stimulation) i de tre eksperimentelle tilstande: øverst A: Hypnotisk hyperalgesi, midterst B: Kontrol (baseline), nederst C: Hypnotisk hypoalgesi. Hjerneaktiviteten ses som overfladeprojektion på tre glashjerner samt T1-vægtede MRI i sagittalt, koronalt, og vandret snit. Farvekodede søjler repræsenterer Z-score. Mørkere farve repræsenterer signifikant øget iltning af blodet (statistisk parametriske kortlægningsmetode.) $P < 0.05$, FEW korrigeret, spatial tærskel > 10 voxels. Bemærk den slående kontrast mellem kontrol og hypnotisk hypoalgesi.

Pin-prick stimulation

	Left		Right	
	Coordinates x / y / z	Max Z score	Coordinates x / y / z	Max Z score
Hypnotic hyperalgesia - control				
No significant voxels				
Control – hypnotic hyperalgesia				
Postcentral gyrus (S1) (BA2)			32 / -40 / 62 (50)	4.11
Hypnotic hypoalgesia - Control				
No significant voxels				
Control – hypnotic hypoalgesia				
Posterior middle temporal gyrus (BA21)			54 / -60 / 2 (47)	4.12
Posterior insula			40 / -38 / 18 (190)	3.91
Inferior parietal lobule (BA40)	-52 / -46 / 26 (18)	3.59		
Inferior parietal lobule (BA40)				
Inferior parietal lobule (BA40)	-48 / -36 / 32 (35)	5.12		

MNI coordinates, corrected Z values and cluster size in parentheses (height threshold $T = 3.958$, except for hyperalgesia – hypoalgesia where height threshold was $T = 6.392$; $P < 0.05$ FWE corrected; spatial extent threshold >10 voxels).

Table 2. Effects of painful pin-prick stimulation in the direct contrasts between control condition versus hypnotic hyperalgesia and hypnotic hypoalgesia conditions.

Tabel 2. Hjerneområder med størst aktivitet under smertestimulation ved en direkte sammenligning af de 3 forskellige tilstande.

Pain scores

Pin-prick stimulation of the mental nerve region caused reports of pain and unpleasantness in all TMD patients. The hypnotic hypoalgesia condition was associated with significantly lower NRS pain scores (2.9 ± 0.4 , $P < 0.001$) and the hypnotic hyperalgesia condition with significantly higher NRS pain scores (7.3 ± 0.4 , $P < 0.001$) compared to the control condition (5.4 ± 0.3). The relative decreases and increases in NRS pain scores from the control condition were $52.2 \pm 23.6\%$ and $47.4 \pm 32.6\%$, respectively.

Also, the NRS unpleasantness scores of the pin-prick stimuli were lower during the hypnotic analgesic condition (2.8 ± 0.3 , $P < 0.002$) and higher during the hypnotic hyperalgesia condition (6.7 ± 0.4 , $P < 0.013$) compared to the control condition (4.6 ± 0.4). The relative decreases and increases in NRS unpleasantness scores were $30.8 \pm 35.2\%$ and $54.2 \pm 40.1\%$, respectively.

There were no significant correlations between NRS present pain scores (clinical TMD pain) and NRS pain scores of the pin-prick stimuli ($R = -0.045$; $P > 0.852$) or NRS unpleasantness scores in the control condition ($R = 0.258$; $P > 0.286$). Furthermore, there was no correlation between NRS pain scores and NRS unpleasantness scores of the pin-prick stimuli in the control condition ($R = 0.361$; $P > 0.129$).

There was a moderate, but significant correlation between hypnotic susceptibility scores and the relative changes in NRS unpleasantness scores of the pin-prick stimuli from control to hypnotic hypoalgesia ($R = 0.561$; $P < 0.047$) (Fig. 1B). No other correlations were found.

Brain activity

In the control condition, the contrast between stimulation with painful pin-prick stimuli versus no stimulation (rest) revealed significant activation in two areas typically assigned to the pain matrix: the right posterior insula and SI. Furthermore, significant activation was detected in the right BA21 and BA6, as well as the left BA40 and BA4 (Table 1) (Fig. 2B).

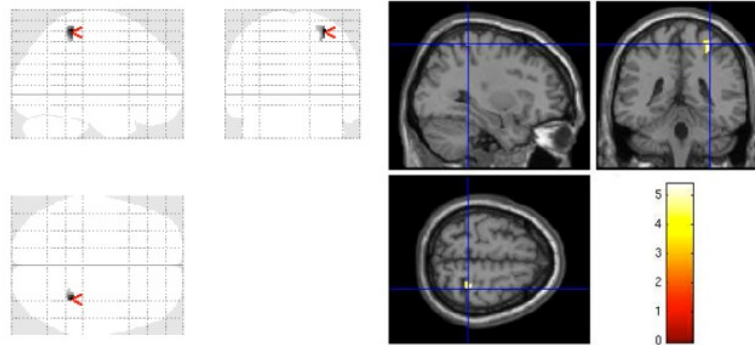
In the hypnotic hyperalgesia condition, painful pin-prick stimulation was associated with significant activation in the right posterior insula and BA6 and left BA40 (Table 1) (Fig. 2A).

In the hypnotic hypoalgesia condition, only a single cluster in the posterior insula was activated by painful pin-prick stimulation (Table 1) (Fig. 2C).

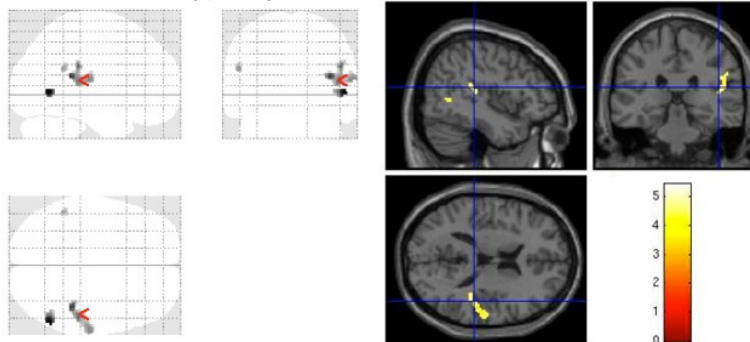
Based on the mask created by the activation pattern in the control condition, the direct contrast between the hypnotic hyperalgesia and control conditions revealed no significant clusters of



A. Control - hyperalgesia condition



B. Control - hypoalgesia condition



C. Hyperalgesia - hypoalgesia condition

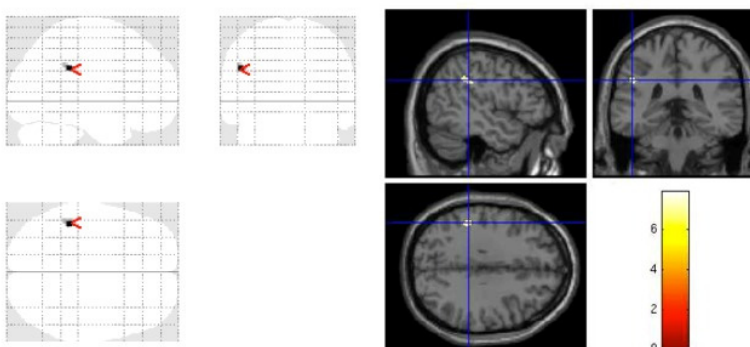


Fig. 3. Direct contrasts between control condition and hypnotic hyperalgesia (top panel A), control and hypnotic hypoalgesia (middle panel B) and hypnotic hyperalgesia and hypoalgesia (bottom panel C) conditions. Note the marked decreases associated with hypnotic hypoalgesia. Three glass brain and T1-weighted MRI sections of the brain represent a sagittal, coronal, and horizontal view, respectively. Color-coded bars represent the Z-scores. All contrasts are based on the mask created by the activation in the control condition and are thresholded at $P < 0.05$, family-wise error (FWE) corrected for multiple comparisons. Moreover, an extent threshold was applied to report only clusters larger than 10 voxels.

Fig. 3. Direkte sammenligninger af hjerneaktiviteten mellem kontrol tilstand og hypnotisk hyperalgesi (øverst A), mellem kontrol og hypnotisk hypoalgesi (midterst B) samt hypnotisk hyperalgesi og hypoalgesi (nederst C). Hjerneaktiviteten ses som overfladeprojektion på tre glashjerner samt T1-vægtede MRI i sagittalt, koronalt, og vandret snit. Farvekodede søjler repræsenterer Z-score. Mørkere farve repræsenterer signifikant øget iltning af blodet (statistisk parametriske kortlægningsmetode.) Alle kontraster er baseret på masken skabt af aktiveringen i kontrol tilstanden med tærskel på $P < 0.05$ og kun cluster > 10 voxels rapporteres. Bemærk den markant reducerede hjerneaktivitet forbundet med hypnotisk hypoalgesi.

Effect of unpleasantness

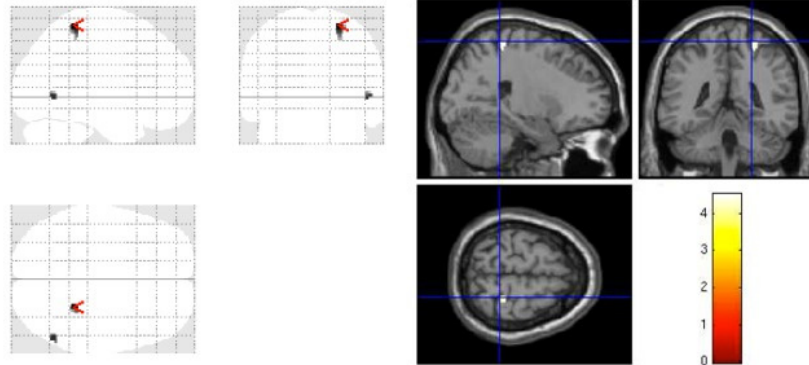


Fig. 4. Results from covariate analysis demonstrating a significant association between activity in the postcentral gyrus (BA5: 24, -42, 66) and changes in NRS (numerical rating scale) unpleasantness scores in the hypnotic hypoalgesia condition. Z score 3.61, cluster size 53 voxels (height threshold $T = 4.020$; $P < 0.05$ FWE corrected; spatial extent threshold >10 voxels).

Fig. 4. Signifikant sammenhæng mellem hjerneaktivitet i postcentral gyrus (BA5: 24, -42, 66) og ændringer i NRS (numerisk rating skala) ubehag under hypnotisk hypoalgesi. Covariat analyse. Z-score 3,61, cluster størrelse 53 voxels ($T = 4.020$, $P < 0.05$ FWE korrigeret, spatial tærskel > 10 voxels).

activation. However, the control condition compared to hypnotic hyperalgesia was associated with significant decreases in the right S1 during hyperalgesia (Table 2) (Fig. 3A).

Again the direct contrast between the hypnotic hypoalgesia condition and the control condition did not show any significant activation. However, the control condition compared to hypnotic hypoalgesia demonstrated significant decreases in the right posterior insula, and inferior insula, right S2 and BA21, as well as left BA4 and BA40 during hypoalgesia (Table 2) (Fig. 3B).

A direct comparison of the hypnotic hyperalgesia versus the hypoalgesia conditions revealed one significant cluster of activation in the inferior parietal cortex (BA 40) (Table 2) (Fig. 3C). The reverse contrast did not reveal any significant clusters.

Finally, the analysis of brain activation related to differences in hypnotic susceptibility and changes in NRS pain and unpleasantness scores only demonstrated one significant cluster located to the right postcentral gyrus (BA5: 24, -42, 66) that was significantly associated with the magnitude of decrease in NRS unpleasantness scores in the hypnotic hypoalgesic condition (Fig. 4).

Discussion

This is the first study to demonstrate that hypnotic modulation can increase or decrease the perception of pain and unpleasantness of painful stimuli in patients with a common musculoskeletal pain condition (TMD) in the orofacial region and that these changes are associated with distinctly different brain activation patterns.

The most striking findings were the marked decrease in brain activity during the hypnotic hypoalgesia condition where only the right insula remained activated with the painful stimulation (Fig. 2C) in accordance with the direct contrast between the control and hypoalgesia conditions showing significant decreases in additional cortical areas (Table 2, Fig. 3B). These findings extend the current knowledge on hypnotic modulation of brain activity in chronic pain patients (12). A number of issues, however, need to be discussed.

Methodological considerations

In order to avoid carry-over effects of hypnotic intervention (2,3), the control condition was always first and followed by the two hypnotic conditions in randomized order. The observed differences in brain activation patterns between hypnotic hyperalgesia and hypoalgesia are nevertheless unlikely to be due to time effects because a direct comparison between the two hypnotic conditions demonstrated a significant difference in nociceptive processing with a single cluster of activity located to the inferior parietal cortex (BA40). Moreover, compared with previous fMRI studies (17,24,27) the present study tested a reasonably large sample of myofascial TMD pain patients and employed a state-of-the-art fMRI acquisition and a conservative statistical thresholding of the fMRI results. However, it should be noted that only one man was included in the study. We originally aimed to include more men, but in accordance with published

studies, TMD pain mainly affects women (42). It is therefore conceivable that the observed brain activation patterns are more characteristic for women and, in fact, women have been shown to have a stronger medial prefrontal cortex response to painful stimulation compared to men (43). So far no studies have demonstrated gender-related differences in the magnitude of hypnotic effects.

Our study differs from previous research on the effects of hypnosis on pain in several ways. We used fMRI scans to increase the spatial and temporal resolution compared to previous PET studies (22,23,44). Another aim was to adjust the study as much as possible to a clinical setting of hypnosis for pain relief. The study was therefore conducted in patients with a common musculoskeletal pain condition (TMD) and with different levels of hypnotic susceptibility (Fig.1). Hypnotic susceptibility was used as a co-variable in the analyses rather than investigating only high (or low) hypnotically susceptible patients. We observed correlations between hypnotic susceptibility and decreases in unpleasantness scores but no direct effects on the associated brain activation patterns. While a control group of healthy individuals would have provided additional information on the effects of hypnotic hypoalgesia and hyperalgesia, we decided to focus on the within-group changes and use the TMD patients as their own controls. This may also in part explain the lack of activation of some of the common areas in the »pain matrix«, for example the ACC and thalamus. It can be speculated that ACC and thalamus were already activated at rest (no stimulation), and that pin-prick stimuli failed to cause more activation. Despite these concerns, we consider the present findings important for the understanding of hypnosis in chronic pain conditions.

Effects of hypnosis

In the control condition, repetitive pin-prick stimuli were rated as moderate painful by all TMD patients and caused activation in a distributed network of brain areas (Fig. 2B). There is indeed an overlap between the activation pattern observed in the control condition and the so-called »pain matrix«, for example the contralateral S1 and insula, but we also noted activation of premotor / motor areas and parietal cortex in accordance with several other imaging studies (22,23,44) including the trigeminal system (45-47). BA40 has been shown to be activated for example in association with experimental jaw muscle pain and hyperalgesia (48) as well as during hypnosis in fibromyalgia patients (27). Interestingly, BA21 which is linked to more extensive associative auditory tasks (49) was also consistently activated during the repetitive pin-prick condition. Another study has nevertheless shown BA21 activation in relation to spinal cord stimulation in patients with refractory angina pectoris (50) and as well as case study of SERP during hypnotic analgesia (51). As mentioned above, there were no indications with the applied conservative thresholds for activation in the ACC or thalamus. It should be noted that meta-analyses of pain

studies indicate a more reliable (frequent) activation of the ACC and thalamus in experimental settings and less often in clinical pain conditions (22,52). Interestingly, Rainville and colleagues attributed an important role of the ACC in hypnotically-modulation of the unpleasantness aspect of painful stimuli in healthy volunteers whereas the S1 was associated with hypnotically-manipulation of the sensory-discriminative component of the painful stimuli (2-4). In accordance, Kupers et al. (53) suggested that the ACC and dorsolateral and orbitofrontal cortices were involved in the endogenous modulation of nociceptive input during hypnosis or placebo-induced conditions (53,54). We could not in our sample of chronic TMD pain patients replicate these findings, perhaps due to differential effects of hypnosis on acute experimental pain versus chronic clinical pain. Compared with the control condition (Fig. 2B), it was a striking finding that hypnotic hypoalgesia was associated with a marked decrease in brain activity during the painful pin-prick stimulation, in fact, only the posterior insula remained activated in this condition (Fig. 2C).

There were fewer differences between the control condition and hypnotic hyperalgesic condition, although the NRS scores of pain and unpleasantness increased. Unexpectedly, the direct contrast between hypnotic hyperalgesia and control did not indicate any significant increases, but the direct contrast between control and hypnotic hyperalgesia revealed significant decreases in the S1 during hyperalgesia despite increases in patient-based scores of pain intensity and unpleasantness of the pin-prick stimuli. It is possible that there could be a »ceiling« effect of the painful pin-prick stimulation or that the subtle shifts within the activated set of brain regions due to the general effect of hypnosis can explain the increased scores of pain and unpleasantness, i.e., pain and unpleasantness are not always associated with linear changes in neural activity within the »pain matrix« but the relative balance and other parts of cognitive and emotional networks may play a significant role in the presentation of chronic pain. However, the observed disconnection between activity in S1 and patient-based scores during the hypnotic hyperalgesia condition needs further studies.

Conclusions

The present findings are the first to describe hypnotic modulation of brain activation patterns associated with nociceptive processing in chronic TMD pain patients and convincingly demonstrate that hypnotic hypoalgesia is associated with a dramatic suppression of cortical activity. Robust ACC activity was not observed which suggests that hypnotic modulation in TMD pain patients may involve other brain mechanisms than placebo or hypnosis in healthy controls.

Acknowledgments

The study was supported by the Research Foundation of the Aarhus University (AUFF). There was no conflict of interest. The

authors are grateful to Svend Daugaard for development and construction of the pin-prick equipment and the staff at Center of Functionally Integrative Neuroscience, Aarhus University Hospital: Dora Zeidler for radiographic assistance and Physicist M.Sc., Ph.D. Ryan Sangill for setting up and performing the scan.

Appendix

Hypnotic suggestions for analgesia

Before the hypnosis:

Patient is informed of hypnosis, the scanning, the noise during the scan, and pin-prick procedures. Autobiographic memories of a nice place and experiences with local anesthetics are recorded.

Hypnosis

1. Induction. Progressive muscle relaxation, guided imaginary to an autobiographic pleasant place according to individual preference (beach, garden, wood). Integration of perceptions of colors, sounds, smells, and kinesthetic feelings. Feelings of success, calm, peace of mind, and inner strengths were anchored.
2. Suggestions to incorporate the fMRI surroundings and noise in the hypnosis.
3. Training the use of glove analgesia and transfer the analgesia to the area of left mental nerve.
3. Suggestions of analgesia using autobiographic experiences of analgesia.

Example: »Just feel how you can remain relaxed and enjoy everything you can do in your nice place. Begin to experience how it is possible for you slowly to change the feeling at the left side of your lower jaw – how you can gradually change the sensation of that specific area. Remember how you once had a successful experience of total anesthesia at the dentist or at the doctor or hospital or whatever you might remember, – remember how you were totally num ... or remember a strange feeling of rubber ... or imagine how that area might be like dry wood without any feeling at all ... or imagine how that specific area has blocked every sensation like all nerves in that area were cut like a wire and no longer able to pass any sensation on. Allow yourself to just let it happen in the way most suitable for you. Nice and wonderfully relaxed without any pain in that area, you will be able to remain wonderfully relaxed and with your mind totally occupied by the things happening in our wonderful place during scan. You will remain in this nice condition throughout the scan. Just let that specific area become totally anaesthetized, like when you have an injection of a very powerful local anesthetic«.mert samtykke.

Abstract (dansk)

Effekt af hypnotisk smertemodulation på hjerneaktivitet hos patienter med kroniske myofasciale temporomandibulære smerter (TMD)
Hypnose kan påvirke smerteopfattelsen, men der eksisterer kun lidt viden om de dertil knyttede centrale processer i hjernen hos patienter med kroniske smertetilstande. Hjerneaktivitet fremkaldt af gentagen smertestimulation (pinprick) over venstre nervus mentalis blev undersøgt ved hjælp af funktionel magnetisk resonans billeddiagnostik hos 19 TMD patienter i kontroltilstand (baseline) og under hypnotisk hypoalgesi eller hypnotisk hyperalgesi. Selv-rapporteret smerteintensitet og ubehag ved den samme smertestimulation blev registreret på en skala fra 0-10 (Numerical Rating Scale (NRS)). NRS smerter og ubehag var henholdsvis væsentligt lavere under hypnotisk hypoalgesi og markant højere under hypnotiske hyperalgesi end ved baseline. I kontroltilstanden resulterede den smertefulde stimulering i aktivering af højre posterior insula, primær somatosensoriske cortex (SI), BA21, og BA6, samt venstre BA40 og BA4. Samme smertestimulation under hypnotisk hyperalgesi var forbundet med forøget aktivitet i højre posterior insula og BA6 samt venstre BA40, mens der under hypnotisk hypoalgesi kun blev registreret aktivitet i højre posterior insula. Uventet viste den direkte statistiske sammenligning mellem de 2 tilstande, baseline og hypnotisk hyperalgesi, et signifikant fald i S1 under hyperalgesi i forhold til baseline. Den direkte sammenligning mellem de 2 tilstande, baseline og hypnotisk hypoalgesi, viste signifikant reduktion af aktiviteten i højre posterior insula og BA21, samt venstre BA40 under hypoalgesi i forhold til baseline. Disse resultater er de første til at påvise hypnotisk modulation af hjerneaktiviteten hos kroniske TMD patienter er associeret til smerteoplevelsen. Endvidere ses at hypnotisk hypoalgesi er forbundet med en markant undertrykkelse af den kortikale aktivitet. Desuden ses en uoverensstemmelse mellem selv-rapporteret scores og kortikal aktivitet i S1 under hypnotisk hyperalgesi

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