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Cerebral somatic pain modulation during autogenic training in fMRI

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Abstract

Background: Functional magnetic resonance imaging (fMRI) studies are increasingly employed in different conscious states. Autogenic training (AT) is a common clinically used relaxation method. The purpose of this study was to investigate the cerebral modulation of pain activity patterns due to AT and to correlate the effects to the degree of experience with AT and strength of stimuli.

Methods: Thirteen volunteers familiar with AT were studied with fMRI during painful electrical stimulation in a block design alternating between resting state and electrical stimulation, both without AT and while employing the same paradigm when utilizing their AT abilities. The subjective rating of painful stimulation and success in modulation during AT was assessed.

Results: During painful electrical stimulation without AT, fMRI revealed activation of midcingulate, right secondary sensory, right supplementary motor, and insular cortices, the right thalamus and left caudate nucleus. In contrast, utilizing AT only activation of left insular and supplementary motor cortices was revealed. The paired *t*-test revealed pain-related activation in the midcingulate, posterior cingulate and left anterior insular cortices for the condition without AT, and activation in the left ventrolateral prefrontal cortex under AT. Activation of the posterior cingulate cortex and thalamus correlated with the amplitude of electrical stimulation.

Conclusions: This study revealed an effect on cerebral pain processing while performing AT. This might represent the cerebral correlate of different painful stimulus processing by subjects who are trained in performing relaxation techniques. However, due to the absence of a control group, further studies are needed to confirm this theory.

1. Background

During the last two decades, many neuroimaging studies have provided a basic knowledge of how the human brain responds to pain and how treatment influences and modulates this response (Derbyshire, 2000; Peyron et al., 2000a; Wiech et al., 2008). These studies suggest that the brain's response to pain is complex and involves multiple brain regions, referred to by some authors as the 'neuromatrix for pain processing' (Derbyshire, 2000; Peyron et al., 2000b); however, this term is not very specific, and many authors relate different areas to this term.

Autogenic training (AT) is a common and clinically used auto-hypnotic relaxation technique (Ernst and Kanji 2000; Stetter and Kupper 2002; Kanji et al.

What's already known about this topic?
- Autogenic training (AT) can have positive effect on, e.g., headache, somatoform pain and anxiety disorders.
- There are indications that AT can have modulating effect on pain perception.
- Meditation led to reduced response to pain within pain-associated brain areas.

What does this study add?
- This fMRI study gives support to an effect on cerebral pain processing while performing AT.
- The posterior cingulate cortex and thalamus correlated with the amplitude of painful electrical stimulation.

2006a). It is a psychophysiological form of suggestive therapy, which can be performed by an individual through passive concentration augmented with certain combinations of psychophysiologically adopted stimuli. It specifically aims at stress prevention and has the advantage that once learned an individual can practise it without further interventions from a therapist. Even elderly patients are able to learn and exercise AT (Kircher et al., 2002).

AT, developed by Johannes Schultz in 1932, encompasses two stages of exercises (Schultz, 1973). The first stage of the autogenic process is focused on relaxation and is composed of a series of six exercises: tranquillity exercise, heaviness exercise, warmth exercise, breath exercise, heart exercise and solar plexus exercise, all of them induced by specific (auto-)suggestive sentences.

The second stage of autogenic training is much more abstract and focuses on self-awareness. Altogether, these exercises result in a relaxed body state and in a relaxed and focused mental state. Especially, the second stage should lead to a deeply relaxed state.

AT supposedly has a positive effect on tension headache/migraine, mild-to-moderate essential hypertension, coronary heart disease, asthma bronchiale, somatoform pain disorder, Raynaud's disease, anxiety disorders, mild-to-moderate depression/dysthymia and functional sleep disorders (Stetter and Kupper 2002; Asbury et al., 2009).

Though there are only few studies analysing the effect of AT on pain (Kwekkeboom and Gretarsdottir 2006), there are indicators for a modulating effect of AT on pain perception (Zsombok et al., 2003; Juhasz et al., 2007; Pakhomova et al., 2008). Up to now, no brain imaging studies have been performed to assess AT effects on pain. However, a study dealing with transcendental meditation showed a longitudinally reduced brain response to acute pain within pain-associated areas (Orme-Johnson et al., 2006). Therefore, functional magnetic resonance imaging (fMRI) studies could quite probably provide some further information concerning the potential effectiveness and the mechanisms of AT. On the basis of the literature, the response to the affective component of acute pain could lead to an activation decrease in the cingulate, prefrontal and insular cortices, as well as the thalamus and further deep brain structures. For example, some areas such as the thalamus and primary sensory and insular cortex are described to be more related to the sensory discriminative aspect of pain processing (Peyron et al., 2000b) and therefore could be modulated by AT.

The purpose of this study was to investigate the cerebral modulation of pain activity patterns due to AT in correlation to the degree of experience with AT. The main hypothesis was that the cue regions for pain processing, the cingulate and insular cortex as well as the thalamus, are modulated under AT during pain perception.

2. Methods

2.1 Subjects

Eight male and five female healthy right-handed volunteers (mean age 34 years, range 19 to 47) familiar with AT were examined. No subject had a history of neurological disease nor showed any brain lesions in the structural MRI. Only subjects with AT experience of more than 5 years and who regularly (more than twice a week) practised the technique were included. The 13 volunteers had a mean time of AT practice of 11 years (range 5 to 21 years). Eleven of them also taught AT in courses. The subjects were recruited out of a local centre for AT. The teachers were contacted by one of the authors (R.N.) first by phone, and these teachers subsequently performed personal recruitment.

Informed written consent was obtained prior to scanning. The ability of subjects to obtain a sufficient state of relaxation during AT was assessed with a questionnaire in a subjective manner. The subjects rated their achieved relaxation and AT state on a visual analogue scale (VAS) with a length of 10 cm (indicating 0 = no relaxation; 10 = best, and similar to the subjects' experience from regular practice). The ethics committee of our university approved the study.

2.2 Experimental design

2.2.1 Elicitation of standardized pain

For painful electrical stimulation, a specifically designed shielded electrical conductor was employed, which had already been tested successfully for preoperative identification of the sensorimotor cortex. The capability of the stimulation system and its MR compatibility has been well documented (Gasser et al., 2004).

The electrical stimuli were applied in each individual to the wrist/forearm (3 cm proximal to the wrist at the level of the malleoli, at the midline). For elicitation of a painful sensation, a 3 Hz stimulus was applied with amplitude, which was individually defined according to the subject's pain threshold. For this purpose, the individual pain level was evaluated by increasing the stimulation amplitude until the subject marked a score of 5 on a numeric pain rating scale (NRS). The scale was designed from 0 (no pain and no sensation) to 10 (pain, not acceptable). On this scale, 5 was defined as a clearly painful stimulus acceptable for about a minute. This evaluation served to normalize the subjective pain experience, and this stimulation intensity was maintained throughout the experiment. Furthermore, the electrodes were not changed between the first evaluation of pain level and the scanning sessions. A motor co-activation was excluded as best as possible by not placing the electrode directly above a motor nerve.

All subjects had to fill in a questionnaire concerning handedness, relaxation state within the scanner and subjective pain intensity rating according to the NRS before and during AT. The ability of subjects to obtain a sufficient state of relaxation during AT was assessed with a questionnaire in a subjective manner as mentioned above; additionally, the subjects rated the success of AT during scanning using the same VAS. Both silicone earplugs and earphones were provided to attenuate acoustic noise.

2.2.2 The scanning protocol

All MR images were acquired with a 1.5 T MRI system (Sonata, Siemens Healthcare, Erlangen, Germany) employing a standard head coil (8-Channel Head Coil). A 3D T1-weighted Fast Low Angle SHot (FLASH) sequence (TR 10 ms, TE 4.5 ms, flip angle 30°, FOV 240 mm, matrix 512, slice thickness 1.5 mm) was acquired for individual co-registration of functional images. Blood oxygenation level dependent (BOLD) contrast images were acquired using an echo-planar technique (Relaxation time (TR) 3100 ms, Echo time (TE) 50 ms, flip angle 90°, Field of view (FOV) 240 mm, matrix 64), with 34 transverse slices with a thickness of 3 mm and 0.3 mm slice gap covering the entire brain. Three 'dummy' scans were eliminated prior to data analysis to account for T1 relaxation effects.

2.2.3 The fMRI paradigm

A block design paradigm alternating every 31 s between painful and resting periods was employed without AT and in another session under the same conditions while performing AT. The order of the sessions was randomized across the subjects. Each run was divided into seven epochs starting with the resting condition. During data acquisition, the subjects were asked to lie relaxed with their eyes closed. In the condition under AT, the subjects were given a defined period of time to comfortably reach the AT relaxation state before functional scanning commenced. This time was adapted to the individual time needed to reach a relaxed state based on past experience and was filled with anatomical scans.

Prior to scanning of the condition 'painful stimulation' both with and without AT and just after finishing scanning of the condition 'painful stimulation', the perceived pain level was documented according to the NRS in order to verify the subjective experience of painful stimulation.

Heart rate and blood oxygenation level were recorded for the entire experiment by an MRI-compatible pulse oximeter (Fabius MRI, Draeger, Lübeck, Germany).

2.3 Data analysis

For statistical data analysis, SPM 02 (Wellcome Department of Cognitive Neurology, London, UK) was used. Prior to statistical analysis, images were realigned utilizing sinc interpolation and normalized to the standard stereotactic space corresponding to the template as supplied by the Montreal Neurological Institute. Bilinear interpolation was applied for normalization. The images were smoothed with an isotropic Gaussian kernel of 8 mm. To calculate differences in activation between active and resting conditions, a voxel-by-voxel comparison according to the general linear model was used. The model consisted of a boxcar convolved with the haemodynamic response function (hrf) and the corresponding temporal derivative. High-pass filtering with a cut-off frequency of 128 s and low-pass filtering with the hrf were applied.

For group analysis, single-subject contrast images were entered into a random-effects model. Significant signal changes for each contrast were assessed by

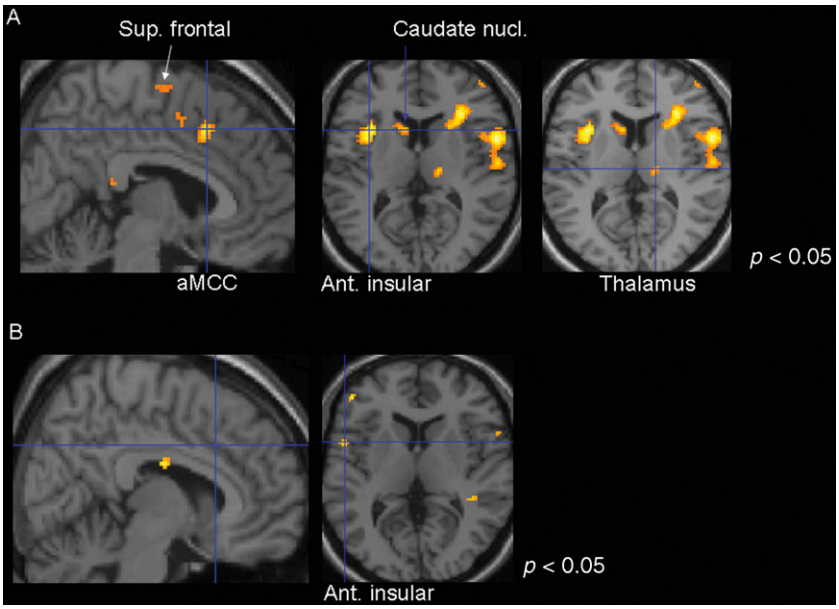

Figure 1 Statistical parametric maps of activation within the groups of volunteers during painful stimulation overlaid on a 2D standard brain. Group analysis in a one-sample *t*-test revealed activation of the cingulate and insular cortex, the thalamus and left caudate nucleus in contrast to resting state in the group of volunteers without performing AT (A). The subjects under AT also revealed activation in the insular cortex during painful stimulation in contrast to resting state (B). The statistically corrected threshold is $p < 0.05$ in both analyses.

means of *t*-statistics on a voxel-by-voxel basis (Friston et al., 1995). The resulting set of voxel values for each contrast constituted a statistical parametric map (SPM) of the *t*-statistic. The threshold was set to $p < 0.001$ [corrected for multiple comparisons, family-wise error correction (FWE)]. A second-level analysis for group differences was performed with a paired *t*-test. A random effects analysis was performed using the intensity of the electrical stimulation and the level of subjective pain experience as confounding variables. For this analysis, a FWE-corrected $p < 0.05$ was chosen. A four-region model of the cingulate cortex was used, established by Vogt et al. (Vogt, 2005) to classify the activations as documented in the study. Here, a small volume correction (SVC) was used in second-level statistics.

3. Results

3.1 fMRI results

During painful electrical stimulation without using AT, group analysis revealed an activation of regions known for pain processing: anterior midcingulate cortex (aMCC), anterior insular cortices, the left caudate nucleus and right thalamus (Fig. 1A). On the other hand, group analysis of the same volunteers revealed no activation of the aMCC, the right thalamus, or the right anterior insular cortex when using AT during the same painful stimulus in contrast to resting state using the same threshold (Fig. 1B). Additionally, activation of the right BA 40 and the left anterior insular cortex were shown in both conditions, but with a larger extension under the non-AT condition (Fig. 1A and B). The exact activated areas with coordinates and activation strength are summarized in Table 1.

The paired *t*-test revealed activation of the aMCC and the dorsal posterior cingulated cortex (dPCC) and also of the left anterior insular cortex for the non-AT condition when compared to stimulation under AT (Fig. 2A). Comparing the condition of stimulation under AT to that without AT, the paired *t*-test revealed an activation of the left ventrolateral prefrontal cortex (VLPFC; BA 47; Fig. 2B). The coordinates of the activated areas are given in Table 2, where additionally

Table 1 Activated areas in a one-sample *t*-test for the condition 'Painful stimulation and resting state' (non-AT) and for the condition 'AT and painful stimulation' (AT) are given. Only results using a $p < 0.05$ (corrected, family-wise error correction) are shown.

Group	Talairach coordinates (mm)	Region (cortex)	Side	*t*-value
Non-AT	6; 18; 44	aMCC	R	6.61
	60; –24; 24	Inf. parietal BA 40	R	7.00
	16; –6; 66	Sup. frontal BA 6	R	7.07
	54; –16; 14	Insular	R	6.64
	60; 6; 6	ant. Insular	R	9.17
	–36; 10; 8	ant. Insular	L	7.90
	16; –18; 10	Thalamus	R	5.66
	–10; 16; 12	Caudate nucleus	L	6.15
AT	54; –28; 24	Inf. parietal BA 40	R	5.08
	–52; 8; 6	ant. Insular	L	4.93

aMCC, anterior midcingulate cortex; AT, autogenic training.

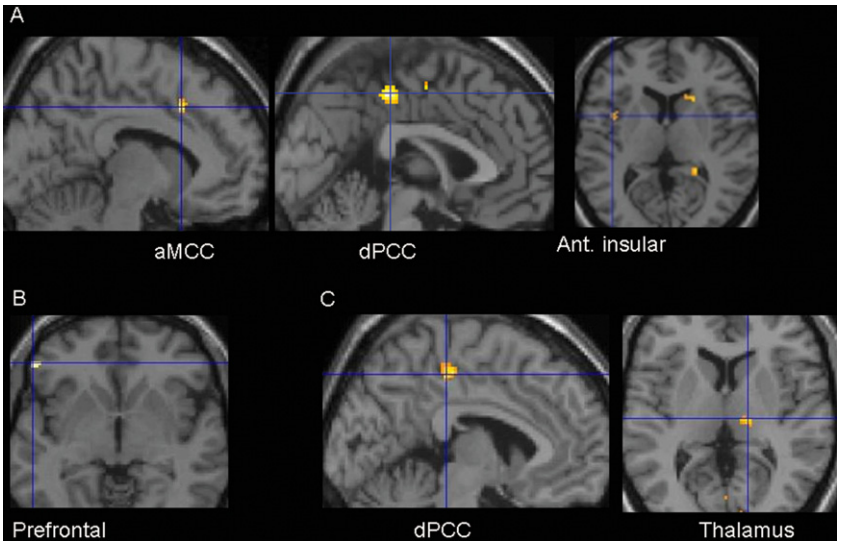

Figure 2 (A) The paired *t*-test revealed activation in the anterior cingulated cortex without AT compared to the run under AT. SVC of insula and cingulate cortex revealed significant activation in ACC and left anterior insula. (B) The contrast of painful stimulation under AT to that without AT revealed only activation of the right prefrontal cortex. (C) Simple regression testing using the intensity of electrical stimulation as a confounding variable revealed significant activation in the dPCC (–4; –30; 48; *t*-value 5.80) and right thalamus (16; –18; 6; *t*-value 5.64).

the results with stimulus intensity as a covariate are given.

Testing the intensity of electrical stimulation in a simple regression analysis, the activation of the dPCC and the right thalamus could be shown for the non-AT condition (Fig. 2C).

3.2 Results of the visual analogue scale

The analysis of the NRS with AT revealed a decrease in the average pain state (sensation) from 5 during 'non-AT' to 1. The correlation between the NRS and the intensity of electrical stimulation is summarized in Table 3.

The applied electrical stimulus varied from 40.8 to 95 mA to reach a subjective painful experience of 5 on the pain rating scale.

3.3 Results of the pulse oximetry recording

No significant reduction of the heart rate or the blood oxygenation level could be demonstrated under AT. The heart rate in the non-AT state was on average 72/min (SD 4.5) and under AT 71/min (SD 5.1).

On average, the blood oxygenation level under pain without AT was 98% (SD 0.3) compared to 98% (SD 0.2) under pain and AT.

4. Discussion

Though there is only little evidence for the effect of AT on pain (Kwekkeboom and Gretarsdottir 2006), some studies indicate that it has an influence on pain perception (Zsombok et al., 2003; Juhasz et al., 2007; Pakhomova et al., 2008). Therefore, we hypothesized that AT would reduce the brain's response to somatic pain stimuli and may reduce anxiety and stress, which might be an additional factor in somatic pain (Kanji et al., 2004; Kanji et al. 2006b; Manzoni et al., 2008).

The activated areas under painful stimulation as revealed in this study are known to be involved in the cerebral response to acute pain (Derbyshire, 2000; Apkarian et al., 2005; Wiech et al., 2008). Activation

Table 2 Activated areas in a paired *t*-test for the condition 'Painful stimulation and resting state' in the non-AT condition compared to this condition under AT. Reported are significant activations at a $p < 0.05$ (family-wise error correction).

Tasks	Group	Talairach coordinates (mm)	Region (cortex)	Side	*t*-value
A: Paired *t*-test	Non-AT versus AT	0; –30; 48	dPCC	L/R	8.26
		8; 16; 40	aMCC	R	5.90
		–40; 6; 8	ant. Insular	L	4.90
	AT versus Non-AT	–54; 40; –4	BA 47	L	5.58
B: Extent of electrical stimulation as a confounding variable	Non-AT versus AT	0; –28; 46	dPCC	L/R	4.04
		–6; 16; 32	aMCC	L	4.78
		8; 16; 40	aMCC	R	5.39
		–40; 6; 8	ant. Insular	L	5.21
	AT versus Non-AT	–	–	-	-

aMCC, anterior midcingulate cortex; AT, autogenic training; dPCC, dorsal posterior cingulate cortex.

Table 3 Results of the numeric pain rating scale (NRS; 0 = no pain to 10 = not acceptable pain, 5 meaning = intense pain acceptable for about 1 min) and the electrical stimulation for each volunteer.

Volunteer	Intensity of painful stimulation (mA)	Pain experience without AT	Pain experience under AT	Difference in painful experience
1	78	5	1	4
2	88	5	2	3
3	69	5	4	1
4	91.8	5	1	4
5	90	5	0	5
6	82	5	0	5
7	40.8	5	0	5
8	73	5	2	3
9	95	5	1	4
10	82	5	0	5
11	68	5	1	4
12	71	5	2	3
13	89	5	0	5

AT, autogenic training.

of the thalamus, postcentral and insular cortex has been related to the sensory-discriminative aspect of pain processing (Peyron et al., 2000b). The insular cortex has also been indicated in autonomic reactions to noxious stimuli, in pain-related learning and memory (Ploner and Schnitzler 2004; Shibasaki, 2004). The cingulate cortex participates in affective and attention aspects of pain sensation (Rainville et al., 1997; Vaitl et al., 2005), and is involved in emotional aspects of pain perception (Vogt, 2005; Vogt et al., 2006). Therefore, the activation of these areas is likely to be modulated during mechanisms influencing pain perception. Many studies do not describe an activation of the caudate nucleus as found in our group. However, some studies describe additional activation during electrically induced pain during a discrimination task (Freund et al., 2007). As in our study, those subjects had to rate the pain level before scanning, and one could assume that a form of 'rating' was also present during scanning.

The missing activation in the aMCC, the right thalamus and the right insular cortex under painful stimulation while performing AT is indicative of cerebral modulation of pain perception during AT; even the left insular and right secondary somatosensory cortex showed less-extensive activation during AT. The reduced activation cannot be related to habituation, as the subjects were randomized for both conditions.

These findings indicate that performing AT influences pain processing, mainly the affective, attention part of pain perception. Autonomic reactions to pain do not seem to be affected, as we could not demonstrate any heart rate reaction. A drawback of this study is that we did not use other, perhaps more specific, parameters like skin resistance for exact measurement of vegetative reaction.

Without AT, pain application led to activation of the aMCC, dPCC and the anterior insular cortex. The aMCC receives nociceptive inputs from midline and intralaminar thalamic nuclei (Hatanaka et al., 2003) indicating a high level of nociceptive activation in the aMCC. Additionally, imaging studies have shown that somatic pain evokes greatest activity in the pACC and MCC and fear is mainly associated with activity in the aMCC (Vogt, 2005). These areas are reportedly responsible for the coding of the intensity of noxious stimuli (Derbyshire et al., 1997; Coghill et al., 1999). Furthermore, voxel-based morphometry of patient groups with chronic pain disorders revealed significant grey matter decreases in the prefrontal, cingulate and insular cortex (Valet et al., 2009). The aMCC receives direct input from the amygdala, thus it is involved in processing of fear and nociception (Whalen et al., 1998). Furthermore, during visceral pain stimuli, a modulation of aMCC could be shown in correlation with anxiety (Elsenbruch et al., 2009). The altered activation of this region under pain during AT is consistent with the idea that fear reduction is part of the analgesic effect mediated by the cerebral cortex and linked in the aMCC. Inducement of analgesia by hypnosis also targets the aMCC (Faymonville et al., 2000). A recent fMRI study regarding pain processing during hypnosis showed diminished activation of the aMCC and decreased subjective pain sensation (Vanhaudenhuyse et al., 2009). AT was established as a self-induced relaxation technique on the basis of hypnosis, so similar modes of cerebral activation are conceivable.

The dPCC has been indicated in body orientation towards the source in response to sensory stimuli, including nociceptive stimuli as well as painful and non-painful electrical stimulation (Vanhaudenhuyse et al., 2009), but also simple finger movements (Huang et al., 2004). Therefore, the dPCC does not seem to have a specific role in pain processing. The absence of activation under AT is another hint for altered pain perception which does not require any body orientation towards the nociceptive stimulus because it is less threatening and intense under AT. Interestingly, when testing the electrical stimulation intensity in a simple regression analysis, an activation of the dPCC and right thalamus could be shown for the non-AT condition, indicating an alteration in the pure perception of stimulus intensity during AT.

The anterior insula is located between the lateral and medial pain system and has been indicated in aspects of

pain processing associated with body state assessment and autonomic regulation (Vogt, 2005). The insular cortex has also been proposed to be involved in pain-related learning and memory (Shibasaki, 2004; Gundel et al., 2008) in memory retrieval of unpleasant experiences (Ushida et al., 2008), but also in a wide range of perception and cognitive processing (Craig, 2009). The anterior insula is, according to this model, part of a network dealing with motivational, cognitive and social conditions. Therefore, the absence of anterior insular activation during painful stimulation under AT could explain the decreased subjective pain and the different attribution to this stimulus ('less threatening'). The anterior insula may also participate in the long-term effect of AT by inhibiting memories of unpleasant pain sensations.

Increased activity of the VLPFC in the condition 'AT versus non-AT' could also be shown in a study analysing the effect of meditation on self-reference (Farb et al., 2007). Transcendental meditation is another, more religiously orientated, relaxation technique, which like AT focuses on concentration and self-awareness. As seen in our results, activation during painful stimulation shifted away from VMPFC toward the more lateral prefrontal cortex (e.g., BA 47), which might support the theory of a more self-detached and objective analysis of interoceptive and exteroceptive sensory events, rather than their affective or subjective self-referential value. This model mirrors neural dissociations between affective and sensory components of the subjective pain sensation, with the former supported by anterior midline structures such as the ACC (Rainville et al., 1997). Another fMRI study supports a key role of the VLPFC in coping with the emotional impact of uncontrollable pain (Salomons et al., 2007). A possible explanation for the decreased subjective pain intensity is the involvement of the VLPFC and aMCC in cognitive modulations, which modify activation in pain-associated regions. This system, referred to as the descending pain modulation system (Wiech et al., 2008), seems to eventually facilitate and/or inhibit pain processing at the level of the spinal dorsal horn. Studies on placebo-related expectations (Petrovic et al., 2002; Wager et al., 2004) and perceived control over pain (Wiech et al., 2006), provide evidence that the VLPFC is involved in cognitive modulations of pain, reflecting reappraisal of the emotional significance of pain resulting in decreased subjective pain.

Further studies are needed to investigate the inhibition level of painful perception, but our results indicate higher inhibition than presumed for a cognitive-related relaxation task. A major limitation of this study is that a priori group differences were not controlled for, as we had no control stimulus apart from the painful stimulus and no control group without experience in AT. Therefore, we also did not perform any structural measurements, as this would only be helpful in a direct comparison between AT and a control group. Volume changes have been described in subjects performing meditative techniques such as Zen or mindfulness practice (Holzel et al., 2011). However, the main focus of this study was the acute influence of AT on a painful stimulus and not the possible long-term effects on pain levels in subjects performing AT regularly. This would be an interesting aim for further studies addressing cerebral alterations due to long-term relaxation practice. A further limitation is that affective and cognitive aspects of pain were not measured separately. The subjects had to rate their relaxation extent and subjective pain levels, but we did not add an unpleasantness rating.

Interestingly, the primary sensory cortices were not activated in both conditions. This may be due to the relative long duration of painful stimulation and the paradigm's block design. The primary sensory cortex was activated in roughly half of previous fMRI and PET studies, and the probability of obtaining that activation appears to be related to the total amount of body surface stimulated (Peyron et al., 2000a). Therefore, the missing activation could be partly related to a peripheral habituation effect due to the relatively long stimulus.

5. Conclusions

The activation changes comparing pain stimulation under AT and without AT indicate that cerebral pain processing can be influenced under autogenic training, and this effect is presumed to be similar to the modulation found under complex meditation and hypnosis. However, further studies are needed including control groups for direct comparison and to address the cognitive and affective aspects of pain.

Author contributions

R.P. Naglatzki: acquisition of data and analyses, drafting the article (text and figures), final approval of the version to be published.

M. Schlamann: acquisition of data and analyses, drafting the article, final approval of the version to be published.

T. Gasser: substantial contributions to conception and design, acquisition of data, drafting the article, final approval of the version to be published.

M.E. Ladd: data analyses and interpretation, revising the article critically for important intellectual content, final approval of the version to be published.

U. Sure: interpretation of data, revising the article critically for important intellectual content, final approval of the version to be published.

M. Forsting: interpretation of data, revising the article critically for important intellectual content, final approval of the version to be published.

E.R. Gizewski: substantial contributions to conception and design, data analyses and interpretation of data, drafting the article and revising it critically for important intellectual content, final approval of the version to be published.

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