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NMDA-receptor antagonist and morphine decrease CRPS-pain and cerebral pain representation

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ABSTRACT

A combination therapy of morphine with an NMDA-receptor antagonist might be more effective than morphine without a NMDA-receptor antagonist for the relief of neuropathic pain in patients with complex regional pain syndrome (CRPS). In order to test the efficacy of this combination therapy we performed a double-blind randomized placebo-controlled study on patients suffering from CRPS of the upper extremity. We used functional magnetic resonance imaging during movement of the affected and unaffected upper hand before and after a treatment regimen of 49 days that contrasted morphine and an NMDA-receptor antagonist with morphine and placebo. We postulated superior pain relief for the combination therapy and concomitant changes in brain areas associated with nociceptive processing. Only the combination therapy reduced pain at rest and during movement, and disability. After treatment, activation in the contralateral primary somatosensory (cS1) and anterior cingulate cortex was significantly reduced when the affected hand was moved. Pain relief during therapy was related to decreased activation in cS1 and secondary somatosensory cortex (S2). Our data suggest that the combination of morphine with an NMDA-receptor antagonist significantly affects the cerebral processing of nociceptive information in CRPS. The correlation of pain relief and decrease in cortical activity in cS1 and S2 is in accordance with the expected impact of the NMDA-receptor antagonist on cerebral pain processing with emphasis on sensory-discriminative aspects of pain.

1. Introduction

Complex regional pain syndrome (CRPS) affects about 5% of patients after limb trauma [4] and leads to chronic pain in the affected limb, which is usually associated with sensory, motor and autonomic dysfunctions [37]. CRPS is usually categorized as neuropathic pain syndrome with the two sub-groups: type I (no measurable nerve damage) and type II (measurable nerve damage) [3]. However, this differentiation is controversially discussed since it does not reflect pathophysiological findings [11]. It has been shown that central neuroplastic changes involving an alteration of the representation zones in somatosensory and motor cortex are common in CRPS [3]. Despite some advances regarding the aetiology of CRPS, treatment is still difficult and several pharmacological agents (such as gabapentin, *N*-methyl-D-aspartate (NMDA)-receptor antagonists and morphine) failed to show lasting effects [2,29,37]. Several studies reported that neuropathic pain can be beneficially affected by morphine (e.g., phantom limb pain: [16]; diabetic neuropathic pain: [15]). Furthermore, a recent study demonstrated a significant effect of an NMDA-receptor antagonist in chronic CRPS-patients [30]. A combination of morphine with an NMDA-receptor antagonist such as memantine, which is effective in blocking NMDA-receptors on the spinal [7], thalamic [28], and cortical [34] levels, might be a promising approach in the treatment of neuropathic pain. In an animal model of neuropathic pain a significantly higher effect of this combination therapy compared to that of morphine alone was demonstrated by increased vocalization thresholds after mechanical and struggle latencies after thermal stimuli [22]. In humans post-surgical pain was significantly reduced by a combination of an NMDA-receptor antagonist and opioids [17]. This superior effect might be related to additive effects of morphine and an NMDA-receptor antagonist, as described before. Chronicity of pain seems to involve learning and memory

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processes and latest models on neuropathic pain postulate that these might be associated with maladaptive cortical plasticity [12]. In the motor domain plastic change in the primary motor cortex has been associated with the NMDA-receptor. For example, pre-treatment with an NMDA-receptor antagonist decreases motor practice-related plasticity [33]. NMDA-receptor antagonists in combination with morphine can reduce the adaptation to morphine: binding of morphine to the opioid receptor results in a release of protein kinase and lipase P that interact with the NMDA-receptor and can enhance sensitivity to pain [8]. NMDA-receptor antagonists might thus prevent this secondary negative effect of morphine use.

These findings suggest that a combination therapy of morphine and an NMDA-receptor antagonist might be beneficial for neuropathic pain such as CRPS. In order to test the effect of a combination treatment on cerebral changes in fMRI-activation we performed a double-blind placebo-controlled study that contrasted morphine and an NMDA-receptor antagonist with morphine and placebo in patients suffering from CRPS. Given the effect of NMDA-receptor antagonist on cortical reorganization, we postulated that predominantly sensory-discriminative aspects of central pain processing would be affected by the addition of an NMDA-receptor antagonist.

2. Methods

2.1. Subjects

Twenty patients (eight males; mean age 50.90 years (SD 11.67; range 29–65) participated in the study. They were recruited by their attending physician (N.S.) in a traumatology care hospital. Demographic and clinical data of the patients are given in Table 1. Fifteen of the patients were diagnosed as CRPS type I and the other five as CRPS type II because they had nerve lesions as quantified with nerve conduction velocity measurements [33]. A detailed description of the clinical reason for the use of nerve conduction delay is given in Table 1. All patients reported pain and allodynia and some showed oedema, vasomotor instability, sudomotor, colour and temperature changes and a limited range of motion of the affected hand [36]. For inclusion in the study all subjects were required to have a minimum of 6 months pain duration and a pain intensity of at least 3 on a visual analogue scale (VAS, 0 cm = "no pain" to 10 cm = "maximum imaginable pain") in either movement or rest pain. Exclusion criteria were age more than 75 years, left-handedness and contraindications for fMRI. All patients were right handed (as assessed with the Edinburgh Handedness Inventory), 12 had their dominant hand affected and the other eight the non-dominant hand. The neurological examination yielded no motor impairment in any of the patients. The first symptoms of CRPS had been diagnosed on average 16.00 months (SD = 10.33) before inclusion in the study. All patients met the current IASP diagnostic criteria for CRPS [32]. Informed consent was obtained from all patients.

2.2. Medication

All patients on medication had a minimum wash out period of 2 days. Morphine medication was provided for 56 days three times a day. From day 1 to day 5 oral intake of morphine was increased from 10 to 30 mg and kept constant for an additional 51 days. Starting on day 8 memantine (in 10 patients) or placebo (in another 10 patients) was added orally for a total of 49 days (Fig. 1). Memantine was titrated from 5 to 40 mg over 15 days and maintained at 40 mg for another 34 days in order to minimize the side effects due to the combination therapy. The treating pain specialist and the investigators were blinded as to whether an NMDA-receptor antagonist or a placebo was applied. The medication was randomized and counterbalanced by the pharmacy of the hospital who supplied the medication. The patients were not allowed to remain on other analgesic medication during the study and did not use additional medication on demand. Memantine is a non-competitive antagonist of glutamate and other excitatory amino acids at the MK-801-binding site of the NMDA-receptor [5]. We used this type of NMDA-receptor antagonist since memantine displays the lowest number of side effects [24] but has been shown to be at least as effective as ketamine or dextromethorphan in animal

Table 1
Demographic and clinical data at baseline and after therapy.

Gender	CRPS-type	Age [years]	Duration of CRPS [months]	Hand[a]	Group[b]	Oedema[c]	Hair growth[c]	Pre-rest pain [VAS]	Post-rest pain [VAS]	Pre-move pain [VAS][d]	Post-move pain [VAS][d]
Male	I	49	20	r	v	0	+	5.49	3.05	5.47	0
Male	I	59	6	l	v	+	+	6.33	0	8.30	0
Female	I	30	12	r	v	+	+	8.51	4.58	10.00	6.67
Female	II[e]	50	26	l	v	0	0	7.67	0	9.8	0
Male	I	29	7	r	v	0	+	0	0	2.98	1.99
Male	I	65	14	l	v	+	+	3.99	2.21	7.91	3.02
Female	I	58	7	r	v	+	+	5.51	1.16	8.46	4.32
Male	I	54	14	l	v	+	+	6.10	3.05	10.00	4.02
Female	I	57	16	r	v	0	+	4.07	0	8.12	1.15
Female	I	69	34	r	v	0	–	7.10	0	8.04	0
Male	II[f]	57	6	l	p	+	0	4.21	0	2.64	2.04
Female	II[e]	50	26	l	p	0	–	7.79	8.21	8.88	10.00
Female	I	44	8	r	p	0	–	8.01	7.79	6.10	5.81
Female	I	68	6	r	p	+	+	9.87	4.22	8.10	8.10
Female	I	37	6	r	p	+	+	8.99	3.35	9.42	4.98
Female	II[f]	62	29	l	p	+	+	7.57	8.55	7.04	9.74
Male	I	55	8	r	p	0	0	4.06	0.88	5.04	1.90
Male	II[g]	44	10	l	p	0	–	4.48	1.00	4.00	4.00
Female	II[f]	40	36	r	p	0	+	5.55	5.55	7.10	6.05
Female	I	41	29	r	p	0	–	7.10	7.10	6.45	5.35

[a] Hand affected (r, right; l, left).
[b] Therapy group: v, morphine + NMDA-receptor antagonist; p, morphine and placebo.
[c] Oedema: + present; 0 not present; hair growth: +, increased; –, decreased; 0, normal.
[d] Move, movement pain;
[e] Ulnaris injury after surgical intervention (CTS, fracture).
[f] Median nerve injury after flexor tendon surgical intervention.
[g] Radial nerve injury after radius fracture.

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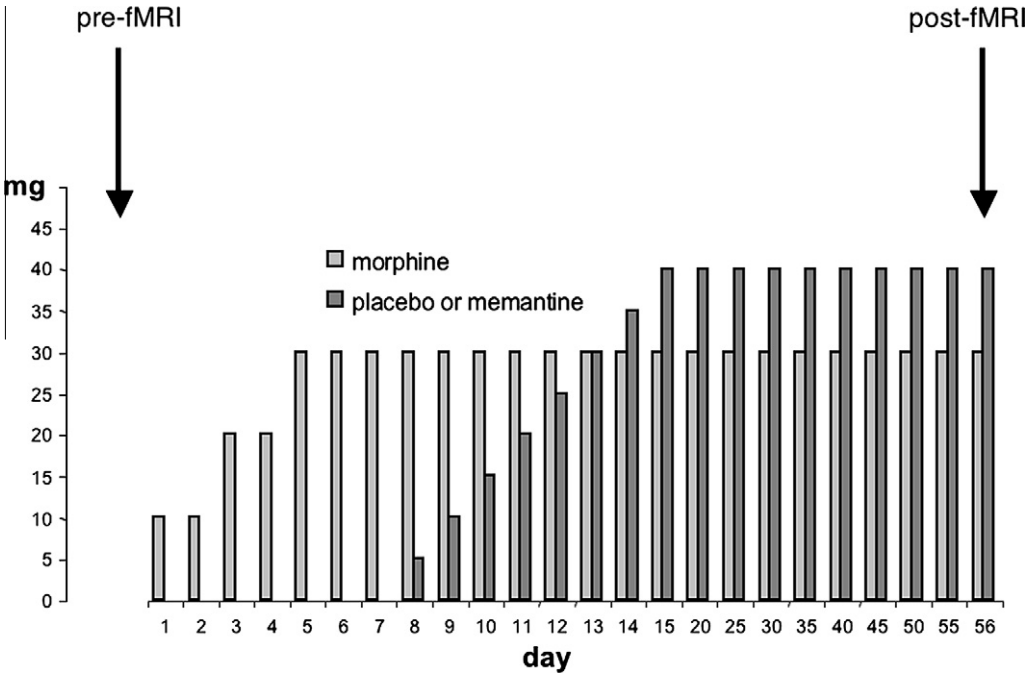

Fig. 1. Schedule of the treatment and dose of medication. fMRI was performed before and after the beginning of medication treatment. Memantine or placebo was titrated after morphine medication had reached the amount of 30 mg per day after 7 days.

experiments [5]. In both treatment groups equal amounts of daily standard physiotherapy were provided following a standardized regimen [18]. This included manual physiotherapy (e.g., traction, compression, massage, and wrist mobilization), manual lymphatic drainage, balneophysical therapy (e.g., electrotherapy and connective tissue massage), and occupational therapy. Importantly, at no stage was the physiotherapy regime permitted to increase the subjects' on-going pain.

For the evaluation of the effects of the combination therapy of morphine with the NMDA-receptor antagonist memantine against the effect of morphine alone we used a double-blinded placebo-controlled design. We chose this comparison based on the previous work that the addition of an NMDA-receptor antagonist might enhance the effects of morphine. Although additional control groups would have been useful, our limited time and economic resources did not permit a full factorial design. For this reason we also included both CRPS types I and II, although there might be differential effects for the two groups. Twenty-six patients were assessed for eligibility, two refused to participate and three did not meet inclusion criteria. Eleven patients were allocated to the intervention placebo and morphine and 10 to morphine and memantine. One person of the placebo group discontinued the intervention. Ten patients of each medication group were analyzed to determine the treatment effects. There were no conflicting interests of the authors. The study was approved by the Ethics Committee of the Medical Faculty of the University of Tübingen.

2.3. Movement task in the fMRI

The patients were investigated in the magnetic resonance (MR) scanner during the baseline condition and after 56 days of treatment. They had to clench the fist of the affected and unaffected hand separately (auditorily paced and trained before scanning, average frequency 0.36 Hz) using a block design. Each block had duration of 3.25 min alternating between activation and rest. To ensure equal hand-grip strength during the pre- and post-measurement, the patient pressed a rubber ball attached to a vigorimeter and trained until constant performance was achieved using visual feedback prior to scanning. Grip force was continuously recorded during functional magnetic resonance imaging (fMRI) and the patients were again trained via feedback in the post-treatment session to perform the movement with the same force and frequency as during the pre-measurement. Three patients of the placebo group and one of the group with NMDA-receptor antagonist medication showed considerable differences in their performance between the pre- and post-measurement (more than 0.5 bar in movement strength and/or more than 0.5 Hz in movement frequency with their affected hand) or strong accompanying head movements (more than 2 mm and/or 2° rotation) and had to be excluded from the fMRI-analysis. For two other patients of the verum group the performance data were not recorded due to technical failure and they were therefore excluded from fMRI-analysis. The remaining 14 patients (seven in each treatment group) showed no differential motor performance between the baseline and post-measurement (placebo: Wilcoxon $z = 0.86$; n.s.; NMDA-receptor antagonist: Wilcoxon $z = 1.56$; n.s.).

2.4. FMRI imaging

We performed echo planar images of the whole head (EPI; 30 axial slices, 3 mm thickness, 1 mm gap; TR = 2.5 s, matrix size = 64∗64, TE = 30 ms, flip angle = 90°) for six times per condition using a 3 Tesla scanner (Siemens Trio, 8 HF-head-coil). A T1-weighted data set (MPRAGE; 160 sagittal slices 1∗1∗1 mm; TR 2.3 s; TE: 3.93 ms) was used for anatomical reference and for improvement of normalization. The subjects were in supine position on the padded scanner couch and wore hearing protection.

2.5. Processing of the fMRI data

Spatial pre-processing and data analysis were performed with SPM2 (Wellcome Department of Imaging Neuroscience, London). Each time series was realigned and resliced after unwarping in phase-encoding direction (anterior/posterior) to account for susceptibility artefacts in mesolimbic areas and movement artefacts. Unwarping of geometrically distorted EPIs was performed using

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the FieldMap Toolbox (from Chloe Hutton, Jesper Andersson) available for SPM2. Images were normalized to the MNI-reference to provide a standardized location of activation maxima and to compare the pre- and post-measurement within the same voxel space. During normalization all patients with affected left side were flipped along the *x*-axis. Therefore the affected hand was always considered as the right hand and the left hemisphere was contralateral to the movement of the affected hand. To correct for intensity inhomogenities EPIs were smoothed with a Gaussian filter of 14 mm (full width at half maximum). Data were high-pass (cut off 128 s) and low-pass filtered (autoregression model AR(1)). For the second level analysis we used random effects statistics. First level contrasts of the time points "pre", "post" and "pre minus post" for the conditions movement of the affected hand and movement of the unaffected hand were used for the second level analysis of within- and between-subject group effects. We performed statistics in regions of interest (ROIs) relevant for pain processing, which included bilateral primary (S1) and secondary (S2) somatosensory cortices, the bilateral insula and the cingulate cortex (CC) [1]. Masks for these ROIs were preselected anatomically (with the "Automated Anatomical Labelling" software; AAL [35]) or using cytoarchitectonic masks (with at least 50% probability; ANATOMY [10]). We corrected for multiple comparisons between areas and hemispheres using an uncorrected *p*-value of 0.007 corresponding to a corrected $p < 0.05$ (Bonferroni correction) within the seven ROIs. Plotted *t*-values refer pre- and post-effects within the highest activated voxel for the given ROI. Coordinates are given for the MNI-system. Pain intensity was correlated with activation magnitude in the ROIs. Correlation analysis were plotted for the highest activated voxel for differences between the pre- and the post-measurement of each subject during movement of the affected hand together with differences in individual pain ratings (Fig. 4C).

2.6. Ratings

Pain intensity during rest (habitual pain) was assessed in a paper and pencil diary three times a day over the period of 8 weeks using a visual analogue scale (VAS; range: no pain to unbearable pain; transformed to a scale from 0 to 10). These data were averaged per day and an average value for the baseline (5 days before therapy onset) and post-measurement (averaged over the last 5 days of the fully dosed combination therapy) was calculated. The time course of the pain ratings over the time of medication is plotted in Fig. 3. The pain following standardized clenching and extension of the fist was classified as movement pain (acute; documented grip strength). In the same diary side effects such as fatigue, drowsiness, dizziness, headache, nausea/vomiting, akathisia, anxiety and hallucinations were assessed on a 3-point scale [none (1); moderate (2); strong (3)] once a day. The side effect ratings were also averaged per day and an average value for the baseline and post-measurement was calculated for the side effect scales. According to the standards for clinical trials on chronic pain [9] we employed additional questionnaires testing mood (Center for Epidemiologic Studies Depression Scale [27]) and disability (Pain Disability Index [26]). For the ratings, we performed a repeated measures analysis of variance (ANOVA) for the

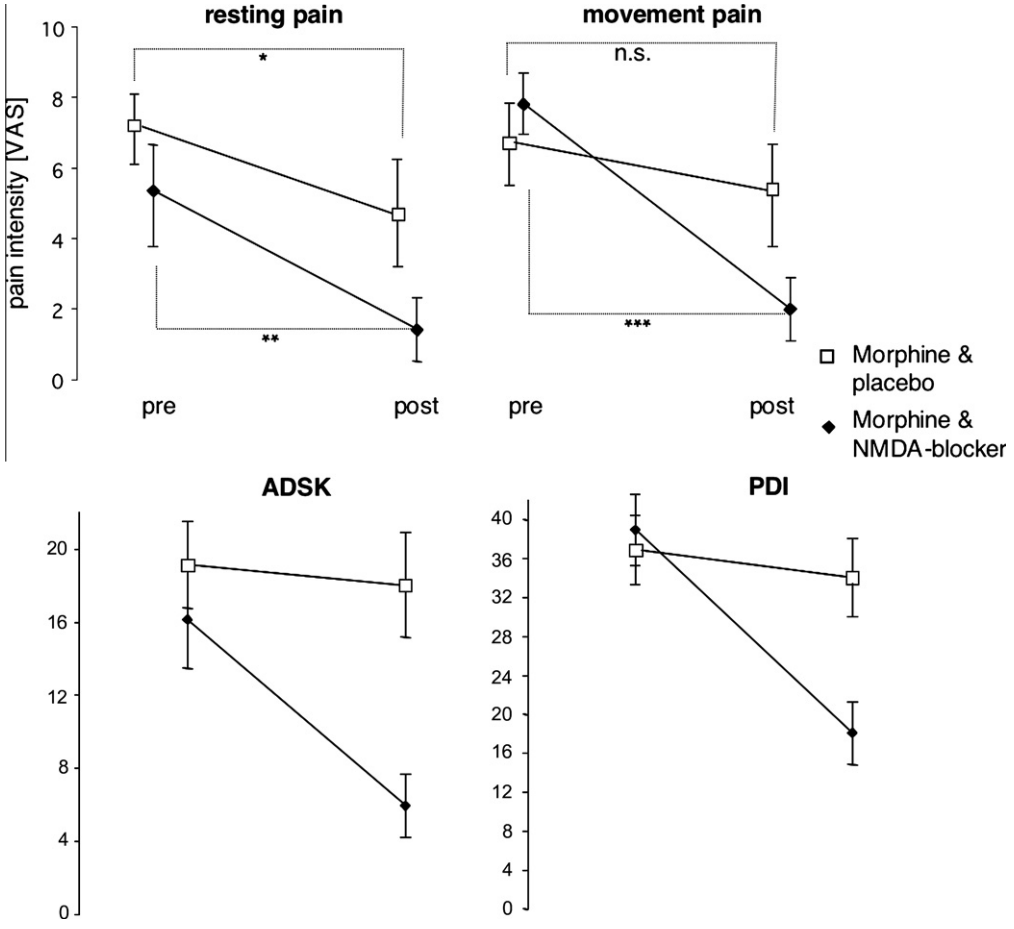

Fig. 2. Pain scores before and after therapy. Rest pain (habitual) and movement pain (acute) as tested with a visual analogue sale (VAS), mood (CESD; Center for epidemiologic studies depression scale) and disability score (pain disability index) for both treatment groups before (pre) and after (post) therapy. Bars indicate standard errors; stars indicate significant differences (***$p < 0.001$; **$p < 0.005$: *$p < 0.05$).

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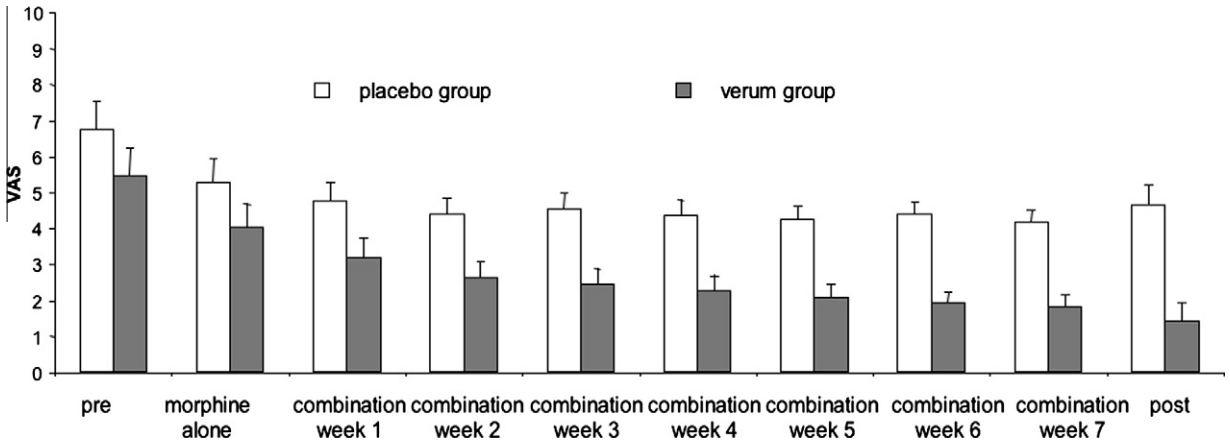

Fig. 3. Mean daily visual analogue scale scores (VAS) for resting pain from the pain diary ratings averaged over all subjects per treatment group. Lines over bars indicate standard errors of the means.

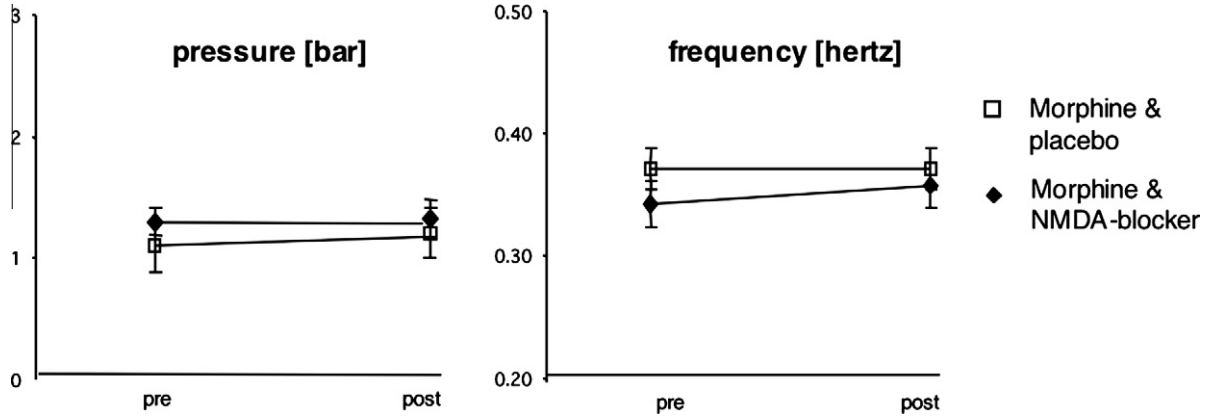

Fig. 4. Performance measures during fMRI-scanning. Performance measures during fMRI-scanning for pressure of the affected fist (left) and frequency of movement (right) separately for the placebo and verum groups during the pre- and post-measurement. Bars indicate standard errors.

within-factor TIME (baseline versus post-therapy) and the between-factor MEDICATION (memantine versus placebo). Post-hoc *t*-tests were corrected for multiple comparisons using a Bonferroni correction and statistics were calculated using SPSS; Version 16.0.

3. Results

3.1. Scores and performance

The ANOVA resulted in a significant interaction of MEDICATION and TIME for both habitual ($F(1, 18) = 3.08$; $p < 0.05$) and movement pain ($F(1, 18) = 15.94$; $p < 0.001$). Post-hoc comparisons showed a significant decrease of pain for the combination therapy of morphine and the NMDA-receptor antagonist (habitual pain: from 5.47 to 1.40; $t(9) = 5.31$; $p < 0.001$; movement pain: from 8.03 to 2.84; $t(9) = 5.73$; $p < 0.001$) and a less pronounced significant effect for the morphine plus placebo treatment for habitual (from 6.76 to 4.66; $t(9) = 2.55$; $p < 0.05$) but not movement pain (from 6.56 to 5.91; $t(9) = 0.94$; n.s.; see Fig. 2, top). Motor performance of the patients included in the fMRI-group analysis did not differ between the pre- and post-measurement (see Fig. 4). The ANOVA also revealed a significant effect for the interaction of MEDICATION and TIME for both mood ($F(1, 18) = 9.17$; $p < 0.01$) and disability ($F(1, 18) = 7.70$; $p < 0.05$). Post-hoc *t*-tests showed no significant effect on mood and disability for the placebo group ($t(9) < 0.90$; n.s.) but a significant improvement in mood ($t(9) = 5.08$; $p < 0.001$) and a significant decrease in disability ($t(9) = 3.66$; $p < 0.005$) for the combination treatment group (see Fig. 2, bottom). There were no significant differences between the pre- and post-measurement of any side effect in each treatment group and also not between treatment groups. After either pharmacological interventions the median of the side effects was 2 (small) for fatigue, and 1 (none) for drowsiness, nausea, akathasia and anxiety. Vertigo and head pain were rated 2 for the NMDA-receptor antagonist group and 1 for the placebo group. Additionally, the therapy groups showed the same median for all side effects assessed in the first week of morphine therapy without comedication. The time course of the pain ratings over the time of medication is plotted in Fig. 3.

3.2. fMRI-activation

During baseline all patients showed activity in pain-associated brain areas during movement of the affected hand (bilateral S1, S2, anterior insula, cingulate cortex; for details see Table 2) together with motor activity. In contrast, during movement of the healthy hand, only brain regions associated with motor function were active (contralateral sensorimotor cortex, premotor cortex and ipsilateral cerebellar hemisphere). In the pre- and post-comparison the morphine and placebo group showed a differential activation in the ACC ($t = 4.09$; coordinates: 9, 45, 3). The combination therapy with memantine resulted in decreased activation in contralateral S1 ($t = 6.23$; coordinates: −33, −45, 75) and ACC

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Table 2
Main effects in fMRI for baseline for all patients; movement of the affected hand.

Area	Brodman area	*t*-value	*x*	*y*	*z*
Ipsilateral primary somatosensory cortex (iS1)	1, 2, 3	6.95	48	−39	66
Contralateral S1 (cS1)	1, 2, 3	6.31	−66	−21	27
Contralateral secondary somatosensory (S2)	OP 1,2,3	5.95	−66	−21	30
Ipsilateral S2	OP 1,2,3	5.29	63	−24	48
Contralateral anterior insula	13	5.12	−60	9	−3
Ipsilateral anterior insula	13	4.55	60	15	−9
Cingulate cortex (CC)	24	3.84	0	−6	48
Differential effects between the pre-minus post-measurement of the memantine group					
Contralateral S1 (cS1)	1, 2, 3	6.31	−33	−45	75
Anterior cingulate cortex (CC)	24	4.70	−6	54	0
Differential effects between the memantine minus p combination group for the pre-minus post-comparison					
Contralateral S1 (cS1)	1, 2, 3	3.54	−39	−42	72

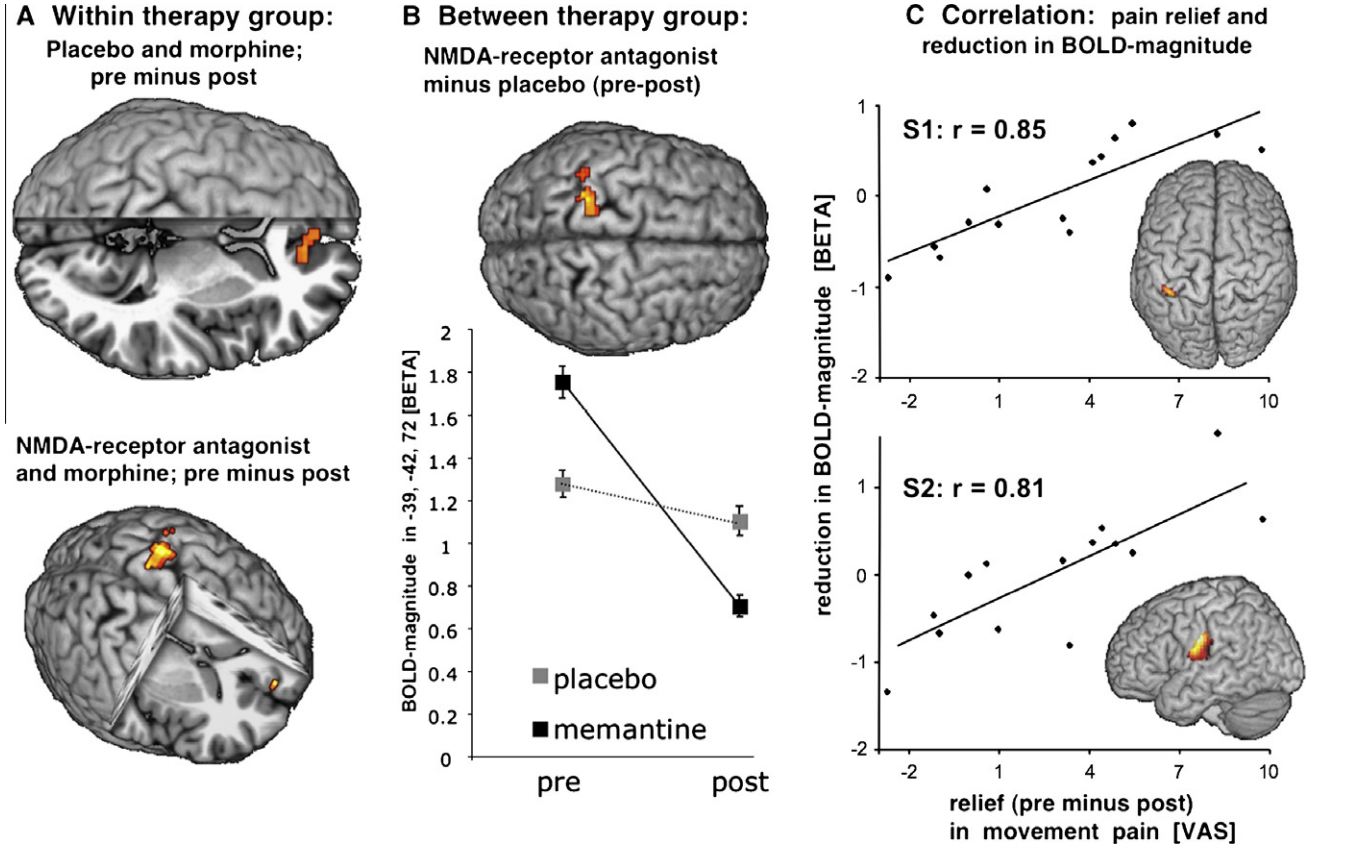

Fig. 5. fMRI results. (A) Within-group contrast before minus after therapy. Patients who received a combination of morphine with placebo showed only significant differences in ACC activation between the pre- and post-measurement (top), whereas those who received the NMDA-receptor antagonist together with morphine (MST) showed decreased activation in S1 and ACC after therapy (bottom). (B) Between group results: The same area was active when the post-measurement contrasts for movement of the affected hand between the combination and the placebo group (top) were compared. BOLD-magnitude within the highest activated voxel of this contrast (cS1: −39; −42; 72) decreased between pre- and post-measurement for the combination therapy with memantine but remained stable for the therapy of opioids with placebo (bottom). (C) Correlation analysis between decrease of pain and changes in BOLD-magnitude: Decreases in pain ratings correlated significantly with activation decreases in cS1 (coordinates: −39; −45; 69; $t = 4.88$; $p < 0.05$; top) and cS2 (coordinates: −60; −12; 21; $t = 3.84$; $p < 0.05$; bottom).

($t = 4$, 70: coordinates: −6, 54, 0; see Table 2; Fig. 5A). The direct comparison between groups (combination therapy pre- and post-minus placebo pre-post) revealed a pronounced decrease of the BOLD-magnitude after treatment for the combination therapy only in contralateral S1 ($t = 3.54$; $p < 0.05$; coordinates: −39; −42; 72; Table 2; Fig. 5B). A post- and pre-comparison showed no significant results. Decreases in BOLD-magnitude in S1 ($r = 0.85$; $t = 4.88$; coordinates: −39; −45: 69; $p < 0.05$) and S2 ($r = 0.81$; $t = 3.84$; coordinates: −60; −12: 21; $p < 0.05$) correlated positively with the decrease of movement pain (Fig. 5C). There was no significant correlation between the duration of CRPS and the pain increase/decrease for both rest pain and movement pain.

4. Discussion

In the present study, the combination of morphine with an NMDA-receptor antagonist led to a significant reduction in pain of the affected limb both during rest and movement in patients with long-standing CRPS and also positively influenced mood and disability.

Previous studies of acute post-operative pain showed promising effects for the combination of an NMDA-receptor-antagonist and opioids [17]. Additionally, a combination of NMDA-receptor blocker with a brachial plexus blockade early after traumatic upper limb amputation revealed beneficial effects on the intensity of chronic

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neuropathic pain processes such as phantom limb pain [6]. Since we did not observe a decrease of pain relief in our placebo group in the course of treatment the beneficial effect of NMDA-receptor antagonist combination with morphine is probably not caused by an antinociceptive tolerance of morphine.

In a multi-center study [14] a combination of morphine sulfate with dextrometorphan hydrobromide showed no additional effect for the relief of chronic pain compared to morphine without the comedication. We assume that the less pronounced effects of the combination therapy might have been caused by the use of an NMDA-receptor antagonist with high side effects and/or differences in the titration of the dosage. In the present study, we used memantine, which shows less side effects than other NMDA-receptor-antagonists. Furthermore, we used a very careful titration protocol until we reached full dosage. By doing this, all patients tolerated the synergistic of morphine and the NMDA-receptor antagonist over the entire time period of the study.

Before treatment, movement of the affected limb resulted in the activation of regions commonly known to be involved in pain processing in CRPS-patients (Table 2; [20,31]). The combination treatment led to a decrease of cerebral activation in cS1 but also in the anterior cingulate cortex (ACC). Activation in the ACC is present both during pain and emotional processing and activation in this area during pain processing is highly associated with the affective dimension of pain. Since the activation change in the ACC was not specific to the NMDA-receptor antagonist medication, but was also present after medication with morphine and placebo, we assume that cS1 and S2, and thus more somatosensory-discriminative aspects of pain, are predominantly associated with the NMDA-receptor antagonist effect in CRPS. Additionally, BOLD-magnitude changes in contralateral S1 and S2 were positively correlated with changes in pain ratings. Pain reduction associated changes in cS1 and S2 have already been described in CRPS-patients [21,25] and our data support the importance of activation reduction in these cortical areas in CRPS. Furthermore, our data underline findings on altered sensorimotor interaction in CRPS-patients described recently [19].

In a recent study, investigating the effect of different dosage of morphine on pain perception in healthy subjects, it has been demonstrated that sensory-discriminative areas in S1, S2 and the posterior insula show a linear decrease of activation in response to morphine concentration, whereas parahippocampal regions, the amygdala and the anterior insula show an on–off phenomena reacting very strongly to any morphine treatment [23].

Interestingly, the effect of the NMDA-receptor antagonist was more pronounced for movement (acute) than resting (habitual) pain. It is possible that morphine has some analgesic effect on pain at rest but that movement-related pain, which is of higher intensity, may not be sufficiently reduced. This added pain might have been reduced by the combination treatment. Moreover, the reduction of pain during movement was highly negatively correlated with BOLD-magnitude in areas related to sensory-discriminative aspects of pain. This reduction of movement pain is especially important for activities of daily living, a fact underlined by the significant improvement of disability ratings of the patients after memantine and opioid combination therapy. However, our study cannot determine the location of the effects of the NMDA-receptor antagonist, which can be central but could also be related to peripheral factors.

Patients who experienced the combination therapy with an NMDA-receptor antagonist showed an improvement of mood during therapy. Memantine in contrast to morphine has no effect on mood, attention and memory [29]. However, the effect on mood observed in our study does not necessarily be related to a decreased tolerance to morphine induced by the NMDA-receptor blocker but might simply be related to the relief of pain.

Overall, the analgesic benefits of opioids can be hypothesized to be related to their effects on both the sensory-discriminative and affective dimensions of pain, but the analgesic effects of NMDA-receptor blockers can be hypothesized to be primarily associated with the effects on the sensory-discriminative component.

Although there were no significant differences between the therapy groups with respect to side effects, vertigo and head pain tended to be more severe under the memantine-combination medication. This trend illustrates that the use of a combination therapy necessitates the careful dosage of both drugs.

It is highly important in follow-up measurements using functional imaging that the performance of the subjects is precisely controlled for, in order to avoid performance-related differences between the pre- and post-measurement. In this study, we carefully controlled for these effects. However, this procedure resulted in a loss of statistic power since we had to exclude a considerable amount of patients investigated.

There are some important limitations of the study. The small sample size might be a reason for observing only peaks of activation differing between subject groups. In fact a larger network might be involved. Furthermore, we treated a quite heterogeneous sample with respect to potential pathophysiology, including both types of CRPS, both sexes and varying pain duration. Additionally, more CRPS-patients with type II, due to the randomisation process, might have biased the effect described. Furthermore, we did not include a memantine alone group, and we therefore cannot determine whether the effects observed are due to memantine alone or to the combination with morphine. We cannot restrict the effect of the NMDA-receptor antagonist on the cortical level, since we did not include a group of subjects with peripheral nerve blockade. The dosage of the morphine medication was quite low in order to avoid side effects [13], which might be potentiated by a combination therapy. Therefore a morphine alone effect might have been larger for a higher dosage. Finally, we did not evaluate long-term effects after the therapy period.

Despite these limitations, our data suggest that a combination of morphine with an NMDA-receptor antagonist is more effective for the therapy of neuropathic pain after chronic CRPS than morphine alone. This increased effect on pain relief is associated with decreased activation in cS1 and S2 pointing to a predominant effect of the combination therapy on areas processing sensory-discriminative aspects of pain processing. Future research should examine larger homogeneous samples of CRPS type 1 or 2.

Conflict of interest

The authors declare that they do not have any conflicts of interests.

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