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Association of Neglect-Like Symptoms with Anxiety, Somatization, and Depersonalization in Complex Regional Pain Syndrome

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Abstract

Background. Many patients with complex regional pain syndrome (CRPS) report some foreignness of the affected limb, which is referred to as "neglect-like symptoms" (NLS). Despite similarities of the NLS reports to symptoms of body image disturbances in mental disorders, no study has been conducted to examine such associations.

Methods. We investigated 50 patients with CRPS and 45 pain control patients (N = 27, chronic limb pain; N = 18, migraine headache). NLS, anxiety, depression, depersonalization, and somatization were assessed using validated questionnaires.

Results. Seventy-two percent of the CRPS patients reported at least one NLS vs 29.6% and 33.3% in the two patient control groups. In limb pain controls, NLS correlated with pain intensity. In CRPS patients, NLS correlated with anxiety (rho = 0.658, $P < 0.001$), somatization (rho = 0.616, $P < 0.001$), depersonalization (rho = 0.634, $P < 0.001$), and pain catastrophizing (rho = 0.456, $P < 0.01$), but not with intensity of pain, duration of pain, or pain disability.

Conclusions. In CRPS patients, NLS could be a result of somatization, depression, anxiety, and depersonalization, but probably not of pain. Whether these associations are causative must be clarified in longitudinal psychological studies.

Key Words. CRPS; Pain Disorder; Psychology; Neglect

Introduction

Complex regional pain syndrome (CRPS) is characterized by severe pain and autonomic, sensory, and motor symptoms. In CRPS patients, so-called "neglect-like symptoms" (NLS) are common [1]. NLS include attention focused on the limb, limb detachments, involuntary movements and motor control, and "dead" feelings about the limb [2]. A large study compared NLS in CRPS patients to a matched pain control group and revealed that the NLS were occurring in both groups, but the incidence rate and the severity was about one-third higher in the CRPS group [3]. The biological cause and the descriptors of NLS are different from neglect in the neurological sense, which is prevalent, for example, in right-sided stroke [4]. In general, the incidence and severity of NLS in CRPS increases with longer disease duration [4].

Reorganization of the central nervous system in CRPS is considered to be one cause of NLS [5]. In a whole series of papers, several groups (including our own) found that shrinkage of the primary somatosensory cortex supplying the affected limb [6], exaggerated brain responses to brushing (allodynia), reduction of laser-evoked potentials as surrogates for sensory loss, and indications for impairment of motor control of CRPS limbs (for review, see [7]). However, it is still not shown that these findings cause NLS. Rather, they could also be the consequences of CRPS itself (maladaptive learning and related brain plasticity) [8]. New results indicate that the driving force behind maladaptive learning may be altered corticolimbic circuit response in fear perception, which is driven or maintained by pain-related fear, as demonstrated by functional MRI [9].

Recent data revealed that CRPS patients had a mismatch between the sensation of the affected limb and how it looked. Hostile feelings about the affected limb were frequently reported, as were different degrees of detachment of the affected limb from the rest of the body [10]. Such descriptions are strongly reminiscent of narratives about body perception disturbances in persons with depersonalization. Depersonalization is a common phenomenon, referring to experiences of emotional detachment and disembodiment [11]. The lifetime prevalence of transient symptoms of depersonalization without indicating a disease is high in the general population. However, severe depersonalization occurs frequently in patients with anxiety and depressive disorders [12], but also in somatic conditions such as vertigo [13], migraine [14], and epilepsy [15]. Interestingly, a small study reported that 21% of chronic pain patients endorsed clinically significant depersonalization [16], and a large epidemiologic survey found a substantial association between depersonalization and chronic pain (odds ratio = ~3) [17].

The aim of the present study was therefore to analyze whether NLS in CRPS might be related to depersonalization, but also to pain, disability, and other psychological symptoms like depression, anxiety, and somatization. These complex behaviors might be part of cognitive dysfunction in CRPS like in other chronic pain disorders. Adequate controls should indicate a specificity of our findings for CRPS.

Methods

The study was approved by the ethics committee of the State Board of Physicians of Rhineland-Palatinate (Germany). All participants provided their written informed consent.

Patients and Controls

The sample consisted of 50 patients with CRPS and 45 patients with other pain syndromes (27 limb pain syndromes of non-CRPS origin and 18 migraine headache patients [migraine without aura according to the international headache society definition] without limb pain). Patients were recruited from the pain clinic of the Department of Neurology of the University Medical Center Mainz. CRPS was diagnosed according to the current IASP criteria for scientific studies [18]. CRPS afflicted the following body parts: right arm/hand, 38% (N = 19); left arm/hand, 38% (N = 19); right leg/foot, 14% (N = 7); left leg/foot, 10% (N = 5). The vast majority of the patients had CRPS-I (94%, N = 47). Seventy-eight percent (N = 39) had primarily warm CRPS. Further clinical characteristics are shown in Table 1.

Questionnaires

Neglect-like symptoms (NLS) were assessed by the questionnaire from Frettlöh et al. [3]. Frettlöh et al. modified the original instrument of Galer and Jensen [2] by using a six-point Likert scale (range: 1 = never to 6 = always) to record the severity of five symptoms [3]. The NLS total score is the arithmetic mean of the five items.

The pain disability index (PDI) was applied to measure the impairment by pain with regard to seven essential everyday activities, for example, family and home responsibilities, activities partly or directly related to work, and frequency and quality of sex life [19]. Scores may range from 0 (no impairment) to 70 (complete disability in all life activities).

Patients rated the intensity of their pain "right now" and their average pain intensity over the previous four weeks on a numerical rating scale (NRS; range: 0 = no pain to 10 = worst imaginable pain).

Patients' cognitive coping with pain was assessed with the Pain-Related Self Statements Scale (PRSS) [20,21]. The PRSS consists of two subscales: Catastrophizing, which includes statements such as "...cannot stand pain," "...pain drives me crazy," and "...need medication"; whereas the Coping subscale covers thoughts such as "...can help myself," "...will soon be better," and "...must relax" [20,21]. Statements are rated on a six-point scale from 0 (= almost never) to 5 (= almost always). Higher mean scores represent more frequent occurrence of the pain-related attitude.

Depression, anxiety, and somatoform symptoms were measured with the corresponding modules of the Patient Health Questionnaire (PHQ). The depression module, PHQ-9, assesses the severity of depression. The nine items on the scale represent the diagnostic criteria of major depression. The items are rated on a four-point Likert scale for the previous two weeks (0 = not at all, 1 = several days, 2 = more than half the days, 3 = nearly every day). A PHQ-9 sum score of 10 or higher was defined as significant for depression [22]. Anxiety was assessed with the generalized anxiety disorder module (GAD-7). The response format is the same as that in the PHQ-9. A sum score of 10 or higher is regarded as the threshold for clinical significant anxiety [23]. Somatoform symptoms were assessed with the

Table 1 Sample characteristics stratified for CRPS patients vs patient controls

	CRPS (N = 50)	Limb pain (N = 27)	Migraine headache (N = 18)		U-test CRPS vs limb pain
Age, y, mean ± SD	51.4 ± 14.7	55.6 ± 11.3	51.3 ± 20.8	ns	ns
Sex, women, % (N)	74 (37)	55.6 (15)	61.1 (11)	ns	ns
Years of school, mean ± SD	10.4 ± 1.6	10.5 ± 1.7	11.3 ± 1.8	ns	ns
Living in a partnership, % (N)	78 (39)	92.6 (25)	77.8 (14)	ns	ns
NRS pain, average 4 wks, mean ± SD	5.7 ± 1.8	5.1 ± 2.3	4.5 ± 2.1	ns	ns
NRS Pain, right now, mean ± SD	4.9 ± 2.3	4.3 ± 3.1	*1.9 ± 2.1*	P ≤ *0.0001*	ns
Number of body parts affected with pain, mean ± SD	1.8 ± 1.3	2.2 ± 1.6	1.4 ± 0.98	ns	ns
Duration since onset of pain, d, mean ± SD	**272 ± 262**	**1989 ± 3080**	*4746 ± 5173*	***P* < 0.0001**	***P* < 0.0001**
Pain Disability Index (PDI), mean ± SD	**38.0 ± 13.1**	**25.7 ± 14.9**	**24.7 ± 17.8**	***P* = 0.001**	***P* = 0.001**
PRSS: Cognition, mean ± SD	2.9 ± 0.85	2.6 ± 0.92	2.9 ± 0.9	ns	ns
PRSS: Catastrophizing, mean ± SD	2.1 ± 1.2	1.9 ± 1.3	2.6 ± 1.6	ns	ns

Data are presented as mean ± standard deviation or percentage (numbers); Kruskal-Wallis test for continuous variables, Chi-square test for categorical variables. Bold print denotes significant differences. Post hoc Mann-Whitney U-tests were performed to compare CRPS and limb pain controls. Migraine is an episodic disease. Therefore, "pain right now" and "duration since onset of pain," which are indicated in italic letters for migraine patients, cannot be compared with the values of CRPS or limb pain. Bonferroni threshold would be $P = 0.004$. CRPS = complex regional pain syndrome; ns = not significant.

PHQ-15. The PHQ-15 measures somatic symptoms that account for more than 90% of symptoms seen in primary care. Patients rate how much they have been bothered by each somatic symptom during the past month on a three-point Likert scale, from 0 (= not at all) to 2 (= bothered a lot) [23]. A recent study demonstrated that patients scoring 9 or higher were most likely to suffer from a somatoform disorder [24]. Based on this report and previous studies, we set 10 as the cut point for clinically significant somatization.

Social anxiety was assessed with the three-item Mini-Social Phobia Inventory (Mini-SPIN). Using a cutoff score of 6 or greater, the Mini-SPIN demonstrated a sensitivity of 88.7% and a specificity of 90.0% for the identification of social anxiety disorder [25].

Symptoms of depersonalization were measured with the Cambridge Depersonalization Scale (CDS) [11]. The CDS consists of 29 items and measures frequency and duration of depersonalization over the last six months. Scores range from 0 to 290. Scores above 65 were determined to be clinically significant depersonalization in the German validation study [26].

Statistical Analysis

Data are presented as means ± standard deviation, or percentages (%) and numbers (N). As not all variables satisfied a normal distribution, nonparametric procedures were applied. The Kruskal-Wallis test was used to test for different distributions of continuous variables between the three groups, and the Mann-Whitney U-test for a post hoc comparison between the groups. Spearman rank order correlation coefficients were calculated for analyzing relationships between NLS with clinical variables (pain intensity, pain disability, duration of pain, symptoms of mental disorders, and PRSS). Correlations were calculated separately for the three groups of pain patients. A two-sided significance threshold of $\alpha = 0.05$ was defined a priori. Categorical variables were compared by the chi-square test. As our analysis was explorative, no correction for multiple comparisons was applied in general. However, the majority of comparisons withheld Bonferroni correction, as indicated in the different legends.

Results

Demographic and Pain Characteristics

CRPS patients were comparable with both control groups regarding gender, age, education, social status, general pain coping strategies (PRSS cognition and Catastrophizing), and average pain during the last four weeks, indicating that the control groups are valid. The Kruskal-Wallis test revealed a difference between groups regarding "pain right now." However, post hoc

Table 2 Occurrence of neglect-like symptoms: Differences between CRPS patients and (a) both groups of patient controls and (b) only the limb pain patients

	CRPS (N = 50)	Limb pain (N = 27)	Migraine headache (N = 18)		CRPS vs limb pain
NLS scale, severity, mean ± SD	**2.4 ± 1.2**	**1.9 ± 1.4**	1.3 ± 0.5	***P* < 0.0001**	***P* < 0.005**
Item 1: If I didn't focus my attention on my painful limb, it would lie still like dead weight, % (N)	**52 (26)**	**22.2 (6)**	16.7 (3)	***P* < 0.0001**	***P* < 0.02**
Item 2: My painful limb feels as though it is not part of the rest of my body, % (N)	**72 (36)**	**22.2 (6)**	16.7 (3)	***P* < 0.0001**	***P* < 0.0001**
Item3: I need to focus all of my attention on my painful limb to make it move the way I want it to, % (N)	**64 (32)**	**33.3 (9)**	22.2 (4)	***P* = 0.002**	***P* < 0.02**
Item 4: My painful limb sometimes moves involuntarily, without my control, % (N)	30 (15)	18.5 (5)	5.6 (1)	Ns	ns
Item 5: My painful limb feels dead to me, % (N)	36 (18)	37 (10)	(0)	P < *0.02*	ns

Data are presented as mean ± standard deviation or percentage (number); Kruskal-Wallis test, Mann-Whitney U-test compared only CRPS with limb pain of non-CRPS origin. Significant differences are indicated in bold. Bonferroni threshold would be $P = 0.008$. CRPS = complex regional pain syndrome; ns = not significant.

test demonstrates that this relates to the difference between migraine and both limb pain groups. This is obviously explained because migraine is an episodic pain disorder. As compared with the control pain groups, pain duration was shorter but PDI scores were higher in the CRPS group. For details, see Table 1.

Neglect-Like Symptoms

Severity of NLS score was increased in the CRPS group compared with both control groups, in particular the limb pain group ($P < 0.004$). Items 1 ("...it would lie still, like dead weight"), 2 ("...is not part of the rest of my body"), and 3 ("...I need to focus my attention...to make it move") of the NLS were more prevalent in the CRPS group as compared with the limb pain controls. Unexpectedly, some migraine patients indicated NLS as well (Table 2). A nerve lesion could influence the body perception and the feeling of ownership of one limb. Moreover, body perception and NLS might be different for arms and legs [3]. Therefore, we reanalyzed our data for CRPS I only (N = 47) and for right and left arms and legs separately. Thirty-five of 47 patients had CRPS-I of the upper extremities. The NLS severity scores did not differ between upper (2.4 ± 1.1) and lower extremity CRPS (2.4 ± 1.1, ns) or between right (N = 24, 2.2 ± 1.1) and left (N = 23, 2.6 ± 1, ns).

Symptoms of Mental Disorders

CRPS patients and patient controls did not differ with respect to depression, generalized anxiety, social anxiety, and somatization severity. However, severity of depersonalization was significantly higher in the CRPS group. For details, see Table 3.

Rank-order correlation analyses of severity of NLS, total score and clinical variables were calculated independently for the three pain groups. In the CRPS group, no associations of NLS were found with severity of pain, duration of pain, or pain disability. However, in particular the features of mental distress and pain catastrophizing strongly correlated with the NLS. Of particular interest might be generalized anxiety, depersonalization, and somatization, which had the highest correlation coefficients. In contrast, in the group of limb pain patients, only the severity of pain correlated with NLS. In the migraine group, which would be expected to express no NLS at all, generalized anxiety correlated with NLS scores (see Table 4). The scatter plots for the correlations of NLS with severity of depersonalization and pain are depicted in Figure 1 for CRPS and limb pain patients.

Discussion

The results of our study are threefold: 1) a confirmation that NLS are more prevalent in CRPS when compared with non-CRPS chronic limb pain; 2) that these NLS were correlated to psychological factors like anxiety, somatization, and depersonalization in CRPS, while NLS only relate to pain intensity in non-CRPS limb pain; 3) with the exception of pain disability and

Table 3 Differences in mental distress between the groups

	CRPS patients (N = 50)	Limb pain patients (N = 27)	Migraine headache (N = 18)	Test	Test CRPS vs limb pain
Depression severity (PHQ-9)	9.2 ± 5.4	7.6 ± 5.8	7.7 ± 5.6	ns	ns
GAD severity (GAD-7)	6.7 ± 4.7	5.0 ± 4.7	5.6 ± 3.7	ns	ns
Social Anxiety severity (Mini-SPIN)	3.0 ± 2.6	2.6 ± 2.7	2.6 ± 2.0	ns	ns
Somatization severity (PHQ-15)	10.7 ± 4.5	8.7 ± 4.0	8.6 ± 4.8	ns	ns
Depersonalization severity (CDS)	**32.9 ± 33.1**	**16.8 ± 19.9**	21.4 ± 33.9	***P* = 0.011**	***P* < 0.01**

Data are presented as mean ± standard deviation or percentage (number); Kruskal-Wallis test for continuous variables, Mann-Whitney U-test for comparison of CRPS and limb pain. Significant differences are indicated in bold. Bonferroni threshold would be $P = 0.01$. CRPS = complex regional pain syndrome; ns = not significant.

Table 4 Correlation of pain indices and symptoms of mental disorders with the severity of neglect-like symptoms

	CRPS patients (N = 50)	Limb pain patients (N = 27)	Migraine headache (N = 18)
Current pain severity	0.178	**0.492****	−0.021
Duration of pain	−0.078	0.039	−0.158
Pain Disability Index (PDI)	0.260	0.091	0.419
Depression (PHQ-9)	**0.481*****	−0.022	0.442
Generalized anxiety (GAD-7)	**0.658*****	−0.145	*0.614***
Social anxiety (Mini-SPIN)	**0.412****	0.057	0.454
Somatization (PHQ-15)	**0.616*****	0.179	0.335
Depersonalization (CDS)	**0.634*****	0.317	0.317
PRSS: Cognition	0.068	0.113	0.013
PRSS: Catastrophizing	**0.456****	−0.148	0.079

Spearman-rho correlation coefficients. Significant correlations are indicated in bold numbers. Migraine patients do not have limb pain and should not have NLS, the correlation coefficient is indicated in italic numbers. Bonferroni threshold would be $P = 0.005$.
**$P < 0.01$.
***$P < 0.001$.
CRPS = complex regional pain syndrome; NLS = neglect-like symptoms; PRSS = Pain-Related Self-Statements Scale.

depersonalization, CRPS patients were indistinguishable from limb pain patients of non-CRPS origin.

NLS and Depersonalization Symptoms Are Prevalent in CRPS

There are several investigations that have already shown that NLS are prevalent in CRPS and that their incidence and strength is higher when compared with limb pain of other origin or healthy controls [1–3,27]. In the CRPS group, the most prevalent NLS feeling was detachment of the affected limb from the body ("...not part of the rest of the body"), a symptom that very rarely occurred in the controls. According to previous studies [28,29], CRPS patients did not differ from pain controls in most of the psychological parameters that were assessed in our study, including depression, anxiety, or somatization. Only depersonalization scores were significantly increased. It is of particular interest because detachment of the affected limb from the body as indicated by the NLS descriptors might be a symptom of depersonalization, or vice versa. The distortion of the body scheme is a hallmark of CRPS symptomatology. This has been demonstrated in a whole series of experiments [30,31]. It has been hypothesized that this body scheme distortion, which might be responsible for the NLS (albeit differentiated investigations are missing), is caused by a dysfunction of the parietal cortex as a part of CRPS pathophysiology [32]. Interestingly, FDG-PET and structural MRI studies revealed that depersonalization

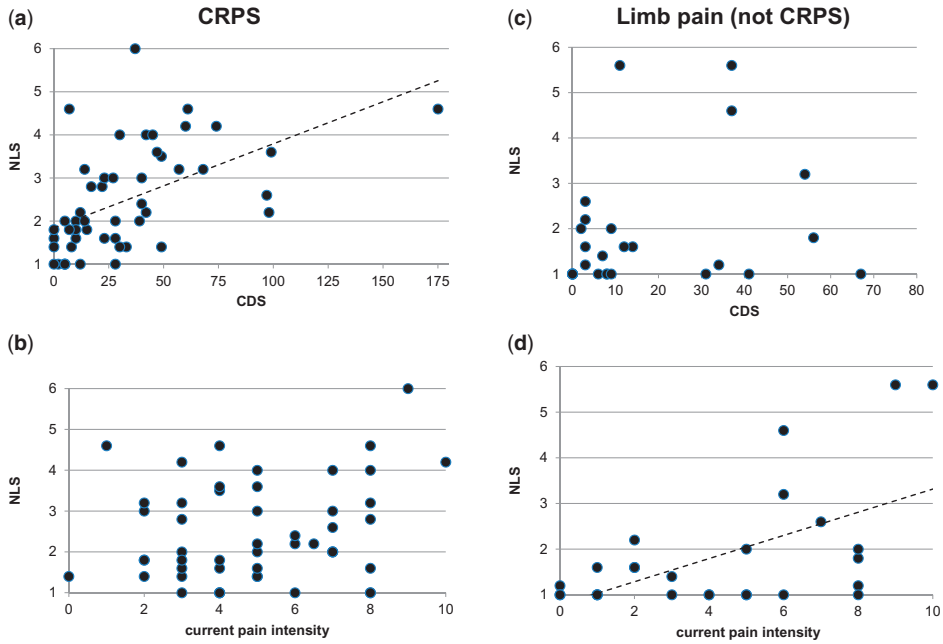

Figure 1 Scatter plot of the Spearman rank order correlations of NLS with depersonalization and pain intensity. **(A)** and **(B)** show scatter plots of the CRPS group (N = 50), **(C)** and **(D)** scatter plots of limb pain patients (N = 27); **(A)** rho = 0.634, $P < 0.0001$ CDS vs NLS; **(D)** rho = 0.492, $P < 0.01$ for current pain intensity vs NLS. CDS = severity of depersonalization; NLS = severity of neglect-like symptoms.

symptoms were correlated with neuronal activity and structural changes of the parietal cortex, this particular brain area that is responsible for encoding an intact body schema [33]. This suggests that a shared brain mechanism might underlie NLS and depersonalization symptoms in CRPS, which might be highly correlated rather than being different symptoms.

Another difference between CRPS and non-CRPS limb pain is the high pain disability (PDI) despite similar pain severity. We did not go into details in our study, but it seems obvious that CRPS, which is by definition a disease of pain plus loss of function must lead to higher disability than pain disorders without loss of function. In addition, passive pain coping strategies in CRPS amplify disability in daily living [34].

NLS Were Correlated to Mental Parameters but Not to Pain Severity in CRPS

We found strong correlations of the severity of NLS with symptoms of common mental disorders in CRPS patients. These correlations had large effect sizes. In contrast to previous studies, we did not find associations of NLS with pain intensity [3,35] or of a clinical measure of body perception disturbances and pain duration [35]. The major difference between those studies and the current investigation is that we included CRPS patients whose condition lasted about one year, while previous studies investigated chronic CRPS patients whose pain lasted between mean one and a half and four years (maximum 10 years) [3,35]. The impact of pain on body perception disturbance increases with the persistence of CRPS [35], which could explain the lacking correlation between pain and NLS in our study of CRPS patients with shorter duration. In contrast, the limb pain controls, who have been in pain for about five years, behave like expected. However, as psychological distress usually increases or at least remains stable during long-standing pain [36,37], it seems unlikely that the remaining correlations disappear in long-time CRPS.

In contrast to the controls, NLS in CRPS correlated with generalized anxiety, social anxiety, depression, somatization, and depersonalization. These findings support that, more than pain, mental distress contributes to the development of NLS in early CRPS patients. The strongest associations were found for symptoms like depersonalization, which was linked to catastrophizing, misinterpretation of perceptions, and subsequent avoidance [38–42]. Recent experiments with healthy persons revealed that pain catastrophizing predicted depersonalization [43] and, in turn, depersonalization led to increased pain [44]. These associations constitute a vicious circle that might be functional in CRPS. However, the psychological symptoms are treatable, and theoretically early psychological intervention could prevent chronic CRPS.

In migraine patients, in whom NLS would be not expected at all, anxiety also correlated with NLS scores.

The concept of a "defensive peripersonal space," the size of which is related to anxiety, may help to explain why anxiety could be related to NLS. According to the "defensive peripersonal space" concept, the magnitude of perceived danger that a stimulus represents is determined by the distance between the stimulus and the body [45]. Detachment from the affected limb (depersonalization expressed as NLS) might constitute a kind of safety behavior.

Limitations

The paper has limitations that must be mentioned before interpreting the results because our cross-sectional approach cannot determine causality. A longitudinal investigation would have been necessary.

Firstly, we cannot prove if mental distress causes NLS or vice versa—only the fact that the peripersonal protection space in healthy subjects depends on trait anxiety [45] and that the anxiety in our patients is not pain specific but generally supports the first assumption. Secondly, our data are questionnaire based. We report symptoms and not mental disorders as this would require validation by expert interviews. Nevertheless, the applied questionnaires are reliable and have shown to be valid in previous studies. Thirdly, the questions of the NLS and five of the 29 items of the CDS are semantically overlapping. Therefore, the association of depersonalization with NLS in our study might be trivial and might indicate that both questionnaires address the same symptoms or even ask the same questions. This seems obvious because the wording of the scales overlaps in the most prevalent item of the NLS scale (NLS item 2: "…as though it is not part of the rest of my body") with corresponding items from the Cambridge Depersonalization Scale (e.g., "...parts of my body feel as if they didn't belong to me…. My hands or my feet have become larger or smaller; I have to touch myself to make sure that I have a body or a real existence") [11]. Alternatively, the similarity between NLS and depersonalization comes from common biological mechanisms, most likely from dysfunction of the parietal cortex. The finding that migraine patients report NLS despite not having limb pain and depersonalization, but having high general anxiety, supports a common biological mechanism. Fourthly, the sample sizes of the two comparison groups were small, which hampers drawing firm conclusions. Despite highly significant results, a replication in a second sample is needed. Furthermore, we included mainly patients with upper limb CRPS I. The findings in CRPS II and lower limbs might be different, although the original study about NLS [2] found no difference in NLS in upper and lower limb CRPS.

In conclusion, the present findings suggest that psychological symptoms play a role in the development of NLS in CRPS, possibly more than previously recognized. Regarding psychology, CRPS differs little from other chronic pain disorders. This does not at all mean that CRPS is a mental disease. The psychological behavior of CRPS patients might be the consequence of CRPS, i.e., of the neuroplastic changes in CRPS brains. Further imaging studies have to cover symptoms of so-called mental disorders (depression, anxiety, somatization, and depersonalization) and related dysfunctional coping behavior (e.g., catastrophizing) as covariates or causal factors. Treatment approaches in CRPS may profit not only from targeting pain and loss of function of the CRPS limb but also from a targeted treatment of psychological symptoms.

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