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Traumatic Events, Posttraumatic Stress Disorder, and Central Sensitization in Chronic Pain Patients of a German University Outpatient Pain Clinic

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ABSTRACT

Objective: Posttraumatic stress disorder (PTSD) and traumatic life events are often coupled to chronic pain, possibly linked by central sensitization. We wanted to assess the prevalence of traumatic events and PTSD in chronic pain patients of a German university hospital outpatient pain clinic. Moreover, we evaluated the extent of indicators and co-occurring traits of central sensitization in comorbid patients.

Methods: We retrospectively divided 914 chronic pain patients into four groups depending on their trauma severity: no trauma, accidental trauma, interpersonal trauma, and PTSD. We collected electronic pain drawings focusing on pain area and widespreadness, as well as information about pain intensity, sleep impairment, disability, stress, anxiety, depression, and somatization. Differences between groups were calculated using Kruskal-Wallis with post-hoc Mann-Whitney tests.

Results: Of 914 patients, 231 (25%) had no trauma, 210 (23%) had accidental traumas, 283 (31%) had interpersonal traumas, 99 (11%) had PTSD, and 91 (10%) could not be classified. We observed statistically significant differences between groups in pain area and widespreadness, as well as maximal pain, sleep impairment, disability, stress, anxiety, depression, and somatization. The severity of symptoms increased with trauma severity.

Conclusions: Traumatic life events and PTSD are frequent in chronic pain patients. The increased pain area and widespreadness, as well as the increased negative impact on co-occurring traits of sensory sensitivity (anxiety, depression, somatization), are compatible with central sensitization in comorbid patients. Therefore, a heightened awareness of the comorbidity between traumatic experiences and chronic pain is recommended.

Key words: chronic pain, posttraumatic stress disorder, pain area, pain widespreadness, central sensitization.

INTRODUCTION

Chronic pain, that is, pain lasting longer than 3 months, is a commonly encountered health issue that decreases quality of life and leads to a great burden on society (1). A meta-analysis showed that 9.7% of chronic pain patients had posttraumatic stress disorder (PTSD) (2). This prevalence was even more pronounced in four university hospital outpatient pain clinics, ranging from 21% to 29% (3–5). This elevated prevalence of PTSD compared with the general population (approximately 7%) (6) suggests that the two disorders often coexist and might exacerbate each other (4,7).

There is some uncertainty about the extent to which psychological trauma and PTSD may promote the development of chronic pain (8). However, early trauma is associated with an increased risk of developing chronic pain in adulthood (9–11), which suggests at least indirect causality. Further research indicates that chronic pain can develop from traumatic psychological events independently of affective factors and in a dose-response relation (11,12).

Early life stress can interact with genetic factors, especially in vulnerable phases of live, and, with the involvement of epigenetic

ICD-10 = International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, **PDI** = Pain Disability Index, **PDS** = Posttraumatic Diagnostic Scale, **PHQ-D** = Patient Health Questionnaire, German version, **PTSD** = posttraumatic stress disorder, **VAS** = visual analog scale, **WPI** = Widespread Pain Index

SDC Supplemental Digital Content

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mechanisms, create the foundation for a persistently disturbed responsiveness of the allostatic systems (13,14). One significant example of such a process is the epigenetic dysregulation of central glucocorticoid receptors, resulting in a disruption of stress processing (15). Both overactivation and underactivation of the hypothalamo-pituitary-adrenal axis can lead to an imbalance of other systems, especially the endocannabinoid (16) and the corticomesolimbic (17) systems. The dysfunction of the latter can be understood as a central neurobiological correlate of chronic pain (17,18), which can remain active even without sustained nociceptive input (17). Childhood trauma also seems be able to directly influence pain sensitivity through epigenetic changes in ion channels (19). This fits with the observation that early life stress is associated with the development of proinflammatory responsiveness throughout life, for example, via priming of microglia (20,21).

Although earlier proxy definitions of central pain sensitization exclusively used pain dimensions such as widespread pain, disproportionate pain intensity, and sensory amplification (22), today a multidimensional nature is assumed, including further factors such as generalized sensory sensitivity, heightened somatic awareness, cognitive disturbance, and sleep difficulties (23). Furthermore, a recent review on studies of central sensitization in chronic low back pain showed that these factors correlate with psychosocial metrics such as depression, anxiety, and somatization (24). We have to rely on this characterization of central sensitization because the direct proof of a "hyperexcitability of the central nervous system" (25) by means of direct electrophysiological recordings is not reasonable in humans.

From a neurobiological perspective, the emergence of central pain sensitization, that is, the hyperexcitability of the central nervous system, was discussed as a significant mechanism for the development of chronic pain in the context of traumatic life events (10,26). In a cross-sectional study on 202 patients with chronic pain, both traumatic events and PTSD symptoms were significantly associated with clinical indicators of central sensitization, such as pain extent, pain intensity, and polysomatic complaints measured by the Central Sensitization Inventory (27). Moreover, compared with controls, pain-free PTSD subjects also showed higher pain ratings and significantly increased temporal summation after intramuscular capsaicin stimulus, indicating acute sensitization (28).

The first objective of this study was to assess the prevalence of traumatic life events and PTSD in a large sample of chronic pain patients of a German university hospital outpatient clinic. Second, we wanted to evaluate the impact of comorbidity on proxy measures for central sensitization such as pain area and widespreadness, as well as co-occurring traits of sensory sensitivity (e.g., anxiety, depression, somatization) (29–31). We also analyzed associated symptoms such as pain intensity, sleep impairment, disability, and stress.

METHODS

This retrospective study took place at Hannover Medical School (Hannover, Germany), was approved by the ethics committee of Hannover Medical School, and was registered at ClinicalTrials.gov (NCT05190367). Between February 2019 and July 2020, 914 of 1047 patients (87%) who visited our outpatient pain department gave written consent to use their routinely collected data anonymously for research purposes. We cannot provide any information about the 133 who did not give their consent to use their data for research purposes. M.D. and M.K. were the attending physicians, and J.M. had access to all anonymized data. Our article follows the REporting of studies Conducted using Observational Routinely collected health Data (RECORD) statement (32).

Participants were divided into four groups depending on their trauma severity: a) no trauma, b) accidental trauma (e.g., illness, accident, natural disaster), c) interpersonal trauma (e.g., assault, rape, war), and d) PTSD (diagnosed according to the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* [*ICD-10*]). This subdivision followed previous reports that interpersonal traumas are more prone to develop into PTSD than accidental traumas (33). Patients fulfilling two or more categories were assigned to the highest group. Patients who could not be classified because of missing information on traumas were excluded from the analysis. Their measures can be found in Supplemental Digital Content, Table S1, http://links.lww.com/PSYMED/A907. All the remaining data were included in the statistical analyses.

Data were collected using the SymptomMapper application (34). Participants provided information about their traumas (first part of the Posttraumatic Diagnostic Scale [PDS] (35)), current pain intensity (visual analog scale [VAS] (36)), mean and maximal pain in the last 4 weeks (VAS), sleep impairment (VAS), acceptable pain (VAS), Pain Disability Index (PDI (37)), pain area (digital drawings), pain widespreadness (Widespread Pain Index [WPI] (38), derived from drawings), stress (Patient Health Questionnaire, German version [PHQ-D] (39)), anxiety (PHQ-D), depression (PHQ-D), and somatization symptoms (PHQ-D).

Differences between groups were calculated using Kruskal-Wallis tests (and χ^2 test for sex), followed by post-hoc Mann-Whitney tests. In a supplementary analysis, we tested for sex differences in all parameters and groups using Mann-Whitney tests. We used the nonparametric equivalents to the analysis of variance and two-sample *t* tests because our data were not normally distributed (Figure S1, Supplemental Digital Content, http://links.lww.com/PSYMED/A907). Moreover, we calculated the Pearson cross-correlation matrix of all measures. All analyses were Bonferroni corrected for multiple comparisons, and we only report corrected *p* values.

Data Availability

Raw data and necessary scripts for reproducing the results of this study are available at Zenodo (https://doi.org/10.5281/zenodo.7498710).

RESULTS

Of 914 patients, 231 (25%) had no trauma, 210 (23%) had accidental traumas, 283 (31%) had interpersonal traumas, 99 (11%) had PTSD, and 91 (10%) could not be classified. There were 623 women (68%), the average age was 54.0 (16.2) years, and the average body mass index was 26.4 (5.4) kg/m^2.

We observed highly significant ($p < .001$) differences between groups in pain area, WPI, sleep impairment, PDI, stress, anxiety, depression, and somatization symptoms. Moreover, there were significant differences ($p = .001$) in maximal pain during the previous 4 weeks and acceptable pain ($p = .010$). Patients diagnosed with PTSD showed more severe symptoms than patients without trauma. Specifically, they showed larger pain area (13.2%

TABLE 1. Group Differences

Measure	No Trauma (n = 231)	Accidental Trauma (n = 210)	Interpersonal Trauma (n = 283)	PTSD (n = 99)	Statistical Significance						
						Post-Hoc Mann-Whitney					
					Kruskal-Wallis	0 versus 1	0 versus 2	0 versus 3	1 versus 2	1 versus 3	2 versus 3
Women	159 (69%)	135 (64%)	195 (69%)	72 (73%)							
Age, y	53.9 (18.0)	55.9 (15.7)	53.0 (16.0)	50.7 (12.0)							
Body mass index, kg/m^2	26.1 (5.0)	26.6 (5.8)	26.4 (5.4)	26.2 (5.7)							
Pain area, %	6.9 (12.6)	7.3 (11.4)	8.5 (12.8)	13.2 (18.5)	***			***		**	*
Widespread Pain Index (0–19)	4.1 (4.4)	4.4 (4.5)	5.6 (5.0)	7.3 (5.7)	***		*	***		***	
Current pain, VAS (0–100)	48.3 (29.8)	52.6 (27.9)	52.9 (27.2)	59.4 (24.5)							
Mean pain, VAS (0–100)	55.8 (24.7)	59.3 (22.7)	59.8 (21.6)	65.0 (20.8)							
Maximal pain, VAS (0–100)	70.3 (25.2)	75.6 (21.0)	79.5 (18.5)	80.6 (17.4)	**		***	**			
Acceptable pain, VAS (0–100)	22.6 (19.4)	25.8 (19.6)	25.4 (17.2)	31.7 (21.4)	**			***			
Sleep impairment, VAS (0–100)	45.6 (32.2)	53.3 (31.6)	52.2 (32.9)	70.6 (28.1)	***			***		***	***
Pain Disability Index (0–70)	31.3 (15.5)	35.3 (15.7)	38.0 (14.7)	42.3 (13.4)	***	*	***	***		***	*
Patient Health Questionnaire											
10-item stress scale (0–20)	5.0 (3.4)	6.1 (3.3)	7.4 (4.1)	10.3 (4.4)	***	***	***	***	**	***	***
7-item anxiety scale (0–21)	6.3 (4.7)	7.3 (4.7)	8.3 (5.0)	12.1 (5.4)	***		***	***		***	***
9-item depression scale (0–27)	9.3 (5.5)	10.4 (5.1)	11.8 (5.3)	15.4 (5.5)	***		***	***	*	***	***
15-item somatic scale (0–30)	10.4 (4.9)	11.8 (4.9)	13.3 (5.1)	16.8 (5.3)	***	*	***	***	**	***	***

PTSD = posttraumatic stress disorder; VAS = visual analog scale.

Data are expressed as mean (standard deviation) unless otherwise stated. (0) no trauma; (1) accidental trauma; (2) interpersonal trauma; (3) PTSD.

* $p < .05$.

** $p < .01$.

*** $p < .001$.

[18.5%] versus 6.9% [12.6%]; $p < .001$; $d = 0.43$), WPI (7.3 [5.7] versus 4.1 [4.4]; $p < .001$; $d = 0.67$), maximal pain (80.6 [17.4] versus 70.3 [25.2]; $p = .005$; $d = 0.45$), acceptable pain (31.7 [21.4] versus 22.6 [19.4]; $p < .001$; $d = 0.45$), sleep impairment (70.6 [28.1] versus 45.6 [32.2]; $p < .001$; $d = 0.81$), PDI (42.3 [13.4] versus 31.3 [15.5]; $p < .001$; $d = 0.74$), stress (10.3 [4.4] versus 5.0 [3.4]; $p < .001$; $d = 1.44$), anxiety (12.1 [5.4] versus 6.3 [4.7]; $p < .001$; $d = 1.17$), depression (15.4 [5.5] versus 9.3 [5.5]; $p < .001$; $d = 1.11$), and somatization (16.8 [5.3] versus 10.4 [4.9]; $p < .001$; $d = 1.28$; Table 1 and Figure S1, Supplemental Digital Content, http://links.lww.com/PSYMED/A907).

We also calculated the Pearson cross-correlation matrix of all measures. WPI, current pain, mean pain, maximal pain, acceptable pain, sleep impairment, PDI, stress, anxiety, depression, and somatization significantly correlated with each other. Age correlated with current pain ($r = 0.15$; $p < .001$) and mean pain ($r = 0.14$; $p = .002$). Furthermore, trauma severity correlated with WPI ($r = 0.20$; $p < .001$), maximal pain ($r = 0.18$; $p < .001$), sleep impairment ($r = 0.19$; $p < .001$), PDI ($r = 0.23$; $p < .001$), stress ($r = 0.38$; $p < .001$), anxiety ($r = 0.30$; $p < .001$), depression ($r = 0.31$; $p < .001$), and somatization ($r = 0.35$; $p < .001$; Figure 1).

Average pain drawings (Figure 2) showed that pain was centered at the lumbar region, spinal cord, shoulders, knees, wrists, and temples. Patients with PTSD additionally reported pain across the limbs, in the back, and in the abdomen.

We did not observe sex differences in any of the parameters (Figure S1, Supplemental Digital Content, http://links.lww.com/PSYMED/A907).

DISCUSSION

We found a PTSD prevalence of 11% in our cohort of 914 patients with chronic pain. Moreover, further 54% reported traumatic life

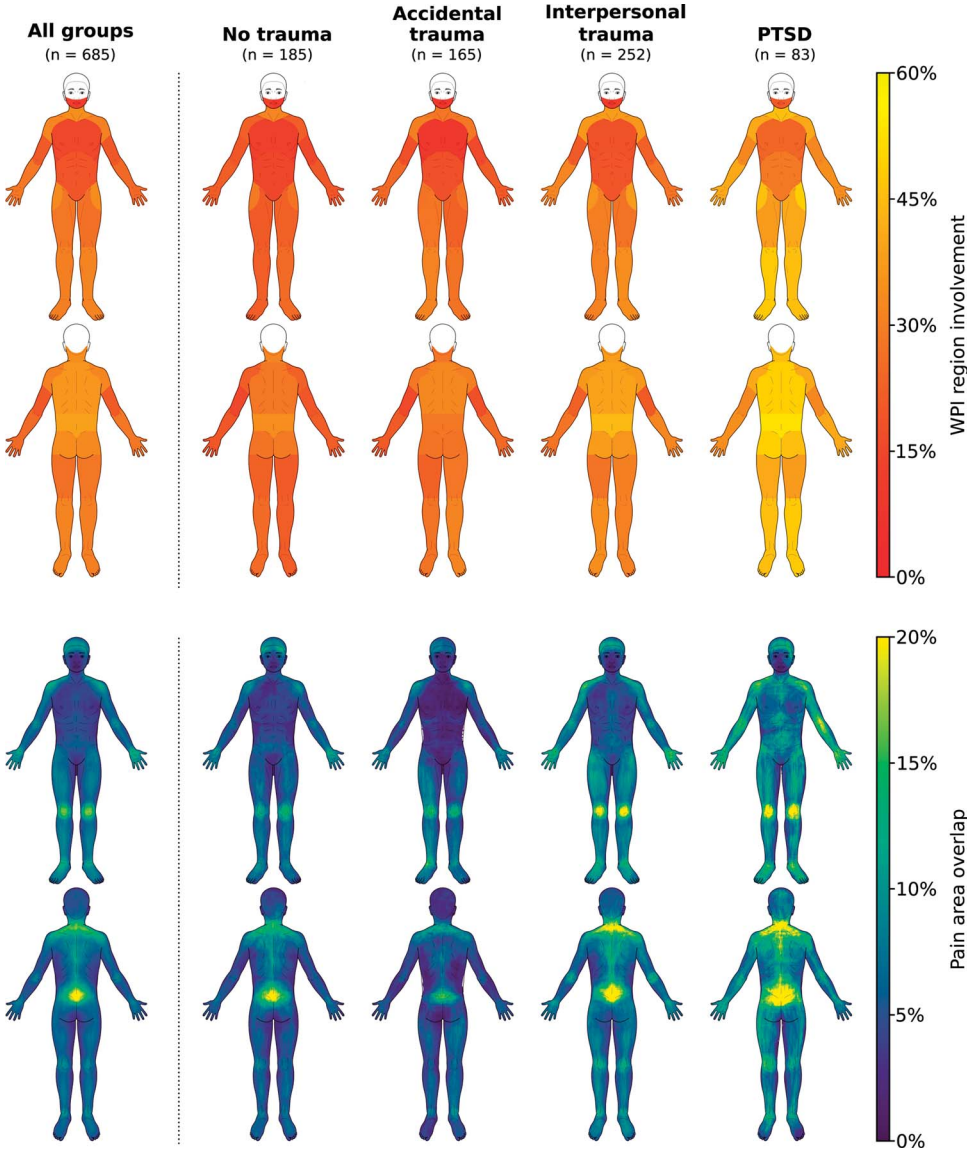

FIGURE 1. Cross-correlation matrix of all measures. $^{**}p < .01$; $^{***}p < .001$. Color image is available only in the online version of the article.

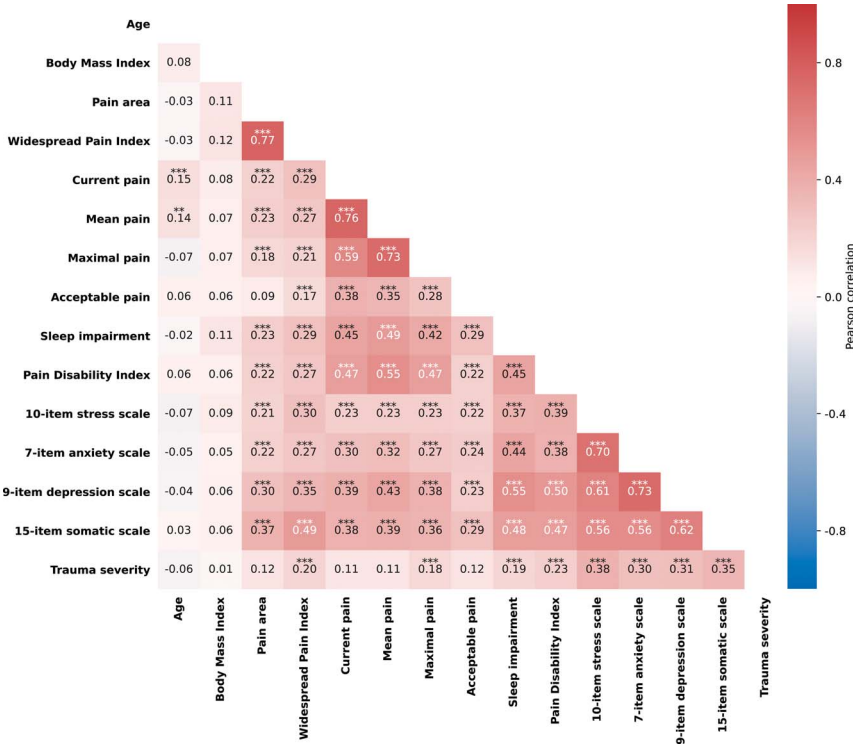

FIGURE 2. WPI region involvement and pain area overlap. Note that the WPI does not include head regions. Moreover, not all patients made pain drawings. WPI = Widespread Pain Index. Color image is available only in the online version of the article.

events. These results are in line with data from a previous meta-analysis (2). In contrast, pain units of four Scandinavian university clinics showed a prevalence rate of PTSD at least twice as high as our sample (3–5).

Moreover, we observed a positive correlation between trauma severity and pain widespreadness, maximal pain, sleep impairment, PDI, stress, anxiety, depression, and somatization (Figure 1). This correlation underpins the notion that trauma severity can be roughly subdivided into accidental and interpersonal traumas, being the latter closer in severity to PTSD (33).

The increased pain area and widespreadness, as well as the impact on outcomes such as pain intensity, sleep impairment, disability, and stress, are compatible with the concept of central sensitization in patients with PTSD as elaborated in Introduction. Both chronic pain and PTSD alter similar nuclei in the brainstem, hypothalamus, and amygdala (40). For this reason, it has been hypothesized by some authors that dysregulation of these regions, which would be exacerbated by the comorbidity, could lead to changes in neurons and glia and hence to central sensitization (41). Other authors found that changes in the amygdala could also lead to affective disorders (42), which could result in increased somatization and pain (43).

Because our sample included a relatively large number of female patients (68%), we conducted a supplementary analysis to figure out whether there were sex differences. We could not find any sex difference in the acquired parameters (Figure S1, Supplemental Digital Content, http://links.lww.com/PSYMED/A907). Nonetheless, the percentage of women in our study was larger than in people with chronic pain in Germany, of which roughly 54% are female (44). One explanation for this discrepancy could be that women visit the pain outpatient department more often.

Limitations

The usage of routinely collected data might distort the results because of missing values or inconsistent data quality. We minimized these errors by acquiring all data electronically. Therefore, no questionnaires had missing values, and pain drawing instructions were standardized. However, some patients were not capable of completing the drawings. We minimized misclassification bias in trauma severity by using the first part of the PDS to reduce free text to a minimum. Moreover, PTSD was diagnosed by experienced physicians following *ICD-10* criteria. Patients who could not be classified because of missing information (10%) were excluded from the analysis. Their measures can be found in Table S1, Supplemental Digital Content, http://links.lww.com/PSYMED/A907. We might hypothesize that these patients felt uncomfortable sharing such sensitive information, which would suggest an underreporting of traumatic events. In addition, the absence of the second to fourth parts of the PDS limits the quantification of trauma severity.

We had no information from specific measures for central sensitization such as quantitative sensory testing, functional magnetic resonance imaging, or blood markers (22). However, pain area, intensity, and widespreadness have been found to be significant proxies for central sensitization (31,45). In addition, patient-reported phenomena relating to psychological and mental impairments seem to be significant cues of central sensitization (see Introduction) (31,46). Given the results from this and previous studies, it may be sensible to screen chronic pain patients for central sensitization using specialized questionnaires like the Central Sensitization Inventory (47) and using quantitative sensory testing for confirmation.

Moreover, neither sociodemographic data nor other relevant factors such as wider social dimensions (e.g., partnership), somatic

and mental comorbidities, and medication were part of the SymptomMapper database. Hence, they were not included in this analysis. Being potential confounders, these parameters should be investigated in further studies to elucidate their impact on chronic pain with comorbid PTSD.

A further limitation of our study is that it did not include people with traumas but without comorbid pain. Such a group could provide insightful information on the risks of developing or exacerbating chronic pain after a trauma. It might well be that people with traumas but without pain develop nonpainful symptoms such as fatigue or no symptoms at all. On the other hand, there is some evidence that pain-free PTSD patients are also affected by central sensitization mechanisms (28).

Clinical Implications

A previous study showed that the majority of a cohort of 83 patients with chronic pain and comorbid PTSD benefited from a 3-week group-based interdisciplinary pain rehabilitation program (48). However, no conclusion could be drawn regarding long-term effects, and a subset of patients experienced no change or even an increase in symptoms. Chronic pain may mask an existing psychological trauma that plays an important role in the way pain is experienced and coped with. On the other hand, chronic pain and the therapeutic interactions themselves can have a (re)traumatizing effect on patients (49). As long as a specific therapy for patients with chronic pain and a traumatic background has not been established, a holistic, person-centered and trauma-informed care approach seems to be elementary. This approach emphasizes the importance of active and compassionate listening from the first encounter (50). The frequent occurrence of PTSD as comorbidity and the severity of symptoms should make healthcare professionals working in pain management aware of and sensitive to their patients.

In conclusion, because of the correlation between severity of traumatic events, anxiety, stress, depression, and pain widespreadness, we believe that chronic pain patients should be screened for trauma and PTSD. A better understanding of the comorbidity of PTSD, chronic pain, and central sensitization may lead to better clinical care for these severely affected patients.

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