



Methodology for self-report of rest pain (or spontaneous pain) vs evoked pain in chronic neuropathic conditions: a prospective observational pilot study

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Abstract

Introduction: The distinction between pain at rest and pain evoked by touch or movement has important clinical implications and may be associated with different mechanisms. However, current methods of clinical pain assessment pay little attention to directly distinguishing between these contrasting components of symptom burden.

Objectives: We developed the 10-item "Functional Impact of Neuropathic Evoked and Spontaneous Symptom Evaluation" questionnaire designed to distinguish between rest and evoked pain.

Methods: A prospective observational pilot study of this questionnaire was conducted in 78 participants with neuropathic pain diagnoses. Other study measures included the self-report version of the Leeds Assessment of Neuropathic Symptoms and Signs questionnaire and a modified Brief Pain Inventory. Exploratory analyses were conducted to evaluate the validity of the Functional Impact of Neuropathic Evoked and Spontaneous Symptom Evaluation questionnaire.

Results: Pain symptoms often/very often/always (1) evoked by touch or movement, and (2) occurring at rest without tactile stimulation were reported by 81% and 65%, respectively. Evoked pain was associated with walking (64%) and standing (35%); and rest pain was associated with watching television (47%), reading (37%), and sitting (36%). Participants reporting both rest and evoked pain tended to report higher levels of pain interference compared to those reporting evoked pain only.

Discussion: These results provide support for the feasibility and validity of new patient-report methods to distinguish between rest pain and evoked pain in chronic neuropathic conditions. Future studies are needed to confirm the reliability and validity of these methods, which may facilitate important improvements in the research and development of new treatments for chronic pain.

Keywords: spontaneous pain, evoked pain, neuropathic pain, stimulus-independent pain, stimulus-dependent pain, questionnaire development

1. Introduction

Human evidence suggests that clinical pain may be experienced and reported at rest (eg, while physically immobile and untouched) or in response to physical movement or somatic stimulation or both.^{14,17} One example of a mechanism that could sustain unprovoked pain is the occurrence of spontaneous discharges from neuromas involving nociceptive neurons^{21,27} or other aberrant spontaneous nociceptor activity that may

be difficult to suppress.³⁰ On the other hand, pain evoked by post-injury movement, or physical stimulation of, inflamed tissue could be generated by: (1) the augmented release of peripheral inflammatory mediators that subsequently activate normal peripheral nociceptors.⁷ While the majority of earlier functional brain imaging studies in chronic pain focused on changes in brain activation following pain-evoking conditions,¹¹ some evidence has suggested that pain at rest (or spontaneous pain) may be

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associated with distinct patterns of abnormal brain activity.^{24,28} The experience of “spontaneous pain” is disconcerting in that it suggests that the occurrence of nociceptive transmission (and subsequent pain experience) is autonomous and inescapable, whereas “evoked pain” can be avoided—although pain avoidance may result in functional limitation. Thus, the contrast between spontaneous pain²⁵ and evoked pain has some compelling experiential and clinical implications. However, controversy continues as to whether or not these are 2 mechanistically distinct phenomena.^{2,22,26} Clearly, advancing our understanding of this apparent dichotomy may have an important impact on the study of pain²⁵ and development of new treatments for pain.³⁸

In clinical care and clinical research settings, distinguishing between pain at rest vs pain with movement has been limited. In postsurgical patients with acute pain, movement pain (compared to pain at rest) has been shown to be more intense,¹⁷ to be more strongly correlated with postoperative physiological impairment^{13,16} and to show differential responses to analgesic treatment.^{15,34,36} Despite these important differences, the majority of postoperative analgesic clinical trials neglect to either measure movement pain or even to distinguish between rest and movement pain when making pain assessments.^{20,32} In chronic neuropathic pain, measurement efforts generally attempt to assess a composite of pain experience (eg, overall pain in the past 24 hours) and, as such, likely include a mix of both rest and movement pain—without distinction. In fact, very few clinical pain measurement instruments make the distinction between rest pain and movement pain. More recently, one instrument—the Neuropathic Pain Symptom Inventory—specifically identifies “spontaneous” pain as being distinct from other evoked symptoms⁵; however, this is in the minority among most neuropathic pain assessment methods.^{4,6}

With continued interest in the potential for mechanism-based pain treatment to better match investigational treatments to patient subgroups most likely to benefit,^{12,19,37,38} there is a need for new pain assessment methods to distinguish between rest pain (or spontaneous pain) and touch-evoked or movement-evoked pain. Thus, the purpose of the present investigation is to provide evidence for the feasibility and validity of questionnaire methods designed to distinguish between pain at rest and pain with movement or stimulation in participants with chronic pain.

2. Methods

2.1. Participants

This study was approved by the Queen’s University Health Sciences Research Ethics Board (Study #ANAE-142-08). Individuals contacting a research coordinator for possible participation in a different interventional neuropathic pain clinical trial were also considered for participation in this prospective observational cohort study. Candidates for this study were included if they met the following criteria: (1) self-report of a neuropathic pain diagnosis given by the study candidate’s physician; (2) reporting pain symptoms for at least 3 months; (3) adult aged 18–89; and (4) sufficient cognitive function and English language skills to complete questionnaires. Candidates were excluded from the study if: (1) Their overall health status prohibited participation in this study, or,

(2) they suffered from another non-neuropathic cause of pain as severe or more severe than their neuropathic pain. A written informed consent form was sent by mail to each eligible participant.

2.2. Pain assessment

Following written informed consent, participants were mailed several questionnaires related to their pain. The questionnaires included: (1) the self-report version of the Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS),³ (2) a modified Brief Pain Inventory (BPI),⁹ and (3) the Functional Impact of Neuropathic Evoked and Spontaneous Symptom Evaluation (FINESSE) questionnaire (Appendix 1). Upon completion of these instruments, participants returned the completed questionnaires by mail.

2.3. The Functional Impact of Neuropathic Evoked and Spontaneous Symptom Evaluation questionnaire and pain symptom classification

The FINESSE Pain Questionnaire (Appendix 1) is a 10-question survey that assesses participants’ pain symptoms in the context of external stimuli (eg, “Does anything touching your skin cause or increase your pain?”), passive conditions (eg, “Do you feel pain while sitting still or doing nothing”), and movement-related activities (eg, “Do you avoid certain activities because they cause you pain?”). Questions were derived from a clinical observation approach to item development³³ that incorporated multiple subject matter experts²⁹ and an iterative series of prior pilot questionnaires. Each of the 10 questions provided 5 response choices: never, sometimes, often, very often, and always. Several of these questions further asked the respondent to provide specific examples of stimuli, activities or situations in which pain is experienced or avoided. Questions 1 and 2 were intended to assess movement-related pain and its functional impact, respectively. Questions 3 and 4 were intended to assess touch-related pain and its functional impact, respectively. Question 5 was intended to assess pain at rest whereas question 6a was intended to assess pain at rest that is not touch-related. Question 6b was intended to assess situations associated with rest pain not related to touch. Question 7 assesses whether the respondent persists with usual daily activities despite his or her pain. Question 8 assesses whether any activities reduce the respondent’s pain. Questions 9 and 10 assess whether the respondent pursues certain activities or movements to reduce or prevent pain, respectively.

We used summary statistics to describe participants’ responses to the FINESSE questionnaire. Participant responses for each question were dichotomized as being negative if the response was “never” or “sometimes” and as being positive if the response was “often,” “very often,” or “always.” For the purposes of exploratory analysis, we described the differential functional impact of pain upon pain-related interference across different subgroups (ie, rest pain, stimulus-evoked pain, both, or neither) using descriptive summary statistics for each pain interference item from the modified BPI. Furthermore, analysis of variance analysis was conducted to explore differences in pain interference across these subgroups.

Table 1
Summary of participant characteristics (n = 78).

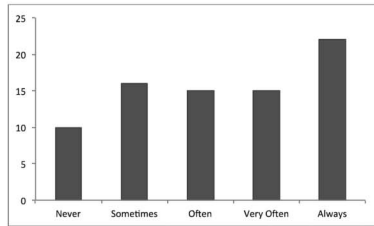
Mean age, y (SD)	Male (%)	Diabetic neuropathy (%)	Postherpetic neuralgia (%)	Idiopathic peripheral neuropathy (%)	Chemotherapy-induced peripheral neuropathy (%)
67.3 (10.1)	40 (51)	45 (58)	16 (21)	15 (19)	2 (3)

2.4. Exploratory analyses

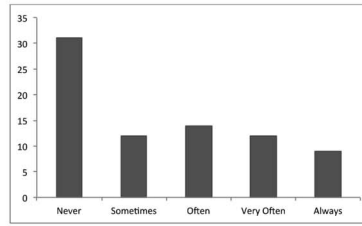
To evaluate the validity of relating rest pain vs stimulus-evoked pain to pain-related interference, exploratory Pearson correlation coefficients between FINESSE questionnaire items and modified BPI items were computed. For example, correlation between frequency of rest pain (eg, FINESSE question #6) and BPI pain interference

with mood (as well as other BPI items) was evaluated; correlation between frequency of evoked pain (eg, FINESSE question #4) and BPI pain interference with general activity (as well as other BPI items) was evaluated. We hypothesized that FINESSE questions addressing evoked pain would be more strongly correlated with BPI pain interference associated with physical function (eg, general activity,

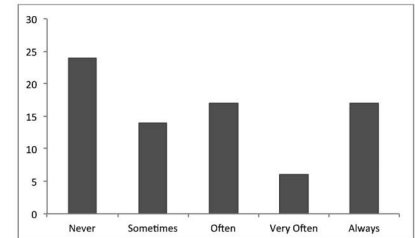
A Q1: Do certain activities or movements cause or increase your pain?



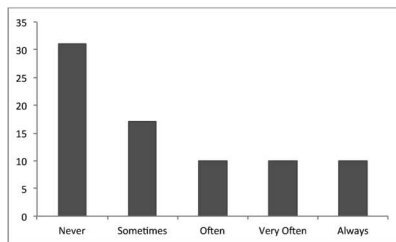
B Q2: Do you avoid certain activities or movements because you think they will cause or increase your pain?



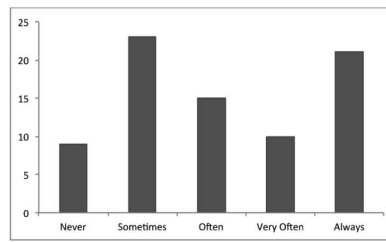
C Q3: Does anything touching your skin cause or increase your pain?



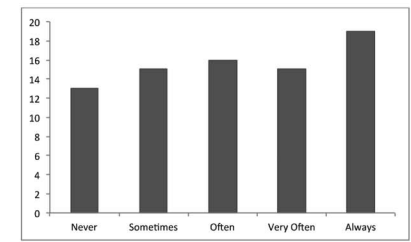
D Q4: Does pain which is caused or increased by touch interfere with any of your activities or movements (including sleep)?



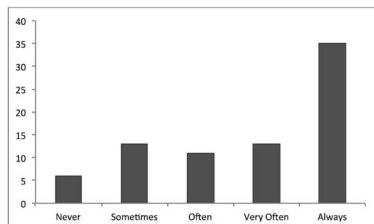
E Q5: Do you feel pain while sitting still or doing nothing?



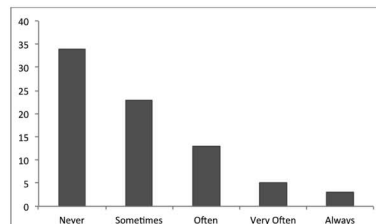
F Q6: While lying in bed, or sitting still, do you often feel pain that is NOT related to anything touching your skin (for example bedsheets)?



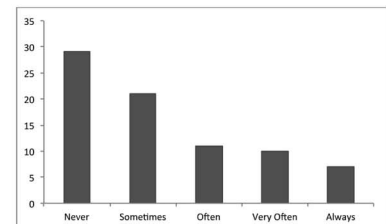
G Q7: Do you continue as usual with all your regular activities of life even though such activities cause or increase your pain?



H Q8: Do certain activities or movements relieve or decrease your pain?



I Q9: Do you specifically do certain activities or movements because you think they will relieve or decrease your pain?



J Q10: Do you specifically do certain activities or movements because you think they will prevent your pain?

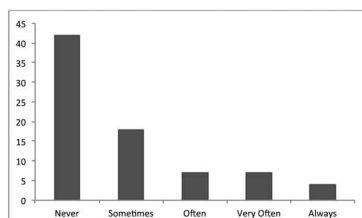


Figure 1. Participant responses ($n = 78$) to the 10 questions of the FINESSE Questionnaire. Each of the figure panels (A–J) correspond to each FINESSE questionnaire item. The y-axis represents the % of study participants reporting each of the 5 responses shown on the x-axis (ie, Never, Sometimes, Often, Very Often, Always). FINESSE, Functional Impact of Neuropathic Evoked and Spontaneous Symptom Evaluation.

work, walking) than would FINESSE questions addressing rest pain. Because rest pain is largely inescapable, we hypothesized that FINESSE questions addressing rest pain would be more strongly correlated with BPI pain interference associated with emotional function (eg, mood, social relations).

3. Results

3.1. Study participants

Seventy-eight participants who self-identified as suffering from a neuropathic pain condition consented to participate. The mean age of the participants was 67.3 years, 40 (51.3%) were men and the mean S-LANSS score (SD) was 15.1 (2.3) (Table 1). Eight participants reported an S-LANSS score just under the cutoff of 12 for (unaided completion) but ≥ 10 (used as the threshold for interview completion), and these were included in the study sample. Reported neuropathic pain diagnoses (Table 1) included painful diabetic neuropathy in 45 (58%), postherpetic neuralgia in 16 (21%), idiopathic peripheral neuropathy in 15 (19%), and chemotherapy-induced neuropathy in 2 (3%). A summary of participant responses to each of the 10 FINESSE questions is shown in Figure 1. Pain often/very often/always evoked by movement (Fig. 1A), by touch (Fig. 1C), or by either one of these was reported by 55 (73%), 42 (54%), and 63 (81%) participants, respectively. Pain reported often/very often/always at rest and unrelated to any tactile stimulation (Fig. 1F) was reported by 51 (65%). Considering whether each participant-reported evoked pain (ie, either movement- or touch-evoked pain) and pain at rest, 48 (62%) reported both evoked and rest pain, 16 (21%) reported evoked pain only, 6 (8%) reported rest pain only, and 8 (10%) reported neither. Thirty-one participants (40%) reported that they never avoid activities or movements as a result of pain (Fig. 1B), and 36 (46%) reported continuing with daily activities even if those activities caused them pain (Fig. 1G). Twenty-one participants (27%) reported experiencing consistent pain relief (often, very often, or always) with certain activities or movements (Fig. 1H). Forty-two participants (54%) reported that they never performed activities or movements to prevent pain (Fig. 1J).

Table 2 describes specific situational examples (eg, activities, stimuli, situations, etc.) reported by participants who are relevant to the specific FINESSE question being considered (eg, pain made worse by walking). Pain was reported to be caused or increased (FINESSE question #1) by walking (64%), standing (35%), climbing or using stairs (13%), and sleeping (12%). Other activities/movements reported by less than 10% included changing body position (9%), sitting (8%), and driving (5%). Activities reported to be avoided because of pain (FINESSE question #2) included walking (40%), standing (18%), normal work (17%), and exercise (12%). Other avoided activities/movements reported by less than 10% included driving/travelling (8%), sitting (8%), using stairs (6%), and recreational activities (5%). Reports of anything touching skin to cause or increase pain (FINESSE question #3) included shoes/socks (37%), bedsheets (28%), and personal contact by one's self or by others (14%). Other less frequent reports included contact with clothing (8%) and warm water/shower (6%). Activities or movements that are interfered with skin touch-evoked pain (FINESSE question #4) included sleeping (45%) and walking (18%) with less frequent reports of sitting (6%), standing (6%) and exercise (5%). Reported situations associated with nontouch-related pain at rest (FINESSE question #6) included watching television (47%), reading (37%), sitting (36%), lying down (17%), and computer/desk work (13%). Less frequently reported situations

Table 2

Participant-reported situational examples provided for specific FINESSE questionnaire items.

Activities or movements that cause or increase pain (item #1), n (%)	
Walking	50 (64)
Standing	27 (35)
Climbing/stairs	10 (13)
Sleeping	9 (12)
Activities or movements that are avoided because of pain (item #2), n (%)	
Walking	31 (40)
Standing	14 (18)
Normal work	13 (17)
Exercise	9 (12)
Anything touching skin that causes or increases pain (item #3), n (%)	
Shoes/socks	29 (37)
Bedsheets	22 (28)
Personal contact by self/others	11 (14)
Activities or movements that are interfered with by touch-evoked pain (item #4), n (%)	
Sleep	35 (45)
Walking	14 (18)
Situations associated with nontouch-related pain at rest (item #6a), n (%)	
Watching television	37 (47)
Reading	29 (37)
Sitting/feet up	28 (36)
Lying down	13 (17)
Computer/desk work	10 (13)
Activities or movements that relieve or decrease pain (item #8), n (%)	
Walking	15 (19)
Sitting/feet up	12 (15)
Activities or movement that are done to relieve or decrease pain (item #9), n (%)	
Walking	13 (17)
Sitting/feet up	10 (13)
Exercise	8 (10)
Activities or movement that are done to prevent pain (item #9), n (%)	
Sitting/feet up	9 (12)
Exercise	9 (12)

Data expressed as # of responses (%). Only items reported by at least 10% of study participants are shown here, see text for additional details. N.B. Some items (eg, walking) may appear as "activities/movements" or as "situations" depending on which question they correspond to.

FINESSE, Functional Impact of Neuropathic Evoked and Spontaneous Symptom Evaluation.

included sleeping (8%), travelling/driving (8%), relaxing (6%), and eating (5%). Activities or movements reported to relieve or decrease pain (FINESSE question #8) included walking (19%) and sitting (15%) with less frequent reports of exercise (9%), bathing/showering (8%), lying down (6%), and massage (6%). Because there is some paradoxical overlap between activities/movements reported to increase pain (question #1) vs decrease pain (question #8), it is important to note that only 6 (8%) participants reported that walking both increased and decreased their pain, 2 (3%) participants reported that sitting both increased and decreased their pain, and one (1%) participant reported that exercise both increased and decreased her pain. Activities/movements reported to be done specifically to relieve or decrease pain (FINESSE question #9) included walking (17%), sitting (13%), and exercise (10%), with less frequent reports of showering/bathing (8%), leg or foot movements (8%), massage (8%), and removing shoes, socks, or bedsheets (6%). Activities/movement reported to be done specifically to prevent pain (FINESSE question #10) included sitting (12%) and exercise (12%) with less frequent reports of walking (9%) and massage/pressure (5%).

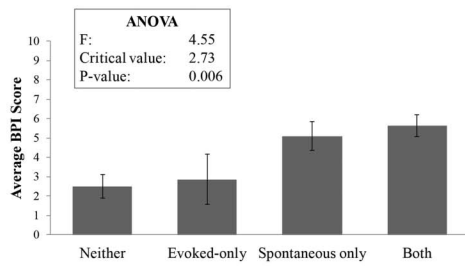
3.2. Pain interference in rest pain vs evoked pain subgroups

For exploratory analyses related to pain interference, participants were categorized into 4 groups based on their symptoms of

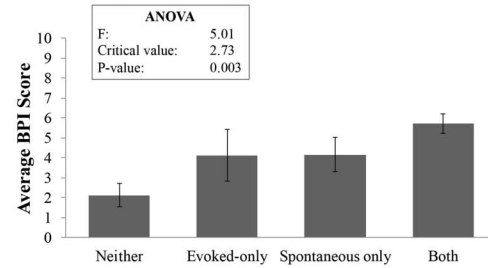
touch-evoked (FINESSE item 3) vs rest (FINESSE item 6) pain. Of the 78 participants, 8 (10%) frequently experienced touch-evoked pain symptoms, but not rest pain symptoms; 18 (23%) frequently experienced rest pain symptoms but not touch-evoked pain symptom; 35 (45%) frequently experienced both pain symptoms; and 17 (22%) rarely experienced either type. To evaluate the differential impact of rest vs evoked neuropathic pain

on various aspects of function, we tabulated BPI interference scores for these 4 different cohort subgroups (**Fig. 2**). Exploratory analysis of variance analyses suggested significant differences across these 4 subgroups for pain interference with general activity, mood, walking, normal work, sleep, and enjoyment of life (**Fig. 2**). Participants reporting both types of pain symptoms tended to report, on average, higher levels of interference in all

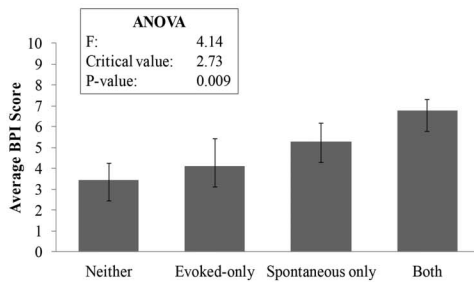
General activity



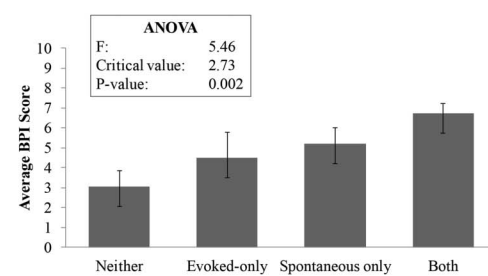
Mood



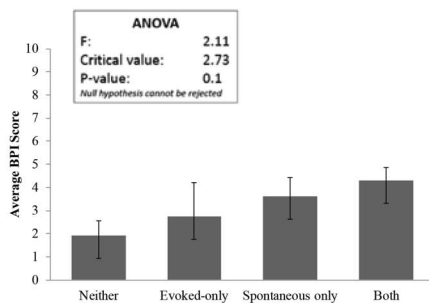
Walking



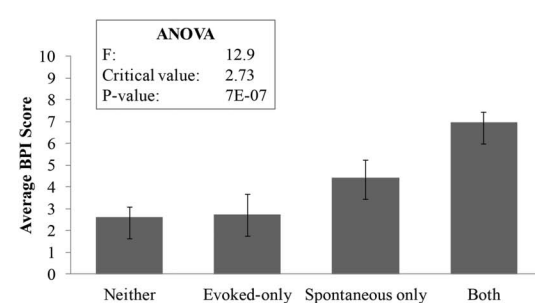
Normal work



Relationships with others (ns)



Sleep



Enjoyment of life

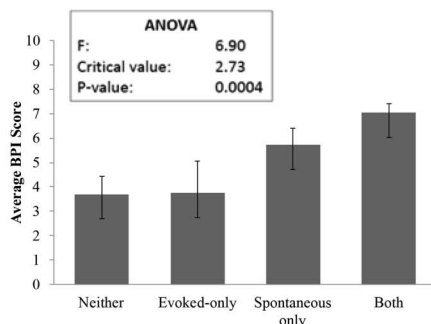


Figure 2. Brief Pain Inventory pain interference scores across cohort subgroups with pain reported as predominantly rest, stimulus-evoked, mixed, or neither. Error bars indicate SEM. ANOVA, analysis of variance; ns, ANOVA results not statistically significant.

areas when compared to those reporting neither type of pain. Participants reporting only rest pain tended to report, on average, comparable or greater interference with all areas compared with those who reported only evoked pain. Notably, the stimulus-independent group tended to report, on average, higher levels of interference with sleep, and enjoyment of life than those reporting only stimulus-dependent pain.

3.3. Correlations between modified BPI and Functional Impact of Neuropathic Evoked and Spontaneous Symptom Evaluation questions

Exploratory analyses of the correlation between individual FINESSE questionnaire items and modified BPI items for pain intensity and for pain interference are shown in **Tables 3 and 4**, respectively. For BPI pain intensity items, a significant correlation with a large effect size was observed between FINESSE item 2 (“Do you avoid certain activities or movements because you think they will cause or increase your pain?”) and BPI “average pain” and also between FINESSE item 5 (“Do you feel pain while sitting still or doing nothing?”) and BPI “pain now.” For BPI pain interference items, a significant correlation with a large effect size was observed between FINESSE item 2 (“Do you avoid certain activities or movements because you think they will cause or increase your pain?”) and BPI “general activity” and between FINESSE item 2 and BPI “normal work.”

4. Discussion

This exploratory pilot study provides evidence to support the feasibility and validity of self-report questionnaire methodology to distinguish between rest pain and evoked pain in chronic neuropathic conditions. In this study, nearly half of the participants reported both rest and evoked pain thus suggesting the importance of both of these components of pain experience in neuropathic conditions. However, it is also interesting to note that some neuropathic pain sufferers almost exclusively experience evoked pain whereas some others almost exclusively experience rest pain. Face validity suggests that FINESSE questionnaire items distinguish between pain at rest and pain evoked by movement or touch. Discriminant validity of the FINESSE questionnaire is suggested by the observation that (1) participants reporting frequent evoked pain but infrequent rest pain

tend to report lower levels of pain-related interference with function and, (2) participants reporting both frequent rest and evoked pain tend to report higher levels of pain-related interference with function. Content validity of the FINESSE questionnaire is suggested by the observation that activities/situations frequently reported with evoked pain (eg, walking and standing) were different than those frequently reported with rest pain (eg, watching television, reading, and sitting). Responses to slightly different, but related, questions 8-10 suggest minimal importance of various activities in preventing or reducing the experience or intensity of neuropathic pain.

As introduced above, the distinction between rest pain and evoked pain may be associated with different underlying mechanisms,^{2,7} differential treatment responses^{15,19,34,36} and thus may have important relevance for the development of new pain treatments. Although such distinctions have been most apparent in acute pain conditions, there is also emerging evidence that differences in the experience of evoked pain may have important implications on response to some treatments for chronic neuropathic pain.^{12,31} In fact, earlier chronic pain trials reporting spontaneous pain as an outcome of interest provided no definition, methods, or measurement metrics for this distinct component of pain experience.^{1,19,23} In another area of interest, the distinction between rest pain and evoked pain may also have important implications on the transition from acute to chronic pain. For example, a recent review reported that postoperative pain studies were more likely to demonstrate a statistical association between acute and chronic pain if they measure acute movement-evoked pain.¹⁸ Furthermore, ketamine which has been shown to preferentially reduce evoked pain early after surgery³⁴ also appears to demonstrate efficacy in the prevention of chronic pain after surgery.⁸ Although the focus of this exploratory study is on distinguishing between rest (spontaneous) pain and evoked pain, there may also be important distinctions between pain evoked by movement vs pain evoked by touch, and there is currently little, if any, human evidence to suggest whether or not these are subserved by different underlying mechanisms.

Another important feature emphasized by the results of this study is the differential functional impact of rest pain vs evoked pain in individuals suffering from chronic neuropathic pain. Previous studies evaluating the functional impact of neuropathic pain have demonstrated the adverse impact of neuropathic pain on various activities of daily living.^{10,39} However, the study

Table 3

Correlations between FINESSE questionnaire items and modified Brief Pain Inventory pain intensity items.

FINESSE item	Brief Pain Inventory item	Worst pain		Least pain		Average pain		Pain now	
		R ²	P	R ²	P	R ²	P	R ²	P
1		0.165	<0.001	0.067	0.022	0.095	0.006	ns	ns
2		0.221	<0.001	0.134	0.001	0.304	<0.001	0.114	0.003
3		ns	ns	0.087	0.009	0.058	0.034	ns	ns
4		0.113	0.003	0.126	0.001	0.107	0.003	0.114	0.002
5		0.129	0.001	0.197	<0.001	0.221	<0.001	0.340	<0.001
6		0.126	0.001	0.131	0.001	0.158	<0.001	0.153	<0.001
7		ns	ns	ns	ns	0.070	0.019	ns	ns
8		ns	ns	0.076	0.015	0.053	0.042	ns	ns
9		ns	ns	ns	ns	ns	ns	ns	ns
10		ns	ns	0.051	0.047	ns	ns	ns	ns

Significant correlations with R² values of 0.25 and 0.09 correspond to large and medium effect sizes, respectively.

R² and P values shown in bold are statistically significant.

FINESSE, Functional Impact of Neuropathic Evoked and Spontaneous Symptom Evaluation; ns, correlation not statistically significant.

Table 4
Correlations between FINESSE questionnaire items and modified Brief Pain Inventory pain interference items.

FINESSE item	Brief Pain Inventory item	General Activity		Mood		Walking		Normal work		Relations with others		Sleep		Enjoyment of life	
		R ²	P	R ²	P	R ²	P	R ²	P	R ²	P	R ²	P	R ²	P
1		0.085	0.009	0.111	0.003	0.147	0.001	0.249	<0.001	ns	ns	0.128	0.001	0.142	0.001
2		0.309	<0.001	0.174	<0.001	0.223	<0.001	0.368	<0.001	0.128	0.001	0.102	0.004	0.188	<0.001
3		ns	Ns	0.062	0.028	ns	ns	0.071	0.018	ns	ns	0.071	0.018	0.059	0.032
4		0.116	0.002	0.141	0.001	0.109	0.003	0.193	<0.001	ns	ns	0.242	<0.001	0.165	<0.001
5		0.125	0.001	0.153	<0.001	0.128	0.001	0.128	0.001	0.084	0.010	0.140	0.001	0.163	<0.001
6		0.075	0.015	0.081	0.012	0.083	0.011	0.094	0.006	ns	ns	0.180	<0.001	0.138	0.001
7		0.120	0.002	ns	ns	0.111	0.003	0.097	0.005	ns	ns	ns	ns	ns	ns
8		ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
9		ns	ns	0.080	0.012	ns	ns	ns	ns	0.073	0.017	ns	ns	ns	ns
10		0.072	0.017	ns	ns	0.051	0.047	0.072	0.017	ns	ns	ns	ns	ns	ns

Significant correlations with R² values of 0.25 and 0.09 correspond to large and medium effect sizes, respectively.

R² and P values shown in bold are statistically significant.

FINESSE, Functional Impact of Neuropathic Evoked and Spontaneous Symptom Evaluation; ns, correlation not statistically significant.

presented here suggests that activities impacted upon by evoked pain (eg, walking and standing) are different from those associated with rest pain (eg, watching television, reading, and sitting) and furthermore that the degree of functional impairment for various activities of daily living vary according to the respective experience of rest vs evoked in each individual. Given the growing emphasis of functional outcomes in pain treatment trials,³⁵ more attention is needed to assessing the experience of rest pain versus evoked pain given their differential associations with functional impairment.

Although this pilot study suggests the feasibility and validity of self-report methods for distinguishing between rest pain and evoked pain, further work is needed to confirm this. In addition to distinguishing between rest and evoked pain, this preliminary exploratory study has also identified sets of participant-identified activities/situations that are preferentially associated with rest pain vs evoked pain. The sample used for this exploratory study was heterogeneous with respect to underlying neuropathic pain diagnosis and anatomical location of pain. Thus, future studies could advance this field by using more homogeneous populations with respect to underlying etiology (eg, diabetic neuropathy, postherpetic neuralgia, HIV or chemotherapy-induced neuropathies, etc.) and painful body region (eg, lower extremities, chest wall, etc.) and would also benefit from larger sample sizes and repeated measurements for evaluation of test-retest reliability. In an effort to keep this pilot questionnaire as simple as possible and to keep the respondents' focus on distinguishing between rest pain and evoked pain, we did not ask respondents to make a distinction between continuous vs intermittent pain. Therefore, this important distinction needs further attention, and future investigations could include distinguishing between continuous and intermittent pain as an added component. Also, it would be useful to subsequently compare the population profile of rest vs evoked pain in neuropathic conditions to that of other non-neuropathic conditions such as osteoarthritis. Finally, upon completion of a validated questionnaire that distinguishes between rest pain and evoked pain, implementation of such a questionnaire in analgesic clinical trial would serve to evaluate treatment effects on each component of pain experience.

In conclusion, this pilot study proposes new patient-report methods to distinguish between rest pain vs evoked pain in chronic neuropathic conditions. Given our observations of the differential

functional impact of rest pain vs evoked pain, further validation of these methods may provide important improvements to the clinical development of new treatments for chronic pain.

Disclosures

The authors have no conflicts of interest to declare.

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References

- 1] Belfrage M, Sollevi A, Segerdahl M, Sjölund KF, Hansson P. Systemic adenosine infusion alleviates spontaneous and stimulus evoked pain in patients with peripheral neuropathic pain. *Anesth Analg* 1995;81:713-7.
- 2] Bennett GJ. What is spontaneous pain and who has it? *J Pain* 2012;13:921-9.
- 3] Bennett MI, Smith BH, Torrance N, Potter J. The S-LANSS score for identifying pain of predominantly neuropathic origin: validation for use in clinical and postal research. *J Pain* 2005;6:149-58.
- 4] Bennett MI, Attal N, Backonja MM, Baron R, Bouhassira D, Freynhagen R, Scholz J, Tölle TR, Wittchen HU, Jensen TS. Using screening tools to identify neuropathic pain. *PAIN* 2007;127:199-203.
- 5] Bouhassira D, Attal N, Fermanian J, Alchaar H, Gautron M, Masquelier E, Rostaing S, Lanteri-Minet M, Collin E, Grisart J, Boureau F. Development and validation of the Neuropathic Pain Symptom Inventory. *PAIN* 2004;108:248-57.

- [6] Bouhassira D, Attal N. Diagnosis and assessment of neuropathic pain: the saga of clinical tools. *PAIN* 2011;152(3 suppl):S74–83.
- [7] Brennan TJ, Vandermeulen EP, Gebhart GF. Characterization of a rat model of incisional pain. *PAIN* 1996;64:493–501.
- [8] Chaparro LE, Smith SA, Moore RA, Wiffen PJ, Gilron I. Pharmacotherapy for the prevention of chronic pain after surgery in adults. *Cochrane Database Syst Rev* 2013;CD008307.
- [9] Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. *Ann Acad Med Singapore* 1994;23:129–38.
- [10] Coplan PM, Schmader K, Nikas A, Chan IS, Choo P, Levin MJ, Johnson G, Bauer M, Williams HM, Kaplan KM, Guess HA, Oxman MN. Development of a measure of the burden of pain due to herpes zoster and postherpetic neuralgia for prevention trials: adaptation of the brief pain inventory. *J Pain* 2004;5:344–56.
- [11] Davis KD. The neural circuitry of pain as explored with functional MRI. *Neuro Res* 2000;22:313–7.
- [12] Demant DT, Lund K, Vollert J, Maier C, Segerdahl M, Finnerup NB, Jensen TS, Sindrup SH. The effect of oxcarbazepine in peripheral neuropathic pain depends on pain phenotype: a randomized, double-blind, placebo-controlled phenotype-stratified study. *PAIN* 2014;155:2263–73.
- [13] Erb J, Orr E, Mercer CD, Gilron I. Interactions between pulmonary performance and movement-evoked pain in the immediate postsurgical period: implications for perioperative research and treatment. *Reg Anesth Pain Med* 2008;33:312–9.
- [14] Garcia-Larrea L, Convers P, Magnin M, André-Obadia N, Peyron R, Laurent B, Mauguière F. Laser-evoked potential abnormalities in central pain patients: the influence of spontaneous and provoked pain. *Brain* 2002;125(Pt 12):2766–81.
- [15] Gilron I, Max MB, Lee G, Booher SL, Sang CN, Chappell AS, Dionne RA. Effects of the 2-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid/kainate antagonist LY293558 on spontaneous and evoked postoperative pain. *Clin Pharmacol Ther* 2000;68:320–7.
- [16] Gilron I, Tod D, Goldstein DH, Parlow JL, Orr E. The relationship between movement-evoked versus spontaneous pain and peak expiratory flow after abdominal hysterectomy. *Anesth Analg* 2002;95:1702–7.
- [17] Gilron I, Orr E, Tu D, O'Neill JP, Zamora JE, Bell AC. A placebo-controlled randomized clinical trial of perioperative administration of gabapentin, rofecoxib and their combination for spontaneous and movement-evoked pain after abdominal hysterectomy. *PAIN* 2005;113:191–200.
- [18] Gilron I, Vandenkerkhof E, Katz J, Kehlet H, Carley M. Evaluating the association between acute and chronic pain after surgery: impact of pain measurement methods. *Clin J Pain* 2016. doi: 10.1097/AJP.0000000000000443. [Epub ahead of print].
- [19] Gottrup H, Bach FW, Juhl G, Jensen TS. Differential effect of ketamine and lidocaine on spontaneous and mechanical evoked pain in patients with nerve injury pain. *Anesthesiology* 2006;104:527–36.
- [20] Kehlet H, Dahl JB. Assessment of postoperative pain—need for action! *PAIN* 2011;152:1699–700.
- [21] Koplovitch P, Minert A, Devor M. Spontaneous pain in partial nerve injury models of neuropathy and the role of nociceptive sensory cover. *Exp Neurol* 2012;236:103–11.
- [22] Loeser JD. Chronic pain is more than a peripheral event. *J Pain* 2012;13:930–1.
- [23] Mailis A, Amani N, Umana M, Basur R, Roe S. Effect of intravenous sodium amytal on cutaneous sensory abnormalities, spontaneous pain and algometric pain pressure thresholds in neuropathic pain patients: a placebo-controlled study. II. *PAIN* 1997;70:69–81.
- [24] Malinen S, Vartiainen N, Hlushchuk Y, Koskinen M, Ramkumar P, Forss N, Kalso E, Hari R. Aberrant temporal and spatial brain activity during rest in patients with chronic pain. *Proc Natl Acad Sci U S A* 2010;107:6493–7.
- [25] Mogil JS, Crager SE. What should we be measuring in behavioral studies of chronic pain in animals? *PAIN* 2004;112:12–5.
- [26] Mogil JS. The etiology and symptomatology of spontaneous pain. *J Pain* 2012;13:932–3.
- [27] Nordin M, Nyström B, Wallin U, Hagbarth KE. Ectopic sensory discharges and paresthesiae in patients with disorders of peripheral nerves, dorsal roots and dorsal columns. *PAIN* 1984;20:231–45.
- [28] Peyron R, Laurent B, Garcia-Larrea L. Functional imaging of brain responses to pain. A review and meta-analysis (2000). *Neurophysiol Clin* 2000;30:263–88.
- [29] Price LR. *Psychometric methods: theory into practice*. New York, NY: Guilford Press, 2016.
- [30] Serra J, Duan WR, Locke C, Solà R, Liu W, Nothaft W. Effects of a T-type calcium channel blocker, ABT-639, on spontaneous activity in C-nociceptors in patients with painful diabetic neuropathy: a randomized controlled trial. *PAIN* 2015;156:2175–83.
- [31] Simpson DM, Schifitto G, Clifford DB, Murphy TK, Durso-De Cruz E, Glue P, Whalen E, Emir B, Scott GN, Freeman R; 1066 HIV Neuropathy Study Group. Pregabalin for painful HIV neuropathy: a randomized, double-blind, placebo-controlled trial. *Neurology* 2010;74:413–20.
- [32] Srikandarajah S, Gilron I. Systematic review of movement-evoked pain versus pain at rest in postsurgical clinical trials and meta-analyses: a fundamental distinction requiring standardized measurement. *PAIN* 2011;152:1734–9.
- [33] Streiner DL, Norman GR, Cairney J. *Health measurement scales: A practical guide to their development and use*. 5th ed. New York, NY: Oxford University Press, 2015.
- [34] Stubhaug A, Breivik H, Eide PK, Kreunen M, Foss A. Mapping of punctuate hyperalgesia around a surgical incision demonstrates that ketamine is a powerful suppressor of central sensitization to pain following surgery. *Acta Anaesthesiol Scand* 1997;41:1124–32.
- [35] Taylor AM, Phillips K, Turk DC, Dworkin RH, Beaton D, Clauw DJ, Gignac MA, Markman JD, Williams DA, Bujanover S, Burke LB, Carr DB, Choy EH, Conaghan PG, Cowan P, Farrar JT, Freeman R, Gewandter J, Gilron I, Goli V, Gover TD, Haddock JD, Kerns RD, Kopecy EA, Lee DA, Malamut R, Mease P, Rappaport BA, Simon LS, Singh JA, Smith SM, Strand V, Tugwell P, Vanhove GF, Veasley C, Walco GA, Wasan AD, Witter J. Assessment of physical function and participation in chronic pain clinical trials: IMMPACT/OMERACT recommendations. *PAIN* 2016;157:1836–50.
- [36] Tverskoy M, Oren M, Dashkovsky I, Kissin I. Alfentanil dose-response relationships for relief of postoperative pain. *Anesth Analg* 1996;83:387–93.
- [37] Woolf CJ, Bennett GJ, Doherty M, Dubner R, Kidd B, Koltzenburg M, Lipton R, Loeser JD, Payne R, Torebjork E. Towards a mechanism-based classification of pain? *PAIN* 1998;77:227–9.
- [38] Woolf CJ, Max MB. Mechanism-based pain diagnosis: issues for analgesic drug development. *Anesthesiology* 2001;95:241–9.
- [39] Zelman DC, Gore M, Dukes E, Tai KS, Brandenburg N. Validation of a modified version of the brief pain inventory for painful diabetic peripheral neuropathy. *J Pain Symptom Manage* 2005;29:401–10.

Appendix 1. Functional Impact of Neuropathic Evoked and Spontaneous Symptom Evaluation (FINESSE) questionnaire

- Do certain activities or movements cause or increase your pain?
 - Never
 - Sometimes
 - Often
 - Very Often
 - Always
 - If so, please list these activities or movements:
- Do you avoid certain activities or movements because you think they will cause or increase your pain?
 - Never
 - Sometimes
 - Often
 - Very Often
 - Always
 - If so, please list these activities or movements:
 - (Note: *You may choose to include some or all activities you listed in #1, and possibly others, depending on which you avoid*)
- Does anything touching your skin cause or increase your pain?
 - Never
 - Sometimes
 - Often
 - Very Often
 - Always
 - If so, please list examples:
- Does pain which is caused or increased by touch interfere with any of your activities or movements (including sleep)?
 - Never
 - Sometimes
 - Often

- Very Often
 - Always
 - If so, please list these activities or movements:
5. Do you feel pain while sitting still or doing nothing?
- Never
 - Sometimes
 - Often
 - Very Often
 - Always
- 6a. While lying in bed, or sitting still, do you often feel pain that is NOT related to anything touching your skin (eg, bedsheets)?
- Never
 - Sometimes
 - Often
 - Very Often
 - Always
- 6b. Please provide examples of different situations when you feel NON-touch-related pain while lying in bed or sitting still (eg, watching television, reading a book, etc.)
7. Do you continue as usual with all your regular activities of life even though such activities cause or increase your pain?
- Never
 - Sometimes
 - Often
 - Very Often
- Always
8. Do certain activities or movements relieve or decrease your pain?
- Never
 - Sometimes
 - Often
 - Very Often
 - Always
 - If yes, please list these activities or movements:
9. Do you specifically do certain activities or movements because you think they will relieve or decrease your pain?
- Never
 - Sometimes
 - Often
 - Very Often
 - Always
 - If yes, please list these activities or movements:
10. Do you specifically do certain activities or movements because you think they will prevent your pain?
- Never
 - Sometimes
 - Often
 - Very Often
 - Always
 - If yes, please list these activities or movements: