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Mechanistic pain profiling as a tool to predict the efficacy of 3-weeks non-steroidal anti-inflammatory drugs (NSAIDs) plus paracetamol in patients with painful knee osteoarthritis

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Abstract

Joint inflammation is present in a subpopulation of knee osteoarthritic (KOA) patients. Pro-inflammatory cytokines are known to sensitize the peripheral and central pain pathways. This can be mechanistically assessed by pressure pain thresholds and temporal summation of pain (TSP). Non-steroidal anti-inflammatory drugs (NSAIDs) combined with paracetamol are recommended as OA treatment. The current study hypothesized that evidence of central sensitization would predict poor responses to peripherally directed therapies in KOA and therefore aimed to investigate the value of mechanistic pain profiling for predicting pain outcome of treatment with NSAIDs plus paracetamol. One-hundred-and-thirty-two patients received Ibuprofen 1200 mg/daily, paracetamol 3g/daily, and pantoprazole 20 mg/daily for 3-weeks. Prior to administration, cuff pain detection, tolerance threshold and TSP were assessed. Worst pain within the last 24-hours and pain during activity (visual analog scales) were assessed before and after treatment.

Facilitated TSP was found at baseline in the non-responders to the 3-weeks treatment as compared with responders for both the 30% and 50% pain alleviation criteria ($P<0.02$). Linear regression models identified facilitated TSP ($P<0.01$) and low clinical pain scores ($P<0.001$) as independent factors for prediction of poor pain alleviation by the treatment.

In conclusion, this study found that mechanistic pain profiling can predict pain alleviation of NSAIDs and paracetamol. Facilitated TSP and low clinical pain scores prior to treatment are independent predictors of poor pain alleviation following NSAIDs and paracetamol. This study adds to the growing evidence that a subgroup of KOA patients with manifested central sensitization may require special management attention.

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Keywords: Osteoarthritis, mechanistic pain profiling, non-steroidal anti-inflammatory drug, temporal summation of pain

Introduction

Musculoskeletal pain is an increasingly large clinical problem and knee osteoarthritis (OA) is the most common joint condition[55]. The mechanisms underlying pain in knee OA are largely unknown[2], but recent studies indicate that inflammation is present in a subpopulation of knee OA patients[53] and that increased inflammation is associated with increased pain severity[17,18].

Pro-inflammatory cytokines are known to sensitize the peripheral nerve endings leading to hyperalgesia[50], which can be assessed as lowered pressure pain thresholds (PPTs). A prolonged intense painful input from the periphery may sensitize the dorsal horn neurons leading to an increased central gain of pain. This phenomenon can be assessed as facilitated temporal summation of pain (TSP)[22]. Widespread hyperalgesia can in part be explained by impaired descending pain control which is considered the net effect of pain inhibitory and facilitatory pathways[6,59]. Mechanistic pain profiling using quantitative sensory testing (QST) has demonstrated local and widespread pressure hyperalgesia and facilitated TSP in patients with severe knee OA compared with pain-free subjects[4]. Further, mechanistic pain profiling of knee OA patients has found preoperative TSP and PPTs to be predictive of the development of chronic postoperative pain following total joint replacement [27,39,40,42,58]. These parameters are normalized after a successful TKA recovery leading to a pain-free outcome [24,31] and this highlights the significance of such mechanisms as targets for pain management.

The combination of non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol is considered the first line of treatment for painful knee OA [26,28]. Analgesic effects have been widely documented even though the mechanisms of action are not completely understood[21]. Further, it cannot be predicted which patients would benefit most from the treatment. NSAIDs may be potentially harmful[34]. Hence patients who do not benefit sufficiently from the treatment should not be exposed to this risk. Both NSAIDs and paracetamol inhibit the synthesis of prostaglandins modulated through cyclooxygenase (COX). In the rat, non-selective NSAIDs and paracetamol enhance the activity of the

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cannabinoid system[1], and studies suggest that the analgesic effect of NSAIDs and selective COX-2 inhibitors is dependent on an intact serotonin system[21]. Further, COX-2 inhibitors modulate widespread hyperalgesia[34,46] suggesting that NSAID treatment may also modulate central pain pathways and that mechanistic pain profiling could identify responders to NSAID treatment. Finally, facilitated TSP prior to treatment has been found to be associated with pain alleviation in responders to selective COX-2 inhibitors in knee OA[3].

The effect size of the combination of NSAIDs and paracetamol is larger than either NSAIDs or paracetamol alone[38]. In this context, the combination of 1.2 gram Ibuprofen and 3 gram paracetamol per day has been found superior to paracetamol alone in osteoarthritic pain[14]. Long-term use of NSAIDS may pose serious health risks [34] and hence tools for predicting the possible benefits are warranted. A recent study found that a reduction in the brain blood oxygen level–dependent signal activation of the sensory cortex and supramarginal gyrus in OA patients was associated with poor pain alleviation following treatment with paracetamol[60]. This indicates that measures of central sensitization could add prognostic information in treatment of OA. Therefore, the current study hypothesized that centrally sensitized OA patients would receive poor or limited analgesic effects of NSAIDs plus paracetamol and aimed to use mechanistic pain profiling as a tool to predict the efficacy of a 3-week NSAIDs plus paracetamol treatment in patients with painful knee OA.

Methods

Protocol

A consecutive cohort of knee OA patients were recruited between January 2016 and February 2018. Data were collected at the Orthopedic Outpatient Clinic at Aalborg University Hospital, Aalborg, Denmark. The study was approved by The North Denmark Region Committee on Health Research Ethics (N-20140077) and registered at ClinicalTrials.gov (NCT02967744). Written informed consent was obtained before patient inclusion. Clinical OA was defined following the American College of Rheumatology criteria[56]. The peak pain intensity within the last 24 hours and the pain during activity (visual analog scale, VAS), the Knee Injury and Osteoarthritis Score (KOOS) and quantitative sensory testing (QST) recordings (pressure pain detection threshold (cPDT), and pain tolerance threshold (cPTT) and TSP) were collected before treatment. The exclusion criteria included the presence of other

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pain problems (e.g. hip OA), sensory dysfunction (e.g. fibromyalgia, neuropathic pain), or mental impairment.

Treatment
Patients were administrated Ibuprofen 400 mg (three times per day), Paracetamol 1g (three times per day) and Pantoprazole 20 mg (once per day) for 3-weeks. Patients were instructed to report all adverse and severe adverse events.

Clinical assessment of pain and function
KOOS, a 42-item self-administered questionnaire[49] assessing five separate dimensions: pain, symptoms, activities of daily living (ADL), sport and recreation function (Sport/Rec), and knee-related quality of life (QOL), was administrated before and after treatment. A percentage score from 0% to 100% was calculated for each dimension; 100% representing the best possible score.

The worst pain within the last 24 hours and the pain during activity were assessed using a VAS before and after treatment. The VAS was anchored at 0 cm: no pain and 10 cm: worst pain imaginable. These assessments have been consistently used in similar studies[27,39,41–43].

Quantitative sensory testing
Deep-tissue pain sensitivity was evaluated by cuff pressure stimuli using a computer-controlled cuff algometer (Cortex Technology and Aalborg University, Denmark) including a 13-cm wide tourniquet cuff (VBM, Sulz, Germany) and an electronic VAS (Aalborg University, Denmark) for recording of the pain intensity. The cuff was placed at the level of the head of the gastrocnemius muscle of the leg most affected by OA. The electronic continuous VAS (sliding resistor) was 10 cm long and sampled at 10 Hz; 0 cm indicated “no pain” and 10 cm indicated “maximum pain”.

Cuff pain detection and tolerance threshold

The pressure (in kPa) was increased by 1 kPa/s and the patient was instructed to rate the pain intensity continuously on the electronic VAS until the tolerance level was reached. The patients were instructed to press a stop button at this point of time. The pressure pain detection threshold (cPDT) was defined as the pressure at which the VAS score exceeded 1 cm[23]. The pain tolerance threshold (cPTT) was defined when the patient pressed the stop button. cPDT and cPTT were assessed bilaterally.

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Temporal summation of pain

Ten short-lasting stimuli (1 s each) at the level of the cPTT were given with a 1 s break between stimuli. The participants were instructed to continuously rate the pain intensity of the sequential stimuli using the electronic VAS and not to return to zero during the breaks. For each cuff stimulus, a VAS score was extracted and TSP was defined as the difference between the tenth and the first VAS score[39].

Statistical analysis

The data are presented as means and standard error of the mean (SEM) if not otherwise stated. Paired sample t-tests were used to compare VAS and KOOS data before and after treatment. The patients were divided into responders and non-responders based on a 30% or a 50% pain alleviation from the treatment using the VAS scale. Pre-treatment parameters (VAS, cPDT, cPTT and TSP) were compared between the two groups (responders and non-responders) using independent sample t-tests. Finally, linear regression models were used to define independent factors and to predict the analgesic effect of the treatment using the mechanistic pain profiles and clinical pain intensity (VAS) prior to treatment. The statistical analyses were performed using SPSS (version 23, IBM Corporation, New York, USA). P-values < 0.05 were considered significant.

Results

Clinical assessments of pain, function and quality of life

One-hundred-and-sixty-two patients were recruited and 132 patients had complete follow-up data after treatment and were included in the current analysis. Significantly decreased pain during activity and worst pain during the last 24 hours (P<0.001), increased KOOS pain (P<0.001), KOOS symptoms (P<0.001) and KOOS ADL (P<0.001) were found at follow-up compared with before treatment values; see table 1.

Clinical and mechanistic pain profiles based on a 30% pain alleviation

Fifty-two (39%) of 132 patients obtained a 30% pain relief based on the worst pain within the last 24 hours. Further, this group showed significantly increased KOOS symptoms (P=0.028), KOOS ADL (P=0.007), a trend towards significantly increased KOOS QOL (P=0.056) and a trend towards significantly increased KOOS Pain (P=0.071) before treatment compared with the group which did not obtain 30% pain relief. These figures are based on worst pain within the last 24 hours. Sixty (45%) of

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132 patients obtained a 30% pain relief based on pain during physical activity. This group had significantly increased KOOS pain (P<0.001), KOOS symptoms (P=0.005), KOOS ADL (P<0.001) and increased KOOS QOL (P=0.010) before treatment compared with the group which did not obtain a 30% pain relief. In addition, based on the 30% pain alleviation criterion of pain during activity and worst pain during the last 24 hours, non-responders compared with responders showed facilitated TSP prior to treatment (P<0.020, figure 1) but no differences in cPDT or cPTT.

Clinical and mechanistic pain profiles based on a 50% pain alleviation

Thirty-three (25%) of 132 subjects obtained a 50% pain relief based on the worst pain within the last 24 hours. This group was not significantly different with regard to any clinical assessments of pain, function or quality of life (P>0.2). Based on the 50% pain relief using the pain during physical activity, 42 patients (32%) had significantly increased KOOS pain (P=0.004), KOOS symptoms (P=0.018), KOOS ADL (P=0.004) and increased KOOS QOL (P=0.007) before treatment compared with the group which did not obtain a 50% pain relief.

Based on the 50% pain alleviation criterion of pain during activity and worst pain during the last 24 hours, non-responders compared with responders showed facilitated TSP prior to treatment (P<0.023, figure 1) but no differences in cPDT or cPTT.

Prediction models of pain alleviation following treatment

Several linear regression models were established to investigate the predictive value using the mechanistic pain measures and clinical pain prior to treatment. Model 1, consists of all the mechanistic pain measures and pain prior to treatment with predictive values (R^2) of 24.6% for worst pain within the last 24 hours and 27.8% for pain during activity and identified pain intensity (P<0.001) and TSP (P<0.008) prior to treatment as significant factors; table 2. Model 2, constricted to significant factors only (using backwards selection), showed with predictive values (R^2) of 24.0% for worst pain within the last 24 hours and 26.9% for pain during activity with pain intensity (P<0.001) and TSP (P<0.009) prior to treatment as significant factors (table 2). The predictive values of model 2 were not significantly different from model 1 (P>0.5), indicating that facilitated TSP and lower pain intensity prior to treatment are the most important features in these models and predict a poor or limited analgesic effect to NSAID plus paracetamol. In addition, linear regression models define independent factors illustrating that pain prior to treatment and TSP are independent factors for the prediction of the analgesic effect of NSAIDs plus paracetamol.

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Discussion

The current study is the first large sized mechanistic pain profiling trial to predict an analgesic response following a 3-week NSAIDs and paracetamol combination in patients with painful knee osteoarthritis. The study found that approx. 40% of the patients obtained a 30% analgesic effect and that approx. 25% of the subjects obtained a 50% analgesic effect following the 3-weeks of NSAIDs plus paracetamol. In addition, non-responders to the 30% and 50% cutoff criteria were characterized by facilitated TSP before treatment compared with responders. Finally, the linear regression models identified facilitated TSP and lower clinical pain intensity prior to treatment as independent factors associated with the poor or limited analgesic effect of NSAIDs plus paracetamol.

Analgesic effect of NSAIDs plus paracetamol for osteoarthritis

NSAIDs and/or paracetamol are considered the first line of medications for treating osteoarthritic pain[26,28]. On average, pain alleviation from analgesics in OA is approx. 20-25% (except the anti-NGF compounds, which show stronger effects)[52]. It is currently debated if and how responders to treatment can be classified. The Osteoarthritis Research Society International (OARSI) Standing Committee for Clinical Trials Response Criteria Initiative and the Outcome Measures in Rheumatology (OMERACT) Committee have defined a responder as either 1) an improvement in pain and function by at least 50% or 2) an improvement by at least 20% in two of the following three categories: pain, physical function or global assessment of the patient [44]. The current study reported a 28.6% pain reduction when assessing the worst pain within the last 24 hours, 31.5% when assessing the pain during activity and a 14.8% pain reduction when assessing the KOOS pain subscale. This illustrates that the method used for pain assessment would greatly affect the OMERACT-OARSI responder criteria.

Studies have found that the majority of the pain improvement occurs within the first weeks of treatment[12,45]. This further supports the short administration period in the current study compared with previous long-term studies showing less convincing long-term effects[9].

NSAIDs plus paracetamol and mechanistic pain profiling

The mechanisms underlying pain in OA are largely unknown complicating the treatment of the pain. Recent evidence suggests that inflammatory markers are associated with osteoarthritic pain[17,51,53] and that inflammatory markers are known to sensitize the peripheral nerve endings resulting in

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hyperalgesia[50]. Both localized and widespread hyperalgesia are found in knee OA patients with high clinical pain intensities [7,16]. NSAIDs inhibit the synthesis of prostaglandins[21], which in turn will blunt the activation of leukocytes thereby minimizing the inflammatory cascade. In theory, this should dampen hyperalgesia. Pre-clinical data suggest that locally upregulated prostaglandins will induce peripheral hyperalgesia and that upregulated prostaglandins in the central nervous system will induce widespread hyperalgesia[46,57]. Interestingly, spinal administration of COX-2 inhibitors in an animal inflammatory model reduces prostaglandin subtype E2 and reduces peripheral mechanical hyperalgesia[46,57] indicating that COX-2 acts on central pain mechanisms as recently shown in knee OA patients[3]. Both COX-2 inhibitors[47] and non-selective COX inhibitors[8,10,25] are found in the cerebrospinal fluid after oral administration in humans. This should modulate locally and widespread hyperalgesia and lead to an analgesic effect. This theory is in contrast to the current study, which found that facilitated TSP (as a measure of central gain of pain) was associated with less pain alleviation following 3 weeks of NSAIDs plus paracetamol.

A previous study has found that approx. 50% of patients experience an additional pain relieving effect when switching from NSAIDs to etoricoxib (a selective COX-2 inhibitor)[33] indicating an additional analgesic effect of administering etoricoxib compared with traditional NSAIDs (COX-1 and COX-2). However, this needs validation in large clinical cohorts.

The predictive value of mechanistic pain profiling in the treatment of osteoarthritic pain

Recent reviews have concluded that there is a neuropathic component in a subpopulation of OA patients[6,13]. The PainDetect questionnaire aims to identify a positive, unclear and negative neuropathic pain component in chronic pain patients[20], and studies have identified 5 - 30%[32,35,37] of OA patients with a positive neuropathic pain component. Furthermore, OA patients with a positive neuropathic pain component have been found to report higher pain intensities and widespread pressure hyperalgesia compared with an unclear or negative neuropathic pain component[35]. Finally, a recent study found that OA patients with a positive neuropathic pain component display preoperatively widespread hyperalgesia, facilitated TSP and report higher pain intensities six months after total knee arthroplasty (TKA) compared with patients with an unclear or negative neuropathic pain component[32].

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The pain sensitivity has been suggested to increase with increasing pain duration and pain intensity in knee OA[7]. Recent phenotyping of knee OA patients based on radiological OA severity and pain intensity has revealed that patients characterized by high pain intensities but low radiological OA are highly pain sensitive[5,19] and respond poorly to TKA[42,48]. Several recent studies have revealed that preoperative pressure pain thresholds[40], TSP[39,42], or CPM[54] are predictive of poor outcome after TKA indicating that highly centrally pain sensitive knee OA patients do not respond well to TKA. Recently, O'Leary et al.[36] found that facilitated TSP and low PPTs were predictive of poor outcome for knee OA patients following physiotherapy. The current study further indicates that knee OA patients with facilitated TSP do not respond optimally to standard anti-inflammatory treatment, which is in line with a previous study regarding topical NSAIDs in knee OA[16].

Conclusively, accumulating evidence suggests that knee OA patients defined as "centrally sensitized" might not respond to the guidelines by OARSI[61] and hence the new pain descriptor "nociplastic" may apply to such conditions[30].

Future research should aim to link mechanistic pain profiling to pain alleviation using these drugs in OA patients who are characterized as centrally pain sensitive to enhance our understanding of the treatment options.

Limitations

It could be argued that this exploratory study is limited by the lack of a placebo group. The aim of the study was not to compare with placebo but to investigate if the outcome after a well-known therapy could be predicted. Several studies have shown that the analgesic effects of NSAIDs plus paracetamol are superior to placebo[11,12,15,29,45]. The aim of the study was to investigate the value of mechanistic pain profiling and its predictive value after NSAIDs and paracetamol treatment as mechanistic pain profiling has previously been shown to identify poor responders to other standardized OA treatments [36,39,40,42,54]. Predicting poor NSAID treatment outcome is valuable as patients not responding adequately should not be treated with NSAIDs due the possible unwanted side effects.

Conclusion

The mechanistic pain profiling identified non-responders to standard pharmacological treatment. This study adds to the growing evidence that a subgroup of OA patients who are specifically centrally pain

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sensitive (facilitated TSP) may require special management attention. Avoiding NSAID treatment in patients not benefitting is important to protect those patients from unwanted side effects.

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Figure legends

Figure 1: Temporal summation of pain in knee osteoarthritic patients grouped into responders and non-responders based on a pain alleviation of at least 30% or 50% following 3 weeks of NSAIDs and paracetamol for the worst pain within the last 24 hours (worst pain) or pain during activity (Activity). * indicate significant differences ($P<0.05$) between responders and non-responders.

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Table 1: Mean and standard error of the mean (SEM) from 132 knee osteoarthritis patients before and after treatment.

	Before treatment Mean (SEM)	After treatment Mean (SEM)	Percentage change	P-value
Age (years)	60.01 (0.81)			
BMI [kg/m^2]	29.15 (0.46)			
Gender (percentage female)	52.6%			
Pain intensity [cm]				
- worst pain within the last 24 hours	6.88 (0.20)	4.91 (0.26)	28.6%	<0.001
- During activity	6.38 (0.23)	4.37 (0.29)	31.5%	<0.001
KOOS subscales				
- Pain	52.45 (1.50)	60.20 (1.63)	14.8%	<0.001
- Symptoms	59.18 (1.71)	64.15 (1.88)	8.4%	<0.001
- ADL	58.63 (1.71)	65.31 (1.84)	11.4%	<0.001
- QoL	36.54 (1.40)	39.36 (2.78)	7.7%	0.242

BMI: Body mass index, KOOS: Knee Injury and Osteoarthritis Score, ADL: Function in daily living, QoL: Quality of life.

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Table 2: Linear regression models using mechanistic pain profiling and pain intensity prior to 3 weeks of non-steroidal anti-inflammatory drugs and paracetamol treatment of patients with knee osteoarthritis.

		Worst pain within the last 24 hours			Pain during activity		
Model	Variable	Standardized coefficient	P-value	R^2	Standardized coefficient	P-value	R^2
1				0.246			0.278
	Pain intensity prior to treatment	0.474	**<0.001**		0.471	**<0.001**	
	cPDT (ipsilateral)	-0.026	0.861		0.084	0.574	
	cPTT (ipsilateral)	-0.064	0.688		-0.024	0.880	
	cPDT (contralateral)	-0.028	0.849		-0.067	0.642	
	cPTT (contralateral)	0.130	0.387		0.096	0.515	
	TSP	0.220	**0.008**		-0.264	**0.002**	
2				0.240			0.269
	Pain intensity prior to treatment	0.472	**<0.001**		0.472	**<0.001**	
	TSP	-0.217	**0.009**		-0.264	**0.001**	

Model 1 included pain intensity, cuff pain detection (cPDT) and tolerance thresholds (cPTT) assessed bilaterally and temporal summation of pain (TSP) assessed prior to treatment. Model 2 included significant factors from model 1 (using backwards selection). R^2 indicate the predictive value of each model.

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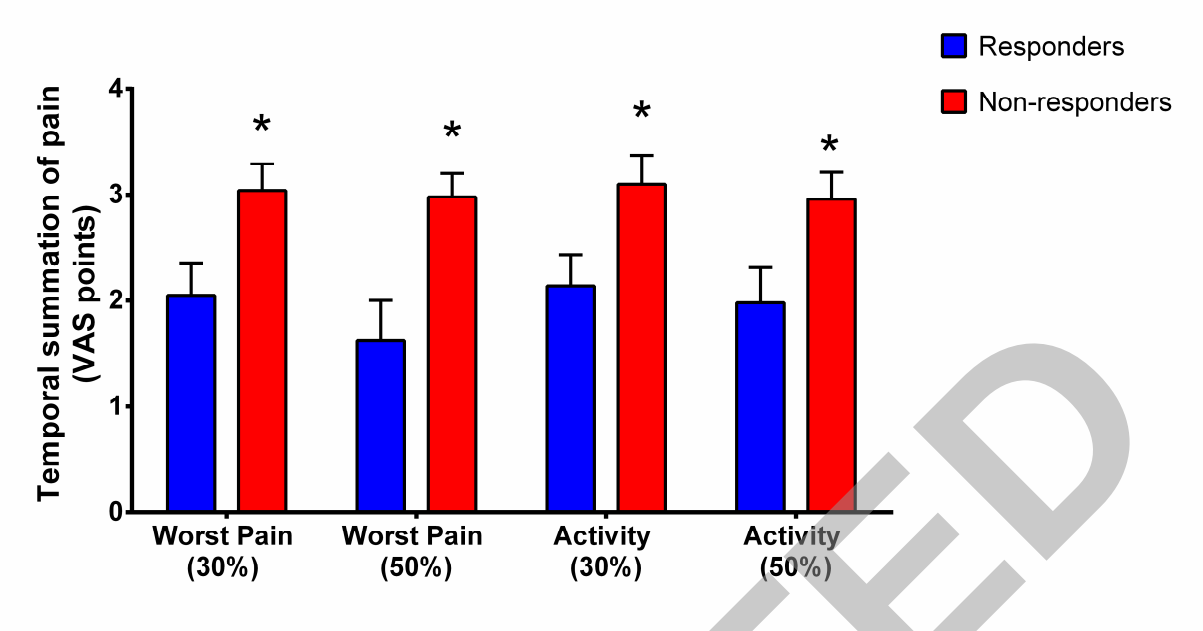

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