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Only Women Report Increase in Pain Threshold Following Fatiguing Contractions of the Upper Extremity

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Abstract

Purpose The perception of pain in response to a noxious stimulus can be markedly reduced following an acute bout of exercise [exercise-induced hypoalgesia (EIH)]. Sex differences in EIH frequently occur after exercise but may be confounded by the sex differences in muscle fatigue. The purpose was to determine if sex differences in pain relief occur after an exercise protocol when muscle fatigue is similar for both young and older men and women. *Methods* Pain perception of 33 men (15 young) and

31 women (19 young) was measured using a pressure pain stimulus on the left index finger before and after maximal velocity concentric contractions of knee extensors or elbow flexors (separate days). During the 2-min pressure pain test, participants verbally indicated the onset of pain (pain threshold) and reported pain intensity (0–10) every 20 s. *Results* Only women experienced an increase in pain threshold (30 ± 27 to 41 ± 32 s) following elbow flexor exercise (trial × sex: $p = 0.03$). Neither men nor women experienced an increase in pain threshold following knee extensor exercise, and pain ratings were unchanged after exercise with either limb ($p > 0.05$). The pain response to exercise was similar in young and older adults (trial × age: $p > 0.05$), despite older adults demonstrating greater fatigability than young adults for the elbow flexor and knee extensor exercise tasks.

Conclusions Under controlled conditions where muscle fatigue is similar, sex differences in EIH occur in young and older adults that is site specific (upper extremity). Only women experience EIH following acute single limb high-velocity contractions.

Keywords
Aging, Gender, Women, Pain perception, Hypoalgesia

Abbreviations
ANOVA Analysis of Variance, EIH Exercise-induced Hypoalgesia, mins Minutes, MVCC Maximal Velocity, Concentric Contraction, MVIC Maximal Voluntary Isometric Contraction

Introduction
The perception of pain in response to a noxious stimulus can be markedly reduced following an acute bout of exercise
[exercise-induced hypoalgesia (EIH)]. Women, in particular, may experience greater hypoalgesia than men following exercise. This sex difference in EIH is not influenced by the phase of the menstrual cycle (Hoeger Bement et al. 2009), and occurs across several types of exercise including dynamic and isometric contractions. For example, following aerobic exercise (10 min of treadmill running at 85 % maximal heart rate) women, but not men, experienced decrease in pain intensity (Sternberg et al. 2001). Likewise, following maximal and submaximal isometric handgrip contractions, women reported increases

Table 1 Demographics, physical activity, and fatigability

Variable	Units	Young Women	Young Men	Older Women	Older Men
Age	Years	20.6 (1.5)	21.7 (3.7)	71.3 (7.6)[b]	71.3 (5.1)[b]
Height	m	1.68 (0.08)[a]	1.83 (0.06)	1.62 (0.06)[a,b]	1.76 (0.06)[b]
Weight	kg	61.9 (6.7)[a]	72.4 (8.2)	68.1 (13.2)[a,b]	81.7 (13.1)[b]
BMI	Kg/m2	22.0 (2.6)	21.6 (2.1)	25.9 (4.0) [b]	26.5 (3.9)[b]
Physical Activity	METhr/week	85.5 (48.5)	89.9 (47.0)	35.9 (21.8)[b]	52.5 (46.3)[b]
Fatigue Measures					
↓ KE Power	%	9(10)	4 (10)	25 (17)[b]	26 (15)[b]
↓ EF Power	%	12(10)	15 (14)	17 (14)[b]	24 (10)[b]

Decreases in muscle power (fatigability) are displayed in the lower panel of the table

a Denotes main effect of sex, $P < 0.05$
b Denotes main effect of age

in pain threshold and decreases in pain ratings while men experienced either no change or only decreases in pain ratings (Koltyn et al. 2001). Similarly, older women experienced larger reductions in pain ratings than men following low- and high-intensity isometric contractions with the elbow flexor muscles (Lemley et al. 2014).

Sex differences in EIH, however, are not always evident (Hoeger Bement et al. 2008) and some studies have reported greater EIH among men compared to women (Umeda et al. 2010). A major confounding variable for many of these exercise protocols is that there are sex differences in muscle fatigue such that women exhibit less muscle fatigue than men for a given intensity of exercise (Hunter 2014). This sex difference is most notable for isometric fatiguing contractions (Hunter and Enoka 2001) and less during single limb fast dynamic exercise (Senefeld et al. 2013). Differences in fatigability can also be specific to the muscle group involved. For example, fatigability of the elbow flexor muscles was greater than the knee extensor muscles for repeated fast-velocity dynamic contractions (Senefeld et al. 2013). Thus, comparison of EIH among the sexes during a dynamic protocol that elicits similar magnitudes of fatigue but in different muscle groups would provide insight into the specificity on the sex difference in the pain response.

The primary purpose of this study was to determine if sex differences in pain relief occur after a fatiguing task of maximal velocity dynamic contractions, a task where muscle fatigue is similar for men and women but differs between upper and lower limb muscles (Senefeld et al. 2013). Because women have shown greater EIH than men with both fatiguing and non-fatiguing contractions (Lemley et al. 2014; Koltyn et al. 2001; Vaegter et al. 2014), we hypothesized that women would experience greater EIH than men following dynamic contractions despite the similar fatigability. Because the magnitude of the EIH response after isometric exercise can decline with age (Lemley et al. 2014; Vaegter et al. 2015), both young and older men and women participated to identify whether potential sex differences were evident with advanced age after dynamic contractions.

Methods

Thirty-three men (15 young) and 31 women (19 young) healthy adults participated in one familiarization and two counterbalanced experimental sessions that involved testing pain before and after fatiguing exercise with either elbow flexors or knee extensors. Participant demographics can be found in Table 1. All participants provided written informed consent prior to involvement in the study and the protocol was approved by the Marquette University Institutional Review Board in accordance with the Declaration of Helsinki.

During the first session, participants were familiarized with the testing equipment and procedures. Each participant performed maximal voluntary isometric contractions (MVICs) and maximal voluntary concentric contractions (MVCCs) with knee extensor and elbow flexor muscles. Participants were also familiarized to the pressure pain test.

Pain

Pressure pain was assessed via a custom mechanical stimulus device (Romus Inc., Milwaukee, WI) (Lemley et al. 2014, 2015; Hoeger Bement et al. 2008, 2009). A Lucite edge (8 × 1.5 mm) was placed on the dorsum of the left index finger midway between the proximal and distal interphalangeal joints for 2 min. A mass (200 g) was applied to a second-class lever such that a 10-N force (1 kg mass) was applied to the Lucite edge (Fig. 1a). The participant reported pain ratings every 20 s on an 11-point scale with the following anchors: 0 = no pain and 10 = worst pain (Williamson and Hoggart 2005) and verbally indicated when the pressure first changed to pain [pain threshold (s)]. During each exercise session, this stimulus was applied twice (prior to and immediately following exercise). EIH was defined as the difference in pain threshold or average pain rating across the six time points before and after exercise. Participants also completed a questionnaire to estimate physical activity (Kriska and Bennett 1992).

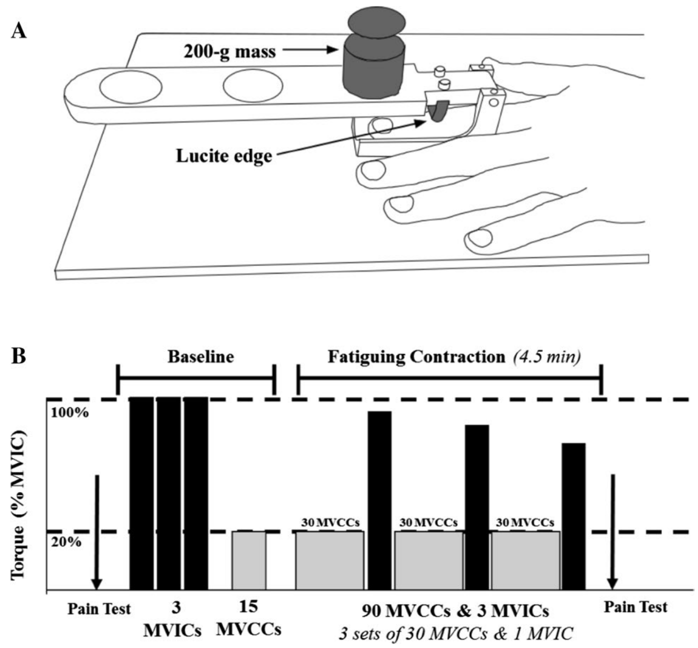

Fig. 1 a Representation of the mechanical stimulus device (Romus Inc., Milwaukee, WI) used for the pressure pain test performed on the left hand. **b** A graphical representation of the protocol during the experimental sessions. Participants performed: (1) pain perception test before and after a fatiguing contraction, (2) baseline maximum voluntary isometric contraction (MVIC) and maximum voluntary concentric contraction (MVCC) measures, and (3) a fatiguing contraction involving 3 subsequent sets of 30 MVCCs and 1 MVIC for a total of 90 MVCCs and 3 MVICs.

Fatiguing protocols

During the experimental sessions (sessions 2 and 3), participants performed a 4.5-min dynamic fatiguing task with either the elbow flexor muscles or knee extensor muscles while the participant was seated in Biodex System 4-Pro dynamometer chair (Biodex Medical, Shirley, NY). Each participant was seated upright in the chair with 90º of hip flexion and secured with padded straps across the shoulders and the waist to minimize auxiliary movements during the fatiguing task. All dynamic contractions during baseline measures and the fatiguing protocol were performed with a load equivalent to 20 % of MVIC because this load (during maximal velocity efforts) corresponds to near peak power (force × velocity) along the force–velocity curve (Caiozzo 2012). Prior to the fatigue task, each participant performed: (1) at least three brief (~4 s) MVICs, additional MVICs were performed if there was a continual increase in torque or if there were not two torque values within 5 %, to determine maximal strength and the load for the MVCCs, and (2) a set of 15 MVCCs to determine maximal velocities and power. After a 2-min rest period, the fatiguing protocol was performed and involved: (1) 3 sets of 30 MVCCs, with each MVCC performed in an isotonic mode with a load equivalent to 20 % MVIC and with one MVCC performed every 3 s, and (2) three MVICs (one MVIC after each set of MVCCs) (see Fig. 1b). MVCCs were performed through 90º range of motion for both muscle groups, between 90º of flexion to 0º of knee flexion and from 55º of flexion to 145º of elbow flexion, with 0º of flexion considered to be full extension for both muscle groups. MVICs were assessed for the elbow flexors muscles at 90ºof elbow flexion and for the knee extensor muscles at 75º. These angles were chosen because they represent the optimal joint angle of the length–tension relationship for these muscle groups (Singh and Karpovich 1966; Smidt 1973). Mechanical recordings of torque, velocity and position from the dynamometer were digitized using a Power 1401 analog-to-digital converter and Spike 2 software (Cambridge Electronics Design, Cambridge, UK) with a sampling rate of 1000 Hz.

Data and statistical analysis

The primary outcome measure of the fatiguing exercise was the reduction in MVCC power during the exercise. MVCC power was calculated by multiplying the torque and velocity signals collected from the dynamometer. The reduction in MVCC power was quantified as the percentage reduction in the average peak velocity of five consecutive MVCCs and relative to the average peak velocity of the five fastest consecutive MVCCs performed prior to the fatiguing task (baseline). Separate mixed-design multivariate repeated-measures analysis of variance was used to measure fatigue (time) and to compare the effects of exercise on pain threshold [trial (pre- vs post-exercise)] and pain ratings [trial × time (pain ratings every 20 s during the 2-min pain test)] for each session, using the Pillai's Trace test statistics (V). Age group or sex was included as a between-subject variable. Because baseline (pre-exercise) pain reports and physical activity may influence EIH (Umeda et al. 2016), two-way ANOVA assessed for differences in physical activity, baseline pain reports, and demographics between groups. Baseline pain thresholds and the average pain rating across the six time points was used for comparison. Pearson correlation coefficients (r) were used to determine associations between physical activity or baseline pain and EIH. Mann–Whitney U test was used to confirm age difference between the two groups. Bonferroni-corrected post hoc tests for multiple comparisons were made when indicated. Significance was determined at $p \leq 0.05$.

Table 2 Measures of pain (pain thresholds and mean pain ratings) before and after the fatiguing contraction with the knee extensor (KE) and elbow flexor (EF) muscle groups

Variable	Units	Young Women	Young Men	Older Women	Older men
Pain Thresholds					
KE pre	s	39 (33)	28 (19)	28 (33)	54 (40)
KE post	s	46 (37)	30 (23)	31 (35)	59 (46)
EF pre	s	31 (23)	31 (24)	27 (34)	50 (41)
EF post	s	42 (25)[a]	28 (19)	39 (43)[a]	51 (42)
Average Pain Ratings					
KE pre	AU	3.0 (1.8)	3.9 (2.3)	4.6 (2.8)	2.5 (2.2)
KE post	AU	2.7 (2.1)	4.0 (2.4)	4.6 (3.4)	2.4 (2.3)
EF pre	AU	3.5 (1.8)	4.4 (2.6)	4.7 (3.4)	2.6 (2.5)
EF post	AU	2.7 (1.7)	3.8 (2.4)	4.6 (3.7)	2.8 (2.7)

Displays the pain thresholds in the upper panel and mean pain ratings of young and old men and women before and after the fatiguing contraction. Young and older women demonstrated an increase in pain threshold after fatiguing exercise with the elbow flexor muscle.
a Time × sex, $p = 0.03$

Results

For both the elbow flexor and knee extensor sessions, there were no significant main effects in baseline pain reports (pain thresholds and pain ratings) for sex [F (1, 60) = 0.8– 2.11, $p > 0.05$] or age [F (1, 60) = 0.02–0.81, $p > 0.05$]. In the knee extensor session there was a significant age × sex interaction for baseline pain threshold [age × sex: F (1, 60) = 5.21, $p = 0.026$] and pain ratings (age × sex: F (1, 60) = 7.36, $p = 0.009$). In the elbow flexor session, there was a significant age × sex interaction for baseline pain ratings [age × sex: F (1, 60) = 5.31, $p = 0.025$], but not pain threshold [age × sex: F (1, 60) = 2.07, $p > 0.05$]. Adjusted pairwise comparisons for all interactions failed to reach significance between groups with post hoc test. Results are summarized in Table 2.

There were no age differences in EIH (reduction in pain ratings or increase in pain threshold) for the elbow flexor or knee extensor sessions. Although there was a trend for young adults to report a reduction in pain ratings following elbow flexor contractions compared with older adults [trial × age: $V = 0.05$, F (1, 62) = 3.55, $p = 0.06$], there were no age-related differences in the pain response to exercise for pain threshold [*knee extensor and elbow flexor*, trial × age: $V < 0.001$, F (1, 62) = 0.01–0.02, $p > 0.05$] or pain ratings [*knee extensor*, trial × age: $V = 0.004$, F (1, 62) = 0.25, $p > 0.05$] in either session.

There was a sex difference in EIH for the elbow flexors but not the knee extensors. Only women [mean difference 11.19, 95 % CI (3.57, 18.82), t (30) = 3.0, $p = 0.005$] reported an increase in pain threshold following elbow flexor contractions [trial × sex: $V = 0.07$, F (1, 62) = 4.97, $p = 0.03$; Fig. 2b]. Following knee extensor contractions, pain thresholds were unchanged [39 ± 34 vs 43 ± 38 s, trial: $V = 0.04$, F (1, 62) = 2.71, $p > 0.05$] for both men and women [trial × sex: $V = 0.002$, F (1, 62) = 0.15, $p > 0.05$; Fig. 2a]. For both the elbow flexor and knee extensor sessions, pain ratings increased over the 2-min pain test [time: $V = 0.79$, F (5, 58) = 43.18, $p < 0.001$ and $V = 0.79$, F (5, 58) = 42.47, $p < 0.001$, respectively], and pain ratings were similar before and after exercise [knee extensor: 3.39 ± 2.3 vs 3.27 ± 2.6, trial: $V = 0.02$, F (1, 62) = 0.98, $p > 0.05$; elbow flexor: 3.66 ± 2.6 vs 3.33 ± 2.6, trial: $V = 0.04$, F (1, 62) = 2.79, $p > 0.05$; Fig. 2c, d]. The rate of rise in pain ratings was less following exercise in the knee extension session [trial × time: $V = 0.21$, F (5, 58) = 3.10, $p = 0.015$], but not the elbow flexor session [$V = 0.12$, F (5, 58) = 1.65, $p > 0.05$]. Post hoc testing corrected for multiple comparisons revealed no significant differences in pain ratings between trials at any of the six time points ($p > 0.008$).

One older man did not complete the physical activity questionnaire. There was a significant main effect of age for physical activity: older adults reported lower levels of physical activity compared to young adults [F (1, 59) = 15.18, $p < 0.001$]. There was no main effect of sex [F (1, 59) = 0.88, $p > 0.05$] or age and sex interaction [age × sex: F (1, 59) = 0.30, $p > 0.05$; Table 1]. There were no associations between estimates in physical activity and any measure of change in pain perception (pain rating or threshold; $p > 0.05$). Baseline pain rating ($r = -0.281$, $p = 0.03$) and baseline pain threshold ($r = -0.291$, $p = 0.02$) were weakly associated with change in pain in the elbow flexor, but not knee extensor ($p > 0.05$) session. Men and women demonstrated similar declines in MVCC power after exercise for both the elbow flexor [time: $V = 0.70$, F (1, 63) = 143.8, $p < 0.001$; sex: F (1, 63) = 2.14, $p > 0.05$] and knee extensor muscles [time: $V = 0.61$, $F(1, 63) = 98.5$, $p < 0.001$; sex: $F(1, 63) = 0.475$, $p > 0.05$]. Older adults demonstrated greater reductions compared with young adults in MVCC power after elbow flexor [21 ± 12 vs 14 ± 12 %, age: $F(1, 63) = 4.739$, $p = 0.03$] and knee extensor exercise [25 ± 15 vs 7 ± 10 %, age: $F(1, 63) = 32.99$, $p < 0.001$] (Table 1). There were no significant correlations of reductions in MVCC with EIH for either muscle group.

Discussion

The primary finding of this study is that women, but not men, report an increase in pain threshold following fatiguing dynamic contractions with the elbow flexor muscles. This dynamic fatiguing protocol was chosen because men

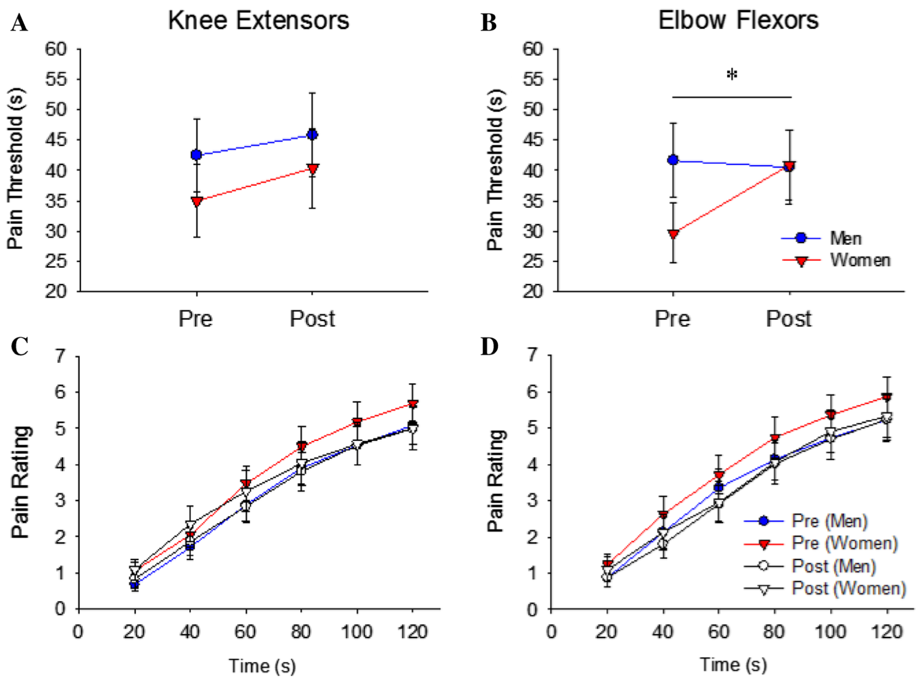

Fig. 2 Pain thresholds did not change for men and women following the knee extensor fatigue task (**a**). Pain thresholds increased for women, but not men, following the elbow flexor fatigue task (**b**). Pain ratings of men and women did not change following the knee extensor (**c**) or elbow flexor (**d**) fatigue tasks. (*Asterisk* denotes women experienced an increased in pain threshold, $p = 0.005$)

and women fatigue similarly during maximal velocity dynamic contractions at the 20 % load, eliminating the confounding effects of sex differences in performance or muscle fatigue that is typically observed for isometric fatiguing contractions (Hunter 2014). Another notable finding was that the sex difference in EIH was prominent among older adults. Although older adults demonstrated greater fatigue in comparison to young adults, fatigue was not different between the sexes.

Sex differences in EIH have previously been demonstrated after isometric (Lemley et al. 2014; Koltyn et al. 2001) and aerobic exercise (Vaegter et al. 2014; Sternberg et al. 2001). The mechanism underlying these sex differences is unclear. Baseline pain has been suggested to be partly responsible for this difference; women have greater baseline pain than men (Fillingim et al. 2009; Riley et al. 1998). This would not appear to explain our findings because despite a weak correlation of baseline pain and EIH in the elbow flexor session, men and women had similar baseline pain thresholds (Table 1). Differences in physical activity has also been proposed to influence EIH (Umeda et al. 2016), and we found no sex-related differences in physical activity and no associations between physical activity levels and EIH.

An additional novel finding of this study was that the EIH was specific to the muscle groups among women. Women demonstrated EIH after elbow flexor exercise, but not knee extensor exercise. Greater EIH in the exercising body part than at distant sites has been found by some investigators (Kosek and Lundberg 2003; Vaegter et al. 2015) suggesting that both systemic and local factors contribute to EIH. Although pain testing was performed on the hand contralateral to the exercising arm, segmental effects may have contributed to the difference in arm versus leg muscles among women.

We found no age-related difference in EIH despite older adults experiencing greater muscle fatigue for the dynamic exercise. Young adults, but not older adults, experience greater EIH after isometric exercise of low-intensity held to task failure compared with other isometric contractions of lesser duration (Hoeger Bement et al. 2008; Lemley et al. 2014). Additionally, greater than 10 min of aerobic exercise may be required for young adults to experience EIH (Hoffman et al. 2004). As our protocol involved intermittent contractions lasting a total of 4.5 min and did not require exercise to task failure, the level of fatigue may have been insufficient for young adults to reach a magnitude of EIH significantly greater than that of older adults. Furthermore, the EIH experienced following the dynamic protocol was less than that seen with isometric exercise. For example, as a group the young adults experienced an elevation of pain threshold of slightly less than 14.5 % in the elbow flexor session, whereas older adults experienced an increase of just over 12.5 %. Using isometric elbow flexion exercise protocols, older adults have been found to experience pain reductions of ~19 % for both pain ratings and pain thresholds, with young adults having even greater reductions in pain reports (Lemley et al. 2014; Hoeger Bement et al. 2008). Thus, the lesser EIH with the dynamic exercise protocol may have contributed to the failure to identify age-related differences.

It is interesting to note that pain threshold, but not pain ratings, was altered in women following elbow flexor exercise. Importantly, EIH indicators (pain threshold and rating) do not always respond in the same manner (Lemley et al. 2014; Hoeger Bement et al. 2008; Koltyn et al. 2001; Naugle et al. 2014). It has been suggested that failure of change in pain ratings following exercise may be a protective response against potential injury or may be a methodological issue when using fixed (the same pressure stimulus for all participants) rather than individualized protocols (Naugle et al. 2014). Thus, experimental pain perception should be assessed using several indicators to adequately describe the phenomenon of pain.

This is the first-known study to show that EIH occurs following repeated maximal velocity single limb dynamic contractions. These contraction velocities parallel those during normal gait (McGibbon 2012). Furthermore, sex differences in EIH are present when muscle fatigue is similar between men and women so that potential sex differences in fatigability did not confound the pain response. Consequently, young and older women, in particular may benefit with reductions in pain sensitivity following repeated dynamic contractions. These benefits may be associated with segmental effects; high-velocity contractions may be most effective when exercising muscle groups closely related to the area of pain.

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Compliance with ethical standards

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Conflict of interest

The authors declare that they have no conflict of interest.

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