Scandinavian Journal of Pain 10 (2016) 6–12

Contents lists available at ScienceDirect

Scandinavian Journal of Pain

journal homepage: www.ScandinavianJournalPain.com

Observational study

COMT and *OPRM1* genotype associations with daily knee pain variability and activity induced pain

Lynn M. Martire[a,*], Stephanie J. Wilson[a], Brent J. Small[b], Yvette P. Conley[c], Piotr K. Janicki[d], Martin J. Sliwinski[a]

[a] *The Pennsylvania State University, United States*
[b] *University of South Florida, United States*
[c] *University of Pittsburgh, United States*
[d] *Penn State College of Medicine, United States*

HIGHLIGHTS

- Multilevel modelling was used to examine daily variability in knee pain by genotype.
- Moderation of lagged associations between activity and pain by genotype was examined.
- Two copies of the Asn^{40} allele of OPRM1 rs1799971 associated with greatest pain variability.
- Val/Val genotype showed the greatest variability and increase in pain after activity.
- Greater fluctuations in daily knee pain may reflect more sensitivity to activity.

ARTICLE INFO

Article history:
Received 13 April 2015
Received in revised form 6 July 2015
Accepted 7 July 2015

Keywords:
Pain
Genetics
Ambulatory
Osteoarthritis
Physical activity

ABSTRACT

Background: Osteoarthritis (OA) of the knee is a common and increasingly prevalent condition that is one of the primary causes of chronic pain. Staying physically active protects against disability from knee OA but is also very challenging. A critical but unexamined question is whether patients at greatest risk for becoming less active are those with a genetic predisposition for greater sensitivity to daily pain.
Aims: We examined day-to-day variability in knee OA pain for patients with different variants of catechol-*O*-methyltransferase (COMT) and mu-opioid receptor (OPRM1) single nucleotide polymorphisms (SNPs), and whether patients with a specific genotype experience more pain following daily physical activity. We predicted that patients having one or more copies of the Met^{158} allele of *COMT* rs4680 (A-A or A-G) and one or more copies of the Asp^{40} allele of *OPRM1* rs1799971 (A-G or G-G) would show greater pain variability. We expected to see the same pattern for these SNPs with regard to moderation (i.e., exacerbation) of the activity-pain association.
Methods: A total of 120 knee OA patients reported on their pain 3 times per day over 22 days using hand-held computers, and wore an accelerometer to capture daily physical activity. Multilevel modelling was used to examine the magnitude of within-person variability in pain by genetic group. We also examined whether lagged, within-patient associations between level of activity in the afternoon (i.e., minutes of moderate intensity activity, and number of steps) and knee pain at the end-of-day were moderated by between-patient differences in genotype.
Results: Regarding *OPRM1* rs1799971 (Asn^{40}Asp), patients with two copies of the Asn^{40} allele showed the greatest day-to-day pain variability. Regarding *COMT* rs4680 (Val^{158}Met), patients with the Val/Val genotype showed the greatest pain variability and also experienced the greatest increase in pain as a result of physical activity. A similar pattern of findings across bi-directional temporal lags was consistent with a negative feedback loop between daily physical activity and pain according to genotype. Consistent with some previous studies, there were no significant between-person differences in daily pain when comparing patients according to *COMT* rs4680, or *OPRM1* rs1799971.

DOI of refers to article: http://dx.doi.org/10.1016/j.sjpain.2015.07.006.
* Corresponding author at: Department of Human Development & Family Studies, 422 Biobehavioral Health Building, Penn State University, University Park, PA 16802, United States. Tel.: +1 814 865 7374; fax: +1 814 863 9423.
E-mail address: lmm51@psu.edu (L.M. Martire).

http://dx.doi.org/10.1016/j.sjpain.2015.07.004

Conclusion: This study provides preliminary evidence that patients with certain genotypes for *COMT* rs4680 and *OPRM1* rs1799971 (G-G and A-A, respectively) experience more variability in their day-to-day pain and exacerbation of pain after daily physical activity compared to patients with other genotypes. Our findings should be replicated in larger study populations.

Implications: Previous clinical research has focused primarily on differences in average level of pain between patients with and without a specific genotype. Assessment of within-person variability through repeated measurements in daily life enhances the reliability, power, and ecological validity of phenotypic measurement.

Perspective: This study provides preliminary evidence that patients with certain variations in the *COMT* and *OPRM1* SNPs experience more variability in their day-to-day pain and exacerbation of pain after daily physical activity.

1. Introduction

Osteoarthritis (OA) of the knee is a common and increasingly prevalent condition that is one of the primary causes of chronic pain [1]. Staying physically active protects against disability from knee OA but is also very challenging [2,3]. A critical but unexamined question is whether patients at greatest risk for becoming less active are those with a genetic predisposition for greater sensitivity to daily pain. In the present study we examined day-to-day variability in knee OA pain for patients with different variants of catechol-*O*-methyltransferase (COMT) and mu-opioid receptor (OPRM1) single nucleotide polymorphisms (SNPs). We also examined the moderation of associations between daily physical activity and knee pain by genotype.

Research on genetics and pain sensitivity has often focused on *COMT* rs4680 (Val^{158}Met), a polymorphism of the *COMT* gene. Relatively little of this research has been in OA. In one study, having one or more copies of the Met^{158} allele (Met/Met or Val/Met; i.e., A-A or A-G) was associated with greater hip OA pain in women [4]. However, a second study did not find an association between symptomatic knee OA and Val^{158}Met [5]. Another focus of research on pain sensitivity is the *OPRM1* rs1799971 (Asn^{40}Asp, A118G) polymorphism [6,7]. As with *COMT* rs4680, virtually none of this research has been in OA. Being homozygous for the Asp^{40} allele of this polymorphism (G-G) has been linked with greater opioid analgesic requirements for pain relief after total knee arthroplasty [8].

Previous research on genetics and pain sensitivity has focused primarily on between-person differences by examining differences in average pain severity between individuals with and without an at-risk genotype. An equally important question, and the first focus of the current study, is whether patients with an at-risk genotype are more variable in their day-to-day pain (i.e., within-person differences; [9]). To our knowledge, only one previous study has taken this approach, showing greater within-person variability in daily pain for fibromyalgia patients with two copies of the Met^{158} allele of *COMT* (A-A), and no differences across variants in *OPRM1* rs1799971 [10,11]. In the current study we used ambulatory data collected from knee OA patients 3 times per day over 22 days to examine the relationships of *OPRM1* rs1799971 and *COMT* rs4680 allelic differences with day-to-day (i.e., within-person) variability in knee pain.

Greater fluctuations in pain, regardless of the level of pain, are likely to reflect greater sensitivity to activities throughout the day. Although previous experimental studies have shown that walking tests increase the level of pain [12], it is not clear if typical daily activity is associated with increased pain for individuals with a specific genotype. Thus, the second novel aim of our study was to determine if knee OA patients with a specific genotype experience more pain following daily physical activity. These analyses incorporated accelerometer data collected over 22 days in tandem with daily pain data. Specifically, we examined lagged, within-patient associations between level of physical activity in the afternoon (i.e., minutes of moderate intensity activity, and number of steps) and knee pain ratings at the end-of-day, and moderation of these associations by genotype. We predicted that patients having one or more copies of the Met^{158} allele of *COMT* rs4680 (A-A or A-G) and one or more copies of the Asp^{40} allele of *OPRM1* rs1799971 (A-G or G-G) would show greater pain variability. We expected to see the same pattern for these SNPs with regard to moderation (i.e., exacerbation) of the activity-pain association.

2. Methods

2.1. Participants

Data presented in this report are from a prospective observational (i.e., non-intervention) study of knee OA patients and their spouses. The purpose of the larger study was to examine spousal influence on osteoarthritis patients' daily and long-term functioning; for a detailed description, see Martire et al. [13]. The current report focuses only on patients. To be eligible for the study, patients had to be diagnosed with knee OA by a physician, experience usual knee pain of moderate or greater intensity, be at least 50 years of age, and be married or in a long-term relationship (self-defined) in which they shared a residence with their partner. Exclusion criteria were a comorbid diagnosis of fibromyalgia or rheumatoid arthritis and use of a wheelchair to get around. Primary sources of recruitment were research registries for rheumatology clinic patients and older adults interested in research, flyers distributed to University of Pittsburgh staff and faculty, and word of mouth. A total of 606 couples were screened for eligibility. Of these, 221 couples declined to participate, and the most frequent reasons were lack of interest ($N = 87$) or illness in the family ($N = 55$). A total of 233 couples were not eligible, and the most frequent reasons were lack of osteoarthritis in the knee ($N = 55$) or knee osteoarthritis pain that was mild ($N = 47$). The total enrolled sample for the larger study was 152 couples.

A total of 145 patients completed the diary assessment and accelerometry components of the study and 120 of these patients agreed to DNA collection as an optional component of the study. Of these patients, 114 had data for *OPRM1* rs1799971 and 120 had data for *COMT* rs4680. Patients with genetic data were compared with the larger phenotyped cohort who did not have genetic data on demographic and illness characteristics (age, sex, ethnicity, years of education, employment status, income, duration of knee OA and severity of knee OA). A greater proportion of patients in the genotyped group were not currently employed, X^2 (1) = 4.93, $p = .027$. This likely reflects that genetic data collection often required a separate visit to participants' homes during the day, when employed participants were less likely to be home, rather than a substantive bias in the cohort. No other differences were found between the two groups.

The University of Pittsburgh Institutional Review Board (IRB) approved this study, and an IRB-approved form was used to obtain written informed consent from all participants. Penn State University's IRB approved the storage of data on Penn State servers and continued analysis of study data.

2.2. Data collection procedures

During a 22-day assessment protocol, patients used a handheld computer to answer questions about pain at the beginning-of-day, in the afternoon (between 2:00 and 4:00 p.m.), and at end-of-day (i.e., upon retiring to bed). Completion and compliance rates for the diary data were over 90% [13].

2.3. Measures

2.3.1. Daily knee pain

Patients provided reports of knee pain over the past 30 min on a scale from 0 to 3 (no pain to severe pain) at the beginning of day, afternoon, and end of day. We also computed a score for pain across the day by averaging the three ratings. The knee pain measure is taken from the Rapid Assessment of Disease Activity in Rheumatology [14] and is often used in daily assessment research. Average daily knee pain for all patients was mild to moderate ($M = 1.44$; $SD = .75$; range = 0–3). Mean levels of morning, afternoon, and evening knee pain were consistent with those averaged across the day ($M_{morning} = 1.33$, $SD = 0.80$, range = 0–3; $M_{afternoon} = 1.42$, $SD = 0.80$, range = 0–3; $M_{evening} = 1.45$, $SD = 0.74$, range = 0–3).

2.3.2. Physical activity

Accelerometers were used to assess amount of time spent in moderate-intensity activity and daily steps taken during the 22-day assessment period. Accelerometers are motion-sensitive monitors that count the number of movements or steps taken per pre-specified time interval. Self-reports of physical activity are often overestimated [15], and thus accelerometers are considered the best way to objectively measure free-living physical activity [16,17]. Participants wore the GT1M or GT3X model of the CSA/MTI tri-axial ActiGraph, with placement on the hip in order to best capture ambulatory activities [18]. Data were collected in 1-minute epochs.

Patients were instructed to wear the monitor during the day and remove it at night; a reminder to put the monitor on in the morning was provided electronically via the handheld computers. Participants used a written log to record any periods during which they did not wear the accelerometer. All times when the monitor was not worn were removed from data analysis. Data were then screened for anomalous values (activity counts greater than 6000 at any given minute), which affected less than 1% of the activity data. The average number of days that the accelerometer was worn was 17.5 ($SD = 4.0$).

Intensity of physical activity is commonly defined using an activity count cut point that corresponds to a range of metabolic equivalents. Previous work confirms that the common cut point for moderate intensity activity (1952 or more activity counts per minute) underestimates walking intensity in older adults as measured by oxygen consumption during treadmill tests [19]. Thus, as reported in a previous publication [13], we relied on work by Matthews [20] and Matthews and colleagues (2002) which combined information from laboratory and field studies to determine a cut point that may better capture moderate-intensity activities of daily living for older adults. Specifically, we defined 760 activity counts per minute or greater as moderate-intensity activity (i.e., moderate-to-vigorous, hereafter referred to as moderate for simplicity). During the afternoon-to-evening epoch that was used for analysis (henceforth called *afternoon physical activity* for simplicity), the average number of minutes spent in moderate physical activity was 17.08 ($SD = 23.03$), and the average number of steps taken was 1815.71 ($SD = 1528.38$).

2.4. DNA extraction and genotyping

Saliva was collected using the Oragene DNA collection kit (DNA Genotek; Ontario, Canada) and DNA was extracted from the saliva according to the manufacturer's instructions.

2.4.1. COMT *genotyping*

We genotyped *COMT* rs4680 (Val^{158}Met). We used TaqMan 5′ exonuclease Assay-on-Demand assays (Applied Biosystems Inc., ABI, Foster City, CA), the ABI7000 for amplification and data collection, and SDS 2.0 software (ABI) for genotype assignment.

2.4.2. OPRM1 *genotyping*

We genotyped three polymorphisms within *OPRM1*, including rs1799971 (Asn^{40}Asp or A118G), rs1799973 (G24A), and rs1799972 (C17T), but we report results for only *OPRM1* rs1799971 due to low or zero frequency of the minor alleles for rs1799973 and rs1799972 in the study cohort. SNPs were genotyped by sequencing a 101bp polymerase chain reaction (PCR) product generated from exon 1 where all 3 investigated polymorphisms reside. Primers to generate the PCR product in the forward and reverse direction were 5′-TCAGTACCATGGACAGCAG-3′ and 5′-GGAGTAGAGGGCCATGAT-3′, respectively. ExoSAP reagents (USBiochemicals, Cleveland, OH) were used to clean up the PCR product and Big Dye Cycle Sequencing reagents (ABI) with the reverse primer were used to sequence the PCR product. Sequencing was conducted with an ABI377 automated sequencer (ABI). Sequencer software (Gene Codes Corporation, Ann Arbor, MI) was used to visualize the sequence and assign genotypes.

For all genotyping conducted for this research, we made double-masked genotyping assignments for each variant, compared them, and addressed each discrepancy using raw data or by re-genotyping.

2.5. Data analysis

Prior to the analysis of the knee pain data, we assessed Hardy–Weinberg equilibrium for all genotypes. Multilevel modelling [21] with SAS PROC MIXED was used to examine within-person variability in daily knee pain, lagged associations between daily physical activity and knee pain, and moderation of these associations by *COMT* rs4680 and *OPRM1* rs1799971. To address the first hypothesis, we fit heterogeneous variance multilevel models to assess whether the magnitude of within-person variability in pain differed by genetic group [22]. These models also tested for differences in average daily knee pain by genotype in order to allow for direct comparisons to previous studies that have taken this approach.

In tests of the second hypothesis regarding lagged associations between physical activity and pain, end-of-day knee pain was modelled as a function of patient physical activity during the afternoon (within-person centred), genotype, and the interaction between physical activity and genotype. These models allowed us to determine whether within-patient associations between physical activity and knee pain were moderated by between-patient differences in genotype. Minutes of moderate physical activity were scaled by 60, such that a one-unit increase is equivalent to 60 min. Steps were scaled by 100, such that a one-unit increase is equivalent to 100 steps. Random intercepts and random slopes of activity, genotype, and the interaction between activity and genotype were tested. These models also included heterogeneous variance terms from the prior set of models. In secondary analyses we tested the

reverse temporal order of afternoon ratings of knee pain predicting level of physical activity during the remainder of the day, and moderation by genotype.

All analyses controlled for age, sex and race (White versus non-White). In addition, each participant's diary days were consecutively numbered and this variable was included in the analyses to adjust for potential linear effects of repeated assessments. Secondary analyses excluding non-White participants ($N = 15$) were conducted to test the generalizability of study results for Whites only.

3. Results

3.1. Sample characteristics

Table 1 summarizes sample characteristics. On average, participants were 65 years of age, half were male and they had completed 16 years of education. Approximately 88% were White and the remainder were Black/African American ($n = 12$, with 1 also identifying as Hispanic) or American Indian/Alaskan native ($n = 3$, with 1 also identifying as White). Participants reported having OA for almost 13 years on average and arthritis severity was moderate according to scores on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC; [23]).

3.2. Genotype frequencies

The frequencies for *OPRM1* rs1799971 and *COMT* rs4680 are shown in Table 2. Analyses showed that both polymorphisms were in Hardy–Weinberg equilibrium ($p > .10$) indicating that the distribution of alleles did not significantly vary from population expectations.

3.3. Genotypic differences in daily pain variability

The intraclass correlation (ICC) indicates the variance attributed to between-person differences, and 1-ICC reflects the proportion of within-person differences. According to ICCs, within-person differences accounted for approximately 36% of the variance in pain at the beginning-of-day, afternoon, and end-of day assessments.

Table 3 displays the within-person estimate, standard error, and statistical significance for pain at each assessment according to *COMT* rs4680 and *OPRM1* rs1799971. As shown in this table, greater day-to-day (i.e., within-person) variability was found in patients with a particular genotype. The first set of columns show that, contrary to our prediction, there was greater within-person variability in afternoon, end-of-day, and across-the-day knee pain for patients with two copies of the Val^{158} allele (G-G) compared to those with at least one copy of Met^{158} (A-A or A-G; $estimate_{Aft} = -0.24$, SE = 0.07, $p = .001$; $estimate_{End} = -0.28$, SE = 0.07, $p = .0002$; $estimate_{Avg} = -0.15$, SE = 0.07, $p = .03$). The difference for beginning-of-day pain was not significant ($p = .16$).

Findings for *OPRM1* rs1799971 are presented in the second set of columns in Table 3. We predicted that having one or more copies of the Asp^{40} allele (A-G or G-G) would be associated with greater pain variability. Contrary to prediction, patients who were homozygous for the Asn^{40} allele (A-A) varied more within-person in their knee pain in the morning, evening, and on average across the day than did those with one copy of the Asp^{40} allele (A-G; $ps = .009$–$.037$). The effect was not significant for afternoon pain but trended in the same direction ($p = .084$).

3.3.1. Analysis of between-person variability in daily knee pain

Consistent with some previous studies [5,10,11,25], there were no significant between-person differences in daily pain when comparing patients according to *COMT* rs4680, or *OPRM1* rs1799971 ($p > .25$).

3.4. Differences in lagged associations between daily physical activity and knee pain by genotype

Table 4 presents the fixed effects for each of the predictors in the lagged multilevel models (i.e., main effects of physical activity and genotype, and the interaction between these terms). Because no analyses converged with the inclusion of random slopes, only random intercepts were estimated in final models.

The first set of columns in Table 4 present the multilevel results for *COMT* rs4680.

These analyses showed that *COMT* rs4680 was a significant moderator of the relationship between minutes of afternoon physical activity and end-of-day pain severity ($p = .014$). This finding is depicted in Fig. 1. Contrary to our prediction, but consistent with our finding for daily pain variability, patients with two copies of the Val^{158} allele (G-G) had significantly higher pain at the end of day following more minutes of moderate physical activity (estimate = 0.30, SE = 0.11, $p = .007$) whereas those with at least one copy of Met^{158} (A-A or A-G) did not experience significant changes in pain following more moderate physical activity (estimate = −0.002, SE = 0.05, $p = .97$). *COMT* rs4680 did not moderate the association between number of steps taken during the afternoon and end-of-day pain severity.

The second set of columns in Table 4 show the multilevel results for *OPRM1* rs1799971. This genotype did not moderate the association of afternoon moderate activity with end-of-day knee pain. Our finding for number of steps was contrary to prediction but

Table 1
Sample characteristics ($N = 120$).

Variable	M (*SD*) or %
Age	65.9 (9.9)
Sex = male	51%
Years of education	16.0 (2.1)
Ethnicity = White	88%
Employed	38%
Household income	$40,000–59,000
Duration of knee OA (years)	12.8 (11.2)
Arthritis severity (WOMAC)	34.9 (14.7)

Table 2
Genotype frequencies.

Genotype	Frequency
OPRM1 rs1799971 ($Asn^{40}Asp$)	
A-A (Asn/Asn)	0.746
A-G (Asn/Asp)	0.254
COMT rs4680 ($Val^{158}Met$)	
A-A (Met/Met)	0.275
A-G (Met/Val)	0.458
G-G (Val/Val)	0.267

Table 3
Differences in within-person daily knee pain variability by COMT rs4680, and OPRM1 rs1799971.

Daily knee pain	*COMT* estimate (SE)	*P*-value	*OPRM1* estimate (SE)	*P*-value
Beginning of day	−0.11 (0.07)	.160	0.21 (0.08)	.009
Afternoon	−0.24 (0.07)	.001	0.13 (0.08)	.084
End of day	−0.28 (0.07)	.0002	0.18 (0.08)	.028
Across the day	−0.15 (0.07)	.030	0.15 (0.07)	.037

Notes. Across the day = average of beginning of day, afternoon, and end of day. All analyses control for age, race, sex, and day in study (i.e., 1–22). Coding of *COMT* rs4680: G-G = 0; A-A, A-G = 1. Coding of *OPRM1* rs1799971: A-G = 0, A-A = 1.

Table 4
Multilevel moderation models of lagged associations between physical activity and knee pain by COMT rs4680 and OPRM1 rs1799971.

Fixed effects	*COMT*		*OPRM1*	
	End of day pain		End of day pain	
	Estimate	(SE)	Estimate	(SE)
Model for afternoon moderate activity				
Intercept	1.942	0.485***	2.214	0.528***
Minutes of moderate physical activity	0.303	0.112**	−0.055	0.093
Genotype	−0.027	0.155	−0.223	0.166
Moderate activity × genotype	−0.306	0.124*	0.145	0.110
Model for afternoon step count				
Intercept	1.939	0.485***	2.215	0.528***
Step count	0.004	0.002	−0.001	0.002
Genotype	−0.023	0.155	−0.219	0.167
Steps × genotype	−0.002	0.003	0.005	0.003†

Notes. Minutes of moderate physical activity were scaled by 60, such that a one-unit increase is equivalent to 60 min. Steps were scaled by 100, such that a one-unit increase is equivalent to 100 steps. All analyses control for age, race, sex, and day in study (i.e., 1–22). Coding of *COMT* rs4680: G-G = 0; A-A, A-G = 1. Coding of *OPRM1* rs1799971: A-G = 0, A-A = 1.
$N_{patients}$ = 115 for *COMT* rs4680; 114 for *OPRM1* rs1799971. $N_{observations}$ = up to 1496.
† $p = .085$.
* $p < .05$.
** $p \leq .01$.
*** $p < .001$.

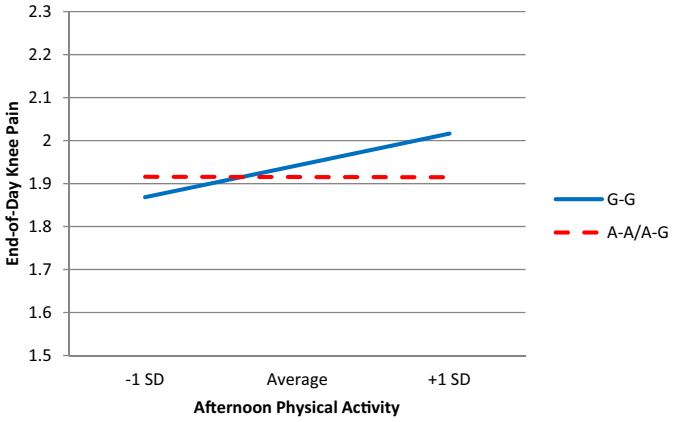

Fig. 1. The moderating effect of *COMT* rs4680 in the association between minutes of afternoon moderate activity and end-of-day pain severity. Estimated values are presented for the within-person association between physical activity and knee pain for patients with one or more copies of the Met^{158} allele (A-A or A-G) and patients with two copies of the Val^{158} allele (G-G), at three levels of physical activity (i.e., the sample average of within-person means and one standard deviation above and below the average, or approximately 15 min).

consistent with our finding for daily pain variability. That is, those with two copies of the Asn^{40} allele (A-A) reported significantly more pain at the end of the day after taking more steps in the afternoon (estimate = 0.004, SE = 0.001, $p = .010$), whereas those with the Asp^{40} allele of the polymorphism (A-G) did not show an association between afternoon steps and end-of-day pain (estimate = −0.001, SE = 0.002, $p = .64$). However, the interaction between steps and *OPRM1* rs1799971 did not reach statistical significance ($p = .085$).

3.4.1. Reverse temporal order

We also examined the effects of afternoon knee pain on physical activity between the afternoon and end-of-day, and their moderation by genotype. No interactions were statistically significant, but some findings trended in the expected direction. Regarding *COMT* rs4680, patients with two copies of the Val^{158} allele (G-G) engaged in fewer minutes of moderate physical activity after greater afternoon knee pain (estimate = −0.06, SE = 0.02, $p = .018$) whereas those with at least one copy of Met^{158} (A-A or A-G) did not show an association between afternoon knee pain and minutes of moderate activity (estimate = −0.01, SE = 0.02, $p = .40$, $p_{interaction} = .13$). Patients with Val/Val also took fewer steps after greater afternoon knee pain (estimate = −2.35, SE = .96, $p = .014$), but patients with Val/Met did not experience a significant association between afternoon pain and steps (estimate = −0.51, SE = 0.63, $p = .42$; $p_{interaction} = .11$). This similar pattern of findings across bi-directional temporal lags is consistent with a negative feedback loop between daily physical activity and pain according to genotype.

3.5. Subgroup analyses

Because we were not able to compare White and non-White participants, secondary analyses focused on only Whites were conducted to determine if population stratification is a threat to the validity of study findings. Two differences emerged in our variability findings. A non-significant difference in pain at the beginning of day for *COMT* rs4680 in all patients (estimate = −0.11, SE = 0.07, $p = .160$) was statistically significant in Whites only (estimate = −0.16, SE = 0.08, $p = .049$). Also, a non-significant effect of *OPRM1* rs1799971 on afternoon pain variability in the full sample (estimate = 0.13, SE = 0.08, $p = .084$) was statistically significant in the Whites-only subsample (estimate = 0.19, SE = 0.08, $p = .015$). Findings for the interactions between genotype and physical activity were consistent across Whites-only and full samples. There were no significant between-person differences in daily pain by genotype for Whites only ($ps > .17$), consistent with the analyses that included all patients.

4. Conclusion

It is estimated that nearly half of U.S. adults will develop symptomatic knee OA in their lifetime [1]. For these individuals, a genetic predisposition for greater sensitivity to daily pain may be a risk factor for physical disability due to inactivity and deconditioning. To our knowledge, this is the first study to examine associations between daily knee OA pain and physical activity by genotype. Although our findings should be replicated in larger study populations, this study provides preliminary evidence that patients with certain genotypes for *COMT* rs4680 and *OPRM1* rs1799971 (G-G and A-A, respectively) experience more variability in their day-to-day pain and exacerbation of pain after daily physical activity compared to patients with other genotypes.

Previous clinical research has focused primarily on differences in average level of pain between patients with and without a specific genotype. Our study posed additional questions and offers several advantages over previous approaches. As noted by Finan and colleagues (2012), assessment of within-person variability through repeated measurements in daily life enhances the reliability, power, and ecological validity of phenotypic measurement and helps to reduce threats to detecting true gene-phenotype associations [9]. Consistent with a previous study on knee OA [5], we found no significant mean differences in pain severity between genetic groups.

Our first aim was to examine differences in daily pain variability by genotype. In our analyses focused on the rs4680 SNP of the *COMT* gene, we found greater within-person variability in afternoon, end-of-day, and across-the-day knee pain for patients with two copies of the Val^{158} allele (G-G), controlling for average level of pain. This finding is contrary to a previous study of hip OA that examined between-group differences in pain [4]. It is important to keep in mind that variability between and within patients reflect different phenomena [24].

Our analyses on the rs1799971 SNP of the *OPRM1* gene showed a consistent direction of effect across time points within the day. Patients who were homozygous for the Asn^{40} allele (A-A) showed more variability in knee pain than did those with one copy of the Asp^{40} allele at the beginning of day, end of day, and across the day. We had predicted that the Asp^{40} allele would be associated with greater pain variability, but this prediction was based on one study of morphine consumption after knee arthroplasty that examined between-group differences in pain [8].

Greater fluctuations in pain, regardless of the level of pain, are likely to reflect greater sensitivity to activities throughout the day. Thus, our second aim was to determine if daily physical activity is more strongly associated with higher levels of pain for patients with a specific genotype. We found that patients with the Val/Val genotype (G-G) for *COMT* rs4680 were not only most variable in their pain but also experienced the greatest increase in pain as a result of physical activity. Similarly, there was a trend-level finding that patients with two copies of the Asn^{40} allele (A-A) for *OPRM1* rs1799971 were most variable in their pain and also experienced greater pain at the end of the day after taking more steps in the afternoon. These findings for *COMT* rs4680 and *OPRM1* rs1799971 are consistent with the idea that greater variability in pain experienced during daily life reflects more sensitivity to physical activity.

These findings extend the experimental literature which shows that walking tests increase the level of pain [12] by demonstrating that typical daily activity may be associated with increased pain for individuals with a specific genotype. The lagged, bidirectional associations between physical activity and pain that were detected in our secondary analyses suggest that there is a negative feedback loop such that activity leads to increased pain and pain leads to decreased activity. This study marks an important step towards understanding how the daily experience and consequences of pain and physical activity may differ for osteoarthritis patients with different genotypes. Smaller differences were detectable with greater power by the use of a repeated-measures design and a commensurate multilevel modelling approach [9]. This is consistent with a previous gene-behaviour study of a similar design that found clinically interesting differences using a sample with half the number of observations (cf. [10]).

It is important to note the limitations of this study. First, our findings are preliminary because of the small sample size and should be replicated in larger study populations. Second, analyzing different ancestry groups separately was not possible due to sample size, although our findings were very similar when excluding non-White participants. Further, though the SNPs of focus were selected due to their empirical importance for the processes of interest, this limited number of SNPs does not reflect the likelihood that daily fluctuations in pain may be influenced by multiple genes.

In conclusion, the current study takes an ambulatory approach to investigating genotypic differences in the dynamics of pain and activity in the daily lives of patients with knee OA. Addressing emergent questions about the role of genetic risk for pain sensitivity in a potential feedback loop of daily pain and activity will be important for a more complete understanding of how knee OA evolves in this rapidly growing clinical population.

Disclosures

This research was supported in part by grants from the National Institute on Aging (R01 AG026010, K02 AG039412).

Conflict of interest

The authors have no conflicts of interest to disclose.

References

[1] Murphy L, Schwartz TA, Helmick CG, Renner JB, Tudor G, Koch G, Dragomir A, Kalsbeek WD, Luta G, Jordan JM. Lifetime risk of symptomatic knee osteoarthritis. Arthritis Care Res 2008;59:1207–13.

[2] Dunlop D, Semanik P, Song J, Manheim L, Shih V, Chang R. Risk factors for functional decline in older adults with arthritis. Arthritis Rheum 2005;52:1274–82, http://dx.doi.org/10.1002/art.20968.

[3] Messier SP, Loeser RF, Miller GD, Morgan TM, Rejeski WJ, Sevick MA, Ettinger Jr WH, Pahor M, Williamson JD. Exercise and dietary weight loss in overweight and obese older adults with knee osteoarthritis: the arthritis, diet, and activity promotion trial. Arthritis Rheumatol 2004;50(5):1501–10.

[4] Van Muers JB, Uitterlinden AG, Stolk L, Kerkhof HJ, Hofman A, Pols HA, Bierma-Zeinstra SM. A functional polymorphism in the catechol-O-methyltransferase gene is associated with osteoarthritis-related pain. Arthritis Rheumatol 2009;60(2):628–9.

[5] Neogi T, Soni A, Doherty SA, Laslett LL, Maciewicz RA, Hart DJ, Zhang W, Muir KR, Wheeler M, Cooper C, Spector TD, Cicuttini F, Jones G, Nevitt M, Liu Y, Arden NK, Doherty M, Valdes AM. Contribution of the COMT Val158Met variant to symptomatic knee osteoarthritis. Ann Rheum Dis 2014;73(1):315–7.

[6] Henker RA, Lewis A, Dai F, Lariviere WR, Meng L, Gruen GS, Sereika SM, Pape H, Tarkin IS, Gowda I, Conley YP. The associations between OPRM1 and COMT genotypes and postoperative pain, opioid use, and opioidi-induced sedation. Biol Res Nurs 2013;15(3):309–17, http://dx.doi.org/10.1177/1099800411436171.

[7] Janicki PK, Schuler G, Francis D, Bohr A, Gordon V, Jarzembowski T, Ruiz-Velasco V, Mets B. A genetic association study of the functional A118G polymorphism of the human – μ opioid receptor gene in patients with acute and chronic pain. Anesth Analg 2006;103(4):1011–7, http://dx.doi.org/10.1213/01.ane.0000231634.20341.88.

[8] Chou W-Y, Yang L-C, Lu H-F, Ko J-Y, Wang C-H, Lin S-H, Lee T-H, Concejero A, Hsu C-J. Association of mu-opioid receptor gene polymorphism (A118G) with variations in morphine consumption for analgesia after total knee arthroplasty. Acta Anaesthesiol Scand 2006;50(7):787–92, http://dx.doi.org/10.1111/j.1399-6576.2006.01058.x.

[9] Finan PH, Tennen H, Thoemmes F, Zautra AJ, Davis MC. Ambulatory monitoring in the genetics of psychosomatic medicine. Psychosom Med 2012;74(4):349–55, http://dx.doi.org/10.1097/PSY.0b013e3182544a74.

[10] Finan PH, Zautra AJ, Davis MC, Lemery-Chalfant K, Covault J, Tennen H. Genetic influences on the dynamics of pain and affect in fibromyalgia. Health Psychol 2010;29(2):134–42, http://dx.doi.org/10.1037/a0018647.

[11] Finan PH, Zautra AJ, Davis MC, Lemery-Chalfant K, Covault J, Tennen H. COMT moderates the relation of daily maladaptive coping and pain in fibromyalgia. Pain 2011;152:300–7, http://dx.doi.org/10.1016/j.pain.2010.10.024.

[12] Wideman TH, Finan PH, Edwards RR, Quartana PJ, Buenaver LF, Haythornthwaite JA, Smith MT. Increased sensitivity to physical activity among individuals with knee osteoarthritis: relation to pain outcomes, psychological factors, and responses to quantitative sensory testing. Pain 2014;155(4):703–11.

[13] Martire LM, Stephens MAP, Mogle J, Schulz R, Brach J, Keefe FJ. Daily spousal influence on physical activity in knee osteoarthritis. Ann Behav Med 2013;45(2):213–23, http://dx.doi.org/10.1007/s12160-012-9442-x.

[14] Mason JH, Anderson J, Meenan R, Haralson K, Lewis-Stevens D, Kaine J. The rapid assessment of disease activity in rheumatology (RADAR) questionnaire: validity and sensitivity to change of a patient self-report measure of joint count and clinical status. Arthritis Rheum 1992;35(2):156–62, http://dx.doi.org/10.1002/art.1780350206.

[15] Ewald B, McEvoy M, Attia J. Pedometer counts superior to physical activity scale for identifying health markers in older adults. Br J Sports Med 2010;44(10):756–61, http://dx.doi.org/10.1136/bjsm.2008.048827.

[16] Matthews CE, Ainsworth B, Thompson R, Bassett Jr D. Sources of variance in daily physical activity levels as measured by an accelerometer. Med Sci Sports Exerc 2002;34:1376–81, http://dx.doi.org/10.1097/00005768-200208000-00021.

[17] Troiano R, Berrigan D, Dodd K, Masse L, Tilert T, McDowell M. Physical activity in the United States measured by accelerometer. Med Sci Sports Exerc 2008;40:181–8, http://dx.doi.org/10.1249/mss.0b013e31815a51b3.

[18] Swartz AM, Strath SJ, Bassett Jr DR, O'Brien WL, King GA, Ainsworth BE. Estimation of energy expenditure using CSA accelerometers at hip and wrist sites. Med Sci Sports Exerc 2000;32:450–6, http://dx.doi.org/10.1097/00005768-200009001-00003.

[19] Brach JS, Wert D, VanSwearingen JM, Studenski SA. The compendium of physical activity underestimates walking intensity in old more so than in young. J Am Geriatr Soc 2009;57:S110.

[20] Matthews CE. Calibration of accelerometer output for adults. Med Sci Sports Exerc 2005;37:S512–22, http://dx.doi.org/10.1249/01.mss.0000185659.11982.3d.

[21] Raudenbush SW, Bryk AS. Hierarchical linear models: applications and data analysis methods. Thousand Oaks, CA: Sage Publications; 2002.

[22] Hoffman L. Multilevel models for examining individual differences in within-person variation and covariation over time. Multivar Behav Res 2007;42(4):609–29, http://dx.doi.org/10.1080/00273170701710072.

[23] Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically

important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 1988;15(12): 1833–40.

[24] Curran PJ, Bauer DJ. The disaggregation of within-person and between-person effects in longitudinal models of change. Annu Rev Psychol 2011;62:583–619, http://dx.doi.org/10.1146/annurev.psych.093008.100356.

[25] Nicholl BI, Holliday KL, Macfarlane GJ, Thomson W, Davies KA, O'Neill TW, Bartfai G, Boonen S, Casanueva F, Finn JD, Forti G, Giwercman A, Huhtaniemi IT, Kula K, Punab M, Silman AJ, Vanderschueren D, Wu FC, McBeth J, European Male Ageing Study Group. No evidence for a role of the catechol-O-methyltransferase pain sensitivity haplotypes in chronic widespread pain. Ann Rheum Dis 2010;69:2009–12.