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Circulating Lipids and Acute Pain Sensitization: An Exploratory Analysis

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Abstract

Background—In individuals with low back pain, higher lipid levels have been documented and were associated with increased risk for chronic low back pain.

Objectives—The purpose of this research was to identify plasma lipids that discriminate participants with acute low back pain with or without pain sensitization as measured by quantitative sensory testing.

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Methods—This exploratory study was conducted as part of a larger parent randomized controlled trial. A cluster analysis of 30 participants with acute low back pain revealed two clusters: one with signs of peripheral and central sensitivity to mechanical and thermal stimuli and the other with an absence of peripheral and central sensitivity. Lipid levels were extracted from plasma and measured using mass spectroscopy.

Results—TAG 50:2 was significantly higher in participants with peripheral and central sensitization compared to the nonsensitized cluster. The nonsensitized cluster had significantly higher levels of PG 34:2, plasmenyl-PC 38:1, and PA 28:1 compared to participants with peripheral and central sensitization. Linear discriminant function analysis was conducted using the four statistically significant lipids to test their predictive power to classify those in the sensitization and no sensitization clusters; the four lipids accurately predicted cluster classification 58% of the time ($R^2 = .58$ ($-2 \log \text{likelihood} = 14.59$)).

Discussion—The results of this exploratory study suggest a unique lipidomic signature in plasma of patients with acute low back pain based on the presence or absence of pain sensitization. Future work to replicate these preliminary findings is underway.

Keywords

acute pain; back pain; lipids; pain sensitization

Musculoskeletal pain affects more than 126.6 million people in the United States and annual estimated costs for direct care and lost productivity exceed \$874 billion (Yelin, Weinstein & King, 2016). One of the most common musculoskeletal pain conditions is low back pain (LBP), and the development of chronic LBP is associated with significant impairment in activities of daily living and work disability. The prevalence of LBP increases with age and has been associated with higher body mass index (BMI) as well as elevated levels of circulating lipid molecules, including low-density lipoproteins and triglycerides (Heuch, Hagen, Heuch, Nygaard & Zwart, 2010; Heuch, Heuch, Hagen & Zwart, 2010, 2013, 2014). It has been posited that the increase in circulating lipids among individuals with LBP contributes to lumbar atherosclerosis, resulting in accelerated degenerative disc disease and higher fat content of the multifidus muscle (Mengiardi et al., 2006). More detailed investigation of the lipid content of the multifidus muscle revealed an increase in intramyocellular lipids in patients with LBP compared to asymptomatic volunteers (Takashima et al., 2016). Although it is currently unclear whether elevated levels of circulating lipids increase vulnerability to developing chronic LBP, both higher BMI and triglyceride levels have been reported in patients with chronic LBP compared to healthy controls (Rinaldo et al., 2016). Alternatively, perturbations within the lipid molecule cascade may have direct mechanistic effects on neuroinflammation and peripheral and central sensitization, processes that underlie the transition from acute to chronic pain (Li et al., 2013; Villarreal, Funez, de Queiroz Cunha, Parada, & Ferreira, 2013).

Nociception, the detection of noxious stimuli, is a protective response that alerts an individual to potential or actual tissue damage (Woolf, 2011). Peripheral and central sensitization can result from damaging stimuli; for example, with sunburn, when peripheral nociceptors become sensitized to normally non-noxious stimuli. The temporary allodynia

following sunburn represents a protective response to heightened risk of further tissue damage. In the absence of ongoing tissue damage, the increased sensitivity of nociceptors returns to normal, requiring high-intensity stimuli to generate pain signaling (Starkweather, Heineman et al., 2016). In contrast, persistent peripheral sensitivity can lead to central sensitization, which occurs when afferent activity induced by peripheral nociceptor activation triggers a long-lasting increase in the excitability of spinal cord neurons. Central sensitization augments pain signaling and is manifested as a reduction in the stimulus threshold required to produce pain, and an increase in responsiveness to noxious stimuli (Woolf, 2011). Alterations in somatosensory function that are consistent with peripheral and central sensitization include reduced thresholds of mechanical or thermal stimuli required to produce pain as compared to age- and gender-matched control thresholds, which can be detected using experimental pain protocols with quantitative sensory testing (QST).

In a cohort of patients with acute low back pain, a standardized QST protocol was used to measure the threshold and tolerance of noxious mechanical and thermal stimuli at the painful site of the lower back and a remote site (dominant forearm) (Starkweather, Lyon, et al., 2016). Some of the participants manifested signs of peripheral and central sensitization to mechanical and thermal stimuli as evidenced by reduced thresholds at both the painful region of the low back and the remote site. As a putative mechanism underlying sensitization, the levels of circulating lipid-based molecules in plasma were analyzed from the first 30 participants enrolled in the case-control observational study conducted by Starkweather, Lyon et al. (2016). Our hypothesis was that pain sensitized and non-sensitized individuals with acute low back pain would have significantly different levels of lipid molecules. The specific aim of this exploratory analysis was to identify plasma lipids that discriminate pain sensitization profiles as measured by quantitative sensory testing among patients with acute LBP.

Methods

Design

This exploratory analysis was part of a larger (parent) case-control observational study that evaluated peripheral and central sensitivity in participants with acute low back pain. The parent study included clinical data, symptom measures, quantitative sensory testing and blood samples collected from participants (clinicaltrials.gov number NCT01981382). The 30 participants in this analysis were a subset of the 220 participants who were enrolled between 2013–2016 at a major academic university medical center in the mid-Atlantic region. Plasma samples available from the first 30 enrolled participants were used for this analysis. The study protocol was approved by the Institutional Review Board of the university. All participants provided voluntary written informed consent before participation in the parent study. Study inclusion criteria were men and women, age 18–50 years old with pain anywhere in the region of the low back bound superiorly by the thoracolumbar junction and inferiorly by the lumbosacral junction, which had been present for >24 hours but <4 weeks duration and was preceded by at least one pain-free month. Exclusion criteria included pain at another site or associated with a painful condition, previous spinal surgery, presence of neurological deficits such as weakness, history of comorbidities affecting sensorimotor

function, pregnancy or within 3-months postpartum, taking opioids, antidepressant or anticonvulsant medications, or history of psychological disorders. Recruitment took place at primary healthcare clinics through advertisements. More detail is available in Starkweather, Lyon, et al. (2016).

Variables and Measurement

Pain—Study measures included well established valid and reliable instruments used frequently in studies evaluating pain. The Brief Pain Inventory Short Form (BPI-SF) was used to assess pain severity and interference with daily activities over the past 24 hours using a self-report Likert-type scale anchored at 0 = *no pain* and 10 = *pain as bad as you can imagine* (Cleeland, 1991). In this sample, Cronbach's α was .91.

Covariates—Since perceived pain, mood, perceived stress, reactivity and level of disability can influence pain sensitization (Starkweather, Heineman et al., 2016), these variables were included in the analysis. The Profile of Mood States (POMS) was designed to measure general distress and mood (McNair, Lorr, & Droppleman, 1992). A total mood disturbance score is derived by summing each of the subscales (vigor is weighted negatively); Cronbach's α was .91. Levels of stress were measured by the Perceived Stress Scale (PSS; Cohen, 1994); Cronbach's α was .92. The Kohn Reactivity Scale (Kohn, 1985) consists of 24 items that assess an individual's level of reactivity or central nervous system arousability. The Kohn Reactivity Scale had a Cronbach's α of .92. The Roland Disability Questionnaire (RDQ) is the most widely used instrument to assess perceived LBP-associated disability (Roland & Morris, 1983); Cronbach's α was .92.

Pain sensitization—Quantitative sensory testing was used to measure sensitivity to experimental pain with standardized stimuli to test both nociceptive and non-nociceptive systems. An established protocol of administration, including examination room conditions and instructions provided to the participant, were strictly followed (Starkweather, Heineman et al., 2016). Sites tested for QST included the most painful region of the lower back and a remote site—the dominant forearm.

Mechanical pain sensitivity (MPS) was assessed using standardized monofilaments that exert a force between 0.25 and 512 mN upon bending. The participant was asked to provide a numerical pain rating score in response to 300 mN of force. To measure mechanical pain threshold (MPT), an adaptive staircase method was used starting with the smallest monofilament in which a mechanical stimulus was detected. The tester applied the next larger-sized monofilament until the participant reported pain. The size of the monofilament and participant's numerical pain rating score were recorded. Wind-up ratio (WUR) represents the sensitization of nociceptors in response to intense activation and is calculated as the ratio of the mean pain rating in response to a series of 10 repetitive pinprick stimuli divided by the mean rating in response to a single pinprick stimuli. Each series was performed using the same physical intensity as the single stimulus.

Thermal testing was performed using the Medoc Pathway System (Ramat Yishai, Israel). The Medoc software guided the examiner through a series of thermal testing procedures in the following order. Cold pain threshold (CPT) was measured first, followed by heat pain

threshold (HPT). The thermal probe was applied to the site being tested and the participant was asked to press the button when the temperature reached a level that was painful. Temperature thresholds were obtained with ramped stimuli (1°C/second) that were terminated when the participant pressed the button on the Medoc machine, and the temperature was recorded. The mean threshold temperature of three consecutive measurements were calculated and used for the analysis.

For pressure pain threshold, the examiner used an algometer (range from 50–600 kPa) attached to the Medoc Pathway system to increase the pressure at a steady rate (30 kPa/s) until the participant indicated first pain sensation by pressing the button. The pressure pain threshold (PPT) was determined by repeating the procedure at the same site until either: (a) two values were recorded within 20 kPa of one another, or (b) three trials were administered. In either case, the mean of the two closest values were recorded as the threshold estimate. During the testing, the computer screen was positioned so that the participant was not able to watch temperature and pressure fluctuations.

Untargeted lipidomic analysis—Blood samples were centrifuged for 20 min at 1600g at 4°C and plasma samples were stored at –80°C. Plasma samples were prepared for analysis using a 2-step methoximation/silylation protocol. Sample preparation involved the addition of extraction internal standards and protein precipitation by organic solvent without other steps. After brief centrifugation, solvent was evaporated from the supernatant and the residue was re-suspended in water containing injection standards for analysis of polar compounds. Lipids were extracted from plasma according to Wijesinghe et al. (2010) and Merrill et al. (2005) with slight modifications as described in Spijkers et al. (2011) and measured using an Applied Biosystems SCIEX 4000 QTRAP mass spectrometer.

Statistical Analysis

Statistical analyses were conducted using SPSS v24 (Armonk, New York) and CAMO software (Woodbridge, New Jersey). Normality of the demographic, psychological, and QST data were tested using the Kolmogorov-Smirnov test and were found to be normally distributed. Thus, *t*-tests were used to assess cluster differences. A hierarchical cluster analysis of the QST data was performed to determine the underlying clustering of the pain sensitivity profiles. The grouping definition was applied to the lipidomic dataset and a partial least squares discriminant analysis (PLSDA) was performed to identify the clusters according to the pain sensitization profiles. PLSDA was selected for this analysis because it defines the features in multidimensional space that best describe the differences between clusters. An orthogonal projections-to-latent structures discriminant analysis (OPLSDA) was used to verify the real separation of the clusters with no overlapping of sensory and lipid profiles. The PLSDA coefficient score with threshold 70 was used to select the lipids for the linear discriminate analysis to determine the predictive power of these lipids to separate the clusters. An internal validation bootstrapping strategy with 1000 repetitions was used to determine the confidence interval of the probable results for the real population.

Results

Sample Description

The study sample was composed of 30 participants with acute low back pain. Participant characteristics, pain, and pain sensitization are shown in Table 1. There were 21 female and eight male participants with an average age of 35.3 years ($SD = 10.07$); average BMI was 29.1 ($SD = 7.78$).

Pain Sensitivity Clusters

The hierarchical cluster analysis of the QST data revealed the existence of two major clusters. Figure 1 demonstrates the two major clusters identified by heat pain threshold, pressure pain threshold, and mechanical pain sensitivity. The clusters were classified as Pain Sensitized (PS) and Nonsensitized (NS). PS participants had quantitative sensory testing values consistent with peripheral and central sensitivity to mechanical and thermal stimuli ($n = 22$; female 72.7%) whereas the NS cluster had quantitative sensory testing values that were consistent with age- and gender matched controls ($n = 8$; female 62.5%). Comparison of demographic, self-reported pain intensity and psychological measures did not demonstrate any significant differences in age, body mass index (BMI), pain, mood, perceived stress, reactivity or disability between clusters.

Lipid Analysis

Analysis of lipid data was conducted using PLSDA to identify the lipids that were most important to discriminate the pain sensitivity clusters. The lipidomic analysis detected 176 lipids with consistent values across the two clusters. To verify the real separation of the clusters based on sensory and lipid profiles, an orthogonal projections-to-latent structures discriminant analysis (OPLSDA) was performed (Figure 2).

Comparison of lipid concentrations between the two clusters using the weighted sum of absolute regression coefficients of PLSDA revealed differences in relative concentration of the following metabolites:

- triacylglycerol (TAG) 50:2 had a coefficient of 100 and was higher in the PS cluster;
- phosphoglyceride (PG) 34:2 with a coefficient of 98 was higher in the NS cluster;
- plasmenyl phosphocholine (plasmenyl-PC) 38:1 with a coefficient of 87 was higher in the NS cluster;
- lysophosphatidylethanolamine (LysoPE) 20:0 with a coefficient of 73 was higher in the NS cluster;
- phosphatidic acid (PA) 28:1 with a coefficient of 70 was higher in the NS cluster; and
- plasmenyl with a coefficient of 66 was higher in the PS cluster.

Of these lipid metabolites, four demonstrated a statistically significant difference between clusters (Table 2). TAG 50:2 was significantly higher in the PS cluster compared to the NS cluster. The NS cluster had significantly higher levels of PG 34:2, plasmenyl-PC 38:1, and PA 28:1 compared to the PS cluster.

The PLSDA coefficient score with threshold of .70 was used to select the lipids for linear discriminate analysis to determine the predictive power of the four lipids to classify between pain sensitization and no sensitization. The four lipids accurately predicted cluster classification 58% of the time ($R^2 = .58$; $-2 \log \text{likelihood} = 14.59$). The bootstrap median and interquartile ranges with the entropy R^2 at the third quartile (75th percentile) was 0.77; at the median (50th percentile) it was 0.66; at the first quartile (25th percentile) it was 0.54. Thus, as lipid levels increased above the median, they were more accurate at predicting cluster classification.

Correlations among the lipids and sensory testing data (using Spearman's rho) revealed significant inverse relationships between TAG 50:2 and pressure pain thresholds at the back ($r = -.62$, $p = .0003$) and remote site ($r = -.64$, $p = .0001$)—with higher levels of TAG 50:2, there was increased sensitization to pressure pain. In addition, significant inverse relationships were identified between plasmenyl-PC 38:1 and heat pain sensitivity at the painful area of the lower back ($r = -.50$; $p = .005$), and PA 28:1 with mechanical pain sensitivity ($r = -.52$, $p = .004$).

Discussion

In this exploratory study, significant differences were identified in plasma lipid levels among participants presenting with acute pain, with and without signs of peripheral and central sensitization. Participants with signs of peripheral and central sensitization (PS cluster) had significantly higher levels of TAG 50:2 while those without peripheral and central sensitization (NS cluster) had higher levels of PG 34:2, plasmenyl-PC 38:1, and PA 28:1.

Increased TAG 50:2 in the PS cluster compared to the NS cluster as well as the inverse association between TAG 50:2 and pressure pain threshold has not been previously reported in the literature. TAG 50:2 is a mono-oleic acid triglyceride, also known as triacylglycerol or triacylglyceride—it is a glyceride in which the glycerol is esterified with three fatty acid groups (i.e., fatty acid tri-esters of glycerol). TAG 50:2 consists of one chain of palmitic acid at the C-1 position, one chain of palmitoleic acid at the C-2 position and one chain of oleic acid at the C-3 position. In a lipidomic analysis performed in 14 pairs of young-adult monozygotic twins discordant for obesity, TAG 50:2 was one of the most abundant glycerolipid species in serum and correlated with total serum triglyceride levels but not BMI or subcutaneous fat (Pietiläinen et al., 2007). It may also be a more sensitive marker to insulin resistance than total serum triacylglycerol concentrations (Koteronen et al., 2009).

Due to the ubiquitous nature of TAG 50:2 in the extracellular compartment, it is unlikely to be directly involved in peripheral and central sensitization. However, elevated levels of TAG 50:2 in circulation may represent the early cascade of alterations in cardiovascular risk factors and intramyocellular storage that have been associated with LBP (Goodson et al.,

2013; Leino-Arjas et al., 2006; Takashima et al., 2016). To date, we are not aware of any studies that have examined lipid levels in relation to peripheral and central sensitivity, although fat distribution has been shown to influence pressure pain threshold. A recent study evaluating pain sensitivity among normal weight, overweight and obese individuals reported that pressure pain threshold was significantly lower in overweight and obese compared to normal weight individuals whereas thermal pain thresholds were not significantly different between groups (Tashani, Astita, Sharp, & Johnson, 2017). Further research regarding how triacylglycerol levels, specifically TAG 50:2, may influence pain sensitivity are needed, with careful attention to controlling for body mass index and fat distribution in mechanical and deep tissue pain sensitivity assessments.

The NS cluster had higher levels of PG 34:2 and plasmenyl-PC 38:1 compared to the PS cluster. Phosphoglyceride is a diacylglycerophosphoglycerol that is ubiquitous in cells as it is a major component of the lipid bilayer of the cell wall, while plasmenyl phosphocholine is a key component of the membranes of muscles and nerves. The NS cluster also had significantly higher levels of PA 28:1, which is one of the simplest diacylglycerophospholipids and acts as a biosynthetic precursor for the formation of all acylglycerol lipids in the cell. The cellular PA levels are dynamic; PA is produced and metabolized by several enzymatic reactions, including different phospholipases, lipid kinases, and phosphatases. PA interacts with various proteins and the interactions may modulate enzyme catalytic activities and/or tether proteins to membranes. The PA-protein interactions are impacted by changes in cellular pH and other effectors, such as cations. PA is involved in a wide range of cellular processes, including vesicular trafficking, cytoskeletal organization, secretion, cell proliferation, and survival (Liu, Su, & Wang, 2013). PA has been shown to possess analgesic activity by inhibiting inflammation-induced C-fiber activation (Kakiuchi et al., 2011). Overall, the current exploratory study results provide additional insight on the lipid molecules potentially involved in early sensitization in individuals with LBP and suggest a pathway, through cardiovascular risk reduction, in which sensitization may be mitigated.

Limitations

We are aware of several limitations of the study including the small sample size and absence of a healthy no-pain control group. Since all of the participants in this study were experiencing acute pain at the time of plasma collection, no inferences can be made regarding whether the levels are within range in comparison to age- and gender-matched no-pain controls. Further research is being conducted to address these issues and to verify the findings in a larger sample of patients with acute and chronic low back pain.

Conclusions

The results of this exploratory study suggest a unique lipidomic signature in plasma of patients with acute low back pain based on the presence or absence of peripheral and central nervous system sensitization. Improved methods within lipidomics (GC/LC mass spectrometry) have been utilized to investigate the role of lipid mediators in peripheral and central nociceptive processes. The results expand upon current understanding of differential

lipid levels between patients with acute pain who exhibit signs of peripheral and central sensitivity and those who do not. The impact of these lipid molecules are of great potential interest to investigations of the transition from nociception to chronic pathological pain states. Further research in this area is needed in order to fully understand the impact of lipid mediators in the process of pain sensitization and vulnerability to chronic pain.

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FIGURE 1.

Pain sensitivity cluster analysis. Quantitative sensory testing results were used to determine the underlying clustering of the pain sensitivity profiles. Two major clusters were identified and classified as the non-sensitized (NS) and pain sensitized (PS) clusters. The figure above shows the two clusters using heat pain threshold (HPT) with temperature in Celsius at the low back site, pressure pain at the control (remote) site in kPa, and mechanical pain sensitivity of the low back site as measured by the numerical pain rating score.

FIGURE 2.

Score plots of the pain sensitivity clusters applied to the lipidomic data. Panel A shows how the partial least squares discriminant analysis (PLSDA) defined two clusters with overlapping lipid profile scores. Lipids that were most important for discriminating between the pain sensitized (PS; dashed line) and nonsensitized (NS; solid line) clusters were identified. The lipidomic analysis detected 176 lipids with consistent values across the two clusters. Panel B shows how orthogonal projections-to-latent structures discriminant analysis (OPLSDA) defined group separation without overlap by separating cluster-predictive variation from cluster-uncorrelated variation in lipid scores.

TABLE 1

Participant Characteristics, Pain Scores, and Pain Sensitization

Category/measure	All (<i>N</i> = 30)			Pain-sensitized (<i>n</i> = 22)			Nonsensitized (<i>n</i> = 8)			<i>p</i> ^a
	<i>M</i>	(<i>SD</i>)	Range	<i>M</i>	(<i>SD</i>)	Range	<i>M</i>	(<i>SD</i>)	Range	
Characteristic										
Age	35.3	(10.07)	20–50	34.1	(2.26)	20–50	38.6	(2.80)	20–45	.29
BMI	29.1	(7.78)	18.5–50.4	27.7	(6.94)	18.5–48.2	32.7	(9.27)	23.9–50.4	.13
POMS (total)	27.1	(30.58)	–9–104	26.6	(31.29)	–9–104	28.5	(30.65)	–6–93	.89
PSS (total)	16.3	(5.54)	5–26	16.6	(5.70)	5–26	15.8	(5.37)	10–26	.73
Kohn (total)	73.2	(11.91)	44–94	74.6	(12.77)	44–94	69.1	(8.56)	56–81	.27
RDQ (total)	8.1	(4.89)	2–20	8.3	(4.93)	2–20	7.7	(5.12)	2–16	.79
Pain										
BPI (worst)	5.6	(2.57)	1–10	5.5	(2.44)	1–10	6.0	(3.02)	2–10	.63
BPI (least)	2.8	(2.28)	0–8	2.9	(2.33)	0–8	2.6	(2.26)	0–5	.62
BPI (average)	4.6	(2.24)	1–9	4.5	(2.06)	2–9	4.9	(2.80)	1–8	.76
BPI (now)	4.1	(2.39)	0–9	3.8	(2.18)	0–9	4.9	(2.90)	1–9	.27
BPI (interference)	4.1	(2.50)	0.1–8.9	4.0	(2.40)	0.1–8.9	4.5	(2.89)	0.7–8.9	.68
Pain sensitization										
MPT (back)	5.6	(1.15)	2.5–6.7	5.3	(1.17)	2.5–6.7	6.3	(0.74)	4.6–6.7	.04
MPS (back)	3.5	(2.47)	0.0–7.7	4.2	(2.08)	1.0–7.7	1.6	(2.57)	0.0–7.7	.01
MPS (remote)	2.1	(1.83)	0.0–6.3	2.6	(1.77)	0.0–6.3	0.9	(1.39)	0.0–4.0	.01
HPT (back)	38.6	(3.40)	34.1–47.5	37.5	(2.55)	34.1–42.5	41.8	(3.53)	37.0–47.5	<.001
HPT (remote)	39.7	(3.94)	34.7–48.9	38.1	(2.58)	34.7–45.1	44.1	(3.87)	39.8–48.9	<.001
CPT (back)	21.7	(8.32)	0.9–44.0	24.1	(7.41)	10.0–44.0	15.1	(7.41)	0.9–22.1	.01
CPT (remote)	19.5	(6.59)	3.0–26.6	21.9	(4.95)	10.0–28.6	13.0	(6.37)	3.0–20.7	<.001
PPT (back)	177.8	(141.51)	0.0–650.0	130.2	(96.91)	0.0–357.4	308.7	(167.57)	151.6–650.0	<.001
PPT (remote)	194.7	(99.97)	16.3–453.4	159.8	(81.12)	16.3–364.6	290.8	(85.29)	186.8–453.4	<.001
Wind-up ratio	2.4	(1.84)	0.0–7.0	2.9	(1.80)	1.0–7.0	1.1	(1.31)	0.0–4.0	.01

Note. BMI = body mass index; BPI = Brief Pain Inventory; CPT = cold pain threshold; HPT = heat pain threshold; MPT = mechanical pain threshold; MPS = mechanical pain sensitivity; POMS = Profile of Mood States; PPT = pressure pain threshold; PSS = Perceived Stress Scale; RDQ = Roland Disability Questionnaire.

^a *t*-test.

TABLE 2

Lipids That Discriminate Pain Sensitivity Clusters

Lipid	Coefficient	T	p	FDR
Triacylglycerol (TAG) 50:2	100 PS > NS	2.4039	.02	.98
Plasmenyl phosphocholine (plasmenyl-PC) 38:1	98 NS > PS	-2.3173	.03	.98
Phosphoglyceride (PG) 34:2	87 NS > PS	-2.3166	.03	.98
Phosphatidic acid (PA) 28:1	73 NS > PS	-2.1032	.05	.98

Note. FDR = false discovery rate. NS = nonsensitized cluster. PS = pain-sensitized cluster.