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ORIGINAL ARTICLE

Familial effects account for association between chronic pain and past month smoking

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Abstract

Background: Smoking is associated with chronic pain, but it is not established whether smoking causes pain or if the link is due to familial effects. One proposed mechanism is that smoking strengthens maladaptive cortico-striatal connectivity, which contributes to pain chronification. We leveraged a twin design to assess direct effects of smoking on pain controlling for familial confounds, and whether cortico-striatal connectivity mediates this association.

Methods: In a population-based sample of 692 twins (age = 28.83 years), we assessed past-month smoking frequency ($n = 132$ used in the past month), presence and severity of a current pain episode ($n = 179$ yes), and resting-state functional connectivity of the nucleus accumbens and medial prefrontal cortex (NAc-mPFC).

Results: Smoking was significantly associated with pain, but the association was not significantly mediated by NAc-mPFC connectivity. In a co-twin control model, smoking predicted which families had more pain but could not distinguish pain between family members. Pain risk was 43% due to additive genetic (A) and 57% due to non-shared environmental (E) influences. Past-month smoking frequency was 71% genetic and 29% non-shared environmental. Smoking and pain significantly correlated phenotypically ($r = 0.21$, $p = 0.001$) and genetically ($r_g = 0.51$, $p < 0.001$), but not environmentally ($r_e = -0.18$, $p = 0.339$).

Conclusions: Pain and smoking are associated; however, the association appears to reflect shared familial risk factors, such as genetic risk, rather than being causal in nature. The connectivity strength of the reward pathway was not related to concurrent pain and smoking in this sample.

Significance: Smoking does not appear to directly cause chronic pain; rather, there may be shared biopsychosocial risk factors, including genetic influences, that explain their association. These findings can be integrated into future research to identify shared biological pathways of both chronic pain and smoking behaviours as a way to conceptualize pain chronification.

1 | INTRODUCTION

Smoking is robustly associated with pain across both adolescence and adulthood (John et al., 2006; Palmer et al., 2003; Scaini et al., 2022) and is more common among chronic pain patients compared to the general population (Orhurhu et al., 2015). Former or current heavy smoking is associated with experiencing multiple pain locations and greater pain intensity, even when controlling for risk factors for pain such as alcohol use, obesity, and biological sex (John et al., 2006).

Some studies have identified a dose–response association between smoking and pain, which supports the causal hypothesis that smoking damages peripheral tissues and exacerbates pain (Ferreira et al., 2013; Hestbaek et al., 2006). Another proposed causal mechanism is that smoking promotes maladaptive plasticity in pain-processing neural pathways over time. Smoking is associated with pervasive cortical thinning (Karama et al., 2015) and decreased subcortical volumes (Hanlon et al., 2016). In one study, the relationship between past-year smoking and later pain chronification was mediated by the strength of the resting-state connectivity between the nucleus accumbens and medial prefrontal cortex (NAc-mPFC) (Petre et al., 2015).

Smoking may be an exacerbating risk factor for chronic pain, but the relationship could arise for different reasons. Chronic pain patients may self-medicate with cigarettes, as nicotine can provide transient analgesic effects (Borsook et al., 2016). Because nicotine is highly addictive (Pontieri et al., 1996), smoking may become frequent. Or, other predisposing factors, such as genetic or shared environmental (e.g., nutrition) effects, may confound the smoking-pain association. Previous twin studies have found that pain and smoking are moderately heritable (Junqueira et al., 2014; Maes et al., 2004) and that smoking shares genetic associations with traits that are genetically correlated with pain (Edwards et al., 2011; Khan et al., 2020).

Co-twin control analyses use monozygotic (MZ) and dizygotic (DZ) co-twins as quasi-experimental controls to estimate effect sizes when controlling for familial similarities, including genetic and familial environmental effects (McAdams et al., 2021). When accounting for familial factors (e.g., when looking at whether the twins who smoke are more likely to have pain compared to their non-smoking co-twins), the relationship between pain and smoking often becomes non-significant (Hestbaek et al., 2006; Suri et al., 2017). For example, a study of male veteran twins found that the association between chronic back pain and smoking status was entirely due to familial effects (Suri et al., 2017). However, another study found that smoking increased musculoskeletal pain risk by two-fold and that odds ratios were similar within families (i.e., when controlling for familial confounds) (Holley et al., 2013).

We examine whether these findings extend to chronic pain in our young adult twin sample. We assess whether smoking frequency increases pain, and using the brain coordinates from a previous study (Baliki et al., 2012), whether the resting-state NAc-mPFC connectivity mediates this relationship. We use a co-twin control analysis to evaluate these associations when controlling for familial confounds. Finally, we use classical twin models to assess the degree of shared genetic and environmental risk between smoking and pain.

2 | METHODS

2.1 | Participants

Participants were 692 same-sex twins (54% female; 46% male) from the Colorado Longitudinal Twin Study (LTS) who had data for at least one measure used in this study. The LTS is a long-standing, ongoing developmental study of twins born between 1984 and 1990. Twins whose families lived within a 3-hour driving range (~300 km) from Boulder, Colorado, and whose birth weights were at least 1000 grams (though 96% weighed 1700 grams or more) were invited to participate; twins were initially assessed at age 14 months. More information on ascertainment and history for the LTS is provided elsewhere (Corley et al., 2019; Rhea et al., 2013).

The data for this study were obtained between June 2014 and July 2019 when the twins completed functional magnetic resonance imaging (fMRI) and questionnaires (mean age = 28.8 years, standard deviation (SD) = 0.56). Exclusion criteria included standard contraindications to MRI (metal in the body, recent tattoo, claustrophobia, and pregnancy). The pain questionnaire was only administered on the scanning day, so individuals who did not attend the scanning session did not have pain data. The smoking questions were administered as part of a phone interview prior to the scanning session and individuals who did not enroll in the scanning study were assessed as part of another study, so more data are available for smoking behaviour. Those who participated in scanning did not significantly differ in smoking frequency ($p = 0.178$) compared to those who did not participate in scanning.

Demographic information and descriptive statistics are provided in Table 1. The sample self-reported their race as being 91.66% white, 4.44% Latino or Hispanic, 2.60% bi- or multi-racial, <1% Pacific Islander, <1% American Indian, and <1% "other." Of the 637 individual twins who responded to the pain questionnaire, 52.12% were MZ and 47.88% were DZ. Of the 687 twins who completed the smoking questionnaire, 51.82% were MZ twins and 48.18% were DZ. A total of 632 individual twins and 298 complete twin pairs completed both the smoking and pain questionnaires.

2.2 | Measures

2.2.1 | Brief Pain History Questionnaire

Participants completed the Brief Pain History Questionnaire (BPHQ) just prior to the MRI scanning session. The BPHQ is a self-report questionnaire developed for the LTS based on the Brief Pain Inventory (BPI), which is a validated tool for assessing pain episode presence and quality (Tan et al., 2004).

TABLE 1 Descriptive statistics of the sample.

Measure	*N*	Mean (SD) or %	Min–max	Skewness	Kurtosis
Age	692	28.83 (0.90)	28.02–34.58	2.45	7.84
Sex	692	46% male; 54% female	—	—	—
Body mass index	646[a]	25.89 (5.65)	15.02–54.02	1.32	2.14
Pain					
Pain episode presence	637	28.1% have pain	—	—	—
Chronic pain	637	27.2% have chronic pain	—	—	—
Pain duration (months)	637	22.56 (50.58)	0–314.3	2.60	6.66
Pain severity	637	8.52 (17.11)	0–100	2.41	6.26
Binned pain outcome		72.37% no pain 15.54% mild-mod pain 12.09% mod-high pain	—	—	—
Pain impact (composite)	637	7.09 (16.58)	0–100	2.84	8.37
Pain location	637	42% single-site pain 54% multisite pain 4% declined to answer	—	—	—
Smoking habits					
Age of initiation[b]	212	18.12 (3.15)	10–28	0.58	0.35
Cigarettes per day[c]	132	7.22 (5.81)	1–30	1.30	1.51
Smoking frequency	687	4.24 (9.82)	0–30	2.08	2.54
Binned smoking exposure		80.79% no smoking 8.15% non-daily smoker 11.06% daily smoker	—	—	—
NAc-mPFC connection[d]	600	0.28 (0.30)	−0.87-1.54	−0.25	1.96

Note: Of the 692 individuals who have either pain or smoking data, 632 have both smoking and pain data. In total, 637 participants of the sample filled out the Brief History Pain Questionnaire and 687 participants the PhenX Substance Use Interview. Chronic pain is defined as a pain episode that has lasted more than 3 months. The pain impact composite is a composite score of participants self-report on how pain has affected their work life, social life, and well-being. The bold face type indicates the variables used in the models; other variables are included to characterize the sample. NAc-mPFC = resting-state functional connectivity of the nucleus accumbens to medial prefrontal cortex. Dashes indicate not applicable for percentage statistics.

Abbreviation: SD, standard deviation.

[a]Only 646 out of 692 individuals filled out the height and weight survey.

[b]These descriptive statistics are of individuals who are former, occasional, or daily smokers.

[c]These descriptive statistics are of individuals who are occasional or daily smokers.

[d]The resting-state connectivity measure presented is z-transformed.

The BPHQ assesses whether participants are experiencing a pain episode as well as what age their pain began, the severity, the location(s) on a body map, and the descriptive quality of the pain episode (tingling, stabbing, etc.). The participants answered (yes or no) whether they were experiencing a "current significant episode of pain." A current significant episode of pain was defined as "A 'significant episode'; is one that has an impact on your quality of life that you consider to be important. An episode could be relatively brief (days to weeks) or prolonged (months to years)." Participants who answered yes then rated the severity of their pain on a numeric pain rating scale of 0–100, with 100 being the worst pain imaginable and 0 being no pain. Numeric pain rating scales are commonly used to measure presence of pain intensity and exhibit moderate to high reliability (0.67–0.96) (Kahl & Cleland, 2005). Of the participants experiencing pain, 42% reported pain in one body location, 54% reported pain in multiple locations, and 4% chose not to report a pain location. Of the total reported pain locations, 35% reported lower-extremity/knee pain, 27% reported back pain, 13% reported head/neck pain, 14% reported upper-extremity/shoulder pain, 3% reported chest pain, 3% reported stomach/bowel pain, 3% reported hip pain, and 2% reported genital pain.

Our measure captured multiple types of pain syndromes (e.g., back pain, head pain) and is thus interpretable as a measure of general chronic pain. Chronic pain may start at an individual location but tends to spread to multiple locations by becoming amplified by the central nervous system, otherwise known as central sensitization (Harte et al., 2018; Tanguay-Sabourin et al., 2023).

While chronic pain conditions at different body sites are diverse in causes, symptoms, and consequences, there is psychometric and genetic evidence for shared aetiology for pain across body sites. A longitudinal, psychometric analysis has supported the validity of a common component underlying pain across body sites (Battaglia et al., 2022). Consistent with this psychometric evidence for a general pain factor, twin and genome-wide association studies have identified a common genetic factor that contributes to many chronic pain conditions (Vehof et al., 2014; Zorina-Lichtenwalter et al., 2023). Of the people who reported pain in our sample, 97.2% reported pain lasting more than 3 months, characterizing the measure as chronic. We decided not to exclude the five participants whose pain episode was less than 3 months (range = 1.18–2.37 months), as our models would then lose information about their co-twins as well.

2.2.2 | PhenX toolkit—substance use interview

The PhenX toolkit (Hamilton et al., 2011) is a web-based toolkit funded by the National Human Genome Research Institute and National Institutes of Health that includes well-established measures of multiple phenotypes, including substance use. The phone substance use interview included multiple self-report questions about substance use behaviours (frequency, quantity, and dependence) with alcohol, tobacco, marijuana, and other substances. Smoking frequency was defined as the participants' self-reported number of days they smoked in the last 30 days (0–30).

2.2.3 | Resting-state functional connectivity

The LTS sample was scanned in a Siemens Tim Trio 3T or Prisma 3T scanner. Resting-state data were acquired with a 6.25-min T2*-weighted echo-planar functional scan (acquisition parameters: number of volumes = 816, TR = 460 ms, TE = 27.2 ms, matrix size = 82 × 82 × 56, voxel size = 3.02 × 3.02 × 3.00 mm, FA = 44.0°, slice thickness = 3.00 mm, field of view (FOV) = 248 mm) (see Reineberg et al., 2020). While the participants were undergoing the resting-state scan, they were instructed to relax and stare at a fixation cross.

The fMRI data were pre-processed using the FMRIB Software Library (FSL) build 509 (FSL) (Jenkinson et al., 2012). Detailed pre-processing information can be found elsewhere (see Reineberg et al., 2020). FSL tools flirt, fslmaths, and fslmeants were used to extract the resting-state functional connectivity between the NAc and mPFC using previously published, priori-defined seeds (Petre et al., 2015). The seed coordinates indicate the center of the regions of interest (ROIs: NAc; 10, 12, −8; mPFC 2, 52, −2) and were 6 × 6 × 6 mm cubed. Average time series for each ROI were created and then correlated within individuals to produce a functional connectivity score. The functional connectivity correlation was Fisher's z-transformed (Silver & Dunlap, 1987). After quality assurance checks, 600 twins' imaging phenotypes were suitable for analyses.

2.3 | Statistical analysis

2.3.1 | Data transformation

Due to non-normality of the smoking and pain variables, we used square-root transformations (see Table 1). However, the distributions were still non-normal, which prompted us to bin the untransformed variables to avoid biased estimates in the twin models (Verhulst & Neale, 2021). In the mediation and co-twin control models, pain (the outcome) was kept ordinal, but the smoking predictor variable was square-root transformed. Normal distribution of independent variables is not an assumption of regression, and the square-root transformed smoking variable allowed for more variability in the between- and within-family scores.

The distribution of past-month smoking frequency was non-normal, with peaks at 0 and 30 days/month. Past-month smoking frequency was binned into three categories to reflect these peaks: past month smoking, no = 0; 1–29 days = 1; 30 days = 2. These bins correspond to daily smokers (30 days), non-smokers (0 days), and social smokers (1–29). The pain severity variable was also categorized into 3 bins: no pain, 0 = 0; mild pain, 1–29 = 1; moderate to severe pain, 30–100 = 2. To ensure that the binned variables were not changing the pattern of results, all analyses were also conducted with the square-root transformed variables (presented in Tables S2–S4) to evaluate consistency.

2.3.2 | Statistical analyses

Phenotypic and twin analyses were completed in Mplus version 8.10 (Muthén & Muthén, 1998). Sex was included as a covariate for all of the models and models appropriately accounted for the non-independence of twins by specifying family clustering (Rebollo et al., 2006). Additional analytic details are provided in Appendix S1.

We conducted a phenotypic mediation model to evaluate whether the data are consistent with a model in

which the NAc-mPFC connectivity (*M*) mediates the direct effect (*c*) of smoking (*X*) on pain (*Y*). If the effect of smoking on pain controlling for *M* (*c*′) is not significant but the indirect effect (*a***b*) is, complete mediation has occurred. If all paths are statistically significant, partial mediation has occurred. If the *c*′ path is significant but *a***b* is non-significant, the significance of a mediation effect is not supported (Hayes, 2009). The NAc-mPFC was regressed on *X*, *Y*, and *Z* plane, head movement covariates.

All significant associations from the phenotypic mediation model were tested in the co-twin control model. The co-twin control design uses one twin in a pair as a matched control for the other twin within a regression framework. We used a mixed-effects logistic regression to investigate the within-twin pair association of pain and smoking while controlling for between-family confounds (genetic and shared environment effects). Specifically, we estimated a multi-level co-twin control model with both within-family and between-family effects. The independent variable for the between-family regressor was the family mean on a trait (here, the mean of smoking frequency for each twin pair). This between-family effect includes familial effects, i.e., shared environmental and genetic effects (Carlin et al., 2005). The independent variable for the within-family regressor was the deviation of each twin from their family mean (here, the deviation of smoking from the mean of both twins). Regressing this discordance estimate on the outcome of interest shows the direct effect while controlling for familial confounding (Carlin et al., 2005). We also tested an interaction of zygosity with the within-family effect since MZ and DZ twins differ in their genetic relatedness.

We used twin structural equation models to decompose the pain and smoking variances and their covariance into genetic and environmental components (Rijsdijk & Sham, 2002). The twin model leverages the fact that MZ twins share 100% and DZ twins share on average 50% of their segregating genetic variants. Common environmental factors (e.g. childhood home environment) are assumed to be shared 100% across MZ and DZ twins (Derks et al., 2006). Thus, when a measure correlates more strongly in MZ twins (*r*MZ) compared to DZ twins (*r*DZ) it suggests genetic influences on that trait. Moreover, when $r\text{MZ} < 2{*}r\text{DZ}$, shared environmental influences are suggested, whereas when $r\text{MZ} > 2{*}r\text{DZ}$, dominance genetic influences are suggested. Using these assumptions, structural equation models can be estimated to decompose the variances and covariances of a phenotype into three latent variables: (1) additive genetic effects (A), which represent the sum of all alleles that add up to the heritability of a trait; (2) genetic dominance factors (D), which represent deviance from additive effects (i.e., when one allele overrides the effect of the other allele at the same locus), or shared environmental factors (C), which are environmental influences that lead siblings to correlate, such as socioeconomic status or parenting styles; and (3) nonshared environmental factors (E), which are environmental influences that lead siblings to not correlate, such as an injury (Rijsdijk & Sham, 2002). The E factor also includes measurement error, as random error will lead twins to not correlate. $r\text{MZ} < 1$ suggests E. In the classical twin model, C and D cannot be estimated simultaneously and the choice of which parameter to include depends on the MZ and DZ correlation patterns. If $r\text{MZ} \leq 2{*}r\text{DZ}$ an ACE model is estimated and if $r\text{MZ} > 2{*}\text{DZ}$ an ADE model is estimated.

We first estimated univariate models for pain and smoking. A univariate AC/DE model estimates the A, C or D, and E parameters for a single phenotype. Nested models in which A and/or C/D are fixed to 0 and compared to the full model can be used to ascertain whether exclusion of a parameter significantly worsens model fit, using a chi-square difference ($\Delta\chi^2$) test (Kline, 2016). To estimate the genetic and environmental correlations between pain and smoking, we estimated a multivariate twin model with both phenotypes which gave us the ACE estimates for each measure and the genetic (*r*A) and non-shared environmental correlations (*r*E) between them (Loehlin, 1996). These correlations provide an estimate of the degree to which genetic (*r*A) and environmental (*r*E) influences overlap across the traits. Similar to the univariate models, nested models can be fit where *r*A or *r*E are dropped to assess their statistical significance.

3 | RESULTS

3.1 | Descriptive statistics

Descriptive statistics are presented in Table 1. The cross-tabs of pain presence and past-month smoking are displayed in Table 2. There were 30 MZ and 44 DZ twin pairs discordant for smoking.

We tested whether smoking's effect on pain was distinct from other PhenX substance use frequency measures (alcohol, cannabis, and a composite measure of any other drug; see Table S1). Smoking frequency was the only phenotype that significantly positively predicted pain, over and above the other substance use phenotypes. Less than 0.5% ($n = 5$) of the sample endorsed any usage (1–30) of painkillers in the last 30 days, which is why it was included in the composite measure; it did not significantly predict pain.

TABLE 2 Cross-tabulation of pain presence and past month smoking.

	Non-smoker	Smoker
No pain	379/632 (58.54%)	75/632 (11.87%)
Yes pain	131/632 (20.73%)	47/632 (7.44%)

Note: The percentages show the crosstabs of pain presence and smoking presence in the past month of the 632 participants who responded to both the Brief Pain History Questionnaire and the PhenX substance use interview.

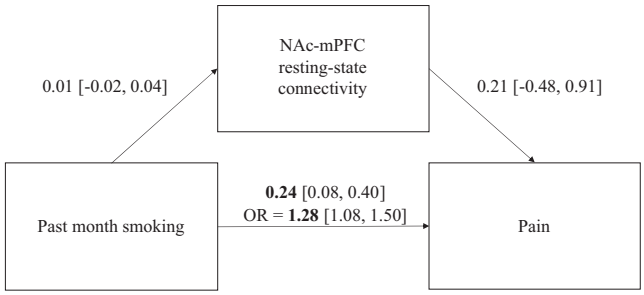

FIGURE 1 Log odds estimates of the mediation model are displayed with 95% boot-strapped (1000 times) confidence intervals. Past month smoking was measured as days smoked in the last 30 days (0–30) and was square-root transformed due to non-normality. Smoking and the brain mediator were *z*-scored. Hence, the estimates are the log odds of increasing one pain level with a standard deviation increase in smoking and NAc-mPFC connectivity. The direct path from smoking to pain is significant; however, the indirect path through the brain mediator is not significant. Smoking does not significantly predict NAc-mPFC resting-state connectivity, nor does NAc-mPFC connectivity significantly predict pain. Sex and 3 head-motion covariates were included (estimates not shown). NAc-mPFC = nucleus accumbens to medial prefrontal cortex connection strength from resting state magnetic resonance imaging. OR, odds ratio.

3.2 | Phenotypic mediation model

Controlling for sex effects, pain and smoking were phenotypically associated (polychoric $r = 0.22$, $p = 0.002$). However, NAc-mPFC connectivity did not significantly correlate with pain ($r = 0.01$, $p = 0.404$) nor past month smoking ($r = 0.02$, $p = 0.294$).

The mediation model is presented in Figure 1. Within the framework of the structural mediation model, the *a* ($a = 0.01$ [95% confidence interval (CI) −0.02, 0.04], $p = 0.441$) and *b* ($b = 0.21$ [95% CI −0.48, 0.91], $p = 0.539$) paths were not significant. Consequently, the indirect path was not significant ($a*b = 0.002$ [95% CI −0.01, 0.02], $p = 0.736$). The only significant path was the direct path from smoking to pain ($c' = 0.24$ [95% CI 0.08, 0.40], $p = 0.004$). Thus, we do not have evidence that the NAc-mPFC resting state connectivity mediates the smoking-pain association in this sample. See Appendix S1 for additional, post-hoc analyses of the NAc-mPFC relationships with pain and smoking.

3.3 | Co-twin control analyses

The co-twin control results do not provide evidence for a causal effect of smoking on pain, but they do suggest familial effects (see Table 3). Since the direct path between pain and smoking was the only significant association from the mediation model, this was the only association included in the co-twin control model. As seen in Table 3, the between-family effect of smoking on pain was significant (Odds Ratio (OR) = 1.31, $p < 0.001$), but the within-family effect was not significant and was estimated as negative (OR = 0.86, $p = 0.386$). Although the within-family effect was not significantly different from zero, it was significantly lower than the between-family effect, as a model that constrained them to be equal fit significantly worse ($\Delta\chi^2(1) = 9.892$, $p = 0.002$). The significantly lower within-family effect compared to the between-family effect suggests familial confounding (Carlin et al., 2005). The interaction of the within-family effect with zygosity was also not significant (OR = 0.90, $p = 0.730$), suggesting that the simple effects for the within-family association (reported in Table 3) do not differ across zygosity groups.

3.4 | Twin models

3.4.1 | Univariate analyses

The univariate twin models suggested that both pain and smoking are due to a mix of genetic and nonshared environmental effects. The observation that the MZ twin correlations were over double the DZ correlations for pain severity (rMZ = 0.46; rDZ = 0.10) implies dominance genetic effects, which are represented by inclusion of the D parameter. The MZ twin correlation for smoking frequency was just about double the DZ correlation (rMZ = 0.70; rDZ = 0.36), suggesting an AE model would fit well.

The variance components and model fit statistics can be found in Table 4. We did not have the power to detect significant A and D components when both were in the model (dominance genetic influences are difficult to detect in even very large samples; Martin et al., 1978), and the pain model fit did not significantly deteriorate when dropping the D parameter. Pain variance was 43% [95% CI 0.18, 0.63] attributable to additive genetic effects and 57% [95% CI 0.37, 0.81] to non-shared environmental effects. For smoking, the AE also fit well. For smoking frequency,

TABLE 3 Results of regression and co-twin control models of pain regressed on smoking.

Model	Independent variable	Effect on pain
Model 1: Individual-level model	Phenotypic smoking	**0.24** [0.09] **OR = 1.28**
Model 2: Co-twin Control model	Between-family smoking	**0.27** [0.08] **OR = 1.31**
	Within-family smoking	−0.15 [0.17] OR = 0.86
	Within MZ	−0.10 [0.21] OR = 0.90
	Within DZ	−0.20 [0.20] OR = 0.82
	Zygosity	0.09 [0.23] OR = 1.09
	Zygosity*Within	−0.10 [0.28] OR = 0.90

Note: Regression estimates [standard errors] for logistic regression models. Pain was ordinal and Smoking was the *z*-score of square root-transformed smoking frequency. Estimates are thus the log odds of increasing one pain level with a standard deviation increase in smoking frequency. The individual-level model regressed pain on smoking and sex without controlling for familial confounds. The co-twin control models separate the individual-level effects into between-family (including familial effects) and within-family (suggestive of direct effects) components. The models used a logit link function and maximum likelihood estimator robust to non-normality and non-independence. Sex was included as a covariate (estimates not shown). Zygosity was contrast coded (MZ = −0.5; DZ = 0.5) to obtain the within-family estimates across zygosity, whereas it was dummy coded to obtain the simple effects within each zygosity (Within MZ and Within DZ). The zygosity interaction coefficient is the difference of the within-family effect between MZ and DZ twins. Bolded font indicates $p < 0.05$.

Abbreviations: DZ, dizygotic twins; MZ, monozygotic twins; OR, odds ratio.

71% [95% CI 0.50, 0.85] of the variance was attributable to additive genetic effects and 29% [95% CI 0.15, 0.50] to non-shared environmental effects.

3.4.2 | Bivariate analyses

The bivariate twin model suggested that pain and smoking share a significant genetic correlation, but not a non-shared environmental correlation. The bivariate model fit statistics are presented below, and the parameter estimates are presented in Figure 2. The cross-twin, cross-trait correlations for MZ twins were about equal to those for the DZ twins (*r*MZ: 0.23; *r*DZ: 0.24). This pattern of correlations would suggest presence of an *r*C. We tried fitting an ACE version of pain, however, the C component in pain was estimated at 0% and in smoking at 1% (see Table 4). A bivariate model including *r*A and *r*E between AE pain and AE smoking fit the data well ($\chi^2(28) = 30.584$, $p = 0.336$, CFI = 0.979, RMSEA = 0.022). The *r*A correlation was significant (*r*A = 0.51, $\Delta\chi^2(1) = 11.525$, $p < 0.001$) but the *r*E correlation was not significant (*r*E = −0.18, $\Delta\chi^2(1) = 0.913$, $p = 0.339$).

4 | DISCUSSION

We found that chronic pain and past-month smoking are related. However, our findings do not provide evidence that smoking directly impacts pain; rather our co-twin control and twin model results suggest that there may be familial, particularly genetic, risk factors that explain their association. The mediation paths through NAc-mPFC connectivity were non-significant.

4.1 | Significant shared genetic influences on smoking and pain

To our knowledge, this is the first twin study employed to estimate the genetic correlation between smoking frequency and chronic pain. Although the genetic correlation we detected may be due to a mixture of genetic and correlated shared environmental effects that we are unable to discriminate, our estimate ($r_g = 0.51$) is similar to a recent estimate from a genome-based method. Lundberg et al. (2020) found a genetic correlation ($r_g = 0.42$) between smoking and wide-spread chronic pain in a genome-wide association study. These results suggest shared risk alleles underlie the pain-smoking association. Another study found that back pain shared a significant genetic correlation ($r_g = 0.35$) with smoking status; interestingly, the correlation became non-significant when controlling for other related traits (e.g., body mass index [BMI], depression), suggesting that those traits might be explanatory variables (Freidin et al., 2019). Many transdiagnostic biopsychosocial factors have been detected for both smoking and pain, such as depression (LaRowe & Ditre, 2020). There may be gene sets that underlie smoking, pain, and other correlated biopsychosocial risk factors.

There are also multiple possibilities for familial environmental risk factors, which may also have

TABLE 4 Model fit statistics of the ADE pain, ACE smoking, and nested models.

		Parameter estimates			Model fit					Chi-square difference		
Measure	**Model**	**A**	**C/D**	**E**	χ^2	**df**	***p***	**RMSEA**	**CFI**	$\Delta\chi^2$	**Δdf**	***p***
Pain	ADE	0.00 [0.00, 0.57]	0.46 [0.00, 0.64]	0.54 [0.34, 0.79]	12.297	10	0.266	0.036	0.898			
	AE	**0.43** [0.18, 0.63]	—	**0.57** [0.37, 0.81]	**13.142**	**11**	**0.284**	**0.033**	**0.905**	**0.837**	**1**	**0.360**
	E	—	—	1.00 [1.00, 1.00]	31.061	12	0.002	0.094	0.154	19.158	2	<0.001
Smoking	ACE	0.70 [0.10, 0.83]	0.01 [0.00, 0.51]	0.30 [0.16, 0.51]	6.446	10	0.777	0.000	1.000			
	AE	**0.71** [0.50, 0.85]	—	**0.29** [0.15, 0.50]	**6.606**	**11**	**0.830**	**0.000**	**1.000**	**0.001**	**1**	**0.981**
	CE	—	0.61 [0.44, 0.74]	0.39 [0.25, 0.56]	10.459	11	0.490	0.000	1.000	5.000	1	0.025
	E	—	—	1.00 [1.00, 1.00]	72.516	12	<0.001	0.165	0.268	84.012	2	<0.001

Note: Model fit statistics for the full ADE pain (rMZ = 0.46; rDZ = 0.10) and ACE smoking (rMZ = 0.71; rDZ = 0.36) models and chi-square difference ($\Delta\chi^2$) tests for the nested models compared to these full models. The A (additive genetic effects), C/D (shared environmental/dominance genetic effects), and E (non-shared environmental effects) estimates presented represent the proportion of variance explained by each of the parameters. Pain and smoking frequency were ordinal and the mean- and variance-adjusted weighted least squares (WLSMV) estimator was used to account for non-normality. The model fit results show whether each model has good fit, indicated by comparative fit index (CFI) > 0.95 and root mean squared error of approximation (RMSEA) < 0.06. Chi-square difference ($\Delta\chi^2$) tests, appropriately scaled for the WLSMV estimator, were conducted to test whether dropping a parameter significantly deteriorated fit, indicated by $\Delta\chi^2$ $p < 0.05$. Dashes indicate the parameter was not estimated. Boldface type indicate the best models (AE) for both pain and smoking.

Abbreviation: df, degrees of freedom.

FIGURE 2 Standardized variance explained [bootstrapped 1000× 95% confidence intervals] and their correlations from the AE correlated factors model. The amount of variance explained by additive genetic effects (A) is 43% for pain and 71% for smoking. The genetic variance components of pain and smoking share a significant genetic correlation ($r_g = 0.51$). The amount of variance explained by non-shared environmental effects (E) is 57% for pain and 29% for smoking. Pain and smoking do not show a significant non-shared environmental correlation ($r_e = -0.18$). Solid lines and asterisks indicate $p < 0.05$ and dashed lines indicate $p > 0.05$, based on chi-square difference tests.

gene–environment correlations with pain and smoking (in which case they might be captured by the genetic correlation for pain and smoking). Lifestyle habits such as nutrition, sleep, physical activity, and obesity, have been linked to chronic pain and smoking, both phenotypically and genetically (Lundberg et al., 2020; Mills et al., 2019).

A gene–environment interaction is also plausible, where genetic risk depends on an individual's environment (Purcell, 2002). Parenting styles have a gene–environment interaction with smoking and BMI, where negative parenting styles during development increased risk of genetic influences expressing for smoking and BMI (Ji & An, 2022). Chronic pain has been conceptualized as an example of gene–environment interaction where a person's genetic variants may make them at higher risk of developing pain when exposed to environmental risk (Mogil, 2012), although this hypothesis has not been

directly tested within a gene–environment twin framework (Purcell, 2002). Shared environmental risk factors during development, such as poor nutrition, could contribute to increased genetic expression of pain and smoking risk alleles.

4.2 | Small, non-significant direct influence of smoking on pain

We did not find a significant non-shared environmental correlation between pain and smoking, which is inconsistent with the hypothesis that smoking directly causes pain. This result is consistent with our co-twin control analysis (McGue et al., 2010), in which we did not find a significant direct effect. Our co-twin control findings did show a significant between-family association, also consistent with the significant genetic correlation we found in the twin model. These results suggest that familial effects account for the relationship between smoking and pain, rather than there being a direct causal effect (McAdams et al., 2021).

The support for predisposition underlying the pain-smoking association corroborates multiple past co-twin control findings, which examined smoking behaviours with low back pain (Hestbaek et al., 2006; Junqueira et al., 2014; Suri et al., 2017). In one study, individual-level analyses showed that being a former or current smoker increased back pain, but when partitioning out familial confounding, the risk was not significant (Suri et al., 2017). In another study, quantity of cigarettes per day showed evidence for dose–response relationships, but within a discordant MZ twin framework, smoking status did not significantly increase concurrent or prospective risk for low back pain (Hestbaek et al., 2006). Our findings extend these conclusions to general chronic pain, which includes multiple pain types in addition to low back pain.

These findings conflict with some studies of causal support found in the literature (LaRowe & Ditre, 2020). Using genomic approaches, Mendelian randomization studies have found contradicting evidence on whether smoking causally increased pain risk (Freidin et al., 2019; Lundberg et al., 2020). This inconsistency may be due to differential mechanisms for specific pain conditions. For example, orofacial pain severity may have a more direct association with smoking frequency, in comparison to general pain (Alamir & Quadri, 2020).

An argument in support of the causal hypothesis, regardless of mechanism, is that the cessation of smoking leads to at least partial reversibility of pain severity. The literature on this phenomenon has mixed results, and these studies are most often observational (Behrend et al., 2012; Leboeuf-Yde, 1999; Shi et al., 2011). The quasi-experimental nature of the co-twin control design is unique in its ability to control for unmeasured genetic and socio-demographic factors within families (McAdams et al., 2021). Within a co-twin framework, being a former or current smoker did not have a significant effect on pain (Suri et al., 2017).

4.3 | Small, non-significant NAc-mPFC mediation of the smoking-pain association

We did not find associations with pain or smoking and maladaptive cortico-striatal connectivity. It is surprising that we did not observe a relationship between NAc-mPFC connectivity and concurrent smoking frequency, as circulating nicotine has been well-supported in activating acetylcholine receptors in dopamine systems (Wittenberg et al., 2020). One possibility is that smoking frequency does not reflect tobacco quantity, which may be a more direct measure of this mechanism; however, smoking quantity and smoking frequency were highly collinear in this sample. The prior study that found the significant mediation had differences in comparison to the current study; it was longitudinal and assessed smoking status within a subacute back pain sample (Petre et al., 2015). Another possibility is that the imaging data may have been noisy, as the nucleus accumbens is small and near many ventricles, making it susceptible to poor data quality.

The lack of relationship between NAc-mPFC connectivity and pain was also unanticipated. The affective dimensions of pain have been shown to correlate with this circuit's functional connectivity (Baliki et al., 2012; Petre et al., 2015). Furthermore, the circuit has been shown to mediate the impact of self-regulation and acute pain intensity (Woo et al., 2015). The pain measure in our study may fail to distinguish between sensory and affective dimensions of pain, which would reduce power.

4.4 | Limitations and future directions

This study was not without its limitations. First, the pain measure was self-reported, which can be biased (Robinson et al., 1997). Substance use self-report measures are especially vulnerable to under-reporting, which may have created artificial discordance in our co-twin design (Johnson & Fendrich, 2005).

Second, the cross-twin cross-trait correlations were suggestive of shared (familial) environmental (C) risk factors underlying the covariation of pain and smoking; however, C estimates for pain and smoking were negligible, so our models focused on genetic associations. We did not detect significant C variance in our pain and smoking measures, consistent with the literature, but that does not

mean they are zero. A larger twin study may be needed to definitively reject the presence of a small C influence (Martin et al., 1978).

Although this is a relatively large study for one that includes imaging data, power for a within-family effect depends on the within-family variance (discordance). A power analysis based on the variances we observed in this sample (see Appendix S1) suggested that we had good power to detect phenotypic and between-family effects similar to those that we observed, but low power to detect a within-family effect of the same magnitude. However, the estimate for the within-family effect was nowhere near that for the phenotypic effect (it was actually negative), which may somewhat reduce concerns that our effects were consistent with a causal model but did not reach significance. While the within-family effect was not significantly different from 0, it was significantly smaller than the between-family effect. Given that we found a significant between-family effect, a non-significant negative within-family effect that was significantly smaller than the between-family estimate, and a significant genetic correlation, the data are suggestive of a familial explanation for the pain-smoking association. However, we cannot rule out the possibility of a small, direct effect of smoking on pain.

This study focused on general chronic pain, but future research would benefit from observing these associations in specific pain conditions. There may be differential mechanisms and shared gene sets for differential pain conditions, such as migraine or low back pain. Future research could examine additional biopsychosocial risk factors and explanatory variables for the pain-smoking relationship, such as inflammation. Furthermore, examining gene–environment interactions between pain and common environmental risk factors, such as stressful life events, may be informative.

5 | CONCLUSIONS

The association between smoking and pain appears to be due to familial effects, likely genetic risk. While cessation of smoking is beneficial to overall health, it may not directly reduce pain. There are likely underlying risk factors that are driving both pain and smoking risk. Identification of these underlying risk factors may be informative in prevention of both pain and smoking exacerbation.

AUTHOR CONTRIBUTIONS

LR, NPF, BP, and TDW assisted in study design. Analyses were performed by LR and AER. This manuscript was written by LR under the supervision of NPF. All authors contributed to improving the manuscript and preparing for final submission.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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