Journal of Dental Research
2016, Vol. 95(10) 1132–1137

DOI: 10.1177/0022034516661151
jdr.sagepub.com

Fear of Pain Mediates the Association between *MC1R* Genotype and Dental Fear

C.L. Randall[1,2], D.W. McNeil[1,3], J.R. Shaffer[1,4], R.J. Crout[1,5], R.J. Weyant[1,6], and M.L. Marazita[1,7]

Abstract

Fear of pain is experienced in acute and chronic pain populations, as well as in the general population, and it affects numerous aspects of the orofacial pain experience, including pain intensity, pain-related disability, and pain behavior (e.g., avoidance). A related but separate construct—dental fear—is also experienced in the general population, and it influences dental treatment–seeking behavior and oral and systemic health. Minimal work has addressed the role of genetics in the etiologies of fear of pain and dental fear. Limited available data suggest that variants of the melanocortin 1 receptor (*MC1R*) gene may predict greater levels of dental fear. The *MC1R* gene also may be etiologically important for fear of pain. This study aimed to replicate the finding that *MC1R* variant status predicts dental fear and to determine, for the first time, whether *MC1R* variant status predicts fear of pain. Participants were 817 Caucasian participants (62.5% female; mean ± SD age: 34.7 ± 8.7 y) taking part in a cross-sectional project that identified determinants of oral diseases at the community, family, and individual levels. Participants were genotyped for single-nucleotide polymorphisms on *MC1R* and completed self-report measures of fear of pain and dental fear. Presence of *MC1R* variant alleles predicted higher levels of dental fear and fear of pain. Importantly, fear of pain mediated the relation between *MC1R* variant status and dental fear (B = 1.60, 95% confidence interval: 0.281 to 3.056). *MC1R* variants may influence orofacial pain perception and, in turn, predispose individuals to develop fears about pain. Such fears influence the pain experience and associated pain behaviors, as well as fears about dental treatment. This study provides support for genetic contributions to the development/maintenance of fear of pain and dental fear, and it offers directions for future research to identify potential targets for intervention in the treatment of fear of pain and dental fear.

Keywords: orofacial pain/TMD, dental phobia, anxiety, genetics, psychosocial factors, behavioral science

Introduction

Experience of orofacial pain—acute and chronic manifestations—is varied (e.g., tooth pulpal, periodontal, musculoskeletal, neuropathic, idiopathic). Orofacial pain is also common; approximately one-quarter of adults report experiencing significant orofacial pain ever in life (Setty and David 2014). The burden is high at societal and individual levels, as orofacial pain is associated with health care expense, lost productivity, and decreased oral health–related quality of life and psychological well-being (e.g., Friction and Schiffman 1995; Vadivelu 2014). To address this burden, a complete understanding of the etiologies, presentations, and implications of orofacial pain is warranted.

Psychosocial factors are important in the experience of acute and chronic orofacial pain (McNeil et al. 2014). Fear represents one of these factors, as it is central to pain etiology, experience, and management. Generally, greater levels of fear (and/or the related emotion anxiety; see comment in Appendix) are associated with more intense acute and chronic pain experience (Robinson and Riley 1999). Not surprising, fear of pain appears to be an especially important emotional determinant of pain. Fear of pain involves irrational apprehension of nociception resulting from any source (Asmundson, Vlaeyen, et al. 2004). Fear of pain

[1]Center for Oral Health Research in Appalachia, School of Dental Medicine, University of Pittsburgh, Pittsburgh, PA, USA
[2]Department of Psychology, Eberly College of Arts and Sciences, West Virginia University, Morgantown, WV, USA
[3]Department of Psychology and Department of Dental Practice and Rural Health, West Virginia University, Morgantown, WV, USA
[4]Department of Human Genetics, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA, USA
[5]Department of Periodontics, School of Dentistry, West Virginia University, Morgantown, WV, USA
[6]Department of Dental Public Health, School of Dental Medicine, University of Pittsburgh, Pittsburgh, PA, USA
[7]Center for Craniofacial and Dental Genetics, Departments of Oral Biology, Human Genetics, Clinical and Translational Science, and Psychiatry, University of Pittsburgh, Pittsburgh, PA, USA

A supplemental appendix to this article is published electronically only at http://jdr.sagepub.com/supplemental.

Corresponding Authors:
C.L. Randall, Department of Psychology, West Virginia University, Box 6040, Morgantown, WV 26505-6040.
Email: CRANDAL1@mix.wvu.edu
D.W. McNeil, Department of Psychology and Department of Dental Practice and Rural Health, West Virginia University, Box 6040, Morgantown, WV 26506-6040.
Email: dmcneil@wvu.edu

can operate to maintain chronic pain over time (Asmundson, Norton, et al. 2004), and also is associated with perceived pain intensity, reduction of physical activity, and occurrence of maladaptive avoidance behaviors in chronic pain patients of many types (McCracken et al. 1996; Vlaeyen et al. 2001; Verbunt et al. 2004). Fear of pain is also associated with self-reported pain intensity in experimental pain (George et al. 2006).

There is minimal literature addressing the relation between fear of pain and orofacial pain. Notably, though, orofacial pain patients report greater levels of fear of pain than do their matched healthy control counterparts (McNeil et al. 2001). Likewise, fear of pain is associated with experiencing more intense and longer-lasting pain following intraoral injection (van Wijk and Hoogstraten 2009), and patients who have experienced dental pain report heightened fears of dental pain (van Wijk and Hoogstraten 2005). Thus, fear of pain and the orofacial pain experience are likely related in a bidirectional or cyclical manner. Still, additional work is necessary to more definitively understand this complex association and the specific role of fear of pain in the orofacial pain experience.

Fear affects not only the orofacial pain experience but also dental treatment–seeking behavior. Indeed, dental fear (see terminology comment in the Appendix) is a prevalent problem, with nearly half of the adult population in the United States reporting at least moderate levels and approximately 1 in 10 patients avoiding dental treatment altogether for this fear alone (for review, see McNeil and Randall 2014). Dental fear is predictive of a host of detrimental health outcomes, including systemic, oral, and psychological ones (McNeil and Randall 2014). Given the potential for pain in dental treatment, those studying dental fear and associated avoidance of dental care have focused on fear and fear of pain. To be certain, fear of pain (and fear of dental pain) is strongly associated with dental fear (e.g., McNeil et al. 2001; van Wijk and Hoogstraten 2003; Binkley et al. 2009), and fear of pain is conceptualized as a primary component and driving factor in dental fear (McNeil and Berryman 1989). Like fear of pain, dental fear is related to more intense experience of orofacial pain, especially during dental treatment (e.g., Klages et al. 2004; Sanikop et al. 2011), and it has even been associated with memory of exaggerated orofacial pain experience at short- and long-term follow-up after tooth extraction (McNeil et al. 2011; Kyle et al. 2016).

Recent data suggest a genetic contribution to the development and maintenance of dental fear. Across anxiety disorders, the degree of heritability is quite high (Timpano et al. 2009), and this appears to be the case for dental fear/anxiety, too. Three studies have demonstrated moderate to high heritability for dental fear (30% to 47%; Ray et al. 2010; Vassend et al. 2011). Notably, only 1 study has addressed the heritability of fear of pain, demonstrating a moderate degree (i.e., 34%) in a community sample of adolescents and adults. Genetic variability may influence in several ways (e.g., anxiety sensitivity, fear conditioning, cognitive vulnerability, pain sensitivity) whether and how a patient acquires fears about pain and/or dental treatment.

Candidate gene analysis has also been applied to the study of dental fear. Given that people with red hair (and associated variants in the melanocortin 1 receptor [*MC1R*] gene) have lower sensitivity to general and subcutaneous local anesthesia as compared with others, Binkley and colleagues (2009) tested and determined that *MC1R* variant status (i.e., having ≥2 gene variants vs. no variants) predicts greater fear of dental pain and dental fear, as well as a 2-fold increase in the likelihood of avoiding dental care, for redheads and for dark-haired Caucasians. It may be that resistance to local anesthesia results in more painful dental experiences, which may condition fears of dental pain and dental treatment. Furthermore, *MC1R* is expressed in brain tissue of the pathways responsible for the experience and processing of pain, anxiety, and fear (Xia et al. 1995; Chaki and Okuyama 2005). The single study on the topic (Binkley et al. 2009) and corroborating evidence suggest that *MC1R* may be particularly important for understanding individual differences in dental fear and fear of pain.

Fear of pain and dental fear are separate and linked phenomena that strongly influence and are influenced by the experience of acute and chronic orofacial pain. To completely understand these phenomena, it is important to elucidate their etiologies and relations. The inclusion of genetic variables makes conceptualizations of fear of pain and dental fear more complete; thus, the aim of this study was to extend limited extant literature suggesting that genetic factors, namely *MC1R*, have a role in fear of pain and dental fear. Specifically, it was hypothesized that the Binkley et al. (2009) finding can be replicated and that *MC1R* variant status is associated with dental care–related fear (hypothesis 1). Two novel hypotheses were additionally tested: that *MC1R* variant status is associated with fear of pain (hypothesis 2) and that fear of pain mediates the relation between *MC1R* variant status and dental care related fear (hypothesis 3).

Materials and Methods

Procedure

The current study utilized existing data from a large, family-based study of the Center for Oral Health Research in Appalachia, Cohort 1. This is the same data set from which the previously reported heritability estimates for fear of pain and dental fear were calculated. The project aimed to identify determinants of oral diseases at the community, family, and individual levels. Data were collected between 2003 and 2009. A comprehensive protocol included a large battery of self-report measures related to several aspects of oral health, standardized interviews, oral health assessment, microbiological assessment, and DNA collection (for a complete description, see Marazita et al. 2005; Polk et al. 2008). Written informed consent was obtained from participants; approval was from the institutional review boards of West Virginia University and the University of Pittsburgh. This study was in accordance with STROBE guidelines for observational investigations.

Table 1. *MC1R* Genetic Variant Information.

SNP	Base Pair[a]	Minor Allele	MAF	Information[b]	Quality[c]	Substitution[d]	*n* (%)[e]
rs1805006	89985918	A	0.011	0.666	0.991	Asp84Glu	10 (1.2)
rs11547464	89986091	A	0.003	0.607	0.997	Arg142His	3 (0.4)
rs1805007	89986117	T	0.068	0.878	0.979	Arg151Cys	126 (15.4)
rs1110400	89986130	C	0.009	0.982	1.000	Ile155Thr	18 (2.2)
rs1805008	89986144	T	0.084	0.947	0.989	Arg160Trp	132 (16.2)
rs1805009	89986546	C	0.007	0.462	0.989	Asp294His	4 (0.5)

MAF, minor allele frequency; SNP, single-nucleotide polymorphism.
[a]Base pair position on chromosome 16, build 37.
[b]Statistical information metric.
[c]Imputation quality score.
[d]Amino acid residue change at protein position.
[e]Number and percentage of participants with the minor allele (N = 817).

Participants

Current participants were members of the 732 households from the Cohort 1 project. Recruitment was completed through a household-based protocol, with eligibility criteria stipulating that households must contain at least 1 biological parent-child pair (i.e., aged 1 to 18 y). All members of eligible households were invited to participate, without regard to biological or legal relationships. Participant exclusion criteria were as follows: psychosis, neurologic impairment, and severe physical or mental disability.

For the current study, to ensure independence among participants, only those who were not biologically related to others in the sample were included (i.e., adult participants' parents and children were not included). Consistent with previous related research involving *MC1R* (e.g., Binkley et al. 2009), only Caucasian participants were included; thus, data for 817 participants were available.

DNA Collection and Genotyping

DNA was collected and genotyped for all consenting participants (see comment in Appendix). *MC1R* variant status was determined for participants by combining genetic data across 6 single-nucleotide polymorphisms (SNPs) to calculate a risk score (i.e., the number of risk alleles present for each participant was calculated; see Appendix for method). Risk alleles at these 6 SNPs are missense (coding) variants responsible for amino acid residue changes that are predicted to be deleterious to protein function (García-Borrón et al. 2005). Ultimately, participants were assigned to 1 of 2 groups based on the number of variant alleles present: those with normal genotype had zero risk alleles, and those with variant genotype had ≥1 risk alleles. This method for establishing participant *MC1R* variant status was utilized because it matches that employed by Binkley and colleagues (2009), which the current study aimed to replicate, and because variations at study SNPs have been shown to be associated with loss of function (García-Borrón et al. 2005).

Assessment Instruments

The Fear of Pain Questionnaire–9 is a self-report measure of fears about pain (FPQ-9). The Dental Fear Survey (DFS) is a 20-item self-report measure of fearful and anxious reactions to dental stimuli and situations (Kleinknecht et al. 1973). Complete descriptions of these instruments and comment on their use can be found in the Appendix.

Statistical Analyses

Statistical analyses performed with SPSS Statistics 21 (IBM SPSS, Chicago, IL) were used to test 3 hypotheses: 1) that variants in *MC1R* are associated with dental fear, 2) that variants in *MC1R* are associated with fear of pain, and 3) that fear of pain mediates the relation between *MC1R* and dental fear. Regression models were used to assess hypotheses 1 and 2. To address hypothesis 3, mediation analysis (single-mediator model) was tested with the PROCESS macro (Hayes 2013) for SPSS Statistics. Relative indirect effects were subjected to post hoc bootstrap analyses with 5,000 samples and a 95-percentile confidence interval estimate. PROCESS allows for dichotomous independent variables in mediational analyses and is the contemporary strategy of choice for determining mediation effects in research with psychological phenomena.

Results

The sample of 817 participants comprised 511 females (62.5%), and mean ± SD age was 34.7 ± 8.7 y (range = 18 to 67 y). Participants had, on average, 13.1 ± 2.5 y of education (range = 4 to 23 y). In total, 546 participants had no *MC1R* risk variants; 249 had 1 risk variant; 22 had 2 risk variants; and no participant had >2 variants. Thus, 271 participants (33.2%) had at least 1 risk allele—a proportion consistent with that observed in the dark-haired Caucasian (i.e., not redhead) subsample of the only other similar study (Binkley et al. 2009). Table 1 summarizes the characteristics of the SNPs and their distribution in the sample.

Mean FPQ-9 score was 39.2 ± 19.2 (range = 20 to 100), and mean DFS score was 23.2 ± 8.1 (range = 9 to 45). Average FPQ-9 and DFS scores were similar to those observed in studies of similar populations (e.g., Randall et al. 2012). As has been reported for this sample, distributions of FPQ-9 and DFS matched existing research: negatively skewed, with nearly 15% of participants reporting extremely high levels of fear of

Table 2. Regression Models for Dental Fear and Fear of Pain.

	Dental Fear Survey Score[a]				Fear of Pain Questionnaire–9 Score[b]			
Predictor Variable	*B*	SE	β	*P* Value	*B*	SE	β	*P* Value
Sex	2.93	2.41	0.07	.002	3.45	0.57	0.21	<.001
MC1R variant status	2.94	1.41	0.07	.002	1.53	0.59	0.09	.009

[a]For Dental Fear Survey score, *P* values represent those of 1-tailed significance tests, given that the hypothesis being tested (hypothesis 1) is replicative and has expected directionality.
[b]For the Fear of Pain Questionnaire–9 score, *P* values represent those of 2-tailed significance tests.

Table 3. Mediation Model: Fear of Pain as Mediator between *MC1R* Variant Status and Dental Fear.

					95% CI	
	B	SE	*t*	*P* Value	Lower	Upper
X → M (a)	1.36	0.60	2.28	0.023[a]	0.1917	2.5369
M → Y (b)	1.17	0.07	16.17	<0.001[b]	1.0306	1.3153
X → Y (c)	2.80	1.42	1.97	0.049[a]	0.0112	5.5895
X → Y (c′)	1.20	1.24	0.97	0.334	−1.2356	3.6358
X → M → Y	1.60	0.71			0.2812	3.0506[a]

CI, confidence interval; M, Fear of Pain Questionnaire–9 score (mediator); X, *MC1R* variant status; Y, Dental Fear Survey score.
[a]$P < .05$.
[b]$P < .001$.

pain and/or phobic levels of dental fear. Women reported higher levels of fear of pain (FPQ-9: 24.6 ± 7.9), and men reported lower levels (FPQ-9: 21.2 ± 7.8; $t_{815} = 5.9$, $P < 0.001$). Likewise, women reported higher levels of dental fear (DFS: 40.3 ± 19.6), and men reported lower levels (DFS: 37.5 ± 18.2; $t_{815} = 2.0$, $P = 0.04$). This sex difference has been widely observed, specifically in dental fear and across many fears (see Craske 2003; McNeil and Randall 2014). Age was not significantly associated with FPQ-9 or DFS scores. In light of these findings, sex was controlled in subsequent analyses.

MC1R variant status was predictive of dental fear ($F_{1,814} = 4.20$, $P = 0.02$, $R^2 = 0.01$). Likewise, *MC1R* variant status was predictive of fear of pain ($F_{1,814} = 21.08$, $P < 0.001$, $R^2 = 0.05$). Presence of ≥1 *MC1R* variants was associated with increased DFS and FPQ-9 scores. See Table 2 for results of regression analyses.

FPQ-9 and DFS scores were strongly correlated ($r = 0.50$, $P < 0.001$). Given this association and the well-supported suggestion that fear of pain is a primary component of dental fear (McNeil and Berryman 1989), a single-mediator model was run, with fear of pain (FPQ-9 score) as the mediating variable to explain the association between *MC1R* variant status and dental fear (DFS score; see Table 3, Fig.). Full mediation was observed. There was a significant indirect effect of *MC1R* variant status on dental fear through fear of pain ($B = 1.60$, bias-corrected and accelerated [BCa] CI: 0.281 to 3.051), representing a small to moderate effect ($\kappa^2 = 0.044$, BCa CI: 0.009 to 0.082).

Associations between each SNP and phenotype were also investigated individually; results of those analyses are presented in the Appendix. Briefly, of the 6 SNPs, only rs1805007 was significantly associated with dental fear and fear of pain. The other SNPs were not significantly related to either phenotype and showed large standard errors of their effect estimates,

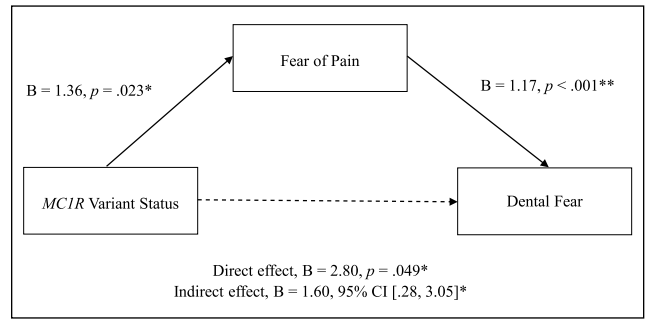

Figure. Fear of pain explains association between *MC1R* variant status and dental fear. *statistically significant at $P < 0.05$; **statistically significant at $P < 0.001$.

indicating insufficient power to precisely model their effects. Additionally, variation at 4 of the 6 SNPs is relatively rare in this sample. Thus, study results appear to be driven predominantly by variation at rs1805007.

Discussion

Results from this study provide additional support for a possible association between *MC1R* variant status and dental fear. As hypothesized, *MC1R* variant status was associated with dental fear in the study sample. Participants with ≥1 risk alleles in the *MC1R* coding region were more likely than those with none to report greater levels of dental fear on the DFS, supporting hypothesis 1. This finding confirms the primary result described by Binkley and colleagues (2009), replicating the result of the only other known study on the topic. *MC1R* variant status also appears to be associated with fear of pain. In support of hypothesis 2, participants with ≥1 variants in the *MC1R* coding region were more likely than those with none to

report greater levels of general fear of pain, as measured by the FPQ-9. Perhaps most interesting—and potentially important—is the finding that the relation between *MC1R* variant status and DFS score was explained by FPQ-9 score. That is, for this study sample, fear of pain fully mediated the relation between *MC1R* variant status and dental fear, providing support for hypothesis 3. One study SNP, rs1805007, appears to drive these observed associations. Although the associations presented here are small to moderate in size and account for a relatively small proportion of the variance in dental fear and fear of pain, they are consistent with effect sizes previously reported in dental fear and behavioral genetics literatures. At this early stage, such significant, even if small, associations provide a window into the potential influences of genetic factors on the experience of dental fear and fear of pain.

Results presented here confirm a well-documented association between fear of pain and dental fear and further highlight the important interaction between pain and fear (for review, see McNeil et al. 2014). Extending study findings, it is conceivable to postulate that the role of genetic factors in the development and maintenance of dental fear may be through pain-related phenomena. The experience of acute and chronic orofacial pain can trigger and/or exacerbate fear of pain, which in turn can influence pain perception and pain behavior. For instance, those who have experienced acute and/or chronic orofacial pain are more likely than those who have not to later report fear of pain (van Wijk and Hoogstraten 2005). Furthermore, those with higher levels of fear of pain are more likely to perceive pain stimuli as more intense (van Wijk and Hoogstraten 2009), to engage in pain catastrophizing (Parr et al. 2012) and avoidance behaviors that worsen chronic pain (Lee et al. 2007). The results showing that fear of pain is the mediating variable in the association between *MC1R* variant status and dental fear suggest that genetically influenced differences in pain experience (e.g., pain threshold, tolerance) may, in some cases, be foundational for the development of fear of pain, which may then underpin dental fear (see comment in Appendix). Of course, this is one of several pathways by which *MC1R* variation may affect dental fear. Future work should utilize experimental measures of the orofacial pain experience (e.g., quantitative sensory testing) to determine how *MC1R* variants are related specifically to orofacial pain perception and to elucidate whether orofacial pain sensitivity bridges the path between *MC1R* variant status and fear of pain (and associated dental fear). Given the results of the current study and those demonstrating that *MC1R* may be important for sensitivity to pain, such an exploration is warranted. Regardless, study results suggest that targeting fear of pain and idiographic pain experiences may promote successful amelioration of dental fear.

Three primary study limitations should be noted. First, the current study relied on analysis of only 1 gene. Certainly, there are genes in addition to *MC1R* that may influence orofacial pain sensitivity and/or be related to fear of pain and dental fear. Given the relatively small effect sizes and minor proportion of variance in fear accounted for by *MC1R* variation observed here—and, thus, the relatively low overall influence of *MC1R* variants on dental fear and fear of pain—studies that include multiple genes may provide a more comprehensive picture. Second, although this study replicates the findings of another demonstrating an association between *MC1R* variation and dental fear (i.e., Binkley et al. 2009), it represents 1 of only 2 known candidate gene studies on the topic. Because candidate gene analysis results observed in single studies are not frequently able to be replicated in follow-up studies (e.g., Bosker et al. 2011), additional candidate gene replication studies and genome-wide association studies aimed at confirming the relation between *MC1R* variation and dental fear are warranted before definitive conclusions can be drawn. Third, mediation analyses were employed on cross-sectional data, which can yield inflated mediational estimates and overestimation of causal association (Maxwell and Cole 2007; see Appendix for detailed comment). Thus, results demonstrating mediation and conclusions suggesting causality should be understood with this potential bias in mind, and future studies on the topic should involve collection and analysis of longitudinal data. Additionally, minor limitations are listed in the Appendix. Notwithstanding, these results provide support for the study hypotheses and offer additional early evidence of a genetic influence on dental pain–related phenomena, including dental fear.

To conclude, this study corroborates previous work suggesting that *MC1R* variants are associated with dental fear. The study is the first to show that *MC1R* variant status predicts general fear of pain. Most important, results presented here indicate that fear of pain plays a mediational role in the association between *MC1R* variant status and dental fear. It is speculated that, by influencing orofacial pain sensitivity, *MC1R* variation may predispose dental patients to experience more pain during dental treatment, setting them up to be more likely to develop fear of pain and then dental fear, an important potential pathway to be explored in future investigations. This study demonstrates a possible future direction for further identification of biomarkers that could aid in the personalization of dental treatment. Moreover, these results have important implications for how we understand psychosocial correlates of orofacial pain and provide possible specific targets for the treatment of orofacial pain, fear of pain, and/or dental fear.

Author Contributions

C.L. Randall, contributed to conception, design, data analysis, and interpretation, drafted and critically revised the manuscript; D.W. McNeil, contributed to conception, design, data acquisition, and interpretation, critically revised the manuscript; J.R. Shaffer, contributed to conception, design, data analysis, and interpretation, critically revised the manuscript; R.J. Crout, R.J. Weyant, and M.L. Marazita, contributed to conception, design, and data acquisition, critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work.

Acknowledgments

This article is based in part on the doctoral dissertation of the first author, for which the second author served as committee chair and the third author as a committee member. The authors acknowledge

with gratitude the families participating in the Center for Oral Health Research in Appalachia, Cohort 1, Study on Determinants of Oral Health in Families. The authors also acknowledge the Behavioral, Epidemiologic, and Health Services Research Group of the International Association for Dental Research, which recognized this study in part and the first author, with an Outstanding Conference Abstract Award: Best Abstract, Pre-doctoral Category. Partial support for this project was provided by the National Institute of Dental and Craniofacial Research (R01-DE014899, F31-DE 023493). The authors declare no potential conflicts of interest with respect to the authorship and/or publication of this article.

References

Asmundson GJG, Norton PJ, Vlaeyen JWS. 2004. Fear-avoidance models of chronic pain: an overview. In: Asmunson GJG, Vlaeyen JWS, Crombez G, editors. Understanding and treating fear of pain. New York (NY): Oxford University Press. p. 3–24.

Asmundson GJG, Vlaeyen JWS, Crombez G. 2004. Understanding and treating fear of pain. New York (NY): Oxford University Press.

Binkley CJ, Beacham A, Neace W, Gregg RG, Liem EB, Sessler DI. 2009. Genetic variations associated with red hair color and fear of dental pain, anxiety regarding dental care and avoidance of dental care. J Am Dent Assoc. 140(7):896–905.

Bosker FJ, Hartman CA, Nolte IM, Prins BP, Terpstra P, Posthuma D, van Veen T, Willemsen G, DeRijk RH, de Geus EJ, et al. 2011. Poor replication of candidate genes for major depressive disorder using genome-wide association data. Mol Psychiatry. 16(5):516–532.

Chaki S, Okuyama S. 2005. Involvement of melanocortin-4 receptor in anxiety and depression. Peptides. 26(10):1952–1964.

Craske MG (2003). Origins of phobias and anxiety disorders: Why more women than men? Oxford, UK: Elsevier.

Fricton JR, Schiffman EL. 1995. Epidemiology of temporomandibular disorders. In: Fricton JR, Dubner R, editors. Advances in pain research and therapy: orofacial pain and temporomandibular disorders. New York: Raven Press. p. 1–14.

García-Borrón JC, Sánchez-Laorden BL, Jiménez-Cervantes C. 2005. Melanocortin-1 receptor structure and functional regulation. Pigment Cell Res. 18(6):393–410.

George SZ, Dannecker EA, Robinson ME. 2006. Fear of pain, not pain catastrophizing, predicts acute pain intensity, but neither factor predicts tolerance or blood pressure reactivity: an experimental investigation in pain-free individuals. Eur J Pain. 10(5):457–465.

Hayes AF. 2013. Introduction to mediation, moderation, and conditional process analysis. New York (NY): Guilford Press.

Klages U, Ulusoy O, Kianifard S, Wehrbein H. 2004. Dental trait anxiety and pain sensitivity as predictors of expected and experienced pain in stressful dental procedures. Eur J Oral Sci. 112(6):477–483.

Kleinknecht R, Klepac R, Alexander LD. 1973. Origins and characteristics of fear of dentistry. J Dent Res. 86(4):842–848.

Kyle BN, McNeil DW, Weaver B, Wilson T. 2016. Recall of dental pain and anxiety in a cohort of oral surgery patients. J Dent Res. 95(6):629–34.

Lee KC, Chiu TTW, Lam TH. 2007. The role of fear-avoidance beliefs in patients with neck pain: relationships with current and future disability and work capacity. Clin Rehabil. 21(9):812–821.

Marazita ML, Weyant RJ, Tarter R, Crout RJ, McNeil DW, Thomas J. 2005. Family-based paradigm for investigations of oral health disparities. J Dent Res. 85(Spec Iss A). Abstract 238.

Maxwell SE, Cole DA. 2007. Bias in cross-sectional analyses of longitudinal mediation. Psychol Methods. 12(1):23–44.

McCracken LM, Gross RT, Aikens J, Carnkike CL Jr. 1996. The assessment of anxiety and fear in persons with chronic pain: a comparison of instruments. Behav Res Ther. 34(11–12):927–933.

McNeil DW, Au AR, Zvolensky MJ, McKee DR, Klineberg IJ, Ho CC. 2001. Fear of pain in orofacial pain patients. Pain. 89(2–3):245–252.

McNeil DW, Berryman ML. 1989. Components of dental fear in adults? Behav Res Ther. 27(3):233–236.

McNeil DW, Helfer AJ, Weaver BD, Graves RW, Kyle BN, Davis AM. 2011. Memory of pain and anxiety associated with tooth extraction. J Dent Res. 90(2):220–224.

McNeil DW, Randall CL. 2014. Dental fear and anxiety associated with oral health care: conceptual and clinical issues. In: Mostofsky D, Forgione A, Giddon D, editors. Behavioral dentistry. 2nd ed. Ames (IA): John Wiley and Sons, Inc. p. 165–192.

McNeil DW, Vargovich AM, Sorrell JT, Vowles KE. 2014. Environmental, emotional, and cognitive determinants of dental pain. In: Mostofsky D, Forgione A, Giddon D, editors. Behavioral dentistry. 2nd ed. Ames (IA): John Wiley and Sons, Inc. p. 89–108.

Parr JJ, Borsa PA, Fillingim RB, Tillman MD, Manini TM, Gregory CM, George SZ. 2012. Pain-related fear and catastrophizing predict pain intensity and disability independently using an induced muscle injury model. J Pain. 13(4):370–378.

Polk DE, Weyant RJ, Crout RJ, McNeil DW, Tarter RE, Thomas JG, Marazita ML. 2008. Study protocol of the Center for Oral Health Research in Appalachia (COHRA) etiology study. BMC Oral Health. 8:18.

Randall CL, McNeil DW, Stuchell RN (2012). Beliefs and fears about the dentist in an emergency clinic. J Dent Res 91(Spec Iss A):A-1412, www.dentalresearch.org

Ray J, Wide Boman U, Bodin L, Berggren U, Lichtenstein P, Broberg AG. 2010. Heritability of dental fear. J Dent Res. 89(3):297–301.

Robinson ME, Riley JL. 1999. The role of emotion in pain. In: Gatchel RJ, Turk DC, editors. Psychosocial factors in pain: critical perspectives. New York (NY): The Guilford Press. p. 74–88.

Sanikop S, Agrawal P, Patil S. 2011. Relationship between dental anxiety and pain perception during scaling. J Oral Sci. 53(3):341–348.

Setty S, David J. 2014. Classification and epidemiology of orofacial pain. In: Vadivelu N, Vadivelu A, Kaye AD, editors. Orofacial pain: a clinician's guide. Cham (Switzerland): Springer International Publishing. p. 15–24.

Timpano KR, Hasler G, Riccardi C, Murphy DL, Schmidt NB. 2009. The genetics of anxiety. In: Berntson GG, Cacioppo JT, editors. Handbook of neuroscience for the behavioral sciences. Vol. 2. Hoboken (NJ): John Wiley & Sons, Inc. p. 1090–1109.

Vadivelu A. 2014. Oral health-related quality of life and facial pain. In: Vadivelu N, Vadivelu A, Kaye AD, editors. Orofacial pain: a clinician's guide. Cham (Switzerland): Springer International Publishing. p. 9–14.

van Wijk AJ, Hoogstraten J. 2003. The Fear of Dental Pain questionnaire: construction and validity. Eur J Oral Sci. 111(1):12–18.

van Wijk AJ, Hoogstraten J. 2005. Experience with dental pain and fear of dental pain. J Dent Res. 84(10):947–950.

van Wijk AJ, Hoogstraten J. 2009. Anxiety and pain during dental injections. J Dent. 37(9):700–704.

Vassend O, Røysamb E, Nielsen CS. 2011. Dental anxiety in relation to neuroticism and pain sensitivity: a twin study. J Anxiety Disord. 25(2):302–308.

Verbunt JA, Seelen HA, Vlaeyen JW. 2004. Disuse and physical deconditioning in chronic low back pain. In: Asmunson GJ, Vlaeyen JW, Crombez G, editors. Understanding and treating fear of pain. New York (NY): Oxford University Press. p. 139–162.

Vlaeyen JW, de Jong J, Geilen M, Heuts PH, van Breukelen G. 2001. Graded exposure in vivo in the treatment of pain-related fear: a replicated single-case experimental design in four patients with chronic low back pain. Behav Res Ther. 39(2):151–166.

Xia Y, Wikberg J, Chhajlani V. 1995. Expression of melanocortin 1 receptor in periaqueductal gray matter. Neuroreport. 6(16):2193–2196.