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Negative social acts and pain: evidence of a workplace bullying and 5-HTT genotype interaction

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Objectives Long-term exposure to systematic negative acts at work, usually labeled workplace bullying, is a prevalent problem at many workplaces. The adverse effects of such exposure may range from psychological symptoms, such as depression and anxiety to somatic ailments like cardiovascular disease and musculoskeletal complaints. In this study, we examined the relationships among exposure to negative acts, genetic variability in the 5-HTT gene *SLC6A4* and pain.

Methods The study was based on a nationally representative survey of 987 Norwegian employees drawn from the Norwegian Central Employee Register by Statistics Norway. Exposure to bullying in the workplace was measured with the 9-item version of the Negative Acts Questionnaire – Revised (NAQ-R) inventory. Pain was rated using an 11-point (0–10) numeric rating scale (NRS). Genotyping with regard to *SLC6A4* was carried out using a combination of gel-electrophoresis and TaqMan assay.

Results The data revealed a significant interaction between exposure to negative acts and the *SLC6A4* genotype with regard to pain (linear regression with 5000 resamples; age, sex, tobacco use and education were included as covariates). The relationship between negative acts and pain intensity was significantly stronger for subjects with the L_AL_A genotype than for subjects with the $SL_A/L_AL_G/SL_G$ genotype. No significant difference between subjects with the L_AL_A genotype and SS genotype was observed.

Conclusions Our data demonstrated that the relationship between bullying and pain was modified by the 5-HTT genotype, ie, genetic variation in *SLC6A4*. The association between negative acts and health among vulnerable individuals appeared more potent than previously reported.

Key terms polymorphism; psychosocial; rs23351; serotonin transporter; SLC6A; 5-HTTLPR.

Exposure to systematic negative social acts at work, usually labeled workplace bullying, is a prevalent issue in contemporary working life, affecting approximately 15% of adults globally (1). Several lines of evidence demonstrate that exposure to such bullying is a major predictor of impaired health and well-being among those targeted (2, 3). The adverse effects of bullying is well documented and range from psychological symptoms, such as depression and anxiety (4, 5), to somatic ailments like cardiovascular disease (6) and musculoskeletal complaints (7). Exposure to bullying is also associated with increased risk of sickness absence (8) and disability retirement (9).

While exposure to bullying in the workplace is a risk factor for pain (10, 11), pain may also be determined by the individuals psychological profile and genetic susceptibility (12). Interestingly, as much as 60% (range 25–60%) of the variance in experimental pain may be explained by genetic variability (13). Thus, pain perception is subject to large variation between individuals. Earlier studies suggest that pain in an experimental setting may be associated with genetic variability important for serotonin (5-HT) signaling (14, 15).

One genetic variant that may be important for 5-HT signaling is the 22-base-pair variable number tandem repeat (5-HTTLPR) in the promoter of the SLC6A4

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gene encoding the serotonin transporter (5-HTT). Two common allelic variants have been described, a short (S) allele of 14 repeats and a long (L) allele of 16 repeats (16). The short allele leads to decreased 5-HTT expression (17). In addition, there is a single nucleotide polymorphism (SNP) in the promoter region of SLC6A4, which also affects the rate of transcription (18). This A to G substitution is in strong linkage disequilibrium with the length polymorphism of the promoter, where the G allele, associated with lower expression, almost always coincides with the long allele (19).

The most important transmitters in the pain pathways may include the excitatory signaling molecule glutamate and the inhibitory modulator GABA. In the central nervous system, 5-HT is a modulator of both glutamatergic and GABAergic neurotransmission (20, 21). Hence, polymorphisms influencing the efficacy of 5-HTT – responsible for 5-HT reuptake into the synaptic boutons – may affect signaling in the pain pathways and nociceptive processing in the brain. Based on the presumed transcription rates from low to high (15), the Caucasian population can be divided in three groups; low (SS), medium ($SL_G/L_AL_G/SL_A$) and high (L_AL_A) expression. Individuals with low, medium and high expression may have different phenotypes.

For example, previous data have suggested that pain evoked by colorectal distention in individuals with SLC6A4 low-transcription-genotype induces an increased activation of brain areas involved in emotion-regulation (22). Moreover, people with SLC6A4 low-transcription-genotype may be associated with anxiety and negative affect (23). On the other hand, individuals with SLC6A4 high-transcription-genotype seem to report more pain evoked by thermal stimuli (24).

Recent data show that exposure to bullying at the workplace is associated with increased distress and somatic health complaints (25). Less is known about conditional factors that govern the health consequences of bullying. However, based on the possible link between bullying, *SLC6A4* genotype and pain, we hypothesized that the effect of bullying on pain may be modified by genetic variation in *SLC6A4*. In the present study, we demonstrate that pain in the working population is associated with a bullying and *SLC6A4* genotype interaction.

Methods

Subjects

This study is based on a probability sampled survey of the Norwegian working force. A random sample of 5000 employees was drawn from The Norwegian Central Employee Register by Statistics Norway. The Norwegian Central Employee Register is the official register of all Norwegian employees, as reported by employers. Sampling criteria were adults aged 18–60 years employed in a Norwegian enterprise. Questionnaires were distributed through the Norwegian Postal Service during the spring 2015. Subjects who gave consent were also sent saliva collection kits. Altogether, 987 subjects who had satisfactorily completed the questionnaire and given a saliva sample were included in this study. The survey was approved by the Regional Committee for Medical Research Ethics for Eastern Norway. Responses were treated anonymously, and informed consent was given by the respondents.

Instruments

Exposure to bullying behaviors in the workplace was measured with the 9-item version of the Negative Acts Questionnaire – Revised (NAQ-R) inventory (26). NAQ-R describes negative and unwanted behaviors that may be perceived as bullying if occurring on a regular basis. The NAQ-R contained items referring to both direct (eg, openly attacking the victim) and indirect (eg, social isolation, slander) behaviors. It also contained items referring to personal as well as work-related forms of bullying. For each item, the respondents were asked how often they had been exposed to the behavior at their present worksite during the last six months. Response categories range from 1–5 ("never", "now and then", "monthly", "weekly" and "daily").

To assess pain, subjects were asked to rate their mean general pain intensity throughout the last week using an 11 point (0–10) numeric rating scale (NRS) with endpoints "no pain" and "worst possible pain".

Genotyping

Collection of saliva and extraction of genomic DNA was done using OrageneRNA sample collection kit (DNA Genotech Inc. Kanata, Ontario, Canada) according to the manufacturer's instructions. Genotyping with regard to *SLC6A4* tandem repeat length in the promoter (short: S versus long: L), and genotyping with regard to the SNP rs23351 (A versus G) were performed.

To determine the length (S versus L) of the polymorphic promoter region of *SLC6A4*, the DNA sequence was first amplified by polymerase chain reaction (PCR) and then separated by gel electrophoresis. PCR was carried out in a total volume of 25 µl containing ~60 ng of genomic template, 6.25 pmol of each primer and 1×Taq DNA Polymerase Master Mix (VWR international, Dublin, Ireland). The forward primer sequence was 5' –GGCGT TGCCG CTCTG AATGC- 3' and the reverse primer sequence was 5' –GAGGG ACTGA GCTGG ACAAC CAC- 3' (DNA technology A/S, Riss-

kov, Denmark). As previously described (27), samples were amplified on a Perkin Elmer GeneAmp PCR 2400 system following an initial denaturing step for 3 minutes at 95 °C. The amplification consisted of 40 cycles including denaturing at 95 °C for 40 seconds, annealing at 60 °C for 20 seconds and elongation at 72 °C for 80 seconds. The PCR yielded a long (529 bp) and a shorter (486 bp) fragment. After four hours separation at 100 V on a 2.5% agarose gel (MetaPhor Agarose, Lonza cologne GmbH, Cologne, Germany), GelRed dye was added and the fragments were visualized by UV light (Biotium Inc, California, USA). A PCR 100 bp low ladder (Sigma-Aldrich CO, St. Louis, Mo, USA) was used to determine the length of the fragments.

The SNP genotyping with regard to rs23351 (A versus G) was carried out using custom TaqMan SNP genotyping assays (Applied Biosystems, Foster City, CA, USA). Approximately 10 ng genomic DNA was amplified in a 5 µl reaction mixture in a 384-well plate containing 1× TaqMan genotyping master mix (Applied Biosystems) and 1× assay mix, the latter containing the respective primers and probes. The probes were labelled with the reporter dye FAM or VIC to distinguish between the two alleles. Approximately 10% of the samples were re-genotyped and the concordance rate was 100%.

Statistical analysis

Exposure to bullying was calculated using the mean-score of the 9 items in the NAQ-R inventory. To explore the hypotheses about main and moderating effects, we conducted a hierarchical regression analysis to test for linear associations between exposure to bullying behaviors and experienced pain, as well as the interactive effects of exposure to bullying and *SLC6A4* genotype (three allele model), with regard to pain. Deviation from the Hardy-Weinberg equilibrium was tested by the Chi-squared test. In order to examine the modifying role of the *SLC6A4* genotype, we followed the recommendations for interaction analyses provided by Baron and Kenny (28). The *SLC6A4* genotype was included as a categorical variable using the L_AL_A genotype as a reference group. The interaction analysis was conducted in two steps. Control variables, exposure to bullying and the *SLC6A4* genotype were entered as predictors in the first step, whereas the interaction term (exposure to bullying×*SLC6A4*) was entered in the second step. A significant interaction term and a significant increase in explained variance (R^2) in the second step were considered as an interaction effect.

As the scores on the NAQ (skewness: 4.18; kurtosis: 26.85) were non-normally distributed, all analyses were conducted using bootstrapping (5000 resamples). The bootstrap method has the advantage that it does not need to meet the assumptions of normality, equal variances, and homoscedasticity that are required in ordinary regression analyses (29). Multicollinearity was not an issue in the current study [variance inflation factor (VIF)=1.01, with cutoff set at VIF=10). Statistical analyses were conducted with Stata 14 (StataCorp, College Station, TX, USA). The level of significance was set to $P<0.05$.

Results

The data showed that 551 of the 987 subjects (56%) included in this study experienced negative acts, ie, NAQ >1 at the workplace during the last six months. Mean NAQ and NRS scores were similar for men and women (NAQ: 1.19 and NRS: 2.52). Genotype frequencies of SS, SL_G, L_AL_G, SL_A and L_AL_A were 18.2%, 7.2%,

Table 1. Characteristics of the subjects grouped by genotype: SS, SLG/LALG/SLA and LALA. [SEM=standard error of the mean; VAS= visual analog scale; NAQ= Negative Acts Questionnaire.]

	SS				SLG/LALG/SLA				LALA				Sum
	N	%	Mean	SEM	N	%	Mean	SEM	N	%	Mean	SEM	
Subjects	180	18.2			555	56.2			252	25.5			987
VAS			2.38	0.16			2.66	0.01			2.29	0.13	
NAQ			1.15	0.02			1.20	0.01			1.19	0.02	
Age			45.08	0.78			45.07	0.43			44.35	0.62	
Male	92	51.1			256	46.1			117	46.4			
Female	88	48.9			299	53.9			135	53.6			
Tobacco	41	22.7			104	18.7			63	25.0			
Education													
Secondary school or less	13	7.2			49	8.8			22	8.7			
High school	55	30.6			163	29.4			75	29.8			
University ≤4 years	65	36.1			182	32.8			78	31.0			
University ≥4 years	47	36.1			161	29.0			77	30.6			

Table 2. Hierarchical regression with genotype LALA as reference (bootstrapping with 5000 resamples). The analyses were adjusted for the covariates age, sex, tobacco use and education. [SE=standard error; CI=confidence interval]

Pain	B	SE	P-value	95% CI
Step 1				
Age	0.009	0.007	0.198	-0.005–0.023
Sex	0.558	0.139	0.000	0.287–0.830
Tobacco use	0.470	0.179	0.009	0.119–0.820
Education				
High school	-0.208	0.295	0.482	-0.787–0.371
University <4 years	-0.809	0.283	0.004	-1.364–-0.255
University >4 years	-1.178	0.286	0.000	-1.738–-0.618
SLC6A4				
SS	0.145	0.201	0.471	-0.249–0.539
SLG LALG SLA	0.376	0.158	0.017	0.067–0.686
NAQ9	0.957	0.259	0.000	0.450–1.464
Step 2				
Age	0.009	0.007	0.170	-0.004–0.023
Sex	0.572	0.139	0.000	0.301–0.844
Tobacco use	0.494	0.178	0.005	0.145–0.843
Education				
High school	-0.182	0.297	0.539	-0.763–0.399
University <4 years	-0.791	0.285	0.005	-1.349–-0.233
University >4 years	-1.155	0.288	0.000	-1.719–-0.591
SLC6A4				
SS	0.563	0.851	0.508	-1.106–2.232
SLG LALG SLA	1.953	0.636	0.002	0.706–3.199
NAQ9	1.768	0.431	0.000	0.924–2.612
SLC6A4 x NAQ				
SS	-0.337	0.734	0.646	-1.776–1.101
SLG LALG SLA	-1.320	0.540	0.015	-2.379–-0.261

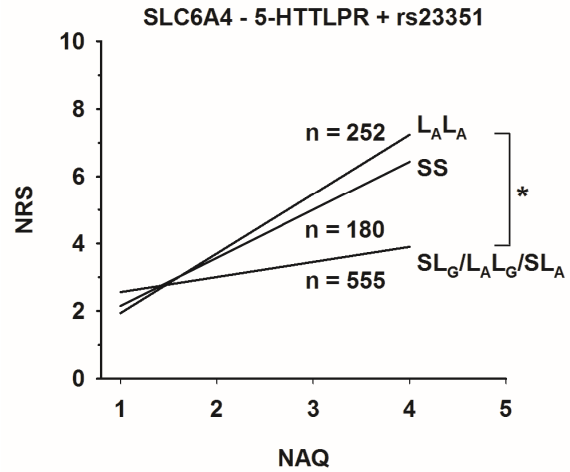

Figure 1. The relationship between negative acts and pain intensity (NRS), after correction for age, sex, tobacco use and education. Subjects were divided into groups based on SLC6A4 genotype: SS, SLG/LALG/SLA and LALA (used as reference for the regression analysis). *P<0.05. [NAQ=Negative Acts Questionnaire; NRS=numeric rating scale.]

6.8%, 41.2% and 25.5%, respectively. No deviation from the Hardy-Weinberg equilibrium was observed. The characteristics of the subjects are presented in table 1.

Findings from the hierarchical regression analyses of linear associations and interaction effects are presented in table 2. In the first step, exposure to bullying was significantly positively associated with pain. The SL_G/L_AL_G/SL_A genotype, but not the SS genotype, reported significantly higher pain than the L_AL_A genotype reference group. Gender, tobacco use, and educational level, but not age, were also significantly related to pain experience. The model was significant (Wald X^2=81.16; P<0.001) and the predictor variables explained 8.36% of the variance in pain experience.

The interaction term (exposure to bullying×*SLC6A4*) was entered in the second step of the analysis. The findings demonstrated a significant interaction between exposure to negative acts and 5-HTT genotype with L_AL_A genotype used as reference with regard to pain experience. The statistical model with the interaction term explained 9.15% of the variance in pain. The model with the interaction term was also significant (Wald X^2=97.83; P<0.001).

The relationship between reported negative acts and pain intensity was significantly stronger for subjects with the L_AL_A genotype than for subjects with SL_G/L_AL_G/SL_A genotype (figure 1). No significant difference between subjects with the L_AL_A genotype and subjects with the SS genotype was observed.

Similar hierarchical regression analyses were performed with the 5-HTTLPR length polymorphism and the SNP genotype separately. The data showed that subjects with LL or AA genotypes also had significantly stronger relationships between negative acts and pain intensity than other subjects (supplementary tables A and B, figures A and B, www.sjweh.fi/show_abstract.php?abstract_id=3703).

Discussion

In accordance with previous findings, our data showed that experiencing negative acts in the workplace is positively correlated with pain intensity (10, 11, 30). The mechanisms behind this association are unknown but may involve psychological distress as an intermediate factor. Previous data suggest that exposure to bullying behaviors results in symptoms such as depression and anxiety (31, 32), which in turn may be associated with pain (33–35).

Several lines of evidence suggest that the short 5-HTTLPR allele may be associated with increased sensitivity to stress (36). Moreover, previous data suggest that the influence of life stress on depression may be moderated by genetic variability in *SLC6A4* (37–39). However, this gene-environment interaction may be debated (40–42).

Our data showed that the association between negative acts and pain may be moderated by genetic variation within the promotor region of *SLC6A4*. Interestingly, subjects with the high expression L_AL_A genotype reported more pain than those with the medium expression SL_G/L_AL_G/SL_A genotype when exposed to systematic bullying behaviors. However, there was no difference between subject with the L_AL_A genotype and those with the SS genotypes. In accordance with earlier data on experimental pain (15), the L_AL_A genotype was associated with the highest pain ratings in the present survey.

A higher frequency of the SS genotype has been observed among patients with fibromyalgia or idiopathic trigeminal neuralgia than healthy controls (43, 44). Moreover, subjects with the SS and SL_G genotypes may also report increased intensity of pain following topical alcohol disinfection of epidermal abrasions (45). In addition, enhanced pain catastrophizing has been reported in S-carriers, suggesting that the low and medium expression (SS / SL_G / L_AL_G / SL_A) genotypes might be a risk factor for emotional pain (46, 47).

On the other hand, animal experiments have demonstrated that knockout mice completely lacking 5-HTT show reduced thermal hyperalgesia compared to wild type mice (48, 49). Moreover, sensory testing of humans show that thermal or electrical noxious stimuli induces increased sensory pain in individuals with the high expression (L_AL_A) genotype (15, 24). Thus, the relationship between the expression of 5-HTT and subjective health complaints may not necessarily be linear.

Hence, although previous data have demonstrated enhanced emotional responses or increased pain catastrophizing in S-carriers (46, 47), testing of humans in the lab shows that individuals with L_AL_A have the strongest pain response to sensory stimuli (15, 24). Therefore, subjects with the SS and L_AL_A genotype are not very different. The SS genotype may be associated with increased emotional pain, whereas the L_AL_A genotype seems to be associated with increased sensory pain. This may explain the result that no significant difference in pain score was observed between subjects with SS versus L_AL_A. In accordance with our earlier observations (15), the present data suggest a u-shaped relationship between presumed *SLC6A4* transcriptional rate and pain intensity.

Anyway, the rate of transcription is dependent on both the 5-HTTLPR and the SNP rs23351 in the promoter region of *SLC6A4*. Therefore, our analyses based on only length polymorphism or alternatively only the SNP genotype resulted in lower explained variance than the model that was based on a combination of 5-HTTLPR and rs23351. Thus, combining these polymorphisms – which are in strong LD – produced a better statistical model. Hence, in accordance with previous observations (14, 15, 18, 50), the present data show that the model based on SS versus SL_G/L_AL_G/SL_A versus L_AL_A may be recommended.

Study limitations

The observed genotype frequencies were in accordance with previous findings (50). However, the overall response rate for the questionnaire survey was only 32%, and <20% of the invited participants returned the saliva samples. These numbers are both lower than the average response rate established for survey studies (51). Hence, we cannot be certain that the final sample is representative for the overall population or survey pool. Still, as response rate and representativity seems to have limited impact on the internal validity (52), the response rate may not be a problem with regard to the actual findings of this study. On the other hand, because measurement instruments for bullying and pain were self-report measures, the study could be influenced by bias such as response set tendencies and social desirability. In addition, a previous longitudinal study from Norway showed that dropout respondents reported significantly higher levels of exposure to bullying at baseline measurement (31). Therefore, non-responders could be more prone to have experienced negative social acts compared to responders.

Concluding remarks

In summary, our data demonstrated that the relationship between bullying and pain was modified by the 5-HTT genotype, ie, genetic variation in the promotor region of *SLC6A4*. Moreover, the present data showed that the effect of bullying on health and well-being among vulnerable individuals might be stronger than previously reported. We conclude that the effect of negative acts and pain is dependent on a gene-environment interaction.

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Conflicts of interest

The authors declare no conflicts of interest.

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