The peer effect on pain tolerance

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Abstract

Background and aims: Twin studies have found that approximately half of the variance in pain tolerance can be explained by genetic factors, while shared family environment has a negligible effect. Hence, a large proportion of the variance in pain tolerance is explained by the (non-shared) unique environment. The social environment beyond the family is a potential candidate for explaining some of the variance in pain tolerance. Numerous individual traits have previously shown to be associated with friendship ties. In this study, we investigate whether pain tolerance is associated with friendship ties.

Methods: We study the friendship effect on pain tolerance by considering data from the Tromsø Study: Fit Futures I, which contains pain tolerance measurements and social network information for adolescents attending first year of upper secondary school in the Tromsø area in Northern Norway. Pain tolerance was measured with the cold-pressor test (primary outcome), contact heat and pressure algometry. We analyse the data by using statistical methods from social network analysis. Specifically, we compute pairwise correlations in pain tolerance among friends. We also fit network autocorrelation models to the data, where the pain tolerance of an individual is explained by (among other factors) the average pain tolerance of the individual's friends.

Results: We find a significant and positive relationship between the pain tolerance of an individual and the pain tolerance of their friends. The estimated effect is that for every one second increase in friends' average cold-pressor tolerance time, the expected cold-pressor pain tolerance of the individual increases by 0.21 seconds (p-value: 0.0049, sample size N=997). This estimated effect is controlled for sex. The friendship effect remains significant

when controlling for potential confounders such as lifestyle factors and test sequence among the students. Further investigating the role of sex on this friendship effect, we only find a significant peer effect of male friends on males, while there is no significant effect of friends' average pain tolerance on females in stratified analyses. Similar, but somewhat lower estimates were obtained for the other pain modalities.

Conclusions: We find a positive and significant peer effect in pain tolerance. Hence, there is a significant tendency for students to be friends with others with similar pain tolerance. Sex-stratified analyses show that the only significant effect is the effect of male friends on males.

Implications: Two different processes can explain the friendship effect in pain tolerance, selection and social transmission. Individuals might select friends directly due to similarity in pain tolerance, or indirectly through similarity in other confounding variables that affect pain tolerance. Alternatively, there is an influence effect among friends either directly in pain tolerance, or indirectly through other variables that affect pain tolerance. If there is indeed a social influence effect in pain tolerance, then the social environment can account for some of the unique environmental variance in pain tolerance. If so, it is possible to therapeutically affect pain tolerance through alteration of the social environment.

Keywords: *Pain tolerance; Social network; Assortativity; Cold-pressor test; Social influence*

Introduction

One hundred and fifty years of twin research has established that most human phenotypes are heritable. Pain is no exception, and the genetic contributions to both clinical and experimental pain are considerable (1). However, genetic influences do not explain all the variability, and environmental causes are typically of equal or greater importance. The often overlooked and frequently disbelieved finding from twin studies is that shared (family) environmental influences have negligible effect on most phenotypes, leaving non-shared (unique) environmental influences as the major source of variance beyond genetics (2). This is also the

case for pain sensitivity. Nielsen et al. (3) found that 54% of the variance in cold-pressor pain was due to genetic factors, with the remaining variance explained by unique environment. Trost et al. (4) found that genetic factors accounted for 55% of the variance in cold-pressor tolerance, and again no evidence of shared environment effects. Likewise, Angst et al. (5) reported 49% heritability and no shared environmental effect for cold-pressor tolerance, though a possible minor effect of shared environment was observed for pain threshold. Finally, a twin study of nine experimental pain assays found shared environmental effects for only one of these (flare area after burn injury) (6).

Though such findings are ubiquitous in the twin literature, an explanation of what exactly the unique environmental factors influencing human health and behaviour are, is lacking. One potential candidate for explaining remaining variance is the social environment beyond the family of origin. Plomin and Daniels (2) hypothesises that the unique environmental variance might increase with age, due to expansion of the social network beyond the family. In a large meta-analysis, Nan et al. (7) demonstrate that the unique environmental influences on body mass index increase with age. They also find that while the family environment has some influence on body mass index in children, the effect is negligible after puberty (18-22 years). This might be due to a shift where adolescents are increasingly affected by their peers rather than their parents.

When ties in a network tend to be between individuals with similar traits, such that connected nodes are more similar, the network is said to be assortative (8). Newman (8) found that in social networks, individuals with many friends tend to be friends with individuals who have many friends. Sex is known to be assortative in social networks (9). Other examples of traits that are assortatively mixed in social networks are obesity, smoking, loneliness and alcohol consumption (10-14). It has also been shown that some genotypes are correlated with social links (15). Two possible processes can explain these observations. Either individuals

are attracted to, and therefore form friendships with, others with similar traits (homophily), or there is a social contagion effect where friends influencing each other cause the similarity. The two processes might also operate simultaneously.

To our knowledge, social network analysis has not been applied in the study of pain phenotypes. In this paper, we investigate whether pain tolerance is assortative in a friendship network of young adolescents.

Methods

Study population

The study sample comprises participants in the Tromsø study: Fit Futures I (TFF1), conducted in the Tromsø and Balsfjord municipalities in Northern Norway in 2010-2011. TFF1 was executed as a single site study, at the Clinical Research Unit, University Hospital of Northern Norway in Tromsø. The study included physical examinations, questionnaire screening and interviews. All first year students at the eight upper secondary schools in the area were invited to participate (N = 1117). Of these, 1038 participated, for a response rate of 93%. From this sample, students with cognitive disabilities (N = 20) were removed, leaving a final sample of N = 1018. However, not all the participants completed the different pain tests, resulting in a sample size of N = 997 individuals for the main outcome measure (the cold-pressor test).

Social network survey

A study nurse interviewed all the students. As part of the interview, they were asked to name up to five friends from their own school or the seven other schools in the area. The friends were defined to be the five individuals whom they had spent the most time with in the preceding week. Follow-up questions were asked where necessary, to ensure unique identification of the named individuals. Friends were then recoded to personal identification

number, which uniquely identifies all Norwegian residents. If a participant named friends who did not participate, these were retained as anonymous nodes in the social network.

Demographic variables and lifestyle factors

Among the interview and questionnaire data collected on the adolescents, we will in this analysis use information about sex, age, school programme (vocational versus general studies programme), smoking and physical activity. For some of the N = 997 individuals, lifestyle information (smoking and physical activity) is missing, resulting in a sample size of N = 982 adolescents for the analysis where lifestyle is considered.

In the statistical analysis in this study, the following coding of the variables is used: sex is 0 if the adolescent is a girl, and 1 if the adolescent is a boy. School programme is 0 if the pupil is attending a vocational programme, 1 if the pupil is attending a general studies programme. Physical activity is an ordered categorical (frequency) variable. The adolescents were asked "If you are actively doing sports or physical activity outside school, how many days a week are you active?", with response options "never", "less than once a week", "1 day a week", "2 to 3 days a week", "4 to 6 times a week" and "almost every day". We use a coding from 0 ("never") to 5 ("almost every day"). Smoking is coded as 0 if the adolescents never smoke, 1 if they smoke sometimes and 2 if they smoke daily.

Experimental pain assessment

The experimental pain procedure encompassed 1) heat pain threshold and tolerance, 2) pressure pain threshold and tolerance on the fingernail and trapezius muscle and 3) the cold-pressor test, in that order.

Heat pain

Heat pain was induced on the ulnar side of the forearm with a MEDOC ATS somatosensory stimulator with a 30×30 mm thermode (Medoc, Ltd, Israel). Stimuli started at a baseline of

32˚C and increased by 1˚C/s until the student pressed a button, at which the temperature was recorded and the thermode returned to baseline by 8˚C/s. Three threshold tests were conducted, where the students were told to press the button as soon as the sensation changed from warm to pain. This was followed by two tolerance tests, where the instruction was to press the button when the pain became unbearable. An upper safety limit was set at 50˚C for all stimuli.

Pressure pain

Pressure pain thresholds and tolerances were assessed with an AlgoMed computerised pressure algometer with a 1 cm^2 probe (Medoc, Ltd, Israel) on the cuticle of the ring finger nail of the non-dominant hand and on the non-dominant trapezius muscle, midway between the neck and shoulder joint. The baseline pressure was 0 kPa, and was increased by a rate of 30 kPa/s until the student pressed a button, at which point the pressure was recorded and the probe was removed. As for heat, thresholds were assessed three times and tolerances were assessed twice. The threshold instruction was to press the button when the sensation changed from pressure to pain. The tolerance instruction was to press the button when the pain became unbearable. An upper safety limit of 1000 kPa was set for all stimuli.

Cold-pressor test

The student was asked to place her/his non-dominant hand and wrist in 3˚C water in a 13-L plexi-glass container connected with a circulating water bath (Julabo PF40-HE; Julabo Labortechnik GmbH, Germany) and maintain it there as long as she/he was able or until the maximum time of 105 s was reached. Pain tolerance was defined as the time (in seconds) the participant kept the hand in the water.

All stimuli

For heat pain and pressure pain thresholds, the two last measurements were averaged. In a few cases, one of the threshold measures is censored while the other is not. In these cases, we set

the threshold to be the minimum value. For heat and pressure pain tolerance, we used the last measurement. For illustrative purposes, the pain tolerance measures were also dichotomised, with subjects reaching the maximum stimulus limit (105 s, 50˚C, 1000 kPa for cold-pressor, heat and pressure stimuli, respectively) defined as pain tolerant and the remaining participants defined as pain sensitive.

Statistical analysis

In order to assess the relationship between friendship ties and individual traits, social network analysis is used. Two different approaches are taken. We calculate pairwise correlations of pain tolerance of two friends, taking into account one friendship at the time. In addition, we fit network autocorrelation models to the data, which relate the pain tolerance of an individual to the average pain tolerance of its friends, considering all the friendships of the individual simultaneously. Though these two measures are clearly not independent, they are not equivalent. It is possible to have a significant effect for one but not for the other. However, if both are significant, then there is stronger evidence of a peer effect. We will use a 0.05 significance level in the statistical analysis.

Definition of the social network

In the friendship network, nodes represent the individuals. There is a directed link going from node *i* to node *j*, if individual *i* nominated individual *j* as a friend. The node *i* is the start node of the link, and the node *j* is the end node of the link. This gives us an adjacency matrix $\boldsymbol{W}$, which contains the friendship information, where the element in the *i*th row and the *j*th column is 1 if individual *i* nominated individual *j* as a friend, and 0 otherwise.

Pairwise correlations

Since there is an upper bound on the pain tolerance measurements, they are right-censored. We thus measure correlations with Kendall's rank correlation coefficient, Kendall's τ, which is straightforward to compute when there is only one fixed censoring point, as in our setting

(16). We compute the correlation between the pain tolerance of the start node and the end node of all the links.

In order to assess the significance of the correlation, we perform permutation tests. This is done by randomly shuffling the pain tolerance observations for all the individuals, while keeping the network structure fixed. The purpose of the permutation is to remove the correlation between the outcome and the network structure, and hence generate a random reference model. Our observed value of τ can then be compared with the correlations obtained for the shuffled data sets. We use 50 000 permutations. The correlations from the permuted data sets are observations obtained under the null hypothesis of no correlation between friends and pain tolerance. We can thus obtain an estimated confidence interval of τ under the null hypothesis, or test if the correlation is significant.

Network autocorrelation model

In order to estimate the effect of friends' pain tolerance on the individual's pain tolerance, we fit a network autocorrelation model (17) to the data. The model is given by

$$\boldsymbol{Y} = \rho \boldsymbol{W}_{\mathrm{N}} \boldsymbol{Y} + \boldsymbol{X}\boldsymbol{\beta} + \boldsymbol{\epsilon},$$

where $\mathbf{Y}$ is the vector of pain tolerance for all the individuals, ρ is the autocorrelation between an individual's pain tolerance and the friends' pain tolerance, $\boldsymbol{W}_{\mathrm{N}}$ is the adjacency matrix, normalised by the number of friends for each individual (so that the rows sum to one), $\mathbf{X}$ is a matrix with other explanatory variables, $\boldsymbol{\beta}$ is the corresponding vector of coefficients and $\boldsymbol{\epsilon}$ is a vector of random normal noise with mean 0 and variance σ^2. The autocorrelation coefficient ρ is a measure of the degree to which an individual has a similar pain tolerance to the overall pain tolerance of her/his friends, and can be interpreted as the expected increase of the individual's pain tolerance with an increase of the average pain tolerance of the individual's friends by one unit (one second for cold-pressor pain, one ℃ for heat, one kPa for pressure).

When fitting this model, we have to take into account both the fact that the observations are dependent (due to the network structure) and censored. In the following, we describe the details of the fitting procedure. We focus on the cold-pressor pain tolerance, and let Y_i be the cold-pressor pain tolerance of individual *i*. We estimate the parameters of the network autocorrelation model as maximisers of a likelihood function, which is a function of the parameters given the observations. Since the full likelihood is intractable, we approximate the likelihood by the pseudo likelihood (18). In the pseudo likelihood approximation, the observations are assumed to be conditionally independent. In addition, we have to take into account that we do not observe the response variable itself, but we observe $Z_i = \min(Y_i, 105)$. Let δ_i be a censor indicator, so δ_i is one if observation *i* is censored, zero otherwise. The pseudo likelihood is given by

$$L(\boldsymbol{z}, \rho, \boldsymbol{\beta}, \sigma, \boldsymbol{y}) = \prod_{i=1}^{N} \left(\frac{1}{\sigma} \varphi \left(\frac{z_i - \boldsymbol{x}_i^T \boldsymbol{\beta} - \rho y_{-i}}{\sigma} \right) \right)^{1-\delta_i} \left(1 - \Phi \left(\frac{105 - \boldsymbol{x}_i^T \boldsymbol{\beta} - \rho y_{-i}}{\sigma} \right) \right)^{\delta_i},$$

where y_{-i} is the average pain tolerance of the friends of individual *i*, $\boldsymbol{x}_i$ is the vector of explanatory variables for individual *i*, N is the number of individuals, φ is the standard normal density and Φ is the standard normal cumulative probability function. The maximum pseudo likelihood estimators are in general good approximations (19). The y_{-i} cannot be evaluated directly, due to the censored observations. Hence, we use an expectation-maximisation (EM) algorithm to maximise the pseudo likelihood. In an EM algorithm, the estimation is performed iteratively, until we have convergence in the estimates. Let $\boldsymbol{\theta} = (\rho, \boldsymbol{\beta}, \sigma)$ be the vector of model parameters. We start with an initial guess for the censored observations as random draws from a truncated normal on $[105, \infty)$. We denote the initial guess by $\widehat{\boldsymbol{y}}_0$. Note that the observed y_i that are not censored are kept at their observed values. A first estimate for the model parameters, $\widehat{\boldsymbol{\theta}}_1$, is then found by

$$\widehat{\boldsymbol{\theta}}_1 = \text{argmax}_{\boldsymbol{\theta}} L(\boldsymbol{z}, \boldsymbol{\theta}, \widehat{\boldsymbol{y}}_0).$$

This estimate for $\boldsymbol{\theta}$ is then used to find a first estimate for $\boldsymbol{y}$, $\widehat{\boldsymbol{y}}_1$, by

$$\hat{y}_i^1 = \begin{cases} y_i, & \text{if } \delta_i = 0, \\ \text{mean of a truncated N}\left(\hat{\rho}_1 \boldsymbol{W}_{\text{N}i}\widehat{\boldsymbol{y}}_0 + \boldsymbol{x}_i^T\widehat{\boldsymbol{\beta}}_1, \hat{\sigma}_1\right) \text{ on } [105, \infty) & \text{otherwise,} \end{cases}$$

where $\hat{y}_i^1$ is the ith element of $\widehat{\boldsymbol{y}}_1$ and $\boldsymbol{W}_{\text{N}i}$ is the ith row of the matrix $\boldsymbol{W}_{\text{N}}$. We continue updating using $\widehat{\boldsymbol{y}}_k$ to find $\widehat{\boldsymbol{\theta}}_{k+1}$ by

$$\widehat{\boldsymbol{\theta}}_{k+1} = \text{argmax}_{\boldsymbol{\theta}} L(\boldsymbol{z}, \boldsymbol{\theta}, \widehat{\boldsymbol{y}}_k).$$

Then $\widehat{\boldsymbol{\theta}}_{k+1}$ is used to find $\widehat{\boldsymbol{y}}_{k+1}$ by

$$\hat{y}_i^{k+1} = \begin{cases} y_i, & \text{if } \delta_i = 0, \\ \text{mean of a truncated N}\left(\hat{\rho}_{k+1} \boldsymbol{W}_{Ni}\widehat{\boldsymbol{y}}_k + \boldsymbol{x}_i^T\widehat{\boldsymbol{\beta}}_{k+1}, \hat{\sigma}_{k+1}\right) \text{ on } [105, \infty) & \text{otherwise.} \end{cases}$$

The updating steps are repeated until we have reached convergence. In order to obtain standard errors for the estimates, we use jackknife procedures which are specific for networks, as explained in (20). The idea behind the jackknife approach is to leave out one individual at a time, and compute the estimates based on the network with this one individual removed. The variance between these estimates is used to estimate the variance of the estimators.

Results

Descriptive statistics for the experimental pain measures are given in Table 1. All pain tolerance and threshold measures were right censored, though this was most pronounced for the cold-pressor test. A histogram of the measured cold-pressor pain tolerance values is given in Figure 1.

Cold-pressor pain tolerance

Main results

A plot of the friendship network, coded by cold-pressor pain tolerance, is shown in Figure 2. At first glance, there seems to be some clustering of individuals with similar pain tolerance. In Figure 3, we plot the proportion of cold-pressor pain tolerant individuals as a function of the

proportion of friends who are pain tolerant. The probability of being pain tolerant seems to be an increasing function of the proportion of friends who are pain tolerant.

We compute Kendall's τ for the continuous cold-pressor pain tolerances, and obtain a value of $\tau = 0.13$, indicating a positive correlation between an individual's pain tolerance and the individual's friends' pain tolerance. There is thus a tendency for friendships among individuals with similar pain tolerance. In order to assess whether this tendency is significant, we perform a permutation test, resulting in τ estimates in the range (-0.072, 0.067). Thus, our observed correlation is much higher than would be expected merely by chance, with a p-value less than 0.00004.

Because sex is assortative in social networks, sex is a potential confounding variable for the association between friendship ties and pain tolerance, since it is also correlated with pain tolerance (21). The estimated partial correlation coefficient of cold-pressor pain tolerance and friendship ties, adjusted for sex, is 0.12. The permutation test for the partial correlation results in values in the range (-0.061, 0.074), and thus there is still significant correlation in friends' pain tolerance after controlling for sex.

We also fit a network autocorrelation model for cold-pressor pain tolerance. The estimated coefficients in a model that only includes the autocorrelation term and an intercept are given in Table 2. The estimated autocorrelation coefficient ρ is highly significant. The estimated size of the effect is that an increase in the average pain tolerance of friends by one second increases the expected pain tolerance of the individual by 0.44 seconds.

In addition, we fit a network autocorrelation model where we control for sex, age and school programme (vocational versus general studies). The resulting coefficients are given in Table 3. The adjusted autocorrelation coefficient ρ is significant and positive. Sex and school programme are highly significant, while age is not, which is not so surprising since most of the adolescents are of same age (15-17 years old). The estimated effect is that by increasing

the average pain tolerance of an individual's friends by one second, the expected pain tolerance of the individual increases by 0.21 seconds. For example, consider two individuals with the same sex, age and school programme, but the friends of the first individual have an average pain tolerance of 30 seconds, whereas the friends of the second individual have an average pain tolerance of 90 seconds. The expected difference in pain tolerance for the two individuals is then 0.21×60 seconds = 12.6 seconds.

Popularity

In order to examine whether the popular individuals have higher cold-pressor pain tolerance, we fitted network autocorrelation models with different network centrality measures of the nodes as covariates. The out-degree of node *i* is the number of links starting at node *i*, thus the number of friends nominated by individual *i* (truncated at five, since the individuals could only nominate up to five friends). The in-degree of node *i* is the number of individuals who nominated individual *i* as a friend, hence this is the number of individuals who consider individual *i* as one of their (likely) top five friends. We also examine whether closeness (how close the individual is to the other individuals in the network), betweenness (a measure of to which extent an individual lies between other individuals) and eigenvector centrality (a measure of the influence of a node in a network), see for instance (22) for details about these measures, have an effect on pain tolerance. The in-degree distribution and out-degree distribution of the network are given in Figure 4. We fitted one network autocorrelation model for each centrality measure and sex, age and school programme were included in all the models. We found no statistically significant relationship between any of the centrality measures and pain tolerance. However, there was a statistical trend for the effect of out-degree on pain tolerance (estimate 1.79, standard deviation 1.04, p-value 0.084), suggesting that individuals who report having more friends may be somewhat more pain tolerant.

Lifestyle factors

We know that lifestyle factors are assortative in social networks. Since lifestyle factors can have an effect on pain tolerance, they constitute possible confounders for the assortativity of pain tolerance in social networks. We therefore control for lifestyle factors in the analysis, by controlling for physical activity and smoking.

The analysis is performed on the subset of the data for whom we have complete information on lifestyle factors. We first refit the network autocorrelation model without lifestyle factors on this subnetwork, in order to compare the fitted model with lifestyle factors on the same subjects. The estimated coefficients are given in Table 4. The estimated coefficients for the network autocorrelation model where we control for lifestyle factors are given in Table 5. We see that smoking has a significant negative effect on pain tolerance, while physical activity has a significant and positive effect. However, controlling for these factors has a minimal effect on the autocorrelation coefficient, and it is still significant. Hence, lifestyle similarities between friends do not explain the association between friendship ties and pain tolerance.

Sex differences in the autocorrelation

We investigate whether the autocorrelation coefficient, ρ, is sex dependent, so that the effect of friends on girls' pain tolerance (ρ_{g}) can differ from the effect of friends on boys' pain tolerance (ρ_{b}). The estimated coefficients for this model are given in Table 6. We see that ρ_{g} (girls) is not significant. The estimated effect for boys is larger than the estimated effect for girls, and it is significant. We thus find a significant correlation between boys and their friends in pain tolerance, but not for girls.

We also investigate whether same-sex friendships have a different effect than different-sex friendships. In the friendship network, there are 3111 same-sex friendships and 582 different-sex friendships. We thus have one autocorrelation coefficient for the friendship

effect of female friends on females ($\rho_{g,ss}$), one for male friends on males ($\rho_{b,ss}$), one effect for male friends on females ($\rho_{g,ds}$) and one effect for female friends on males ($\rho_{b,ds}$).

The estimated coefficients for the model are given in Table 7. The only significant effect is the effect of same-sex friendships for boys ($\rho_{b,ss}$), that is, the effect of boys on boys. Neither the effect of girls on girls nor the effect of boys on girls were significant.

Test sequence

One possible explanation for the effect of friends' pain tolerance on the individual's pain tolerance is the competition between peers. The adolescents are tested consecutively, so they are able to brag to their peers about being able to endure the maximum testing time. This might induce peer pressure, where others also want to perform as well. Thus, we hypothesise that if test sequence has an effect on pain tolerance, then the effect will be positive, so that those who are tested later have a higher pain tolerance. We therefore control for test sequence in the network autocorrelation model. The results are given in the Supplementary Materials. We find that test sequence has a positive and significant effect. When controlling for test sequence, the estimated correlation coefficient ρ decreases, but it is still significant.

It is also possible that the test sequence effect is larger among friends. We therefore also fit a network autocorrelation model, where we control for the test order among friends. We find that the test order among friends does not have a significant effect on the pain tolerance of the individual (see Supplementary Materials). In addition, including this covariate does not seem to affect the network autocorrelation coefficient. Hence, there seems to be an effect of the number of adolescents who have been tested before the individual, and it is not confined to friends. However, even though controlling for this induced peer pressure effect reduces the estimated effect of friends' average pain tolerance on the individual's pain tolerance, there is still a significant autocorrelation effect.

Other pain modalities

In order to study whether pain tolerance is also assortative for other pain tolerance measures, we repeated the analysis for heat pain tolerance, pressure pain tolerance at the fingernail and pressure pain tolerance at the trapezius muscle. The full results are given in the Supplementary Materials. We find a positive and significant pairwise correlation between friendship ties and pain tolerance for all pain modalities, also after controlling for sex. Considering network autocorrelation effects, we find that for pressure pain tolerance at the fingernail, there is a significant effect of friends' pressure pain tolerance on the individual's pressure pain tolerance. For pressure pain tolerance at the trapezius muscle, the effect is not significant, but borderline significant on the 0.05 level, indicating that there is possibly an effect. As an exception, we find no indication of an effect of the friends' average pain tolerance on the individual's heat pain tolerance.

Pain threshold

We also study the friendship effect on pain threshold. When considering the pairwise correlations of friendship ties and pain threshold, there is a significant effect for heat pain threshold and pressure pain threshold at the fingernail, but no effect for pressure pain threshold at the trapezius muscle. For the network autocorrelation effects, there is a significant effect of the average pain threshold of friends on the individual's pain threshold for pressure pain threshold at the fingernail, but not for heat pain threshold and pressure pain threshold at the trapezius muscle.

Popularity

We examined whether popularity or centrality had a positive effect on pain tolerance or pain threshold, for heat pain, pressure pain at the fingernail and pressure pain at the trapezius muscle. For heat pain tolerance and heat pain threshold, the in-degree has a significant effect.

For pressure pain tolerance at the trapezius muscle, none of the centrality measures are significant, but out-degree is borderline significant with a p-value slightly above 0.05 (0.051).

Discussion

We studied the effect of friendship ties on cold-pressor pain tolerance in a group of upper secondary school students, and found that their social network is assortative in terms of pain tolerance. Hence, there is a significant tendency for pupils with high pain tolerance to be friends with other pupils with high pain tolerance, and vice versa.

Investigating further how this effect depends on the sex of the individual, and whether the friendships are same-sex friendships or different-sex friendships, we find that the only significant effect is the effect that male friends have on males. We find no significant effect of friends for girls on pain tolerance in stratified analyses.

Considering other pain modalities, we found that even though the relationship was most significant for cold-pressor pain tolerance, it is clear that there is a positive association between friends and pain tolerance. For pain threshold, we found that the relationship between friendship ties and pain threshold was not as clear as the relationship between friendship ties and pain tolerance.

There are two possible reasons why we find a significant and positive correlation between individuals and their friends in pain tolerance. Either individuals select friends based on similarity in pain tolerance (homophily), or it could be due to friends influencing each other so that one becomes more similar to one's friends (social transmission). If the latter is true, this would provide an explanation for some of the unique environmental contribution to pain, which is not explained by genes and family environment. Compelling evidence of both homophily and social transmission has been reported for several other phenotypes, including obesity, alcohol consumption and smoking (11-14). To the extent that these phenotypes

influence pain tolerance, it is quite plausible that social transmission of pain tolerance could occur as a downstream effect.

Pain tolerance is not a directly observable trait and, in our experience, research subjects are frequently surprised by their own response to the cold-pressor test. The direct selection of friends based on their pain tolerance therefore seems unlikely. However, there is good reason to believe that such selection might occur indirectly, for instance by individuals selecting friends with similar lifestyle, or other characteristics that are also associated with pain tolerance. In other words, the lifestyle arguments that hold for social transmission also hold for homophily. Therefore, it is reasonable to assume that at least part of the observed assortativity is due to homophily, and not explained by social transmission alone.

We have partially controlled for lifestyle by controlling for smoking and physical activity, as a substitute for lifestyle. Though we do have information on multiple lifestyle factors (smoking, snuff use, alcohol consumption, obesity and physical activity), we do not include all of these lifestyle factors in the analysis, because they are highly correlated with each other. To avoid multicollinearity issues, we only include smoking and physical activity. Since the lifestyle covariates are highly correlated, the effect is likely to be similar for other lifestyle factors. Though such adjustments reduce the effect of friends' pain tolerance on the individual slightly, it is still significant. However, there may be other factors which we have not controlled for, which are both associated with pain tolerance and friendship ties. One potential candidate is socioeconomic status. We did try to control for education of parents as a substitute for socioeconomic status. We found no significant effect of the education of parents on the pain tolerance of the individual, and the friendship effect did not decrease when controlling for the education of the parents (results not shown). The fact that the effect that boys have on boys is the only significant effect in stratified analysis, indicates that there is possibly a "macho effect" present, where "tough" boys tend to be friends with other "tough"

boys and vice versa, or that boys influence each other's pain tolerance, perhaps as a peer pressure effect. Here it is worth noting that participants may report to each other whether or not they endured the full time for the cold-pressor test, thus inducing peer pressure on friends tested later. We controlled for test sequence, and found that it had a positive, significant effect. Hence, adolescents who are tested later have, on average, higher pain tolerance than adolescents tested earlier. Controlling for test sequence does decrease the effect of friends' pain tolerance on the individual's pain tolerance, but it does not explain all of the friendship effect. The friendship effect is still significant after controlling for test sequence.

For cold-pressor pain tolerance, there was no significant effect of any of the centrality measures, but the estimated effect of out-degree (the number of nominated friends by the individual) showed an indication of a possible effect. Out-degree was also borderline significant for pressure pain tolerance at the trapezius muscle, and in-degree (the number who nominated the individual as their friend) had a significant effect on heat pain tolerance and heat pain threshold. Thus, there is an indication of more central individuals being more pain tolerant, but we did not find significant evidence for this. This supports (but does not confirm) previously published results indicating that pain tolerance is higher for individuals with more friends (23).

One limitation of the study is the fact that we use the pseudo likelihood approximation and not the full likelihood, to estimate the parameters in the network autocorrelation models. The reason why we use the pseudo likelihood approximation is due to the censoring. An alternative to using the pseudo likelihood approximation is to use the dichotomised pain tolerance outcomes instead of the continuous measurements. We have chosen not to do this, due to the information loss related to dichotomising continuous variables (24). Another limitation of the study is that we do not have the full social network for the individuals, since they could only nominate up to five friends, all within the upper secondary school in the

Tromsø area. In addition, the adolescents were not asked to name their five closest friends, but they were asked to name the five individuals with whom they had spent most time the preceding week. This does not necessarily coincide with the top five friends, causing uncertainty in the strength of these friendship ties. The friendships are also not weighted, so we cannot distinguish strong friendships from weak ones. Another source of error in the friendship network is the fact that the network is self-reported. Last, and most importantly, without longitudinal information, we are unable to determine to what the degree pain tolerance is assortative due to homophily (similar people becoming friends) or due to social transmission.

Authors' Statements

Conflicts of interest

We have no conflicts of interest to declare.

Informed consent and ethical approval

Data collection for TFF1 was approved by the Norwegian Data Protection Authority, and the Regional Committee for Medical and Health Research Ethics of Norway, Northern health region. The study procedures were conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent before inclusion. For participants younger than 16 years, written or oral consent from one parent was also obtained. In cases of oral consent, two study nurses provided confirmation that oral consent from a parent was obtained, in accordance with procedures laid out in the ethics approval.

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Tables

Table 1. Descriptive statistics for the various pain measures.

	N	Girls	Boys	Cens.	Med.	Min.
Cold-pressor tol.	997	481	516	502	105	9.30
Heat pain tol.	983	478	505	278	48.40	37.90
Press. tol. f.	902	440	462	316	798	182
Press. tol. t.	886	428	458	228	570	84
Heat pain th.	983	479	504	13	44.90	35.45
Press. th. f.	905	443	462	21	400	99
Press. th. t.	882	428	454	3	253.75	55
	Med. girls	Med. boys	Min. girls	Min. boys		
Cold-pressor tol.	78.10	105	11	9.30		
Heat pain tol.	47.50	49.40	37.90	39.40		
Press. tol. f.	667	994.50	182	252		
Press. tol. t.	478	684	84	136		
Heat pain th.	44.75	45.15	36.30	35.45		
Press. th. f.	364	459	99	116		
Press. th. t.	227	278	55	92		

The Tromsø Study: Fit Futures I: Number of participants, number of girls, number of boys, number of censored individuals (cens.), median (med.), minimum value (min.), median for the girls, median for the boys, minimum value for the girls and minimum value for the boys, for the different pain measurements. Cold-pressor tol. is the cold-pressor pain tolerance, heat pain tol. is the heat pain tolerance, press. tol. f is the pressure pain tolerance at the fingernail, press. tol. t is the pressure pain tolerance at the trapezius, and th. is the threshold.

Table 2. Fitted network autocorrelation model.

	ρ	Intercept
Estimate	0.44	55.45
Std. dev	0.062	6.19
P-value	$1.40 \cdot 10^{-12}$	$<2.0 \cdot 10^{-16}$

Estimated coefficients in the network autocorrelation model using data from the Tromsø Study: Fit Futures I, standard deviation (Std. dev) and p-values.

Table 3. Fitted network autocorrelation model, controlling for sex, age and school programme.

	ρ	Sex	Age	School p.	Intercept
Estimate	0.21	18.44	-1.19	32.58	72.22
Std. dev	0.073	2.54	0.95	3.29	18.44
P-value	0.0049	$3.61 \cdot 10^{-13}$	0.21	$<2.0 \cdot 10^{-16}$	$9.08 \cdot 10^{-5}$

Estimated coefficients in the network autocorrelation model using data from the Tromsø Study: Fit Futures I, standard deviation (Std. dev) and p-values. School p. denotes school programme.

Table 4. Fitted network autocorrelation model, controlling for sex, age and school programme, on the individuals for whom we have lifestyle information.

	ρ	Sex	Age	School p.	Intercept
Estimate	0.24	17.31	-1.36	31.40	73.32
Std. dev	0.072	2.50	0.87	3.24	17.39
P-value	0.0010	$4.62 \cdot 10^{-12}$	0.12	$<2.0 \cdot 10^{-16}$	$2.47 \cdot 10^{-5}$

Estimated coefficients in the network autocorrelation model using data from the Tromsø Study: Fit Futures I, standard deviation (Std. dev) and p-values. School p. denotes school programme.

Table 5. Fitted network autocorrelation model, controlling for sex, age, school programme, physical activity and smoking.

	ρ	Sex	Age	School p.	Phys. act	Smoke	Intercept
Estimate	0.22	17.00	-1.27	27.75	1.87	-5.29	71.53
Std. dev	0.074	2.53	1.44	3.32	0.62	2.28	26.75
P-value	0.0035	$1.94\cdot 10^{-11}$	0.38	$<2.0\cdot 10^{-16}$	0.0028	0.020	0.0075

Estimated coefficients in the network autocorrelation model using data from the Tromsø Study: Fit Futures I, standard deviation (Std. dev) and p-values. School p. denotes school programme and phys. act denotes physical activity.

Table 6. Fitted network autocorrelation model with sex-dependent ρ, controlling for sex, age, school programme, smoking and physical activity.

	ρ_g	ρ_b	Sex	Age
Estimate	0.15	0.27	5.30	-1.36
Std. dev	0.10	0.089	11.80	1.70
P-value	0.16	0.0022	0.65	0.42
	School p.	Smoke	Phys.act	Intercept
Estimate	27.80	-5.62	1.92	79.09
Std. dev	3.40	2.28	0.64	33.47
P-value	$2.22 \cdot 10^{-16}$	0.14	0.0026	0.018

Estimated coefficients in the network autocorrelation model using data from the Tromsø Study: Fit Futures I, standard deviation (std. dev) and p-values. School p. denotes school programme and phys. act denotes physical activity. ρ_g is the effect of friends on girls' pain tolerance and ρ_b is the effect of friends on boys' pain tolerance.

Table 7. Fitted network autocorrelation model with sex-dependent ρ, and separating the effect of same-sex and the effect of different-sex, controlling for sex, age, school programme, smoking and physical activity.

	$\rho_{\mathrm{g,ss}}$	$\rho_{\mathrm{b,ss}}$	$\rho_{\mathrm{g,ds}}$	$\rho_{\mathrm{b,ds}}$	Sex
Estimate	0.12	0.25	0.065	-0.030	7.70
Std. dev	0.10	0.077	0.048	0.055	11.39
P-value	0.27	0.0012	0.17	0.59	0.50
	Age	School p.	Smoke	Phys. act	Intercept
Estimate	-1.38	29.12	-5.71	1.84	79.73
Std. dev	1.97	3.45	2.36	0.64	37.37
P-value	0.48	$<.2.0\cdot 10^{-16}$	0.016	0.0041	0.032

Estimated coefficients in the network autocorrelation model using data from the Tromsø Study: Fit Futures I, standard deviation (Std. dev) and p-values. School p. denotes school programme and phys. act denotes physical activity. $\rho_{\mathrm{g,ss}}$ is the effect that female friends have on a female, $\rho_{\mathrm{b,ss}}$ is the effect that male friends have on a male, $\rho_{\mathrm{g,ds}}$ is the effect of male friends on a female and $\rho_{\mathrm{b,ds}}$ is the effect that female friends have on a male.

Figure legends

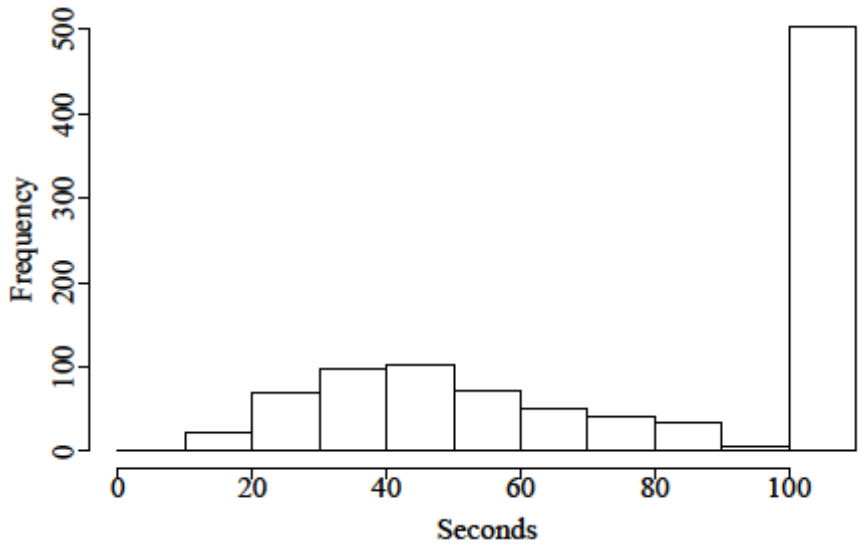

Figure 1: Histogram of the cold-pressor pain tolerance. Observed pain tolerance in seconds in the Tromsø Study: Fit Futures I.

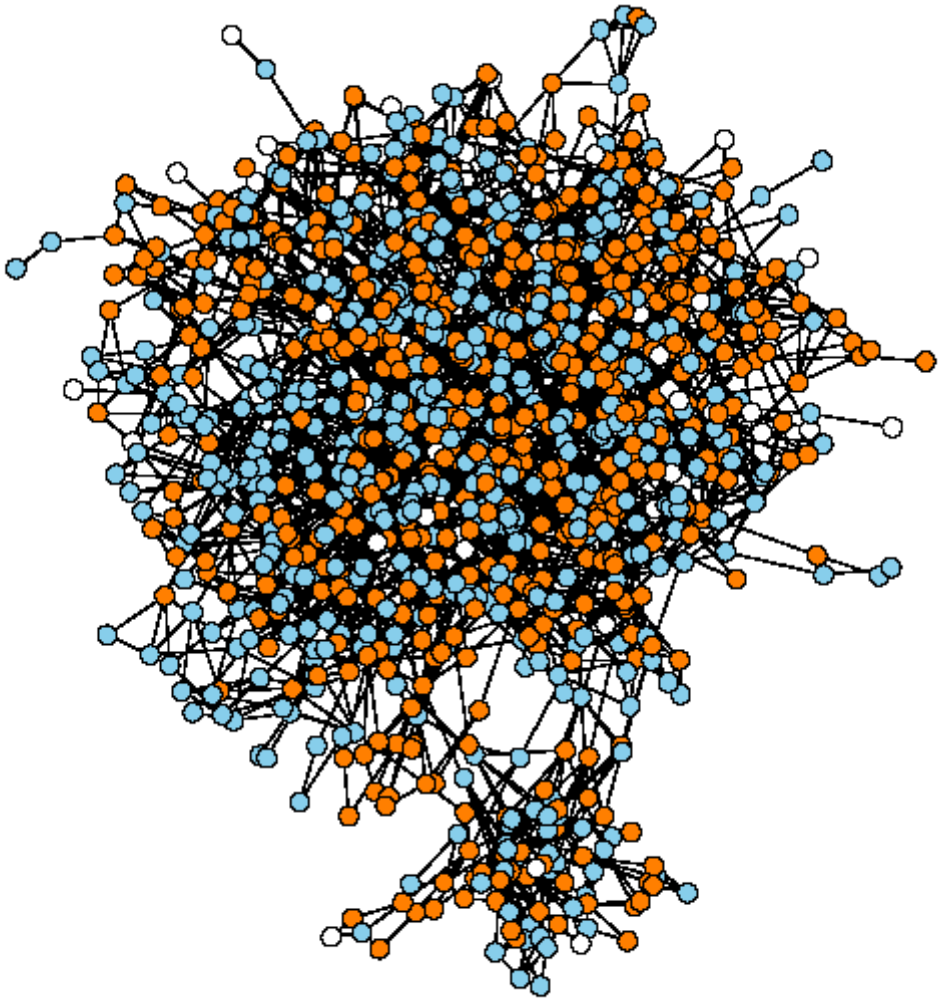

Figure 2: Friendship network. Social network of the adolescents in the first year of upper secondary school in Tromsø in the Tromsø Study: Fit Futures I, where the nodes are coloured by cold-pressor pain tolerance. Orange: pain tolerant. Blue: pain sensitive. White: not

measured (non-participants or not tested). The isolates (i.e. individuals with no friendship ties) have been removed to reduce visual clutter. Out of the isolates, there were three pain sensitive individuals and two pain tolerant individuals.

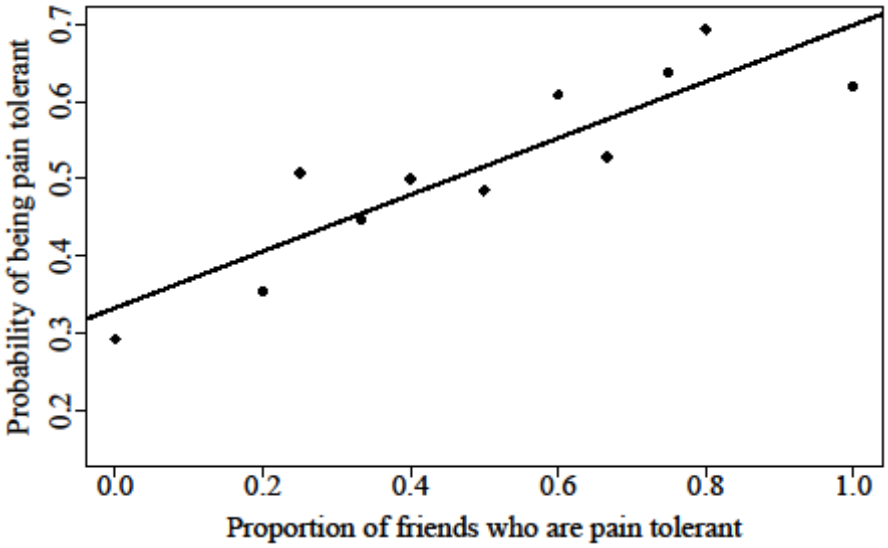

Figure 3: Cold-pressor pain tolerance versus friends. Proportion of cold-pressor pain tolerant individuals as a function of the proportion of their friends who are pain tolerant in the Tromsø Study: Fit Futures I. The best linear fit to the points is also plotted.

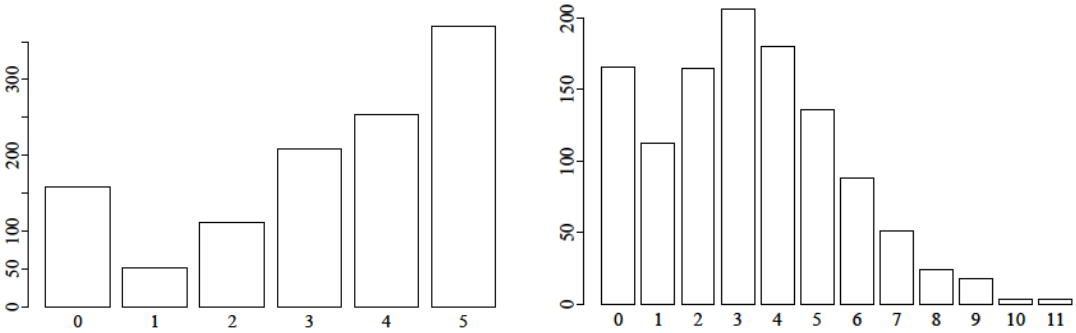

Figure 4: Degree distributions. Degree distributions for the adolescent network in the Tromsø Study: Fit Futures I. Left: out-degree. Right: in-degree.