



## Determinants of pressure pain threshold in adult twins: evidence that shared environmental influences predominate

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### Abstract

The objective of this study was to examine the relative contribution of genetic and environmental factors in determining pain perception in a classical twin study. Dolorimeter measurements of pressure pain threshold (PPT) were recorded in 609 healthy female-female twin pairs of whom 269 pairs were monozygotic (MZ) and 340 were dizygotic (DZ). There was a strong correlation ( $R$ ) in PPT in both MZ and DZ pairs ( $R_{MZ} = 0.57$ , 95% confidence interval (CI): [0.49, 0.65];  $R_{DZ} = 0.51$ , 95% CI: [0.42, 0.59]). The slight excess in intraclass correlation observed in MZ when compared with DZ twins corresponds to a heritability for PPT of only 10% and is not statistically significant. Neither estimate of intraclass correlation was substantially altered after adjusting for a range of potential confounding variables including age, current tobacco and alcohol use, current analgesic use, psychological status assessed by the general health questionnaire, and social class. The dolorimeter measurements were shown to be reliable (between observer agreement  $R = 0.66$ ; within observer agreement  $R = 0.70$ – $0.76$ ) and stable over time. In conclusion, these data suggest that there is no significant genetic contribution to the strong correlation in PPT that is observed in twin pairs. These findings reinforce the view that learned patterns of behaviour within families are an important determinant of perceived sensitivity to pain. © 1997 International Association for the Study of Pain. Published by Elsevier Science B.V.

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### 1. Introduction

There is wide variation in the appreciation of pain between individuals in human populations. In members of the same family, however, levels of pain sensitivity have been reported to show similarity (Violon and Giurgea, 1984; Edwards et al., 1985). This clustering has hitherto been interpreted as reflecting the influence of the shared environment within families. In particular, family dynamics and learning of early pain behaviour have been implicated as causes (Edwards et al., 1985). The clustering may equally have a genetic basis. Genetic mechanisms have been demonstrated to underlie a number of pain appreciation traits in laboratory animals (Mogil et al., 1996). In humans, racial variation in pain threshold has been described (Woodrow et al., 1972). A number of genetic polymorphisms have also recently been identified to be associated with

pain perception (Wood, 1996). One example is the CYP2D6 isoenzyme polymorphism which has been shown to be related to cold sensitivity (Sindrup et al., 1993).

Given this recent recognition of new genetic models of pain perception in man, it is appropriate to re-explore the relative contribution of genetic and environmental factors in determining the appreciation of pain in human populations. Examining twins is a classical epidemiological approach to this problem and to our knowledge has not been previously used in this area. In this study we compare pressure pain threshold (PPT) measurements assessed by dolorimetry in pairs of monozygotic (MZ) and dizygotic (DZ) twins.

### 2. Subjects and methods

#### 2.1. Twin ascertainment

Twin pairs included in this analysis were ascertained

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through a UK nationwide media campaign conducted between 1992 and 1996. A small proportion were also recruited through a normal twin register at the Institute of Psychiatry. Details of the twin recruitment method are given elsewhere (Spector et al., 1996). In brief, the media campaign focused on recruiting twin pairs for studies into osteoporosis. The majority who volunteered were healthy postmenopausal women with characteristics similar to those of the general population. All twins in this sample had been reared together as children by their natural parents.

Respondents were invited to attend for a full medical assessment at the Twin Research Unit at St Thomas' Hospital. All completed a detailed nurse-administered questionnaire relating to their twin history, medical history and to a range of environmental and lifestyle variables. All were subjected to a sequence of physical investigations which included PPT measurement by dolorimetry. Zygosity was assigned using a validated questionnaire (Cederlöf et al., 1961), with DNA fingerprinting undertaken in those pairs in whom zygosity was uncertain or disputed.

As part of the twins' assessment, information was obtained relating to variables which were judged to have a potential confounding influence on the comparison between PPT measurements. The variables identified were age, height, weight, blood pressure, tobacco and alcohol use, current analgesic use, social class and general health questionnaire (GHQ) score. The GHQ score was determined using the 28-item questionnaire in which responses are classified under four factors representing somatic symptoms (factor A), anxiety and insomnia (factor B), social dysfunction (factor C) and severe depression (factor D) (Goldberg and Hillier, 1979). Responses were scored using a Likert scale and the total score for each category was analysed separately.

## 2.2. Dolorimetry

Pressure pain thresholds were assessed using a variable pressure dolorimeter with a footplate surface area of 0.5 cm<sup>2</sup> and a scale range from 0 to 9 kg. The measurements were undertaken at the forehead following a standard protocol (Fischer, 1987). All measurements were carried out with the subject sitting. Prior to the test the subject was instructed to say 'yes' at the moment that they started to feel pain or discomfort. The dolorimeter was placed perpendicular to the forehead and the pressure was raised continuously at a rate of 2 kg/cm<sup>2</sup>/s. When the subject said 'yes' the pressure was stopped and the dolorimeter removed. Measurements were made once only for each subject.

The test was carried out by one of two nurses trained in the technique prior to the study. One observer made measurements on both members of the pair. In all examinations twins and their co-twins were present in the same room when tested. Both twins were blinded to the result of the test.

The consistency and independence of the dolorimeter

measurements were assessed in a sequence of analyses. First the intra- and interobserver agreement between the two nurse examiners was measured in a group of 24 unrelated healthy volunteers. All these tests were carried out in a 2–4-h period. Second, the consistency of readings over a longer time interval was assessed by one of the nurse examiners who repeated the analyses in a subgroup of MZ and DZ twins 12–24 months apart. Third, a possible influence resulting from the circumstances of the test, in which twins were examined together in the same room rather than apart, was assessed. In this analysis, measurements were carried out by one of the nurse examiners (a) in a subset of MZ twins where co-twins were assessed apart in separate examination rooms and (b) in unrelated individuals examined as pairs, both together in the same room and separately.

## 2.3. Statistical methods

Similarity in PPT in MZ and DZ pairs was assessed through measurement of the intraclass correlation coefficient (*R*) calculated in a one-way analysis of variance. The coefficient was adjusted for the influence of potential confounding variables by a validated technique in which (a) the dolorimeter score for each individual was entered in a multiple linear regression against all potential confounding variables and (b) an adjusted *R* was calculated for MZ and DZ groups using the residuals of the regression analysis (Williams et al., 1992). Before adjustment, the data were log-transformed to retain a normal error distribution and to satisfy the assumptions for the analysis of variance. The relative contribution of genetic factors in determining PPT was assessed through measurement of the heritability coefficient. This is an estimate of the extent to which phenotypic variation in PPT can be explained by additive genetic variance alone (Falconer, 1989). The distribution of characteristics in MZ and DZ pairs was compared using the intraclass correlation coefficient for continuously distributed variables and the kappa statistic for categorical data. The agreement between dolorimeter readings in the analysis of its repeatability was also assessed by measuring the intraclass correlation coefficient. The analyses were carried out using the statistical software packages STATA (StataCorp, 1997) and TWINAN90 (Williams et al., 1992).

## 3. Results

### 3.1. Correlation in PPT in MZ and DZ pairs

Pressure pain threshold measurements were carried out in 269 MZ and 340 DZ pairs. The median PPT and range of PPT was similar in both MZ and DZ twin groups (MZ twins: median 3.0 kg/cm<sup>2</sup>, interquartile range 2.2–4.0 kg/cm<sup>2</sup>; DZ twins: median 3.0 kg/cm<sup>2</sup>, interquartile range 2.0–4.0 kg/cm<sup>2</sup>). These measurements are comparable to values reported in a number of other studies of PPT in normal

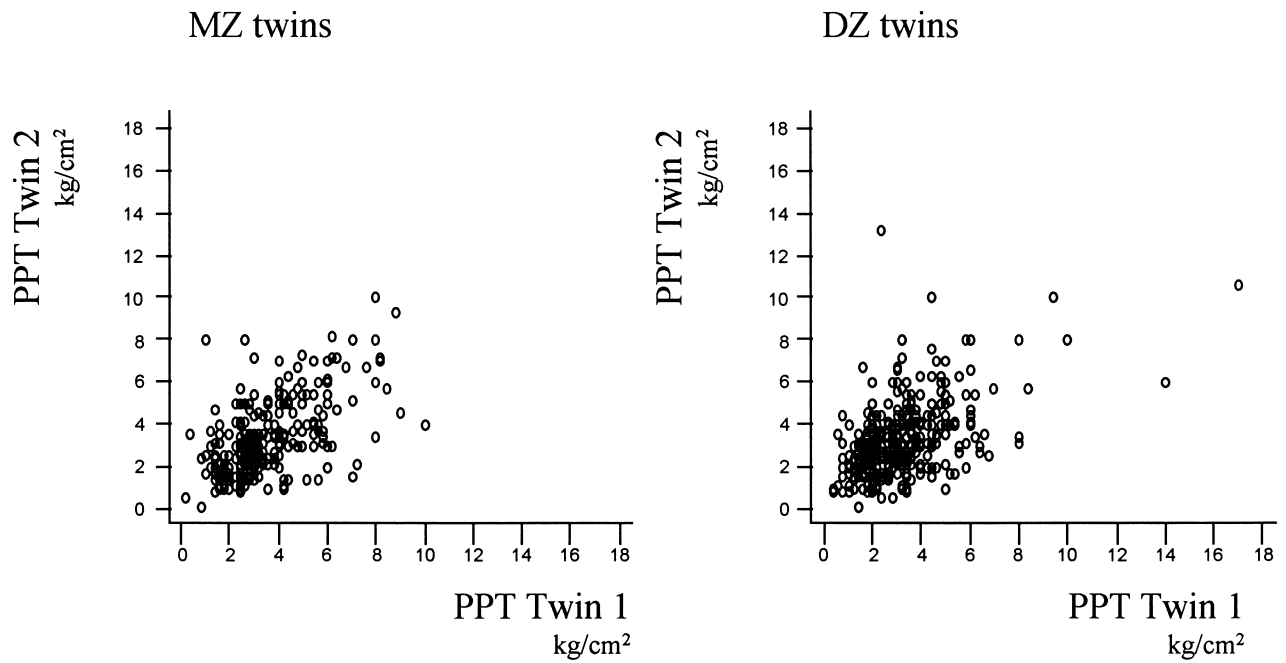


Fig. 1. Scatterplot of PPT in MZ and DZ twins. The labels ‘Twin 1’ and ‘Twin 2’ are allocated arbitrarily to co-twins from each pair.

females (Fischer, 1987; Lautenbacher et al., 1994; Spector et al., 1996).

Scatterplots of PPT measurements are shown in Fig. 1. There was a strong correlation in PPT in the group overall ( $R = 0.54$ , 95% confidence interval (CI): [0.48, 0.59]). PPT was strongly correlated in both MZ and DZ twins (Table 1). A slight excess in correlation was observed in MZ when compared with DZ twins, however this was not statistically significant ( $R_{MZ} = 0.57$  vs.  $R_{DZ} = 0.51$ ;  $P = 0.14$ ). This MZ excess corresponds to a heritability coefficient for PPT of approximately 10%, and indicates that only a small proportion of the overall variation in PPT in the twins might be accounted for by genetic factors.

The distribution of potential confounding variables identified prior to the analysis is shown in Table 2. Greater similarity in MZ compared with DZ pairs was seen for current smoking, alcohol use, and score on the general health questionnaire. The average age was higher in the MZ twins than the DZ twins. Although the pairs themselves were, by definition, matched for age, this difference could have influenced the comparison between MZ and DZ twins if age itself was related to variance in PPT. After adjusting for the influence all of these confounding variables by linear regression both MZ and DZ intraclass correlations remained virtually unaltered (Table 1).

Table 1

Correlation in pain threshold					
	<i>n</i> (pairs)	<i>R</i>	95% CI	Adjusted <i>R</i>	95% CI
MZ	269	0.57	[0.49, 0.65]	0.60	[0.52, 0.67]
DZ	340	0.51	[0.42, 0.59]	0.57	[0.49, 0.64]

### 3.2. Reliability of dolorimetry measurements

The sequence of tests examining the reliability of the dolorimeter measurements is summarised in Table 3. There was good agreement in PPT measurements within and between the two observers both in the twins and in unrelated individuals. Tests examining the stability of the measurement over time using one observer showed that the

Table 2

Characteristics of the twins

	MZ ( <i>n</i> = 538)		DZ ( <i>n</i> = 680)	
	Mean (SD)/%	<i>R</i> /kappa <sup>a</sup>	Mean (SD)/%	<i>R</i> /kappa
Age (years)	57.4 (6.7)	1.00	52.3 (8.8)	1.00
Height (cm)	161.1 (5.8)	0.86	162.2 (6.0)	0.54
Weight (kg)	63.2 (9.7)	0.72	64.8 (11.4)	0.37
Mean blood pressure (mmHg)	107 (15.2)	0.57	107 (14.3)	0.35
Regular current alcohol use (%)	54	0.39	54	0.33
Current smokers (%)	16	0.42	17	0.11
Current analgesia (%)	29	0.25	17	0.26
GHQ <sup>b</sup>				
Factor A	4.2 (3.3)	0.43	4.5 (3.5)	0.28
Factor B	3.9 (3.8)	0.46	4.3 (4.2)	0.26
Factor C	7.0 (2.0)	0.24	7.2 (2.1)	0.21
Factor D>0 (%)	55	0.24	57	0.21
Social class I–II (%)	47	0.39	40	0.32

<sup>a</sup>The association between values measured in co-twins in each pair is expressed as the intraclass correlation coefficient for continuous variables and kappa for categorical variables

<sup>b</sup>GHQ, General health questionnaire. Factors are defined in the text. Factors A, B and C were examined as continuous variables. Factor D was examined as a categorical variable D = 0 and D > 0.

Table 3

Reliability of dolorimeter measurements

Design	<i>R</i>
Agreement over 2–4 h (observer 1) ( <i>n</i> = 24, unrelated subjects)	0.76
Agreement over 2–4 h (observer 2) ( <i>n</i> = 24, same subjects as above)	0.70
Agreement between observer 1 and 2 ( <i>n</i> = 24, same subjects as above)	0.66
Agreement in MZ and DZ twins tested 12–24 months separately ( <i>n</i> = 20 subjects)	0.33
MZ pairs assessed singly ( <i>n</i> = 48 subjects)	0.35
Agreement in unrelated subjects assessed as pairs ( <i>n</i> = 24 subjects)	<0.0
Same pairing as above but individuals assessed singly	<0.0

PPT remained stable in the shorter timespan of hours (representative of the variation in the timing between different twins' assessments) and over a period of 12–24 months. Analysis of the effect of carrying out the test with the partner present showed that the twin correlation was lower when the twins were examined separately ( $R = 0.35$ ) than when they were both present in the same examination room, despite being blinded to all the results. In the unrelated individuals no positive correlation between results was seen when the subjects were examined as pairs either separately or together.

#### 4. Discussion

This study has demonstrated that PPT levels are strongly associated within members of both MZ and DZ twin pairs, with only a small excess in correlation observed in MZ when compared with DZ pairs. The results can be interpreted as suggesting that environmental factors unique to each twin pair have the most important aetiological contribution to PPT. The influence of genetic factors appears to be substantially less important.

In analysing these data we have attempted to quantify the potential bias that may have arisen through the influence of confounding variables acting differently in the MZ and DZ groups and through the variation of the dolorimeter measurements themselves. Confounding variables considered by prior review to be possible influences on pain threshold included age and blood pressure (Woodrow et al., 1972; France et al., 1994). Anxiety and depression also influence pain experience (Unruh, 1996) and were taken into account using scores recorded on individual components of the general health questionnaire.

Bias may also have arisen in this study through the recruitment method which may have selected for subjects with an interest in osteoporosis and musculoskeletal disease. Pain threshold has been described as being altered in a number of musculoskeletal diseases including fibromyalgia (Lautenbacher et al., 1994). In the analysis we attempted

to account for this potential bias by including current analgesic as a proxy measure of musculoskeletal symptoms. Analgesia itself is not thought to influence PPT (Beecher, 1959).

Although differences in the distribution of several potential confounding variables were observed in the MZ and DZ twin groups (Table 2), none had a quantitative influence on the measurement of the absolute level of correlation in MZ and DZ pairs. We recognise, however, that fully accounting for all known and unknown confounders involved in determining a trait as complex as PPT is impossible and the effects of residual confounding are likely to remain. In this regard, it should be stressed that for an environmental confounding variable to influence these results so as to lead to an underestimate of a genetic influence, its variation would have to be greater in MZ than DZ twins, irrespective of the direction of the association with PPT. Such a pattern is rarely observed in twin data.

Logistic constraints in a study of this size limited the number of PPT measurements on each subject to one. It was therefore important to quantify the extent of measurement error in the data. The variation in dolorimeter readings was assessed in several analyses in the twins themselves and in a group of unrelated individuals. In our hands, the PPT measurements showed good repeatability both between and within examiners and the results were stable over time. This concurs with other reports of the reliability of this technique (Fischer, 1987). Because errors are likely to have been equally distributed in MZ and DZ twins, the effect of measurement variation will have tended to lead to an underestimate of the degree of correlation in the MZ and DZ twins. The comparison between MZ and DZ twins is unlikely to have been biased as a result of measurement variation as each pair was examined by one observer and both observers saw an equal proportion of MZ and DZ pairs.

The analysis did, however, suggest that the circumstances of the test itself may influence the level of correlation between pairs. In a sample of 24 pairs of MZ twins examined in separate rooms the correlation in PPT was lower than in the twins examined in the same room (Table 3). A similar effect was not observed when unrelated individuals were examined in pairs. These observations suggest that factors unique to the twins themselves, such as their behavioural responses to the painful stimulus, may have an important contribution to the association.

No quantitative method of measurement of pain threshold or tolerance is ideal (Chapman et al., 1985). Furthermore, there is no clear relationship between pain threshold measurements by dolorimetry and the clinical experience of pain in humans (Beecher, 1959; Chapman et al., 1985). The fact that we have not demonstrated an important genetic influence in the generation of PPT does not preclude the possibility that other pain perception mechanisms are strongly genetically determined. Indeed, recently published data show a clear genetic link with pain perception in humans for specific pain pathways. Mutations of the

TRKA receptor gene, for example, have been associated with type 4 hereditary insensitivity to pain with anhidrosis, a disease in which there is loss of unmyelinated C fibres and small diameter myelinated A fibres (Indo et al., 1996). Polymorphisms of CYP2D have been shown to be specifically associated with cold insensitivity but not the response to painful pressure stimuli (Sindrup et al., 1993). It would be of interest to test the quantitative contribution of these genetic loci to pain perception in population-based family studies.

The results from this twin study underline the importance of shared environmental factors as opposed to genetic factors in determining the threshold to pain. Whilst requiring confirmation in adoption studies and studies of MZ twins reared apart, the present data lend support to earlier observations in families which showed current pain experience to be the result of learned patterns of behaviour reinforced by family members (Violon and Giurgea, 1984; Edwards et al., 1985). Our findings suggest that understanding of the precise environmental factors shared by twin pairs would be a fruitful area of further pain research.

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