

INDIVIDUAL DIFFERENCES IN PAIN SENSITIVITY:
MEASUREMENT AND CAUSATION

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DEDICATION

I dedicate this thesis to my father, Claus Sivert Nielsen, who unfortunately did not live to see it completed.

ACKNOWLEDGEMENTS

Most of this study was conducted while I was employed by the Department of Psychology, Faculty of Social Sciences, University of Oslo. When funding ran out, Arne Holte offered me a position at the Division of Mental Health, Norwegian Institute of Public Health, where I am currently employed, and I feel strongly indebted to him for rescuing me from a difficult situation. The main funding for the study was provided by the Norwegian Research Council. Additional funding was provided by: the Norwegian Foundation for Health and Rehabilitation; the Faculty of Medicine, University of Oslo; Medinnova AS; and by the Department of Psychology, Faculty of Social Sciences, University of Oslo. Laboratory space was provided by Rikshospitalet University Hospital.

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Pain measurement is, as pointed out in the thesis, crucially dependent on subjective report. Valid and reliable measurement of pain is therefore only possible when research subjects take their task seriously, and actively engage in the challenge of assessing and communicating their private experience. Our results serve as testimony to the high standard of the contribution made by the twins who participated in this study.

Though it is hoped that this thesis will be of interest to researchers and clinicians in the field, no one will experience greater relief at its completion than my wife, Marie, and children, Yngvild and Helene. They have suffered my absence evenings, weekends and vacations with little complaint, and I thank them for their patience. I also extend my apologies to my friends, who have heard little from me these last years. Finally I would like to thank my mother-in-law and father-in-law, Kari and Leif Anisdahl, for their substantial contribution to babysitting, and my mother, Mary Lee Nielsen, for proof-reading this manuscript.

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LIST OF PAPERS INCLUDED

- I. Nielsen CS, Price DD, Vassend O, Stubhaug A, Harris JR. Characterizing individual differences in heat-pain sensitivity. *Pain* 2005;119:65-74.
- II. Nielsen CS, Stubhaug A, Price DD, Vassend O, Czajkowski N, Harris JR Individual Differences in Pain Sensitivity: Genetic and environmental contributions. *Pain* 2007; In press.
- III. Nielsen CS, Vassend O, Harris JR, Stubhaug A. The genetics of pain and attention. *Pain* 2007; Submitted.

1. BACKGROUND

1.1. THE FUNCTION OF PAIN

The functional significance of pain is to protect the body from harm, by informing of impending or ongoing tissue damage and to motivate the organism to do something about it. Thus pain has both a sensory (informative) and affective (motivational) dimension, as is reflected in modern definitions of pain (Price 1999). To a limited extent this function can be served by automated processes, such as withdrawal reflexes and conditioned responses, but ultimately it must involve the full range of complex cognitive, emotional and behavioral resources available to the individual. Consequently pain is defined as a *conscious* experience, whereas “nociception” refers to the objective response of the nervous system to noxious stimulation (Price 1999). Though conceptually different, pain and nociception are normally closely related. For instance, the correlation between pain ratings and brain potentials evoked by different stimulus intensities ranges from 0.60 to 0.80 in within-subjects studies (Carmon et al. 1980). Under certain circumstances, however, nociception may occur without pain, as during hypnotic analgesia where evoked potentials may persist in the absence of pain (Friederich et al. 2001), or pain may occur without nociception, as is presumed to be the case with “psychogenic” pain (Robinson 2007). Such exceptions aside, though brain activity and other psychophysiological measures can provide some indication of pain levels at the group level, there is general agreement that the only valid and reliable method of assessing pain in the individual is therefore direct inquiry by means of questionnaires, pain rating scales, and similar instruments (Turk and Melzack 2007). Strictly speaking it is therefore impossible to demonstrate that a patient is lying about or exaggerating his/her pain, or to know the degree of pain experienced by an animal or a child that cannot communicate. Rightly or wrongly, inferences are nevertheless made, based on observable behavior, prior knowledge of the patient, and knowledge of the assumed cause of pain.

Pain is the primary reason for visits to general practitioners in nearly 30% of cases (Hasselstrom et al. 2002), and is among the most important initial symptoms considered in diagnosis. The reliability and validity of pain, as a sign of underlying disease, is therefore of crucial importance to medical diagnosis. This is most dramatically illustrated by rare cases of congenital insensitivity to pain. These patients may bite part of their tongues or lips off, suffer bodily harm without noticing, and, typically, die from undetected concomitant infections (Indo 2004). A more common example is unrecognized (“silent”) myocardial infarction, where reduced pain sensitivity or complete insensitivity to cardiac pain is thought to be

responsible for heart attacks not being noticed by the patient (Sheifer et al. 2000). However, the major problem of pain is its presence and not its absence. Pain becomes a problem when it occurs without cause, when it is disproportionate with its cause, or when it persists after all relevant behavioral and medical actions have been taken to rectify the condition. In these cases pain loses its functional role, and is purely a source of suffering. It is in this sense that pain is a problem of epidemiological proportion and possibly the most widespread, costly and debilitating medical issue in developed countries today.

1.2. THE PROBLEM OF PAIN

According to the *Pain in Europe* survey, 19% of the adult European population and an astounding 30% of the adult Norwegian population suffer from chronic pain (Breivik et al. 2005). The latter finding is supported by two other Norwegian studies reporting a prevalence of 24.4% and 28.7% (Rustoen et al. 2004; Statistics Norway 2005). Though these numbers may seem high, they most likely underestimate the true prevalence, since hospitalized patients and patients in nursing homes were not included. The prevalence of most chronic pain conditions increases with age, and for nearly all pain conditions it is higher among women than men (LeResche 1999). Muscular-skeletal pain conditions were registered a primary diagnoses in 46.0% of the sick-leave, 35.8% of the disability, and 40.2% of the rehabilitation compensation covered by Norwegian national social security in 2005 (Rikstrygdeverket 2006). The cost of this coverage was 30.7 billion NOK or slightly more than half the total cost of all public hospital treatment that year. This figure does not include other causes of pain; treatment and medication; costs carried by the private sector, such as the first period of sick-leave and private insurance compensation; and indirect costs such as reduced tax income and lost productivity.

In addition to putting a large number of people out of work, pain has serious consequences for the individual's well-being. Depression and anxiety are far more prevalent among pain patients than in the general population. For instance, a large-scale population based study of arthritis, migraine, and back pain reported odds ratios for co-morbid depression, panic attacks, and generalized anxiety disorder ranging from 2.06 to 3.20 after controlling for sex and demographic variables (McWilliams et al. 2004). Suicide rate among pain patients is at least doubled, compared to the general population (Tang and Crane 2006). The WHO Collaborative Project of Psychological Problems in Primary Care found that whereas prevalence of chronic pain was 8.6% among patients without anxiety or depression, it was 32.4% among patients with depression, 35.3% among patients with anxiety, and 47.2%

for patients with both anxiety and depression (Sartorius et al. 1993). Of persons reporting pain lasting 6 months or more, 29% report having been diagnosed with depression by their doctor as a result of their pain (Breivik et al. 2005). Though the direction of causation between pain and psychiatric conditions is still a matter of debate, and most likely there is some degree of bi-directionality, it seems likely that pain is a major contributing cause of depression and anxiety in the population.

1.3. INDIVIDUAL DIFFERENCES

Pain is normally associated with physical trauma or disease, but this relationship is tenuous. For instance, among rheumatoid arthritis patients inflammation and other measurable physiological parameters are uncorrelated with pain intensity (Hagglund et al. 1989), untreated pain after arthroscopic knee surgery varies from no pain to severe pain (Rosseland et al. 2003), and several studies have failed to find an association between the invasiveness of breast surgery and acute post-surgical pain (Montgomery and Bovbjerg 2004; Katz et al. 2005). Though some conditions may be more painful than others, the variation between individuals suffering from the same condition is greater by far than the difference in painfulness across conditions, as illustrated in Fig. 1. Certainly it can be argued that this is no more unusual than the fact that the same disease has different outcomes for different patients. After all, it is hardly a major revelation that some patients survive breast cancer and others do not. However, though it may not be a major revelation, it is an important *observation*. Just as we would like to know the factors determining death or recovery from breast cancer in the hope that this may lead to better treatment strategies, understanding the causes underlying individual differences in pain may be crucial to its prevention and treatment, and to the utility of pain in diagnosis. There are several possible explanations for the apparent lack of correspondence between cause of pain and reported pain, and we will briefly consider each in turn.

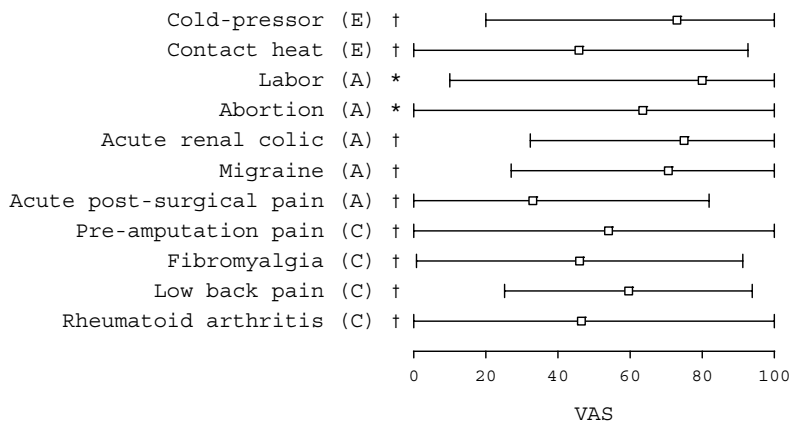


Fig. 1. VAS pain intensity ratings for acute pain (A), chronic pain (C), and experimental pain (E). Where available the median and range is shown (*), covering 100% of the study population. Where the range was not given the mean \pm 1.97 standard deviations is shown (†), which encompasses 95% of the population assuming normal distribution. Means and standard deviations were pooled for study groups that did not differ significantly. The following studies were included: cold-pressor pain (N=70) (Pud et al. 2004), contact heat pain (N=148) (Wise et al. 2002), labor pain (N=100) (Chao et al. 2007), abortion (N=40) (Pud and Amit 2005), renal colic (N=110) (Engeler et al. 2005), migraine (N=113) (Cete et al. 2005), pre-amputation pain (N=35) (Nikolajsen et al. 2000), post-surgical pain (N=77) (Rosseland et al. 2003), fibromyalgia (N=277) (Staud et al. 2006), low back pain (N=161) (Bannwarth et al. 2005), and rheumatoid arthritis (N=100) (Pollard et al. 2006). The studies were selected unsystematically and no attempt was assess the quality of the studies beyond the methods used in pain measurement. Subjects had not received analgesic medication at the time of measurement in the following studies: labor, post-surgical pain, cold-pressor, and contact heat. Pain ratings for migraine patients were registered before analgesic treatment, but use of medication prior to admittance was not controlled for.

Pathology

Even if every effort is made to measure all relevant disease characteristics, there is no way of knowing whether important parameters have been overlooked or are unknown. According to this view, characterizing certain pain syndromes as diffuse, or the patient's suffering as disproportionate with its physical cause, reflects lack of knowledge of the true causes of pain, rather than characteristics of the patient pain perception or reporting. A variant of this interpretation is that the disease or injury, though initially the same, develops differently dependent on the patient's physiological condition or genetic disposition. In either case, the understanding is that variance in reported pain reflects actual differences in the cause of pain, and is not a feature of pain perception itself. Though one cannot deny the logic of the argument, and undoubtedly better prediction of pain could be achieved through better

description of pathology, there are at least two good reasons to doubt that this is the only or even a major explanation of individual differences in pain. First, as shown in Fig. 1, large individual differences in reported pain are ubiquitous and are as large for diagnoses that are well defined, as for diagnoses with diffuse or unknown cause. Second, individual differences in reported pain are as large for experimental pain stimuli which are precisely controlled and identical for all subjects (Chen et al. 1989; Fillingim 2004).

Psychological factors

Such considerations have led to an alternative interpretation, which is that psychological characteristics of the patient are responsible for the observed differences. In fact a number of studies have shown that psychological dimensions, including depression, anxiety, and pain catastrophizing, are as good or better predictors of pain than physiological parameters (Hagglund et al. 1989; Dworkin et al. 1992; Ozalp et al. 2003; Montgomery and Bovbjerg 2004; Katz et al. 2005; Strulov et al. 2007). One problem with this view is that the prospective relationship between psychological dimensions and experienced pain, though significant, is normally not strong, explaining 10% or less of the variance. In other words, though psychological traits of the patient may be better predictors of pain than physiological characteristics of the disease, they are still not very good predictors. As mentioned above the relationship between pain and psychological states is often stronger in cross-sectional studies, but in these studies it is not clear whether states such as depression and anxiety are a cause or consequence of pain. Most likely causation is bi-directional, but given the weak and frequently inconsistent associations between personality traits and pain in prospective studies (Pietri-Taleb et al. 1994; Bisgaard et al. 2005; Asghari and Nicholas 2006), it seems unlikely that the psychological disposition of the individual is the major cause of the observed differences between patients.

Measurement error and bias

A third possibility is that differences in reported pain do not reflect differences in actual pain, but arise from idiosyncrasies in patients' interpretation of pain rating scales or from some patients exaggerating or underreporting pain (Dionne et al. 2005). Arguably the very high reliability of pain ratings of repeated experimental pain stimuli (Rosier et al. 2002) indicate that measurement error in the classical sense is not a major issue. Furthermore, triangulation studies, where subjects rate both experimental pain stimuli and clinical pain, show that subjects use pain rating scales in a consistent manner (Price et al. 1983). The issue, however, is to what degree there is scaling invariance across subjects, e.g. does what one

person denotes as “strong pain” correspond to other persons’ definition of the same term. This issue is not unique for pain and is ultimately a philosophical issue which cannot be conclusively resolved by empirical studies. However, it can be approached empirically if certain assumptions are made. One approach was used in a PET study of pain-related brain activity where it was shown that brain activity during pain stimulation was greater for pain sensitive than for pain tolerant subjects (Coghill et al. 2003). Assuming that the observed differences in brain activity reflect pain, rather than the process of rating pain, this study shows that differences in *reported* pain reflect actual differences in *experienced* pain. However, the proportion of “true” score variance was not estimated, and given the small sample and the uncertain relationship between nociceptive brain activity and pain it is questionable whether such estimates would be of much value. A second approach was based on the assumption that pain rating scales, when used for rating different types of pain, are used in the same manner. If so, systematic bias in scale will increase correlation between ratings of different pain modalities. However, since correlation between ratings between different types of laboratory pain is frequently low, and sometimes approaches zero, it was argued that bias is negligible (Janal et al. 1994). By this reasoning pain ratings show a high degree of scaling invariance.

Pain sensitivity

The final perspective, which constitutes the major point of departure for this thesis, is that observed differences in clinical pain arise from individual differences in pain sensitivity. Support for this hypothesis comes from laboratory studies showing large variations in pain ratings of identical stimuli (Chen et al. 1989; Fillingim 2004). Though this demonstrates that large individual differences in pain sensitivity exist, it remains to be proven that the observed differences in sensitivity to laboratory stimuli are relevant to clinical pain. Yet there is some evidence that this may be so: Cross-sectional studies have found increased pain sensitivity among patients suffering from a variety of chronic pain conditions, including fibromyalgia (Carli et al. 2002; Petzke et al. 2003; Staud et al. 2003), low back pain (Giesecke et al. 2004b), cluster and tension headaches (Ladda et al. 2006; Schmidt-Hansen et al. 2007), irritable bowel syndrome (Rodrigues et al. 2005), and vulvodynia (Giesecke et al. 2004a). Measurements in these studies were made at unrelated anatomical sites (e.g. the hand for migraine patients) and/or unrelated stimulus modalities (e.g. heat pain sensitivity among fibromyalgia patients). Though this is hardly conclusive, since increased pain sensitivity may be a result rather than the cause of these conditions, it is highly suggestive and consistent with

the hypothesis. More recently prospective studies have emerged showing that increased pain sensitivity is associated with risk of developing chronic pain conditions (Diatchenko et al. 2005; Kasch et al. 2005; Tegeder et al. 2006), but these studies have been small and results must be considered preliminary. A final piece of evidence comes from studies of the relationship between blood-pressure and pain. Human and laboratory animal studies have documented that pain sensitivity to experimental stimuli is inversely related to both tonic and phasic blood-pressure (Ghione 1996; Campbell et al. 2003). In a large scale epidemiological study it was shown that the prevalence of headaches and of muscular skeletal pain was negatively correlated with resting blood pressure (Hagen et al. 2002; Hagen et al. 2005). Admittedly, evidence for the pain sensitivity perspective is not conclusive, but there is growing evidence suggesting that increased basal pain sensitivity is a contributing factor to the development and severity of chronic pain conditions.

1.4. ASSESSING PAIN SENSITIVITY

Pain sensitivity can be broadly defined as the relationship between a noxious stimulus and resultant pain. The assessment of pain sensitivity therefore requires a means of measuring relevant features of the noxious stimulus and of registering pain in the subject (e.g. a pain rating scale). For clinical pain conditions the noxious stimulus is the disease or trauma causing pain, which varies across subjects and can rarely, if ever, be completely measured and described. For clinical pain, individual differences in pain sensitivity are therefore confounded with individual differences in pathology. For this reason, precise measurement of pain sensitivity can only be performed in the laboratory setting where pain is induced by controlled and quantifiable experimental stimuli.

Measurement of pain sensitivity also presupposes a precise *concept* of pain sensitivity, amenable to operational definition in empirical terms. Unfortunately the concept of pain sensitivity is far from clear in the literature and problems related to its conceptualization have received too little attention. Three indices of pain sensitivity are commonly used: pain threshold, pain tolerance, and the magnitude relationship between stimulus and pain intensity, and we will discuss each in turn.

Pain threshold

Pain threshold refers to the lowest stimulus intensity that induces a painful sensation. It may be quantified directly in terms of the stimulus parameter (e.g. the temperature of a heat stimulus) or indirectly in terms of time-to-pain for stimuli that increase in intensity. Though this sounds straightforward, the measurement of pain thresholds is problematic. Unlike sensory modalities such as vision or hearing, experimentally induced pain is nearly always preceded by non-painful sensations such as touch, heat or cold. Furthermore, since pain typically lingers beyond the end of the stimulus, pain thresholds are hard to assess for descending stimulus intensities. Common methods of signal detection theory are therefore inapplicable for pain thresholds. In addition, clinical pain only becomes a problem when it reaches supra-threshold intensities, so the relevance of threshold measures for clinical conditions is questionable.

Pain tolerance

Pain tolerance refers to the amount of pain the subject is able to or willing to endure. Obviously this will depend on the subject's motivation which may or may not be considered a problem. A more serious issue is that nearly all studies that claim to measure *pain* tolerance actually measure *stimulus* tolerance which is a different matter all together. One example is the cold-pressor test, where most studies measure pain tolerance based on whether the subject is able to endure the stimulus for a given number of seconds (Chen et al. 1989). By this procedure a subject that endures 180 s with a final pain intensity of 40 on a 0-100 scale is classified as more pain tolerant than a subject who endures 170 s with a final pain intensity of 90, which is clearly incorrect since the former subject endured less pain. Measuring pain tolerance as stimulus tolerance confounds the amount of pain evoked by the stimulus with pain tolerance. Assessing pain tolerance in the true sense requires that pain intensity reaches tolerance levels for all subjects, which for most stimulus methods is impossible due to ethical and safety limitations.

Magnitude relationships

In its simplest form, magnitude relationships can be expressed as the level of pain induced by a fixed stimulus. Though this may work in small samples or as rough classification of high and low pain sensitivity, it is normally inadequate for describing pain sensitivity as a continuous trait in the population. This is because the variance in pain sensitivity among healthy individuals is so great that for most stimulus modalities no stimulus

intensity is both painful to all subjects and, at the same time, tolerable to all subjects. Using fixed stimuli will therefore fail to discriminate between the most pain sensitive subjects, the least pain sensitive subjects, or both. A possible solution to this problem is to use variable stimulus intensities and to extrapolate data below or beyond the stimulus range. This is made possible by assuming a model describing the relationship between the stimulus intensity and pain. Thus a complex, but nevertheless tenable method of quantifying pain sensitivity as a continuous trait in the population is using stimulus-response function analysis (Price et al. 1994).

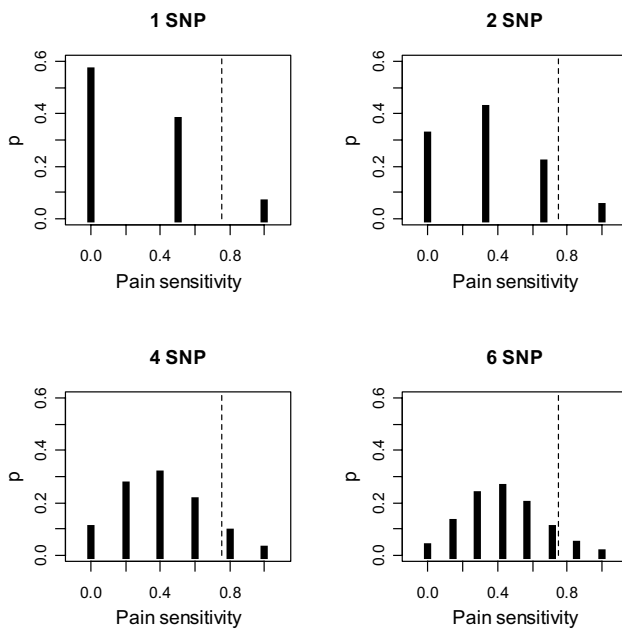


Fig. 2. Expected population distribution for phenotypes influenced by 1, 2, 4, and 6 SNPs. For simplicity, the model assumes two alleles, designated 'A' and 'a', at each SNP with probabilities 0.25 and 0.75 respectively. The phenotypic effect of each SNP is assumed to be equal. Allelic effects are assumed to be additive, i.e. that the phenotypic effect of 'Aa' lies midway between 'AA' and 'aa'. Environmental effects are not included in the model.

1.5. PAIN GENETICS

Pain is a complex phenotype involving processing at several levels in the nervous system, including transduction of stimuli to nervous activity at the receptor level; pain

regulation in the spinal cord and brain stem; sensory, cognitive and emotional processing in the cerebral cortex; and finally, the cognitive and motor activities involved in reporting pain (Price 1999). Each of these processing stages is potentially affected by genetic variation. Consequently, pain sensitivity is thought to be a polygenetic trait, meaning that it is influenced by single nucleotide polymorphisms (SNPs) at several genetic loci, with each SNP explaining a portion of the observed variance in the phenotype (Mogil and Devor 2004). Unlike phenotypes that depend on one SNP, polygenetic traits are continuously distributed in the population, as illustrated in Fig. 2.

The most obvious approach towards the study of genetic causes of individual differences in polygenetic phenotypes is to attempt to identify the genes involved. In humans, this is typically done by association studies, where relationships with SNPs or correlated sets of SNPs (known as haplotypes) in candidate genes are tested. To the extent that the role of the protein that the gene encodes is known, results from such studies can be directly related to physiological mechanisms, and can potentially lead to novel treatment strategies. Unfortunately, there are a number of problems with genetic association studies which make their utility less clear cut. The human genome includes 20,000-25,000 protein coding genes and several million SNPs. An undisciplined search for associations in this vast sea of possibilities carries a high risk of false positive findings even in large samples. The problem of statistical power is further aggravated if each individual SNP has a modest effect on the phenotype. As a result more than half of the reported genetic associations for polygenetic diseases fail to replicate in follow-up studies (Lohmueller et al. 2003). Though improvements in statistical techniques and larger sample sizes may reduce the problem of false positive findings, there is still reason to caution against uncritical acceptance of findings from association studies. Furthermore, though association studies can potentially identify SNPs that contribute to individual variation, they are uninformative about what remains to be identified, since the number of genes influencing the phenotype is not known a priori. One way of approaching this issue is through twin or family studies, which estimate the amount of variance in the phenotype that is due to genetic variation (heritability). Though the number of associated genes cannot be determined, knowing the heritability of the phenotype provides a benchmark for assessing the progress of association studies in identifying the genetic variance of the phenotype. Heritability studies can also determine the degree to which phenotypes are genetically distinct or related, which can be of value for selecting candidate genes, for determining the processing stage at which genes have their impact, and for making informed choices about whether to aggregate measures in genetic studies.

At the time when this study was initiated, information about genetic mechanisms in pain sensitivity came mainly from animal studies. SNPs in a number of genes had been identified as contributing to differences in pain sensitivity among rodents, and some of these had also been shown to predict related variables, such as analgetic response to endogenous and exogenous opioids (Mogil 1999). Comparison of different animal strains indicated heritabilities ranging from 30 to 76% for various pain assays (Mogil et al. 1999a; Mogil et al. 1999b; Lariviere et al. 2002), and cluster analysis identified at least three and possibly five genetically distinct classes of pain in mice (Mogil et al. 1999b; Lariviere et al. 2002). Pain sensitivity was also shown to be genetically related to swim-stress analgesia and to opioid analgesia, possibly indicating that part of the genetic variation was related to opioid pain-regulatory mechanisms (Elmer et al. 1998; Mogil 1999). The only available human genetic study of pain sensitivity was a twin study of pressure-pain threshold which concluded that an insignificant portion (10%) of the variance in pain sensitivity was attributable to genetic factors (MacGregor et al. 1997). This stood in strong contrast to findings from animal studies, and to twin-studies showing considerable heritability for a number of clinical conditions (Battie et al. 2007; Larsson et al. 1995; Morris-Yates et al. 1998; Treloar et al. 1998; Hakim et al. 2002; Zondervan et al. 2005; Fejer et al. 2006). There was therefore reason to doubt whether the estimated heritability for pressure pain threshold is representative for pain in general. More recently a number of human genetic association studies have reported positive findings. Pain sensitivity has been associated with the polymorphisms in the catechol-*O*-methyl transferase gene (*COMT*) (Zubieta et al. 2003; Diatchenko et al. 2005; Diatchenko et al. 2006), the μ -opioid receptor gene (*OPRM1*) (Kim et al. 2004; Fillingim et al. 2005; Lotsch et al. 2006), the GPT cyclohydrolase gene (*GCHI*) (Tegeeder et al. 2006), and the melanocortin-1 receptor gene (*M CIR*) (Mogil et al. 2005). However, several of these findings have failed to replicate in independent studies (Kim et al. 2004; Kim and Dionne 2007b), giving grounds for caution in drawing firm conclusions. One possible reason for the discrepancies among human association studies is that different experimental pain modalities were applied in different studies. If findings from animal studies also hold for human pain, one would expect genetic mechanisms to differ across pain modalities. Determining the degree of genetic correlation across pain modalities is therefore of importance for interpreting existing studies and for planning future studies.

1.6. THE FUNCTIONAL GENOMICS OF PAIN

Genetic research is not limited to identifying the genes contributing to individual variation, but ultimately attempts to explain the function of these genes at a mechanistic level. The negative correlation between pain sensitivity and opioid analgesia among laboratory mouse strains has led many human genetics studies to focus on genes that are directly or indirectly related to the opioid system. However, drawing a direct analogy from laboratory animals to human subjects may be problematic. Though low-order peripheral and spinal pain regulatory mechanisms may be similar, human pain is also modulated by high-order processes for which there are questionable or no analogies in animal models. Such high-order regulation includes hypnotic analgesia (Rainville et al. 1997), effects of emotions (Zachariae et al. 1991), and effects of attention (Petrovic et al. 2000). These functions are complex, most likely polygenetic, and poorly understood at a biological level. If high-order regulatory functions are a major target of genetic variation, the functional genomics of human pain may prove challenging to elucidate. Thus a question of considerable interest is to what degree genetic influences on human pain sensitivity act through high-order functions, and to what degree they act through peripheral and spinal mechanisms that are more amenable to translational research.

A common feature of high-order regulatory mechanisms is that these appear to be driven by endogenous states, whereas low-order processing stages tend to be stimulus driven. One tentative assumption about high-order pain regulation is therefore that these effects will tend to be less dependent on pain modality than low-order mechanisms of the nociceptive system. Based on this assumption one would expect genetic factors influencing pain through high-order regulation to be the same across pain modalities. A low degree of genetic commonality between different types of pain could therefore be taken as an indication that high-order regulatory functions are a minor concern for human pain genetics. However, since this argument rests on uncertain premises, the high-order pain regulatory mechanisms must ultimately be examined individually. Here we will focus on cognitive distraction.

1.7. COGNITIVE DISTRACTION

Cognitive distraction from pain entails distracting attention away from pain by performing a concurrent cognitive task (Eccleston 1995). This intervention has been the subject of extensive research in experimental pain studies, and is frequently a component in cognitive behavioral pain therapy. That cognitive distraction is effective in reducing brief experimental pain has been documented in numerous experimental studies using pain ratings

and/or brain activity as outcome measures (Hodes et al. 1990; Petrovic et al. 2000; Veldhuijzen et al. 2006). This effect is most commonly explained in terms of the resource allocation model of attention (Eccleston and Crombez 1999). According to this model, attention is a limited resource and allocation of attention to one activity leaves less attention available for other activities. Allocating attention to a cognitive task will therefore reduce attention to pain. This model also predicts that the presence of pain will reduce the performance on cognitive tasks, which has in fact been shown in studies of chronic pain patients (Dick et al. 2002; Harman and Ruyak 2005). Cognitive abilities have moderate to high heritability (Rijsdijk et al. 2002; Kuntsi et al. 2006), so it is a reasonable hypothesis that the genetic factors may be of importance in determining the individual's ability to reduce pain by cognitive distraction. If so, the genes that influence the individual's ability to distract attention from pain may also influence tonic pain sensitivity. This is analogous to findings for opioids where analgesic effect is genetically related to tonic pain sensitivity (Mogil 1999).

2. STUDY AIMS

The main aims of this thesis were to:

1. Develop methods for quantifying pain sensitivity (Paper I & II)
2. Describe the variation in pain sensitivity (Paper I, II and III)
3. Estimate the contribution of genetic factors to individual differences in pain sensitivity (Paper II and III)
4. Determine to what degree genetic findings can be generalized across pain modalities (Paper II)
5. Estimate the contribution of genetic factors to individual differences in the analgesic effect of cognitive distraction (Paper III)

3. METHODS

3.1. SUBJECTS

Main study

The sample was, with small variations, the same for all three papers included. It was comprised of 189 subjects (78 males and 111 females, aged 23 to 35 years) recruited from the twin registry at the Norwegian Institute of Public Health (Harris et al. 2006), and included 53 identical (MZ) and 40 fraternal (DZ) twin pairs, and 3 twins whose co-twin was not examined. Paper I was written before the data collection was completed and included the first 175 subjects examined.

Control study

In addition to the main study, a control study was carried out to assess the test-retest reliability of the measures and to characterize the stimulus-response function for cold-pressor pain, as described below. The subjects in this study were 53 students recruited from the University of Oslo: 33 women and 20 men, aged 19 to 40 years.

Ethics and data security

The study was approved by the regional ethics committee and by the Norwegian Data Inspectorate. All subjects signed informed consent forms before the examination. Data that could be used to identify the subjects (name, date of birth, phone number, postal and e-mail address) were stripped from the main data file and stored on physically isolated media to secure the subjects anonymity.

3.2 MEASURES

The study was designed to address a range of topics beyond what is presented in this thesis. Only measures analyzed in the constituent papers will be described in detail.

Health screening questionnaires

Prior to the examination subjects filled out a health questionnaire used to exclude subjects with neurological disorders, psychotic disorders and substance abuse. On arrival, an additional health questionnaire was administered in order to exclude subjects that felt physically ill on the day of the examination, and subjects that had taken pain medication or

had drunk alcohol within the last 24 h. Further details on the application of inclusion and exclusion criteria are given in the constituent papers.

Pain measurement

Detailed description of the stimulus procedures are given in the constituent papers, and will not be repeated here. Briefly, pain testing was performed with cold-pressor stimulation (CP) and with contact heat stimuli (HP) presented in ascending and random order. The subjects used visual analog scales (VAS) to rate pain intensity (VAS-I) and discomfort (VAS-A) after each stimulus (Price et al. 1994). VAS-I and VAS-A ratings were highly correlated and only the results for VAS-I data will be presented here. Since HP stimulus temperatures and CP duration differed across subjects, data extrapolation techniques were used to compute indices of HP and CP sensitivity, as described in the constituent papers.

Cognitive tests

Cognitive tests served the dual purpose of measuring cognitive performance and of distracting the subject's attention from pain. Subjects were tested using the color interference condition of the Stroop Test (Stroop 1935) and a Working Memory Test consisting of immediate recall of five two-digit numbers.

3.3. EXPERIMENTAL DESIGN

An overview of the experimental design for the main study and the measurements used in each paper is given in Table 1. The procedure consisted of three blocks. In Block I, HP was given in ascending order. The primary purpose of this measurement was to calibrate HP stimulus temperatures used in Blocks II and III. Block I also included 180 s CP testing (not analyzed). In Block II baseline measurements of cognitive performance, 60 s CP, and random order HP testing were performed. In Block III pain stimulation and cognitive testing were performed concurrently in order to measure the effect of pain on cognitive performance and the effect of cognitive distraction on pain. The entire procedure took approximately 3 ½ h to complete. The control study followed a similar experimental design, with the exception that the cognitive tests were not included. The control study was conducted to provide estimates of test-retest reliability for CP, used in Paper II and III.

Table 1. Experimental design for the main study

	Item	Paper I	Paper II	Paper III
Preliminaries	Health screening questionnaire	X	X	X
Block I	HP - ascending order	X	X	
	CP - 180 s			
	Hypnotic susceptibility testing (~45 min)			
Block II	Working Memory Test			X
	HP - random order	X		X
	Color Stroop Test			X
	CP - 60 s		X	X
Break	Questionnaires (~45 min)			
Block III	HP - random order /w Working Memory Test			X
	CP – 60 s /w Color Stroop Test			X

HP = contact heat pain. CP = cold-pressor test. The Color Stroop Test (Stroop 1935) and Working Memory Test, which consisted of immediate recall of five two-digit numbers read at a rate of one per second, were included to tests effects of cognitive distraction on pain and to test the effect of pain on cognitive performance in Block III. Questionnaires completed during the break included the NEO-PI-R personality questionnaire (Costa and McCrae 1992), the Giessen Symptom Check List (Brähler and Scheer 1983) and questions related to pain and anxiety in connection with dental treatment. Hypnotic susceptibility was tested with the Experiential Scale of Hypnosis, an instrument that was developed for this study. Test order for Block II and III was randomized twin-pair wise, so that the same order was used for both twins in any given pair.

3.4. STATISTICAL METHODS

3.4.1. Stimulus-response function analysis

HP stimulus-response functions were modeled using Stevens' power function (Stevens 1961). The accuracy of this model in describing individual stimulus-response functions is documented in Paper I. CP stimulus-response functions were modeled by linear extrapolation,

as described in Paper II. Integrals of these functions (43 to 50°C for HP; 0 to 60 s for CP) were used as measures of pain sensitivity in Paper II and III in order to achieve continuous distribution of pain scores across the entire sample.

3.4.2 Heritability analysis

Heritability analysis was performed in Paper II and III. Since the statistical approach introduced certain innovations, a brief description of these methods is appropriate. The most common approach to twin analysis in contemporary publications is to define structural equation models describing the genetic and environmental relationships between co-twins and to use maximum likelihood optimization to estimate the parameters of the model (Posthuma et al. 2003). Analysis then typically proceeds by dropping model parameters and comparing fit between sub-models and the full model in order to arrive at the most parsimonious description of the data. This approach is not unproblematic, since it has been shown that significance levels and fit statistics based on difference in $-2 \log$ likelihood between models in heritability analysis are too conservative (Dominicus et al. 2006). This can lead to false negative results and incorrect rejection model parameters. Consequently, the analysis of sub-models was not performed in the analyses presented here. Instead, results were reported in terms of confidence intervals for parameters in the full model. These confidence intervals were calculated by bootstrap sampling (Efron and Tibshirani 1986), which is not dependent on $-2 \log$ likelihood differences and should therefore be more robust with respect to the above issue.

A second and more practical problem is that optimization is a heuristic method which can lead to incorrect results. Optimization entails trying out various parameter values in order to find the result under which the observed data has the highest likelihood of occurring. Since it is impossible to test every possible combination of parameter values, software algorithms use various heuristic methods to arrive at the correct solution. Unfortunately, there is no way of proving that the correct global minimum has been reached or whether the program has arrived at a local minimum. To test whether this was an issue for the software used here, multiple analyses were run with random parameter starting values. For univariate analyses the correct result or an error message was consistently reached in nearly all cases. For bivariate and multivariate analyses incorrect solutions were frequent, and replicating the global minimum could in some cases take several hundred trials. To minimize this source of error, each bootstrap sample was analyzed repeatedly with random starting parameter values until the lowest $-2 \log$ likelihood was replicated three times. This procedure is illustrated in Fig. 3.

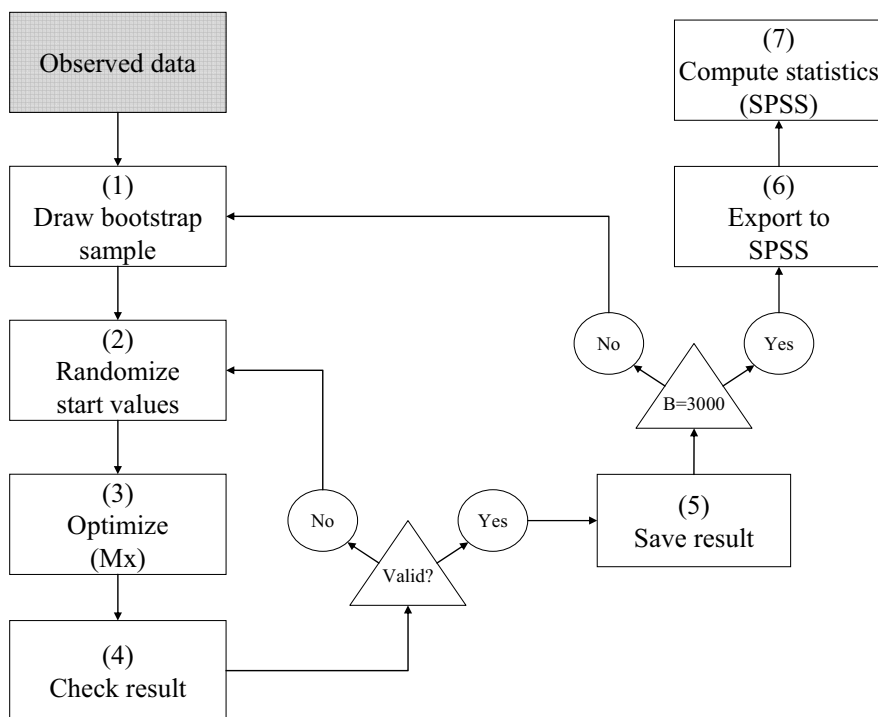


Fig 3. Flow chart of the heritability analysis. (1) A random sample of twin pairs is drawn with replacement, stratified by gender and zygosity. (2) Start values for the structural equation model parameters are randomized. (3) Maximum likelihood optimization is performed in Mx. (4) The result of the analysis is checked for error messages and for replication. The replication check entails that the lowest $-2 \log$ likelihood found must replicate three times with different start values. Steps 2-4 are repeated until the replication check is passed. (5) The result is saved and steps 1-5 are repeated until 3000 bootstrap samples have been analyzed. (6) The data are exported to SPSS. (7) Indices are computed for each sample, and confidence intervals and other statistics are estimated.

3.4.3. Software

Statistical analysis was performed with SPSS version 14.0 (SPSS Inc.), R version 2.3.1 (R Development Core Team 2007), Mx version 3.2 (Neale et al. 2002), and with proprietary software written by the author. Graphics were produced with Sigmaplot version 10.0 (Systat Software, Inc.), and R version 2.3.1. Proprietary software was written in Assembler code, C, and C++, using the (somewhat antiquated) Borland C compiler version 3.1 for DOS (Borland International, Inc.). Software written for this study encompassed approximately 40 programs,

ranging in size from small utility programs to large-scale data analysis and data recording tools encompassing several thousand lines of code. The examination of the twins was programmed in its entirety, including computer assisted interview for questionnaire items, computerized VAS scales, randomization and timing of stimuli, cognitive testing, online registration of blood-pressure, etc. Other major programs covered curve fitting, bootstrapping procedures and reliability analysis of heat pain stimulus-response functions, and added bootstrap functionality for structural equation model analysis.

4. SUMMARY OF PAPERS

4.1. PAPER I

The main purpose of this paper was to examine whether individual stimulus-response relationships for heat pain could be described in terms of Steven's power function, and to what degree data extrapolation produced reliable and unbiased results when this model was used. Though the power function has been used by several authors to describe stimulus-response relationships for group data, the application of this model to individual data has not been documented previously.

VAS-I and VAS-A ratings given by 175 subjects (104 women, 71 men) during ascending order (Block I) and random order (Block II) HP stimulation were analyzed. For each subject \times condition \times measure curve fitting was performed, using bootstrap sampling to estimate within-subject variability. Applying classical reliability theory, methods were developed to assess the reliability of the derived indices, including the exponent of the function, extrapolated VAS ratings and temperature estimates corresponding to fixed VAS values. Results showed excellent model fit. On the average, predicted values deviated from observed values by 2.08 VAS units for both scales in the ascending series, and 3.53 VAS-I units and 3.31 VAS-A units in the random series on a scale from 0 to 100. For VAS-I the average difference between observed and predicted group averages at individual temperatures was 0.34 (range = -0.60 to 0.52) in the ascending series and 0.98 (range = -1.78 to 1.65) in the random series, indicating minimal bias in the model. Results for VAS-A were similar. The reliability of VAS estimates was ≥ 0.93 within the 43 to 50°C stimulus range and for the ascending series it remained so when extrapolating several degrees upwards. It was also notable that predicted scores had higher reliability than the observed values. The reliability of temperature estimates corresponding to VAS ratings 0 to 100 was also satisfactory (ascending series ≥ 0.93 ; random series ≥ 0.87). Power function exponents showed good reliability for the ascending series (0.92 VAS-I; 0.91 VAS-A), but not for the random series (0.69 VAS-I; 0.71 VAS-A). Inter-subject variability in pain ratings was large and accounted for 60% of the variance in pain ratings, whereas stimulus temperature (43 to 50°C) only accounted for 40%. The methods documented in this paper were applied in further analyses performed in Paper II and III.

4.2. PAPER II

In this paper we estimated the heritability of HP and CP pain intensity. We also examined the degree to which genetic and environmental factors are the same for both pain modalities. We estimated 60% heritability for cold-pressor pain and 26% heritability for heat pain, after correction for sex differences and measurement error. Sex differences accounted for 8% of the variance in cold-pressor pain, but were insignificant for heat pain. Measurement error accounted for 10% of the variance in cold-pressor pain and 1% of the variance in heat pain. The correlation between the phenotypes was 0.34 after correction for sex and measurement error. Genetic factors that were common to both pain modalities accounted for only 6% of the variance in cold-pressor pain and 3% of the variance in heat pain, whereas environmental factors common to both pain modalities accounted for 5% of the variance in cold-pressor pain and 8% of the variance in heat pain. The remaining variance was explained by genetic and environmental factors that are specific to each phenotype. We conclude that the two pain modalities are mainly distinct phenomena from both a genetic and environmental standpoint. These findings are of obvious relevance to research on pain genetics, where the indiscriminate aggregation of pain measures is not to be recommended. In addition, our findings indicate that biased use of pain rating scales and other factors that influence pain sensitivity independent of pain modality account for a minor portion of the observed variance in pain sensitivity. The study therefore gives strong support to the notion that individual differences in pain ratings of identical stimuli or clinical conditions reflect actual differences in experienced pain.

4.3. PAPER III

In this paper we examined to what degree genetic factors influence a) the efficacy of cognitive distraction in reducing pain intensity, and b) the impact of pain on concentration. For each pain modality (HP, CP) and for each cognitive test (Stroop, Working Memory), bivariate heritability analysis was performed using data from baseline (Block I) and intervention (Block II) conditions (see Table 1). In addition, univariate analysis of difference scores (Block II – Block I) was carried out. The effect of cognitive distraction on HP pain intensity ($Z = -0.54$) was almost twice as large as on CP pain intensity ($Z = -0.31$). Conversely, the effect of pain on cognitive performance was greater for the Stroop Test ($Z = -0.77$) than for the Working Memory Test ($Z = -0.22$). Thus CP induced greater reduction in cognitive performance but was less affected by cognitive distraction, than HP. These data are consistent with a limited resource model of attention which states that attention allocated to

one task (pain) reduces attention available for allocation to another (cognitive performance). Stimulus-response function analysis was carried out for HP and indicated that the effect of cognitive distraction was the same in terms of percentage-wise pain reduction over all baseline pain levels. Thus the data indicate that the duration of the stimulus, rather than stimulus intensity, was the most likely cause of differences in effects over stimulus modality. The phenotypic correlation between conditions was high for both pain modalities and both cognitive tests, and approached or reached the theoretical limit given by the reliability of the measures. This finding alone gives substantial evidence that any lack of correlation between the two conditions is due to measurement error. The heritability analysis confirmed this result, since the genetic correlation between conditions was estimated close to or at 1.0 for all four analyses. We therefore conclude that the genetic influences on pain during baseline and on pain during cognitive distraction are most likely similar. The same conclusion was drawn for cognitive performance with and without concurrent pain, albeit somewhat less definitively for the Working Memory Test, due to the lower reliability of this measure. Analysis of difference scores confirmed these results, showing no or minimal genetic influence on the effect of intervention. Though three of the four pain variables analyzed differed from those examined in Paper II, reliability corrected heritability estimates for pain phenotypes were nearly identical to estimates reported in that paper: 59% for CP and 31% for HP. Reliability corrected heritability was 70% for the Stroop Test and 53% for the Working Memory Test. The most important conclusion to be drawn from this study is that though cognitive distraction has significant effect on brief experimentally induced pain, and though pain has significant effect on cognitive performance, variance in these effects is not at all or only minimally influenced by genetic factors. The study also gives one reason to question the efficacy of cognitive distraction for reducing long term pain, and raises concerns about pain as a confounder in neuropsychological testing.

5. DISCUSSION

5.1 INDIVIDUAL DIFFERENCES AND THEIR MEASUREMENT

In this study we have documented large individual differences in pain sensitivity as expressed by subjective pain ratings. For both pain modalities examined, pain tolerance for some subjects lay well below stimulus intensities considered non-pain by others, as illustrated for heat pain in Fig. 4. We have emphasized this point in all three papers because we believe it is an important observation, not because it was surprising. In fact, similar conclusions can be inferred from measures of distribution reported by most experimental pain studies. However, few studies have systematically described the range of variation as we have done. For instance, in planning this study we were unable to find normative data for heat pain sensitivity describing the population distribution of pain ratings at different stimulus temperatures. Consequently we underestimated the range of variation, and the upper temperature limit in our protocol was lower than desirable to differentiate between the least sensitive subjects. Though the emergence of pain genetics as a field of study has sparked interest in individual differences in pain sensitivity, our underestimation of the range of variation may still be symptomatic of a persisting disbelief in the magnitude and validity of these differences.

That pain ratings vary is an empirical observation. That this variation reflects actual variation in experienced pain is less obvious, but the contention has gained increasing support from brain imaging studies (Coghill et al. 2003; Schweinhardt et al. 2006) and studies examining relationships between pain modalities (Lynn and Perl 1977; Janal et al. 1994; Bhalang et al. 2005). Our argument in this respect is not original, but builds on the reasoning first set forth by Janal et al. (1994). They argued that systematic bias in pain ratings should result in correlation between ratings of different pain modalities. Since cross-modality correlations are generally low they concluded that bias was minimal. Our unique contribution has been to refine this analysis by estimating genetic and environmental sources of covariation separately. This makes it possible to address more specific hypotheses about genetic and environmental sources of error in pain ratings. One such hypothesis is that the use of pain rating scales is dependent on previous pain experiences (Dionne et al. 2005). However, since we find that environmental factors common to both pain modalities explain only 5% of the variance in cold-pressor pain and 8% of the variance in heat pain, previous pain experience seems unlikely to be a major factor influencing pain ratings. Thus we

conclude that pain ratings are valid measures of experienced pain and that the observed differences between individuals mainly reflect actual differences in pain sensitivity.

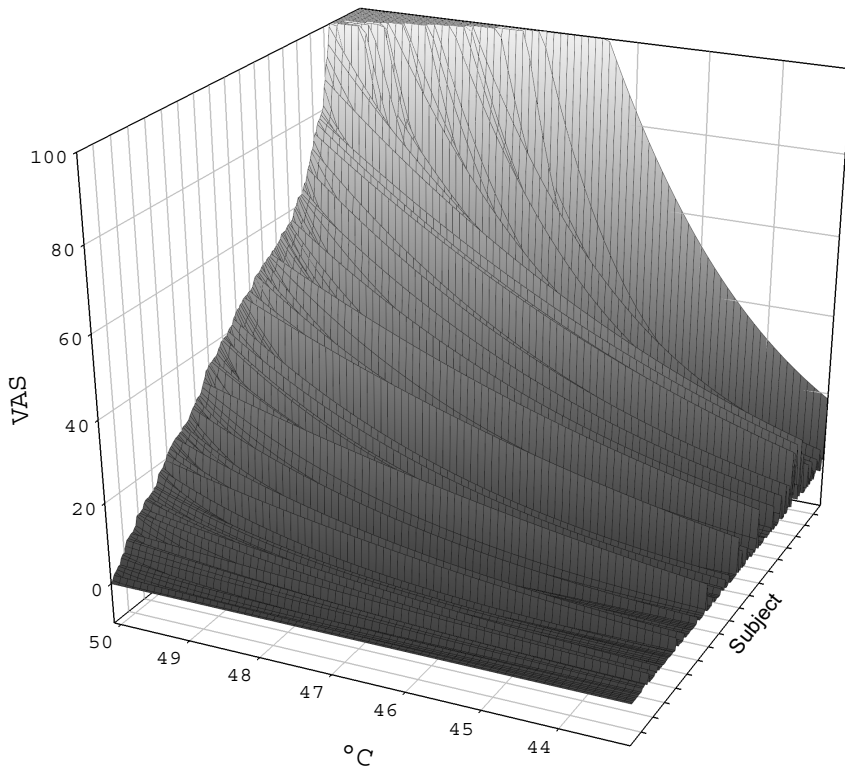


Fig. 4. Contact heat pain stimulus-response functions for individual subjects. Estimated VAS intensity from 43-50°C for 188 subjects in the ascending order condition (Block I) is shown. Estimates exceeding VAS = 100 were truncated.

Large individual differences in pain sensitivity present a number of challenges for pain research and for clinical practice. Among the most obvious consequences is that adequate pain measurement is difficult to achieve in experimental studies, due to floor and ceiling effects in pain ratings of fixed stimuli (censoring). In Paper I we developed methods for quantifying heat pain, using stimulus-response function analysis. In Paper II a somewhat simpler approach was used for cold-pressor pain. By these methods a continuous distribution in pain sensitivity was achieved, making parametric analysis possible. Undoubtedly, a number of different strategies could be used to quantify pain sensitivity as a continuously distributed

measure in the population, and the methods used in this study are perhaps better seen as illustrative rather than definitive. Nevertheless, using variable stimulus intensity combined with some type of empirically founded method of data extrapolation appears to be the only viable approach to avoid censoring in measurement of magnitude relationships in experimental pain sensitivity. Though our analysis was restricted to magnitude relationships, censoring is equally an issue for pain tolerance. The 180 s cold-pressor stimulus in Block I (not analyzed in the constituent papers) was tolerated by 56% of subjects, meaning that pain tolerance was not measurable for more than half the subjects. Heat stimulus temperatures were below tolerance levels for nearly all subjects in this study, but other studies typically report setting an upper temperature limit, indicating that tolerance levels for some subjects lie above safety levels necessary to avoid burns. The problem can be circumvented by dichotomizing variables and using non-parametric statistics, but at the cost of loss of power. For pain thresholds these issues may be less pertinent, but as discussed in the introduction above, threshold measures have other weaknesses and may be less relevant to clinical pain.

Lack of attention to issues of score distribution and censoring in pain research gives reasonable cause to question whether parametric analyses in experimental pain studies have been correctly applied and reviewers would be well advised to demand histograms of pain measures when assessing experimental pain studies. In addition to these technical issues, there also appears to be considerable conceptual confusion, as seen when threshold and tolerance measures are combined in aggregate scores (Diatchenko et al. 2005; Tegeder et al. 2006), or when VAS ratings of cold-pressor pain are analyzed without taking endurance time into consideration (Robinson et al. 2003). Future studies would gain by clarifying the concept of pain sensitivity, and paying closer attention to methods of quantifying pain. The consequences of poor pain measurement are aggravated when pain measures are used to measure change over experimental conditions in intervention studies. Most obvious is that subjects reporting no pain in baseline cannot report less pain in the intervention condition. If variables are dichotomized, pain reduction is effectively not measurable for subjects classified as pain tolerant. A more subtle point is that intervention effects may, and probably do, depend on baseline values. In Paper III we demonstrate that this is the case for the effect of cognitive distraction on heat pain, where pain reduction is a near constant percentage of baseline values. This application of stimulus-response function analysis exemplifies that the utility of the analysis justifies the effort expended on its execution.

Individual differences in pain sensitivity also represent a challenge for clinical diagnosis. Pain is among the most common reasons for seeking medical attention

(Hasselstrom et al. 2002), and the presence, location, and intensity of pain is among the most important symptoms guiding the general practitioner in early diagnosis. Initial diagnosis is therefore critically dependent on the accuracy of pain as an indicator of disease, which in view of the differences in pain sensitivity is dubious. If other diagnostic criteria, such as blood tests or MRI scans, showed the same degree of inaccuracy they would certainly be banned from use in clinical practice. This does not mean that pain is without value in medical diagnosis, but there needs to be awareness that pain is a highly unreliable indicator of pathology. Conversely, if the cause of disease is known, it is meaningless to state that the pain expressed is out of proportion with its cause. As shown in this study, a stimulus that is barely painful to one subject can be intolerable to another. In absence of compelling evidence to the contrary, pain must therefore be treated at face value. Moralizing about pain is an unproductive activity that builds on the misinformed view that pain is experienced similarly by all patients.

Our findings are based on pain ratings of experimental stimuli made by healthy individuals, and one should be cautious in generalizing to clinical settings where a number of different factors come into play. This would seem to be especially true in clinical cases where major financial consequences such as insurance compensation or eligibility for disability are at stake. Translating experimental findings to the clinic, let alone to the individual patient, will always be a challenging exercise. While this may be true, our evidence and the evidence of others indicate that subjects *can* use VAS scales to rate pain in an inter-subjective manner if given proper instruction, and skeptics would need to demonstrate a) in which situations this is not the case and b) the superior validity of alternative indicators of pain, before basing pain treatment on other criteria than subjective pain reporting.

A more troublesome issue is that our study and similar studies supporting the validity of subjective pain ratings as measures of experienced pain is performed within a limited context. For instance, we found that a number of subjects rated the cold-pressor stimulus as VAS = 100, while enduring the entire 60 s. In the control study, where VAS ratings were given at 10 s intervals we found that maximum VAS rating was reached by many subjects well before the end of the stimulus and maintained until the end. At face value this means that these subjects are voluntarily enduring the “the most intense pain imaginable” for an extended period of time. Apparently these subjects either have an extreme sense of duty or a very limited imagination as far as pain is concerned, or something else is going on. One possibility is that the anchor for the upper end of the VAS scale is contextually interpreted, e.g. that it is understood as “the most intense pain imaginable in this situation”. Thus, while our findings

support the use of VAS ratings for comparing pain between subjects within the same context, they do not necessarily imply that such comparisons are valid across contexts.

5.2 THE HERITABILITY OF PAIN SENSITIVITY

In Paper II and III we reported estimates of heritability for cold-pressor pain (60% and 59% respectively) and for heat pain (26% and 31% respectively). As discussed in Paper III, the difference in estimated heritability for heat pain reported by the two papers has to do with the methods used in correcting for reliability and does not reflect a substantive difference between results for ascending and random series presentation. The heritability of heat pain was significantly lower than for cold-pressor pain in this study, albeit marginally so. One interesting hypothesis about this difference is that cold-pressor pain may be a more stable trait than heat-pain. Random fluctuations over time that are unsynchronized between co-twins will increase the environmental component (E) in the analysis, but can be corrected for using two or more measurements widely spaced in time.

Apart from one twin study of pressure pain threshold (MacGregor et al. 1997), ours are to our knowledge the only reported heritability estimates of human experimental pain sensitivity and should therefore generate considerable interest. When this is said, the implications of these heritability estimates may be less important than would appear at face value. Obviously, our results show that a substantial portion of the variance in pain sensitivity is related to genetic differences between subjects. Identifying the genetic mechanisms involved would therefore appear to have importance beyond mere academic curiosity. However, though heritability estimates are helpful in determining whether genetic effects are sufficiently large to be of clinical importance, they are uninformative with respect to the likelihood of finding genetic associations for polygenetic traits. If the major portion of the genetic variance is caused by polymorphisms in a few genes, significant associations may be found even if the heritability is low. Conversely, if genetic variance is due to polymorphisms in a large number of genes, each of which has minor impact, false negative results may occur even in large studies of highly heritable traits. Thus the higher heritability for cold-pressor pain does not of itself imply that this phenotype is better suited for genetic studies than heat pain. The situation is somewhat different where genetic associations have been identified, as to some extent is the case for pain. In these cases, knowing the heritability of the phenotype provides a benchmark to which the variance explained by the identified polymorphisms can be compared. However, since heritability estimates are specific to the population from which the sample is drawn, and may depend on factors such as environmental exposures, age, and

ethnic composition of the sample, this type of comparison is strictly speaking only valid when carried out within the same study or at least among samples drawn from the same population.

The heritability of pain sensitivity in general or the higher heritability of cold-pressor pain in particular should not be misconstrued as evidence for individual differences arising at low-order stimulus driven stages of nociceptive processing, as opposed to high-order cortical modulation induced by endogenous factors, such as psychological states. Most human traits show significant heritability, and objectively measurable physiological traits with known biological mechanisms are not necessarily more heritable than diffusely defined psychological constructs measured by subjective reporting. For instance, heritability estimates for blood-pressure (Kupper et al. 2005) are typically similar to those reported for personality traits (Ebstein et al. 2007). Thus the heritability of pain sensitivity is in itself not relevant to distinguishing between low-order and high-order functions. Our tentative conclusions with regard to this issue are based on the genetic and environmental relationships between phenotypes, rather than on the heritability of the individual phenotypes, as discussed below.

5.3 GENETIC AND ENVIRONMENTAL RELATIONSHIPS

Heat and cold-pressor pain sensitivity show a phenotypic correlation of 0.32 in our study. It could be argued that different transformations were used to achieve normal score distribution for the two pain phenotypes and that this might have affected the magnitude of the relationship. However, the observed sex corrected correlation between untransformed values was 0.30 (data not reported elsewhere), which is virtually identical to our estimate for transformed values, so the results are not seriously effected by transformation. In Paper II the relationship between pain modalities is dissected into its constituent genetic and environmental components (see Fig. 5). This analysis essentially shows that both the genetic and the environmental factors creating variance in pain sensitivity differ for the two pain modalities. For the unique environmental components some difference is to be expected, since estimates of environmental influences include measurement error which is by definition uncorrelated across phenotypes. However, even if the test-retest correlations between baseline and distraction conditions are used as conservative estimates of the reliability, the predicted environmental factor correlation is 0.71 (data not reported elsewhere), whereas the estimated environmental factor correlation is 0.34 with a 97.5 % confidence limit of 0.50. It is therefore clear that environmental influences differ considerably for the two pain modalities, beyond what is predicted by measurement error alone. This issue is not pertinent to genetic relationships, where our findings show that only a minor portion of the variance is attributable

to genetic factors that are common to both pain modalities. Somewhat simplified this means that there are different genes involved in each phenotype, but strictly speaking the correct interpretation is that the relative impact of individual polymorphisms differs across phenotypes. Be that as it may, our evidence shows that pain genetics is modality specific, as has been demonstrated in animal research previously, although not for heat and cold, as is discussed in Paper II.

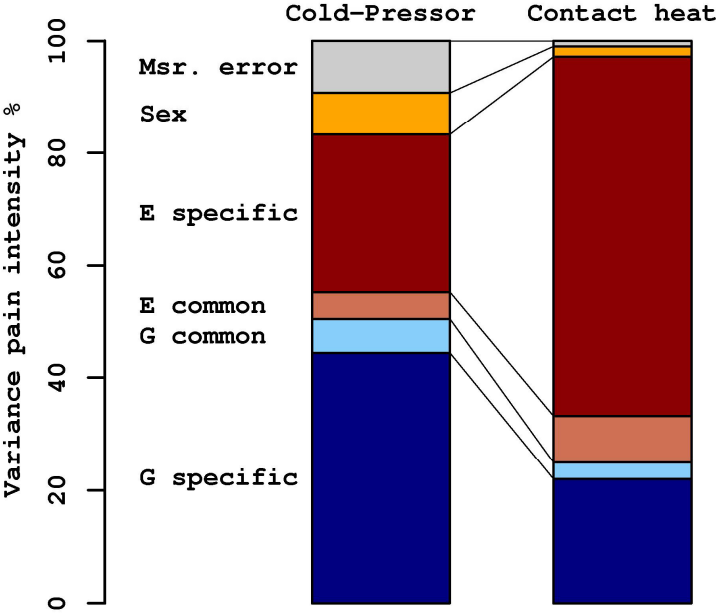


Fig. 5. Breakdown of variance components for contact heat pain and cold-pressor pain. Genetic (G) and environmental (E) effects are decomposed into components that are specific to each pain modality and components that are common to both pain modalities. Measurement error for cold-pressor pain was estimated as test-retest reliability in the control study. Measurement error for heat pain was estimated as internal consistency of scores within the same testing session. Reproduced and rendered in color with permission (Nielsen et al. 2007).

We argue that the lack of genetic and environmental commonality between pain modalities provides strong evidence for the lack of systematic error in the use of VAS scales to rate pain. The same argument can be extended to encompass a variety of factors that affect pain, irrespective of stimulus modality. It seems reasonable to assume that factors that influence pain at high-order stages of processing, such as personality, emotions, attention, and

the scaling of pain will tend to be independent of stimulus modality. The sex corrected correlation with neuroticism was about equal for cold-pressor pain intensity ($r = 0.16$) and heat pain intensity ($r = 0.20$) in this study, which is consistent with this hypothesis (data not reported elsewhere). If the hypothesis is true, it would mean that our estimates of variance attributable to environmental and genetic factors that are common to both pain modalities represent an estimate of the total contribution of all such late processing factors. Ultimately, however, these late processing factors will need to be examined individually as we have done for cognitive distraction.

On the strength of the above argument, it is tempting to conclude that modality specific genetic effects act on low-order stages of processing, rather than on mechanisms dependent on cortical processing. This conclusion is most likely premature. There are a number of differences between cold-pressor and heat stimuli used in this study and several of these differences may be relevant to high-order stages of processing. The cold-pressor stimulus involved longer stimulus duration, greater pain intensity, and larger stimulus area than heat pain testing. In addition a substantial increase in blood-pressure occurred in response to cold-pressor stimulation, which was not seen during heat stimulation. Though many of these differences affect nociception through spinal mechanisms, such as temporal summation and spatial summation (Price et al. 1992), they are also experienced subjectively and may result in differential activation of descending pain modulating pathways. To resolve this issue, larger studies will be needed where a range of stimulus modalities are examined, and where stimulus parameters such as duration and intensity are systematically manipulated.

The moderate genetic correlation between pain modalities implies that aggregating measures in pain genetics studies may be a bad idea. This issue has recently been raised by Kim and Dionne (2007a) with respect to Diatchenko, et al.'s study of temporal mandibular joint dysfunction (TMJD), where threshold and tolerance measures were aggregated within pain modalities (Diatchenko et al. 2006) and across pain modalities (Diatchenko et al. 2005). In response to criticism the authors of the study argued that TMJD patients have elevated scores on a number of pain measures and that the use of an aggregate measure reflects the clinical syndrome more accurately than individual measures of pain sensitivity (Diatchenko et al. 2007). While conceding that this may be the case, it does not necessarily follow that genetic risk for developing TMJD follows the same pattern. It is quite possible that elevated scores on certain measures are genetically associated with risk for development of TMJD, whereas elevated scores on other measures are environmentally associated with risk for development of TMJD. Even if all pain measures examined are associated with genetic risk

factors for TMJD, it is not necessarily true that the genetic risk factors are the same for all pain measures. Finally, it is possible that hypersensitivity to some pain modalities is prospectively associated with TMJD, whereas hypersensitivity to other modalities develops after the onset of the syndrome. The authors also argue that pain threshold and pain tolerance are highly correlated within the same pain modality and load on the same factor when analyzed with factor analysis, thereby implying that the two measures are expressions of the same underlying phenomenon. However, it remains to be shown that this is the case for all clinical conditions. For instance, in certain types of hearing impairment (recruitment) thresholds may be increased with unchanged or increased sensitivity to supra-threshold stimuli, resulting in loss of dynamic range (Brunt 2007). There is no reason to assume that similar phenomena do not exist in clinical pain conditions. Since the Diatchenko et al.'s study only identified 16 new cases of TMJD it seems premature to conclude on these issues. However, their follow-up analysis (Diatchenko et al. 2006) showed that only one of the pain modalities examined was positively associated with the COMT haplotypes examined, which is in line with our finding of modality specific genetic effects.

Whether to aggregate measures or not depends on the purpose of the study and the assumptions made. If the study aims to identify genes that are common to all pain phenotypes, then aggregation of several distinct pain measures may in fact be the best approach. It can be argued that all experimental pain stimuli involve processes that are not specific to pain processing. For instance, pressure pain threshold may depend on muscle size, cold-pressor pain may conceivably depend on the amount of sub-dermal fat affecting thermal transfer to deeper tissues, and heat pain could depend on the ratio of the stimulated skin area to the total skin area of the body which might be related to the number of nociceptive fibers activated. Such spurious factors are typically not the object of study in pain genetics and could be factored out by combining pain measures across a wide range of stimulus modalities. However, the case rests on the assumption that a major portion of the variance in pain ratings of experimental stimuli is due to factors that are not inherent to pain processing – an assumption for which there is little concrete evidence and which, if true, would invalidate much of the experimental pain research to date. As of now, the lack of large scale prospective studies demonstrating predictive value for various experimental pain measures, and the lack of human heritability studies examining the genetic relationships among multiple pain modalities makes an informed choice in this matter difficult. In view of our finding that genetic factors that are common to both heat and cold-pressor pain account for a minor

portion of the genetic variance, the use of aggregate measures seems less likely to achieve success.

5.4 EFFECTS OF ATTENTION

Though both cognitive performance and pain sensitivity are heritable traits we did not find that the effect of one on the other was heritable to any significant extent. This does not mean that pain is unaffected by attention, in fact we found that heat pain was reduced by 40-50% by cognitive distraction. Rather, our findings show that individual differences in this effect are not dependent on genetic factors. On this basis we conclude that differences in subjects' ability to ignore pain are unlikely to contribute to the heritability of pain sensitivity.

Our findings were based on the analysis of genetic correlations between conditions, and the analysis of difference scores. Since the latter typically have low reliability, it is of interest to examine how this may have influenced our results. The reliability of a difference score (r_d) is given by:

$$r_d = \frac{[(r_{xx} + r_{yy})/2] - r_{xy}}{1 - r_{xy}}$$

Where r_{xx} is the reliability of the first measure, and r_{yy} is the reliability of the second measure, and r_{xy} is the correlation between the first and second measure.

It follows from this definition that the reliability of a difference score approaches zero when the correlation between the two measures approaches their reliability. Consequently the difference score may have low reliability either because the measures are unreliable, or because the two measures are highly correlated. Given the high reliability of our pain measures, it is the latter issue which is at stake. For cold-pressor pain the test-retest reliability was 0.90 and the correlation between conditions was 0.85, yielding a very low reliability of 0.33 for the difference score. This would have major impact if the purpose of our analyses were to compare this difference score with another variable, such as drug dosage. However, since our purpose was to decompose the variance in the difference score, the low reliability simply informs us that 67% of the variance is stochastic. If genetic differences between individuals had been a major determinant of the efficacy of cognitive distraction in reducing pain, then the correlation between conditions would have been much lower, and the reliability of the difference scores much higher than we have found.

Our results are consistent with the limited resource model of attention (Eccleston and Crombez 1999) in that the pain modality that was least affected by cognitive distraction had the greatest effect on the subject's cognitive performance, and visa versa. For heat stimuli, pain reduction was a near constant percentage of baseline pain, so the greatest pain reduction in absolute terms is to be expected for the most intense stimuli. Though this may sound promising in terms of therapeutic applications, cold-pressor pain was only marginally influenced by distraction. On this basis we propose that cognitive distraction is mainly effective for brief stimuli, and that the subject is unable to ignore pain for extended periods of time. In the competition for limited attentional resources, it seems that pain predominates over willful cognitive activities, which is hardly surprising given the crucial importance of pain to the survival of the organism. If our conclusions are true, the usefulness of cognitive distraction for treating persistent clinical pain is questionable.

Though the effect of pain on cognitive performance was not the major focus of this study, our findings give reason for concern with regard to the validity of neuropsychological testing in pain patients. Though the reduction in cognitive performance during cold-pressor testing was not large in absolute terms, it is sufficient to shift test results from the normal to the pathological range for a substantial number of subjects. But more important than the diagnostic issue are the possible implications that reduced cognitive function might have for quality of life among chronic pain patients. Minor reduction in core cognitive functions, as seen in mild head injury, is frequently accompanied by considerable fatigue (Lezack 1995) and one might usefully speculate whether reduced cognitive functioning and associated mental fatigue contribute to the social isolation, withdrawal from activities, and depression experienced by many chronic pain patients (Breivik et al. 2005). Despite the considerable focus on cognitive interventions against pain, the cognitive consequences of pain have received little attention in the literature. Knowledge about which cognitive functions are reduced and how this impacts on quality of life is at best limited.

5.5 LIMITATIONS

The most important limitation of this study is the small sample size. Though this has not been a major issue for the main analyses performed, where confidence intervals are acceptable, it has severely limited the analyses that *could* be performed. For instance, an attempt was made to determine whether the relationship between neuroticism and pain was indeed mediated by genetic and environmental factors that were common to both pain modalities. Though the results of the analysis were consistent with this hypothesis, the

confidence intervals were too large to merit publication of these data. As noted in Paper II, sample size also prohibited the analysis of sex specific genetic effects. In other words, though the sample size limited the issues that were addressed, it was sufficient to answer the main study questions with reasonable confidence. The second major limitation was that the study only tested two stimulus modalities, rendering conclusions in terms of neural mechanisms speculative. It is hoped that these limitations will be rectified in future studies.

5.6 FUTURE DIRECTIONS

Historically, experimental pain research and clinical pain research have to a large extent lived in separate worlds. Though progress has been made since Beecher and Hardy debated this issue in the 50's (Beecher 1956; Hardy 1956), translation of results from one domain to the other is still problematic. Laboratory pain stimuli may be referred to as "models" for clinical pain conditions, but the analogy is typically anecdotal and unsupported by hard evidence. Understanding the relevance of specific experimental pain modalities to specific clinical pain conditions is therefore of prime importance. Though recent prospective studies have shown that experimental pain sensitivity may predict later development of chronic pain conditions (Diatchenko et al. 2005; Kasch et al. 2005; Tegeder et al. 2006), these studies have been small, identifying less than 20 clinical cases in the follow-up period. Large scale prospective studies, describing the relationship between experimental pain sensitivity and clinical pain will be needed to demonstrate the clinical relevance of experimental methods.

Equally important to genetic pain research is furthering the understanding of the genetic relationships between different stimulus modalities. Animal studies have found that there are at least three and possibly as many as five genetically distinct classes of pain stimuli (Mogil et al. 1999b; Lariviere et al. 2002), but the relevance of these studies to human pain is questionable. Animal studies rely primarily on behavioral pain thresholds, such as paw withdrawal or tail-flicks. Supra-threshold stimuli are used to a lesser extent, and the dependent measures, such as number of stomach writhings, are hardly analogous to intensity ratings made by humans. Factor analysis of multiple experimental pain modalities in humans has identified four distinct factors (Hastie et al. 2005), indicating that pain is as heterogeneous in humans as it is in laboratory animals, but the genetic relationships between multiple pain modalities remain to be elucidated. In this study we have shown how genetic relationships between different pain modalities can be examined without knowledge of the specific genes and SNPs involved. Data from a larger twin-study testing a range of stimulus modalities and

manipulating parameters such as stimulus intensity and duration could be analyzed using genetic factor analysis to clarify which pain modalities are genetically related and which are not. Though candidate gene studies have made rapid progress, with a number of positive findings, further research would still profit significantly from this knowledge.

Finally, greater focus should be placed on the methods used in measuring pain in large scale samples. This includes both conceptual clarification and improved procedures for quantifying pain sensitivity across the entire range of variation. One of the biggest assets of experimental pain studies is precise stimulus control which cannot be achieved in many other areas of research. Unfortunately, the strong focus on stimulus control and on finding stimuli that selectively activate specific fiber types or spinal mechanisms has not been accompanied by the same level of sophistication when it comes to quantifying subject responses. This study has illustrated approaches for two pain modalities, but further studies will be needed to find good models for quantifying pain sensitivity for the wide variety of stimulus methods in common use.

6. CONCLUSIONS

The main findings of this study were:

1. Heat pain stimulus-response relationships for individual subjects are adequately described by Stevens' power function. The cold-pressor stimulus-response function can be approximated by linear extrapolation up to 60 s. In both cases, the integral of the function yields a continuously distributed and reliable score of pain sensitivity.
2. Pain intensity ratings of contact heat stimuli covered nearly the entire VAS scale (0-95). Individual differences accounted for 60% of the variance in pain ratings, whereas stimulus intensity (43 to 50°C) accounted for 40%. Cold-pressor pain ratings covered the entire VAS scale (0-100). No stimulus temperature (heat) or stimulus duration (cold-pressor) was both painful to all subjects and tolerable to all subjects.
3. Corrected for sex and measurement error, the estimated heritability for cold-pressor pain was 60% and for heat pain was 26%. Heritability for heat pain was marginally higher (31%) when corrected for lack of stability over experimental conditions. The heritability of heat pain was equal for random order and ascending order stimulus presentation.
4. The genetic and environmental factors causing individual differences in heat and cold-pressor pain sensitivity are mainly modality specific. Approximately 11% of the variance in pain sensitivity is explained by genetic and environmental factors that are common to both pain modalities.
5. Genetic factors have little or no impact on the efficacy of cognitive distraction in reducing pain. For heat pain, the reduction was a near constant 40-50% of baseline pain. Data indicate that cognitive distraction is less effective for longer pain duration. Pain produced significant reduction in cognitive performance. In absolute terms the reduction was small, but sufficient to confound neuropsychological test results.

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