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Genetic Factors in Social Pain

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Social exclusion, rejection, or loss are among the most profoundly impactful experiences that human beings undergo. This observation is consistent with the evolutionary perspective that underscores the significance of group living for human survival. In human pre-history, rejection or exclusion from the social group could be tantamount to a death sentence. Accordingly, complex systems for detecting, preventing, and responding to experiences of social pain would have adaptive significance. As such, there are likely to be a number of genetically-based biological regulatory systems involved in the experience of social pain.

As yet, there is not a field devoted to the genetics of social pain, and so the task of this chapter is to provide directions as to how such a field may be constructed. This chapter will progress in step-by-step fashion from the psychological level through the neurochemical to the genetic level. In the process, we will underscore the utility and promise of the genetic approach for furthering the understanding of social pain at both the psychological and biological levels.

As is described in other chapters in this volume, social pain is a complex, multi-faceted response to situations of real or potential relational devaluation (Leary, 2005; Williams, 2001). Therefore, identifying genetic contributions to social pain is likely to be facilitated by subdividing it into component processes, as there is unlikely to be a single gene influencing all the different forms and components of social pain (Kendler, 2005). For the sake of this discussion, we have chosen to restrict our focus to the areas of research on social pain that have received the most study with genetic methods, specifically the experience of social pain as well as processes associated with its counterpart, social support. Interwoven with this discussion will be a consideration of personality factors which are known to influence perceptions of both social pain and support. Finally, we will conclude with a discussion of how the early childhood environment interacts with genetic makeup to influence responses to social pain.

Genetic Contributions to Social Pain

Genetic Contributions to Social Pain: Twin Studies

The foundational assumption of this chapter is that there is a genetic contribution to social pain. The traditional first step for verifying this assumption has been the twin study. Using loneliness as a measure of social pain, researchers estimated that as much as 50% of the variance in the experience of loneliness may have genetic bases (Boomsma, Willemsen, Dolan,

Hawkley, & Cacioppo, 2005). Similarly, researchers have estimated that as much as 30% of the variance in the experience of social support stems from genetic factors, possibly involving the ability to construe one's social environment as supportive or the ability to attract a socially supportive network through social competence skills (Kessler, Kendler, Heath, Neale, & Eaves, 1992). Conversely, people high in neuroticism, prone to experiencing negative affect, or low in extraversion are less likely to construe their environments as socially supportive. These personality traits have a strong genetic basis, with estimates of the variance explained by genetic factors ranging from 30 to 60% (Fanous, Gardner, Prescott, Cancro, & Kendler, 2002). Although the evidence from these twin studies is not comprehensive, it is certainly suggestive that there is a genetic component to different facets of social pain. Hence, the next question becomes how does one identify specific genes associated with social pain processes?

One approach to solving this needle-in-the-haystack problem is to propose genetic hypotheses based on pharmacological and neurochemical studies of social pain that have been conducted over the last several decades. These studies have implicated the opioid, dopamine, serotonin, and oxytocin systems in social pain-related processes, and hence it is likely that variation in the genes controlling signaling within these systems are involved in social pain. Therefore, the following discussion centers on how variation in genes belonging to each of these systems is related to social pain and discusses each of these systems in succession.

Before beginning that discussion however, we should note that we have deliberately avoided technical genetic jargon to make the article more comprehensible for psychologists not trained in the physiological sciences. Nonetheless, several key terms need to be defined. When a portion of the DNA sequence is variable, it is referred to as a polymorphism, and the different forms of variation at this position in the DNA are referred to with the interchangeable terms, variant or allele. Each person has two alleles, and the combination of the two alleles is referred to as a genotype, which will be denoted with a slash (e.g. allele A/ allele B). For a more detailed primer on genetic variation and its applications to psychology, readers are referred to other sources (Robinson, 2005; Way & Gurbaxani, 2008).

Physical Pain and Social Pain Overlap: The Opioids

The hypothesis that social pain and physical pain share overlapping physiological substrates provides a useful foundation for identifying potential genes influencing the experience of social pain. Support for this hypothesis comes from multiple sources. At the neuroanatomical

level, brain regions that are involved in the unpleasant, affective component of pain (e.g. dorsal anterior cingulate; dACC) are also critically involved in the subjective distress of being excluded by peers (Eisenberger et al., 2003). Similarly, at the neurochemical level, drugs used to blunt physical pain (e.g., morphine) also appear to blunt the social pain of being separated from loved ones and attachment figures (Herman & Panksepp, 1978). Because morphine acts on the opioid system, particularly the μ-opioid receptor, Panksepp (1998) hypothesized that the tonic level of endogenous opioid activity is a barometer of the quality of the social environment. Consistent with this notion, monkeys being groomed by a conspecific exhibit increased brain levels of endogenous opioids that act on the μ-opioid receptor (Keverne, Martensz, & Tuite, 1989). In addition, inhibiting opioid transmission by blocking the μ-opioid receptor leads to increased need for affiliation (Martel, Nevison, Simpson, & Keverne, 1995).

Although there are still missing pieces to the puzzle, evidence in humans indicates that tonic levels of endogenous opioid signaling may also be related to social connectedness. According to one line of work, when participants recalled a time of separation distress (e.g., the ending of a romantic relationship), endogenous opioid transmission decreased (Zubieta, Ketter et al., 2003). Thus, imagined social pain decreases μ-opioid dependent signaling in humans, as in animal studies.

Based on the centrality of the μ-opioid receptor to social pain, the gene coding for this receptor is a logical starting place for identifying genetic contributors to social pain. Within the μ-opioid receptor gene (*OPRM1*), there is a polymorphism (A118G) that influences the amount of receptor produced (Zhang, Wang, Johnson, Papp, & Sadee, 2005). The less frequent G allele is associated with reduced receptor expression, relative to the A allele.

Preliminary analyses from our laboratory indicate that the G allele is associated with higher levels of self-reported rejection sensitivity (Mehrabian, 1994). Physiologically, the G allele carriers also had greater increases in salivary cortisol responses during the Trier Social Stress Test, a laboratory procedure in which subjects perform mental arithmetic and give a speech in front of an unreceptive audience. These associations of the G allele with greater response to social threat were primarily limited to females.

We have also recently assessed the relationship between the A118G polymorphism and social pain responses during a different laboratory measure of social pain. To study social exclusion within the confines of an MRI scanner, participants play an online, virtual ball-tossing game in which the other players gradually exclude the participant (Williams & Jarvis, 2006).

Previous research has found that this task induces feelings of rejection and invisibility, self-assessments that are positively correlated with neural activity in the dACC (Eisenberger, Lieberman, & Williams, 2003). Carriers of the G allele, relative to individuals with two copies of the A allele, exhibited greater ACC responses during social exclusion. Thus, across multiple measures of social pain, the G allele is associated with greater distress.

Further support for a role of the G allele in social-related distress comes from studies in the rhesus monkey. Fortuitously, this species has a very similar polymorphism (C177G) to that of humans in the μ-opioid receptor (Miller et al., 2004). Infants with the rare G allele exhibit greater distress vocalization upon repeated separation from their mothers and also spend more time clinging to their mothers upon reunification (Barr et al., 2008). In addition, the G allele has also been associated with alterations in basal plasma cortisol concentrations (Miller et al., 2004). This commonality of effects across species strongly indicates that this polymorphism is indeed functional and has broad effects on social pain.

With respect to the physiological overlap between social pain and physical pain, the A118G polymorphism has also been linked to differences in responses to physical pain in laboratory paradigms (Fillingim et al., 2005), as well as to dosage of analgesia required in clinical patients (Lotsch & Geisslinger, 2006). Thus, in addition to evidence provided at the neurochemical and neuroanatomical levels, there is now genetic evidence supporting the overlap between physical pain and social pain. This multi-method convergence strongly indicates that physical pain and social pain share common foundations and that each field can serve as a source of hypotheses for the other.

Methodologically, the genotyping approach for the study of social pain experience has several advantages over traditional neurochemical methods. For example, the required use of a PET scanner to measure opioid levels has obvious methodological limitations, and the less invasive genotyping approach (only a saliva sample is required) creates the opportunity to study opioid involvement in a greater diversity of contexts and paradigms. Hence, genotyping methods can be a useful complement to traditional research methods and thereby facilitate a better understanding of which components of social pain are governed by the opioid system.

Monoamine Oxidase A and the Social Pain Experience

In addition to the opioids, other neural systems are also likely to influence the experience of social pain. To identify one of these additional systems, we used a slightly different

theoretical approach than in the previous example that built upon the overlap between physical pain and social pain. We hypothesized that chronic social pain and clinical depression are likely to share some common physiological underpinnings, and accordingly, the endogenous targets of antidepressant drugs may influence sensitivity to social pain. One such target is monoamine oxidase A (MAOA), an enzyme that breaks down neurochemicals such as serotonin and dopamine (Shih, Chen, & Ridd, 1999), and that is present in high concentrations within the anterior cingulate (Ginovart et al., 2006), a brain region closely associated with the distress of social pain (Eisenberger, Lieberman, & Williams, 2003).

Within the gene coding for MAOA, there is a particular form of variation (referred to as the MAOA-uVNTR) that is associated with differences in the production of MAOA (Sabol, Hu, & Hamer, 1998). Using the previously-described social exclusion task in the scanner, our group found that the MAOA-uVNTR was associated with degree of exclusion-related neural activation, such that the individuals with the low expressing alleles had the greatest response within the portion of the dACC associated with self-reported distress (Eisenberger, Way, Taylor, Welch, & Lieberman, 2007). Thus, it appears that the MAOA gene also influences the degree of distress experienced in response to social exclusion.

In addition to providing a marker for individual differences in social pain, these data also provide an example of how genetics can help to clarify basic psychological processes. In epidemiological studies, men with the low expressing alleles of the MAOA-uVNTR are more likely to engage in aggressive and antisocial behavior than men with the high expressing alleles, particularly when exposed to maltreatment as a child (Caspi et al., 2002; Kim-Cohen et al., 2006). However, what is difficult to ascertain from epidemiological studies is the psychological pathways by which this polymorphism influences aggressive behavior. According to theories of aggression (e.g., (Buss, 1961), men with low expressing alleles may be more aggressive either because of a callous indifference to the suffering of others or because of a proclivity to overreact to social slights. In support of the latter social hypersensitivity hypothesis, our group found that both men and women with the low expressing alleles reported higher trait aggression and higher levels of trait interpersonal hypersensitivity (e.g., “How bothered do you feel about your feelings being easily hurt”). Importantly, the relationship between genotype and trait aggression was mediated by the dACC response (Eisenberger, Way, Taylor, Welch, & Lieberman, 2007). Thus, in light of the well-documented link between rejection and aggression (Leary, Twenge, & Quinlivan, 2006), it appears that those with a genotype predisposing them to feel greater social

pain are also more likely to behave aggressively, and this proclivity to reactive aggression appears to be due to hypersensitivity to social slights. The ability to study correlates of the same biological marker in both laboratory and epidemiological investigations is another benefit of the genetic approach and this integration will hopefully lead to improved understanding of the relationship between laboratory experiences of social pain and responses to real world events.

Dopamine, Catechol-O-methyltransferase (COMT), and Social Pain

One of the neurochemical systems influenced by the MAOA-uVNTR is the dopamine system (Ducci et al., 2006), and unlike most of the other neurochemical systems discussed in this chapter, it is possible to measure dopamine signaling in the human brain during social pain. Accordingly, rather than using pharmacological evidence to derive hypotheses concerning candidate genes in the dopamine system involved in social pain, one can use neurochemical evidence. Using a modified Trier Social Stress Task, researchers have found that the magnitude of the cortisol response to social threat is positively correlated with the magnitude of dopamine released in the striatum, as measured either during the actual stressor (Pruessner, Champagne, Meaney, & Dagher, 2004) or on a separate occasion using a pharmacological probe (Wand et al., 2007).

In light of this relationship between dopamine signaling and pain in a socially evaluative context, it is logical to ask if variation in genes regulating dopamine signaling also affect these pain processes. One gene with potential for such a role is the COMT (catechol-o-methyltransferase) gene, which codes for an enzyme that regulates levels of dopamine in the synapse. A particular polymorphism in the *COMT* gene (val^{158}met) leads to two different alleles that appear to affect activity of the COMT enzyme (Lotta et al., 1995). The reduced activity of the met allele is thought to lead to higher synaptic levels of dopamine, because the enzyme is less able to metabolize the neurotransmitter. Consistent with the evidence found for dopamine signaling during social stress, individuals with two copies of the met allele (met/met) have been found to have greater subjective and hormonal responses to social evaluative threat than individuals with other allele combinations (Jabbi et al., 2007).

In terms of other situations eliciting social pain, our group did not find a relationship between COMT val^{158}met and the magnitude of dACC response to social exclusion. Thus, it is possible that COMT is associated only with particular types of social pain experiences. Alternatively, the lack of an effect could be due to recently identified complexity in the COMT

gene. Polymorphisms in the vicinity of COMT val^{158}met also influence COMT activity (Nackley et al., 2006). Accounting for the effects of these additional polymorphisms has helped to clarify the relationship between COMT and physical pain (Diatchenko et al., 2006), so it may also prove useful to incorporate these additional markers into future social pain studies.

Although clarifying the role of *COMT* in pain processes requires more work at the genetic level, a psychological perspective may also help to clarify this relationship. There is an extensive overlap between anxiety levels and the experience of physical pain (Tsao, Lu, Kim, & Zeltzer, 2006). The *COMT* val^{158}met polymorphism has been linked to various anxiety-related constructs, with the bulk of the studies associating the met allele with heightened anxiety, particularly in women (Enoch, Xu, Ferro, Harris, & Goldman, 2003; Olsson et al., 2005). These studies have also been supported by functional neuroimaging studies, which show that met allele carriers have stronger responses to anxiety-eliciting stimuli within limbic brain areas than individuals with two copies of the val allele (Drabant et al., 2006; Smolka et al., 2005). This influence of the met allele upon anxiety suggests that social and physical pain studies of *COMT* should incorporate anxiety-related measures, because at least part of the effect of *COMT* on physical and social pain may be attributable to the propensity of anxious people to construe their circumstances as painful. Thus, these data underscore the valuable contributions that psychological perspectives can make to genetic studies.

It is worth noting that although this chapter has discussed each gene and its corresponding neurochemical system separately for the purposes of conceptual clarity, there is likely to be extensive interaction among them. This has been best demonstrated with respect to *COMT* and the opioid system. For example, *COMT* val^{158}met genotype is correlated with the degree of μ-opioid-related peptide release in response to sustained pain. Met/met individuals not only had the highest negative affect in response to pain induction, but they also had the least endogenous activation of μ-opioid signaling (Zubieta, Heitzeg et al., 2003). In addition, met/met individuals exhibit the greatest cortisol release in response to blockade of the μ-opioid receptor (Oswald, McCaul, Choi, Yang, & Wand, 2004). Similarly, *COMT* val^{158}met genotype also affects morphine dosage requirements (Rakvag et al., 2005; Reyes-Gibby et al., 2007). Thus, there are multiple psychological and neurochemical routes by which opioids in conjunction with *COMT* affect social pain. The ability to assess such interactions between multiple neurochemical systems has been greatly facilitated by genotyping methodologies, because multiple systems can

be probed more readily than has been possible with traditional neurochemical or pharmacological methodologies.

The *COMT* and *OPRM1* genes also point to an additional consideration that is likely to be of importance in genetic studies of social pain: sex differences. Based on findings in the physical pain literature (Craft, Mogil, & Aloisi, 2004), it has been hypothesized that sex differences in pain sensitivity may not just be the result of different levels of activity in a common pain system, but rather reflect different genetic organizations of the pain system in the two sexes. Thus, different sets of genes may be involved in social pain for women than for men. For example, most of the associations of *COMT* val^{158}met with physical pain and anxiety are limited to women (Diatchenko et al., 2005; Enoch, Xu, Ferro, Harris, & Goldman, 2003; Hagen, Pettersen, Stovner, Skorpen, & Zwart, 2006; Kim, Mittal, Iadarola, & Dionne, 2006; Olsson et al., 2005). In addition, although evidence is still preliminary, there may be opposite effects of the *OPRM1* A118G polymorphism in males and females, with the presence of the G allele being associated with reduced pain sensitivity in males and heightened sensitivity in females (Fillingim et al., 2005). Consistent with this latter finding, our preliminary data discussed earlier indicates that women, but not men, with the G allele exhibit greater increases in cortisol during social evaluative threat. Moreover, Chong et al. (2005) found in a primarily male sample that the G allele was associated with blunted cortisol responses during the same social stressor. Thus, the genetic approach may reveal that the pain system in the two sexes is constructed differently, which is an observation that would have been unlikely to have been made based on behavioral data alone.

Social Support

One of the most critical influences on the social pain experience is likely to be social support. High levels of daily social support are correlated with lower levels of dACC activation during a social exclusion experience and lower cortisol release during an experience of social evaluative threat, indicating a blunting effect of social support on social pain (Eisenberger, Taylor, Gable, Hilmert, & Lieberman, 2007). Consistent with the overlap between social and physical pain, social support also blunts the experience of physical pain in clinical conditions (Zaza & Baine, 2002) as well as in experimental studies (Brown, Sheffield, Leary, & Robinson, 2003).

A neurochemical system likely to affect social support is the serotonin system. For example, free ranging rhesus monkeys with higher levels of central serotonin, as measured by metabolites in the cerebrospinal fluid, are more "popular." They spend more time grooming and in the vicinity of other monkeys and have more monkeys sitting close to them than monkeys with low central serotonin levels (Mehlman et al., 1995). Similarly, in humans, pharmacological facilitation of serotonin signaling can increase affiliative behavior (Knutson et al., 1998; Tse & Bond, 2002) and agreeableness (aan het Rot, Moskowitz, Pinard, & Young, 2006). As these studies require rather invasive methodologies (spinal tap or drug administration, respectively), progress in understanding the physiology of social support processes is likely to be aided by the less invasive genotyping approach. Using this methodology, genetic variation in the seorotonin system has been associated with social popularity in humans. Specifically, variation in the serotonin 2A receptor gene (*HTR2A* G-1438A) has been linked to sociometric ratings after participants work together on cooperative tasks (Burt, 2008). Participants were liked better if they were homozygous for the G allele. Accordingly, these individuals may be better able to recruit social support, which may diminish both their vulnerability to and their subjective experience of social pain.

Another gene that may be related to the ability to develop social networks is the dopamine 4 receptor gene (*DRD4*). In a recent meta-analysis (Munafo, Yalcin, Willis-Owen, & Flint, 2008), allelic variation in *DRD4* was associated with novelty seeking, a psychological construct closely related to extraversion. Accordingly, *DRD4* variation may influence the establishment of social networks by affecting behavioral and social approach in novel situations. The relationship between this polymorphism and approach-related traits appears to be fairly robust, as the association has been made across multiple species, including monkeys, horses, dogs, and birds (Bailey, Breidenthal, Jorgensen, McCracken, & Fairbanks, 2007; Fidler et al., 2007; Hejjas et al., 2007; Ito et al., 2004; Momozawa, Takeuchi, Kusunose, Kikusui, & Mori, 2005).

Neuroticism, characterized by chronic negative affect, also appears to influence the construal of social circumstances as painful or supportive. Higher levels of neuroticism are associated with a propensity to experience multiple forms of social pain (Macdonald & Leary, 2005) as well as physical pain (Wade, Dougherty, Hart, Rafii, & Price, 1992). A meta-analysis has revealed a small effect of the short allele of a polymorphism in the serotonin transporter gene (5-HTTLPR) on higher levels of neuroticism (Schinka, Busch, & Robichaux-Keene, 2004).

However, attempts to identify other reliable genetic correlates of neuroticism with larger effect sizes have been unsuccessful (Shifman et al., 2008).

Oxytocin and Vasopressin

In addition to genes related to the serotonin, dopamine, and opioid systems, polymorphisms in the the oxytocin (OT) and vasopressin (AVP) systems may be associated with both social affiliation and pain experiences. At present, the specific roles of oxytocin and vasopressin in social pain and support have not been clearly elucidated in humans, and little is known about which genes within these systems are associated with social processes. Thus, our discussion of the genetic bases of these systems has a greater focus upon animal models and is more conjectural than has been true for discussion in other sections.

Elevated plasma OT may be a signal of social pain, as both human (Taylor, Gonzaga et al., 2006; Turner, Altemus, Enos, Cooper, & McGuinness, 1999) and animal (Grippo et al., 2007) studies have found that elevations in OT accompany social isolation or deficits in social contacts. This elevation may act as a biological signal that prompts affiliative activity. Both exogenous administration of oxytocin and endogenous oxytocin have also been tied to a broad array of affiliative activities. For example, OT has been related to increases in physical proximity, maternal behavior, grooming, and preferences for familiar conspecifics in multiple animal studies (e.g., (Carter, 1998; Carter, Lederhendler, & Kirkpatrick, 1997). Thus, paradoxically, increases in oxytocin have been found in conjunction with both social pain/isolation and affiliation/support experiences. Clearly, further research is needed to clarify these effects, and the use of genetic methodologies is likely to be a valuable approach toward this end.

Consistent with a role for oxytocin genes in social processes, deletion of the gene responsible for making oxytocin prevents mice from developing social memory (Ferguson et al., 2000). Infant OT knock-out mice are deficient in vocalization following separation from their mother and, as adults, show more aggression in isolation-induced and resident-intruder tests of aggression (Winslow et al., 2000). Thus, the absence of exposure to oxytocin during development appears to lead to abnormalities in socioemotional behavior (Winslow et al., 2000). In humans, variation in the oxytocin receptor gene (OXTR) has been tied to social behavior. Carriers of the A allele of a single nucleotide polymorphism (rs 53576) are at heightened risk for

autism (Wu et al., 2005) as well as insensitive parenting (Bakermans-Kranenburg & Van Ijzendoorn, in press).

The vasopressin system may also be involved in social affiliation. For example, transfer of the vasopressin 1A receptor gene has been found to enhance male social affiliation in animal studies (Keverne & Curley, 2004). In humans, a polymorphism within the vasopressin 1A receptor (AVPR1A) gene has recently been identified and appears to be related to empathy and altruistic behavior (Bachner-Melman et al., 2005; Knafo et al., 2008). Hence, this polymorphism provides an opportunity to examine the role of the human vasopressin system in social pain and support and determine if findings in animal models translate to the human.

Moderation of Genetic Associations with Social Pain by the Environment

Up to this point, we have largely been discussing unidirectional effects of genetic variation on the dependent measures. However, one of the key advances made possible by the genotyping approach is the ability to study the interaction of life experience and markers of neurochemical function. One of the most salient environmental influences on emotionality and social behavior across the lifespan is the harshness/nurturance of the early environment (e.g., (Liu et al., 1997; Repetti, Taylor, & Seeman, 2002). These social effects are moderated by many of the same polymorphisms already discussed.

One such polymorphism is in the regulatory region of the serotonin transporter gene (5-HTTLPR). People with two copies of the 5-HTTLPR short allele (short/short) who have experienced childhood maltreatment are more likely to be diagnosed with major depressive disorder than individuals with one or two copies of the long allele who have experienced similar environments (Caspi et al., 2003; Kaufman et al., 2004). A study from our laboratory (Taylor, Way et al., 2006) suggests that the short allele may not only function as a risk allele for depression in the face of an adverse environment, but as a general sensitivity allele, providing protection from symptoms of depression when the environment is nurturant. Using a non-clinical sample of 118 adult men and women, we assessed nurturance of the early family environment, depressive symptomatology, and 5-HTTLPR genotype. As expected, a stressful early family environment by itself was significantly related to depressive symptomatology. However, we also found that a significant gene-by-environment interaction between the 5-HTTLPR and the nurturance of the early family environment qualified the risk for depression. Specifically, individuals with two copies of the short allele had greater depressive

symptomatology if they had experienced early familial adversity compared to participants with the short/long or long/long genotypes, but significantly less depressive symptomatology if they reported a supportive early environment. Notably, the adverse early family environments studied were ones in which the degree of social pain was fairly mild, consisting of some conflict, moderate household chaos, and/or cold, unaffectionate, and distant behaviors, rather than explicit maltreatment in the form of physical or sexual abuse.

Of interest, this differential sensitivity to the environment does not appear to be limited to childhood, but is present in adulthood as well. Thus, people with the short/short genotype who reported being in a currently highly stressful environment had higher levels of depressive symptomatology, relative to those with short/long or long/long variants, whereas those who reported currently being in an low stress environment had significantly lower levels of depressive symptomatology. Reports of the early and current environment were only modestly correlated with each other, and so these results are fairly independent of each other. Thus, with respect to depressive symptoms, the short/short genotype appears to be risky in harsh environments but protective in nurturant environments. Consistent with this latter point, short/short individuals have been found to be more responsive to the protective effects of social support as well (Kaufman et al., 2004; Kilpatrick et al., 2007).

Thus, it appears that genetic variation affecting social pain may also affect responses to social support and nurturance, reflecting a sensitivity to the social environment in general, rather than just its negative aspects. Whether such influences on social sensitivity apply to all genes affecting social pain is not clear; however, a similar effect has been documented for the DRD4 receptor gene (Exon 3 48bp VNTR) and externalizing behavior, as we next discuss.

Like early studies of environmental moderation of the effects of the 5-HTTLPR, the initial focus of the DRD4 studies was on interaction of variation in this gene with negative outcomes resulting from emotionally distant and insensitive parenting. Multiple research laboratories found that when exposed to non-nurturant parenting, people with a particular allele at this polymorphism (though not always the same allele) were at higher risk for either externalizing behaviors (Bakermans-Kranenburg & van Ijzendoorn, 2006; Propper, Willoughby, Halpern, Carbone, & Cox, 2007) or high levels of novelty seeking (Keltikangas-Jarvinen, Raikkonen, Ekelund, & Peltonen, 2004; Sheese, Voelker, Rothbart, & Posner, 2007) than individuals with the other alleles. However, recent evidence indicates that the long allele may increase sensitivity to positive as well as negative parental influences. Thus, when the

environment is nurturant, individuals with the long DRD4 allele had low levels of externalizing behavior, but when the environment was one of frequent social pain, individuals with the very same allele had high levels of externalizing behavior. The behavior of individuals with the other alleles was less responsive to parenting quality (Bakermans-Kranenburg & van Ijzendoorn, 2007).

Providing experimental support for the differential sensitivity hypothesis, Bakermans-Kranenburg and colleagues (2008) found that toddlers with the long allele were the most responsive to a parental educational program designed to reduce externalizing behavior through increasing the attentiveness of parenting. This finding is especially interesting for clinical researchers, as it indicates that particular therapies may be more effective with people who have particular genotypes. Furthermore, it may even be worthwhile to specifically design and target therapies according to individual genotypes.

Findings such as these offer significant evidence that the social environment can powerfully shape genetic effects. For researchers, these data raise intriguing questions concerning the mechanisms by which social pain and the DRD4 and 5-HTTLPR variants affect lasting changes in behavior. There are multiple possibilities. One is that because the 5-HTTLPR polymorphism lies within the upstream regulatory region of the serotonin transporter gene, it is poised to modulate transporter expression in response to environmental factors, including social ones. Over time, such changes could lead to alterations in the structure of the brain, particularly in areas such as the ACC which are integral to social pain processes. Stressful early life experiences, most of which involve social pain, appear to reduce the volume of the ACC in adulthood (Cohen et al., 2006). Although such sequelae of social pain have never been analyzed in combination with genetics, the ACC is likely to be a neural site of gene-environment interaction, as the 5-HTTLPR (Pezawas et al., 2005), DRD4 exon 3 VNTR (Shaw et al., 2007), and the MAOA-uVNTR (Meyer-Lindenberg et al., 2006) have all been shown to relate to ACC volume.

Thus, variation in these genes may affect sensitivity to the social environment by setting the degree to which neural networks are under environmental control. In a nurturant family environment, synaptic connectivity would flourish, leading to a richly connected neural network that might, for example, yield better emotion regulation capabilities. Conversely, in an environment of social pain, there would be less synaptic integration, which would presumably lead to diminished emotion regulation capabilities.

In addition to environmental moderation of genetic influences, the maternal environment can also induce lasting changes in the function of genes, which is an additional mechanism by which experiences of social pain can induce long-term behavioral alterations. In animal studies, Meaney and colleagues have shown that rat pups exposed to highly nurturant mothering show less emotionality to novel circumstances and more normative social behavior including mothering in adulthood, compared to recipients of normal mothering (Francis, Diorio, Liu, & Meaney, 1999; Weaver et al., 2004). Studies with monkeys have shown similar effects. For example, Suomi (1987) reports that highly reactive monkeys cross-fostered to nurturant mothers develop good socioemotional skills and achieve high status in the dominance hierarchy, whereas monkeys with reactive temperaments who are peer-raised develop poor socioemotional skills and end up at the bottom of the dominance hierarchy.

Such long-term effects of maternal care appear to be a result of epigenetic structural alterations (methylation) to the glucocorticoid receptor gene that occur in the first week after birth and affect its expression throughout the lifespan (Meaney & Szyf, 2005). This process is affected by each of the neurochemical systems discussed in this chapter and thus polymorphisms in these systems that affect signaling are likely to have downstream effects upon this process. Mothers showing high levels of nurturant behavior exhibit greater increases in oxytocin receptors during pregnancy, which is the thought to trigger maternal responsivity (Meaney, 2001), and have higher levels of dopamine release when caring for their pups (Champagne et al., 2004). This more nurturant mothering triggers greater increases in serotonin turnover in the pup, which initiates the cascade leading to the altered glucocorticoid receptor expression that affects adulthood reactivity to stress (Meaney & Szyf, 2005). Identifying the specific manner in which the genetic variants discussed in this paper affect such processes will be a productive area for future research.

Conclusions, Caveats, and Future Directions

The study of genetic factors in the experience of social pain is in its infancy, yet several variants have been identified that are likely to influence individual differences in response to social pain. Each of the discussed variants appears to be involved in physical pain as well, supporting the hypothesis that the distressing aspects of physical and social pain share similar physiological underpinnings. The identification of these variants was a result of hypotheses

developed from prior neurochemical studies, which we believe is likely to be a useful means of identifying future variants affecting social pain.

A key advantage of the genetic approach is that its easy-to-use methodology provides the opportunity to examine how genes affect responses to life experiences outside the laboratory. In particular, variation within each of the genes described in this chapter influences individual sensitivity to the environment, either amplifying or dampening down the effects of experience. Far from being a deterministic process, genetic influences on psychological endpoints reflect an interaction with environment variables.

As should be clear from this discussion, not all genes implicated in social pain may be specific for the experience of social pain; rather, genes that more generally predispose to psychological and social distress, such as those implicated in anxiety, neuroticism, and depression, may be involved as well. As such, these genes may exert their effects on the experience of social pain by affecting the ability to develop social skills, extract social support from others, and construe the social environment as a beneficent one.

Although we have advocated for the merits of the genetic approach in this chapter, there are methodological problems involved in linking genetic variation directly to the experiences of social pain or social support. A principle one concerns insufficient understanding of the molecular mechanisms by which polymorphisms, particularly the interacting effects of adjacent polymorphisms, effect the function of proteins and thus the function of neurons and neural circuits. In addition, the small effect sizes involved with any one particular variant, and heterogeneity in the methods used to evaluate the relations of genetic and psychological factors are also problems with studies conducted to date. Complex phenotypes typically show small relations to specific genes, and so methodological differences between studies can obscure the relations between polymorphisms and psychological characteristics. Moreover, complex phenotypes are likely to be influenced by several, perhaps many, genes, and thus, efforts to tie a phenotype to a particular gene may be hampered by not knowing about and controlling for the other genes involved. Genetic heterogeneity within a population also represents a difficulty, as many of the samples that researchers recruit are multiethnic, and even efforts to explore relations within ethnically homogeneous samples may nonetheless include substantial heterogeneity. In light of these factors, it is prudent to treat results of the genetic association studies reported here cautiously until multiple replications have been performed.

Several factors, however, provide bases for optimism, particularly with respect to the phenotype of social pain. First, experiences of social pain can be reliably induced in the laboratory and in neuroimaging studies, rendering the phenomenon highly tractable to controlled experimentation. Second, social pain is continuously distributed (unlike most disease processes which are defined categorically; e.g., affected or unaffected). This makes the social pain experience sensitive to detecting genetic effects, because normal allelic variation most likely influences position of the phenotype within a continuous distribution (Plomin, 2003). Although studying extremes of phenotypes (such as people diagnosed with depression or anxiety disorders) has been used as a method to try to address genetic bases of social pain, in so doing, investigators may inadvertently restrict the range of psychological characteristics. In such a case, true effects or interactions with environmental factors can be obscured (see Taylor, Way, et al., 2006, for a discussion of this issue).

To take full advantage of the genetic approach, it will be necessary to have a narrowly defined phenotype. Due to the infancy of the field, we have deliberately used a broad definition of social pain and focused on genetic variation that is likely to be common to different subtypes of social pain. However, in the future, genes may be identified that are involved in different subtypes of social pain. For example, social evaluative threat may involve somewhat different genetic mediators than separation distress.

In the future, incorporating a genetic approach into the study of social pain will not only improve understanding of the neurochemical systems influencing social pain, but is also likely to generate new conceptual insights into the process of social pain. Thus, as each additional gene becomes linked to social pain, social pain then becomes associated with other traits or psychological processes associated with this gene. Just as associating social pain with physical pain has been a rich source of hypotheses, associating social pain with these as yet unknown processes could function like a psychological Rosetta Stone, providing new theories about social pain.

Although this article has centered on deriving genetic hypotheses from neurochemical data, one of the great advantages of the new genetic technologies is the opportunity to go beyond previous neurochemically-derived hypotheses to discover new genes and pathways involved in social pain. One approach to doing so is by studying rare disorders related to physical and social pain, such as Williams Syndrome, congenital indifference to pain, and autism. For example, Williams syndrome is characterized by excessively friendly behavior and an apparently reduced

capacity to experience social pain (Meyer-Lindenberg, Mervis, & Berman, 2006). Identifying the particular deleted genes that cause excessive gregariousness will help determine if these genes are related to normal variation in social pain processes.

An additional way to identify novel genes involved in social pain is through large-scale studies that sample the entire genome in a non-hypothesis driven manner. Such whole-genome association studies have recently successfully identified many disease genes and are likely to be influential in studying normal variation in physiological processes as well (McCarthy et al., 2008).

Clearly, the next decades will advance the understanding of the genetic contributions to social pain greatly. As the field unfolds, some of the suggestions and concerns offered here may prove to be misplaced. That is an inherent risk of reviewing a field that is in its early stages. Nonetheless, the effort to bring coherence to these diverse investigations is a first step to pointing researchers in useful directions for the discoveries of the future.

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