Social Influences on Health: Is Serotonin a Critical Mediator?

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The influence of social relationships on health has been well documented for many years, yet identifying the physiological mechanisms responsible for these effects has proved more challenging. This review assesses the potential role of the serotonin system in affecting sensitivity to the health-related effects of the social environment. Building on recent studies of genetic variation in the serotonin system, particularly focusing on a polymorphism (5-HTTLPR) in the serotonin transporter gene, we provide evidence that activity within the serotonin system is critically involved in setting sensitivity to social experiences. Furthermore, we highlight the effects of the 5-HTTLPR on sensitivity to both positive and negative social experiences. In a positive environment, individuals with the short allele, and particularly the short/short genotype, function better psychologically than those with the long/long genotype. Conversely, when exposed to adverse environments or in the absence of social support, individuals with the short allele are at high risk for a variety of negative health outcomes. This serotoninergic involvement in social sensitivity seems to occur in concert with other neurochemical systems, such as the opioid system, which will also be discussed. Although this differential sensitivity to social experiences is initially determined in the brain, it has physiological effects on downstream pathways that more directly affect disease mechanisms, such as the hypothalamic-pituitary-adrenal axis, which is a particular focus of this review. The serotonin system, as indexed by the 5-HTTLPR, is an important link between the social environment and health. **Key words:** social, serotonin transporter, polymorphism, gene, health, A118G.

5-HTTLPR = serotonin transporter gene-linked polymorphic region; **HPA** = hypothalamic-pituitary-adrenal; **SERT** = serotonin transporter.

INTRODUCTION

Since the 1960s when it was first recognized that social isolation of mice induced decreases in serotonin turnover (1), it has been clear that there is a close relationship between the serotonin system and the social environment. Building on this notion with recent human genetic data, we review evidence indicating that the serotonin system affects individual sensitivity to positive and negative aspects of the social environment. Because social support and stress have well documented effects on health outcomes (2), we propose that the serotonin system may serve as a critical link between the social environment and downstream pathways that affect health outcomes.

The following discussion primarily focuses on a particular genetic marker of differential function in the serotonin system, the 5-HTTLPR (3). The 5-HTTLPR refers to a location in the serotonin transporter gene where there are two principal alleles, long (16 repeats of a 20–23 bp sequence) and short (14 repeats), that affect expression of the gene. The serotonin transporter is perhaps best known as the primary target of serotonin reuptake inhibitors (e.g., Prozac) and therefore initial studies of the 5-HTTLPR and the environment focused on depression. We begin by discussing this early work, including a study from our laboratory, which serves as a scaffolding from which we outline a larger theory of serotoninergic involvement in moderating social influences on health.

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The 5-HTTLPR, Early and Adult Life Events, and Depressive Symptomatology

In a seminal study, Caspi et al. (4) found that the 5-HTTLPR moderated the effects of childhood maltreatment on depression. They also found that the 5-HTTLPR had a similar role in moderating the depressogenic effects of recent stressful events (e.g., divorce, bankruptcy). Building on this finding, we analyzed the relationship between such adverse events and depressive symptomatology (5), but additionally examined the effects of positively valenced experiences on depressive symptomatology in a sample of healthy young adults. Thus, we asked the question: Does the 5-HTTLPR moderate the affective consequences of a loving and caring family environment? And, similarly, do positive recent life-changing events have different effects on affect according to 5-HTTLPR genotype?

Looking at the effects of being raised in a harsh, conflict-ridden, family environment, we found that young adult homozygous carriers of the short allele had the highest levels of depressive symptomatology in the sample, replicating the findings of Caspi and colleagues (4). A common interpretation of such findings is that the short allele, and particularly the short/short genotype, is a risk allele for psychopathology after experiences of adverse events. However, when individuals with the same genotype were raised in a nurturant family environment, they had the lowest levels of depressive symptoms in the sample (Fig. 1). Thus, in addition to its effects on sensitivity to a negative social environment, the short/short genotype also conferred greater sensitivity to the positive social environment. Therefore, we postulate that the short allele's association with vulnerability to psychopathology in the face of adverse social experiences is a reflection of its larger role in affecting overall sensitivity to the social environment, including positive social experiences.

We asked the same question with respect to the effects of life-changing events that had occurred in the last 6 months. On this measure, participants recorded major life events and then rated the magnitude of negative or positive influence they had (this rating of recent events was not signif-

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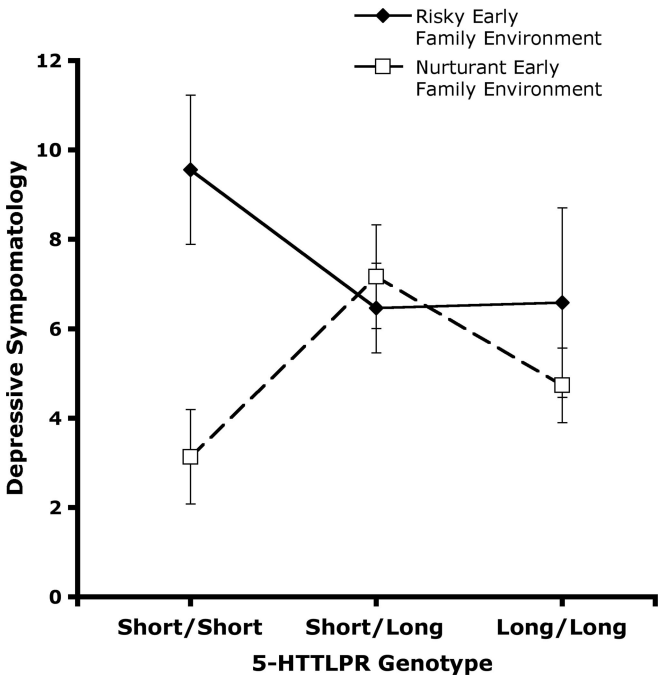

Figure 1. Relationship of the 5-HTTLPR and the quality of the early family environment to depressive symptomatology. *5-HTTLPR* = serotonin-transporter-linked polymorphic region. Reprinted from *Biological Psychiatry*, with permission from Elsevier (5).

icantly correlated with the measure of the early family environment). Again, we found that the depressive symptomatology of individuals with the short/short genotype was the most affected by such recent events. Thus, these individuals had the highest levels of depressive symptomatology if their recent experiences were predominantly negative, yet they had the lowest levels of depressive symptomatology if their recent experiences primarily entailed positive events. This pattern of effects is in line with prior theories of temperament (6,7) and biological reactivity (8,9), which suggest that people at highest risk for psychopathology in the face of adverse experiences are also the people most likely to benefit from positive experiences. Here, we extend this model to the 5-HTTLPR, as has been done recently by Belsky and colleagues (10), and we place particular emphasis on the role of the 5-HTTLPR in mediating sensitivity to social experiences (11).

To specifically examine the role of recent social events on affect, we subsequently recoded these recent life events into social and nonsocial categories. Of all reported life events, 38% were social in nature, including such events as breaking up with a romantic partner, conflict with family or friends, or death of a loved one. Events in the nonsocial category were related to achievement (e.g., receiving a low grade in class), financial status (e.g., lost job), or other events, such as being in a car accident. The net rating of the social events was more negative than the nonsocial events ($t_{(2,117)} = 2.94$, $p < .01$).

Using a median split, the interaction between this social life events measure and the 5-HTTLPR was significantly associated with depressive symptomatology when controlling for ethnicity, gender, early family environment, and socioeconomic status ($F(2,112) = 3.21$, $p = .044$). However, when the interaction between nonsocial life events and the 5-HTTLPR was assessed, there was not a significant relationship with depressive symptomatology ($F(2,112) = 1.56$, $p = .21$), suggesting that the effects in the study by Taylor et al. (5) were primarily driven by the social events. Again, it was the individuals with the short/short genotype whose affective state was the most dependent on their social environment. Only among individuals with the short/short genotype was there a significant correlation between depressive symptomatology and life events that were social in nature ($r = -.40$, $p = .025$). For the same individuals, the correlation between depressive symptomatology and nonsocial life changing events was not significant ($r = -.22$, $p = .24$). As the slopes of these correlations were not significantly different, we do not claim that nonsocial life-changing events have no impact on affect, only that the 5-HTTLPR was more associated with the effects of social life events than nonsocial life events.

There are three conclusions that we draw from these data that shape the remainder of this discussion. First, the 5-HTTLPR is particularly associated with individual differences in sensitivity to the social environment. This suggests that the serotonin system is likely to be critically involved in the signaling pathways activated by social interaction, with potential downstream effects on a variety of health outcomes, in addition to depression. Second, these results indicate that the serotonin system not only affects sensitivity to negative social influences, but positive ones as well. Third, given that the two measures of the social environment (early family environment and social events in adulthood) were not correlated ($r = -.03$, $p = .79$), moderation of their effects on depressive symptomatology by the 5-HTTLPR likely occurs via different cellular mechanisms due to the different time periods of influence. Insufficient attention to delineating such developmental influences, as well as measuring the positive aspects of the environment, particularly the social environment, may help to explain some of the variability in studies assessing the role of the 5-HTTLPR in moderating the effects of life experiences on psychopathology (12). Therefore, the following review of evidence in support of the serotoninergic social sensitivity hypothesis discusses developmental influences apart from contemporaneous influences. In this discussion, we will also allude to potential health-relevant pathways by which the serotonin system may mediate social influences, particularly the hypothalamic-pituitary-adrenal (HPA) axis. Finally, we conclude with a discussion of the potential clinical implications of the social sensitivity hypothesis.

The 5-HTTLPR and Social Sensitivity: Developmental Influences

Our findings of 5-HTTLPR-related differential sensitivity to the social environment during development are consistent

with an accumulating body of research. Two additional studies of depression have also shown such social sensitivity effects (13,14). In one of these (14), the interaction effect was limited to females, but it is a particularly strong demonstration of the differential sensitivity hypothesis because the effects of the positive environment had a greater magnitude of effect than the negative environment, as highlighted in a recent reanalysis of these data (10). Similar gender differences in 5-HTTLPR-related social sensitivity have been seen in adult samples as well (15).

With respect to other phenotypes, studies of suicide risk (16), anxiety sensitivity (17), and attention deficit hyperactivity disorder (18) not only showed that the short allele was associated with greater risk for psychopathology, but also showed that individuals with the short allele and a positive family environment, or at least the absence of an abusive one, fared better than individuals with the long/long genotype. It should be noted that, in two of the aforementioned studies (14,18), the measure of the early life environment was composed primarily, but not exclusively, of social measures.

Animal models showed similarly robust effects in response to manipulations of the social environment during development. For example, rhesus monkeys with the short allele of an orthologous polymorphism exposed to impoverished maternal care were more likely than monkeys with the long/long genotype to exhibit low levels of central serotonin, as indexed by 5-hydroxyindoleactic acid levels in the cerebrospinal fluid (19), as well as increased anxiety (20), sensitivity to alcohol (21), and adrenocorticotropic hormone activation in response to separation stress (22). Although the effects of a positive social environment have not been assessed in the monkey, there is evidence in support of serotoninergic-mediated sensitivity to positive, as well as negative, social influences in serotonin transporter (SERT) knockout mice. The heterozygous SERT null mutant mice, which have a 50% reduction in the SERT (23), serve as a model system for humans or rhesus monkeys with the 5-HTTLPR short allele (24). Conversely, wild-type animals are a model of the long/long genotype. In a study assessing maternal behavior (24), the heterozygous null mutants exposed to low maternal care had heightened depression-like (tail suspension test) and anxiety-like (open field and elevated plus maze) behavior, akin to humans with the 5-HTTLPR short allele exposed to a stressful family environment. Conversely, the heterozygous SERT null mutants receiving high levels of maternal care exhibited the lowest levels of depression-like and anxiety-like behavior in the entire sample. This is a compelling validation of the social sensitivity hypothesis derived from the human 5-HTTLPR data, because it is not subject to the same environmental and molecular confounds present in human studies.

These results also suggest a potential mechanism by which serotoninergic social sensitivity may affect adult psychopathology. Maternal licking and grooming of rat pups activate serotonin release which, in turn, initiates a cascade of events that ultimately prevent epigenetic alterations of the glucocorticoid receptor gene (26). As expression of this gene regulates feedback inhibition of the HPA axis, the epigenetic alterations associated with low levels of maternal care increase HPA axis reactivity in adulthood (27). In human clinical samples, individuals suffering from abuse during childhood show signs of similar epigenetic alterations of the glucocorticoid receptor gene (28) and also exhibit similar reductions in central serotonin turnover, as indexed by cerebrospinal fluid 5-hydroxyindoleactic acid (29), as well as SERT binding (29). Thus, it is conceivable that the 5-HTTLPR moderates social influences on such epigenetic alterations and may thereby affect HPA axis reactivity in humans as well.

Social Sensitivity and the 5-HTTLPR: Adult Studies

As excessive HPA axis reactivity is a risk factor for multiple mental and physical health outcomes (30), we examined the relationship between the 5-HTTLPR and cortisol response to an acute social stressor in the laboratory (Trier Social Stress Test). The study design allowed direct experimental evaluation of the social sensitivity hypothesis (31). Participants performed public speaking and mental arithmetic tasks either in front of an evaluative audience or in the absence of an audience (but in the presence of a video camera and an experimenter off to the side of the participant). This stressful experience elicited significant cortisol increases in both the audience and no audience conditions (32). However, only when a socially evaluative audience was present was there a significant association between cortisol response and the 5-HTTLPR (Fig. 2). This finding suggests that the 5-HTTLPR is particularly associated with the social nature of the stressor. However, due to the greater cortisol response in the social stress condition, we cannot rule out the possibility that low cortisol reactivity in the nonsocial condition obscures any effect of the 5-HTTLPR in that condition.

The greater cortisol reactivity of individuals with the short/short genotype to social stress is also consistent with other studies that did not directly assess the social sensitivity hypothesis, including a sample of adolescent girls (33) and a sample of adult males, conditional on having recently experienced stressful life events (34).

Social Support and the 5-HTTLPR

Because heightened cortisol exposure has been argued to be a causal factor in depression onset (35), cortisol exposure could be one mechanism by which individuals with the short/short genotype are more vulnerable to depression. However, such assessments of risk are predicated on the absence of social support, which can act to buffer against the adverse effects of stress. Individuals with the short/short genotype seem to be especially sensitive to this social input as well. After experiencing a natural disaster (a hurricane), individuals with the short/short genotype were at no higher risk for depression than individuals with the long/long genotype if they had a strong social network providing instrumental and emotional support (36). However, if short/short individuals exposed to this disaster did not have good social support, they

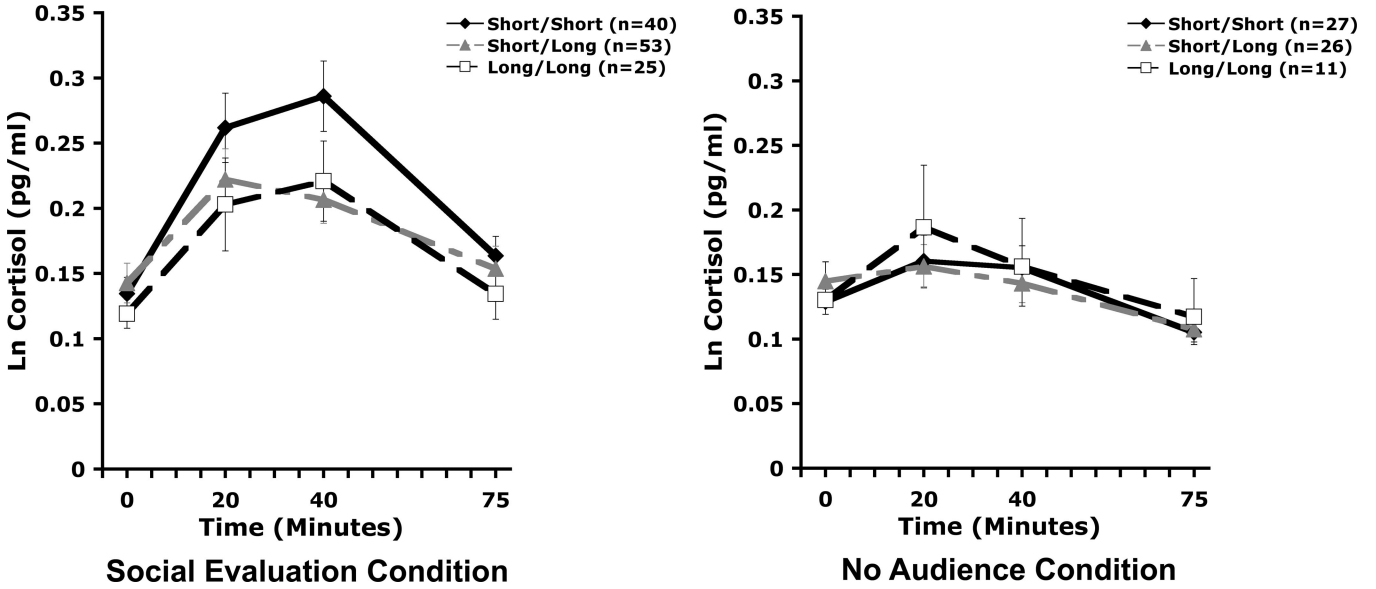

Figure 2. Mean (± SEM) cortisol response to the Trier Social Stress Test as a function of 5-HTTLPR in the social evaluation condition (*left*) and the no audience, control condition (*right*). 5-HTTLPR = serotonin-transporter-linked polymorphic region. Reprinted from *Biological Psychiatry* with permission from Elsevier, (32).

had a 4.5 times greater risk for depression than those with good social support. A similar result was found among individuals raised in the foster system (37). Short/short individuals with a supportive mentor had no higher levels of depressive symptomatology than long/long individuals raised in the same environment, whereas short/short individuals without this support had significantly higher levels of depressive symptoms. In both of these examples, the long/long individuals were relatively unaffected by social support. Such effects of social support are consistent with the stress-buffering model of social support (38) and indicate that the serotonin system is involved in this process.

To test whether the 5-HTTLPR is associated with differential sensitivity to social support processes in more controlled settings, our work has begun to focus on romantic relationships. In preliminary data from a longitudinal study of married couples, short allele carriers exhibited more crossover of affect, including positive affect, from their partner across a series of structured social interactions in the laboratory than did long/long individuals (Schoebi D, Way BM, Karney BR, Bradbury TN, manuscript in preparation). Thus, the mood of short allele carriers moved in concert with their partners. In preliminary data from a daily diary study, when short allele carriers felt their partners were more attuned to them and supportive of them, they were more likely to engage in reciprocal thoughtful behaviors than long/long individuals (Way BM, Algoe SB, Frederickson BL, manuscript in preparation), indicating that the greater responsiveness to social support of short allele individuals carries over into behavior as well.

Interaction of the 5-HTTLPR With Other Neurochemical Systems

Although the focus of this review has been on the serotonin system, other systems are also involved in setting sensitivity to social experiences. In particular, another neurochemical system with a similar anatomical distribution in limbic, and particularly paralimbic, brain areas (39,40) is the opioid system. Like the serotonin transporter (41), the μ-opioid receptor is concentrated in the hypothalamic paraventricular nucleus, which is the site of corticotrophin-releasing factor cells that initiate activation of the HPA axis (42). Within the coding region of the μ-opioid receptor, there is a functional polymorphism (A118G) that we have found to be associated ($F(3,333) = 2.34$, $p = .074$) with the cortisol response to the Trier Social Stress Test in the sample described previously. The A118G polymorphism was genotyped, using a Taqman allelic discrimination assay, as described in our previous work (43); genotypes did not deviate from Hardy-Weinberg equilibrium. These are preliminary analyses, but, as with the 5-HTTLPR, the A118G polymorphism was associated with cortisol response only in the social evaluation condition and not with responses in the nonsocial evaluation condition, suggesting that it influences differential sensitivity to social challenge. Carriers of the G allele were the most reactive to this social stressor, which is consistent with our prior work showing that G allele carriers had greater self-reported as well as neural (anterior cingulate and insula) response to social rejection (44).

When combined, the 5-HTTLPR and A118G polymorphisms had an additive association with cortisol reactivity in the social evaluation condition ($F(6,327) = 3.33$, $p = .003$); there was no association in the no audience condition ($F(6,168) = 1.38$, $p = .22$). Those with the combination of the most responsive genotypes (5-HTTLPR short/short and A118G allele carriers) exhibited over 3-fold greater cortisol response than those with the low socially responsive genotypes (long/long and A/A), who showed no greater response to

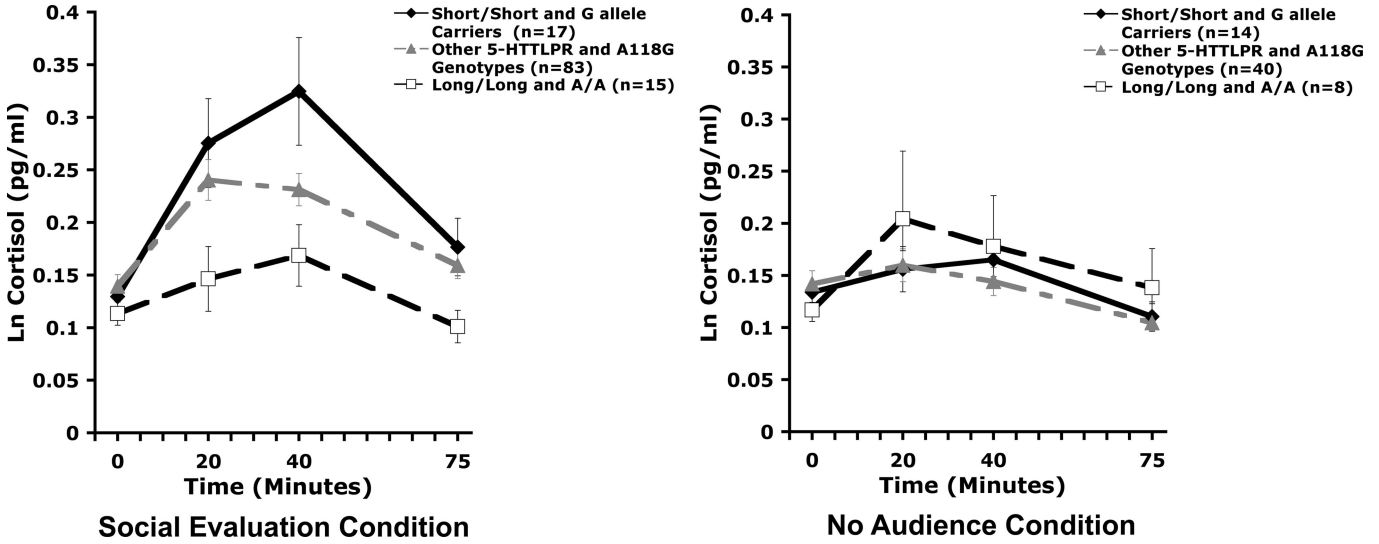

Figure 3. Association of 5-HTTLPR and A118G polymorphisms with cortisol response to stress. The category "Other combinations of 5-HTTLPR and A118G Genotypes" includes: short/long + G allele carriers; long/long + G allele carriers; short/long + A allele homozygotes; long/long + A allele homozygotes. *5-HTTLPR* = serotonin-transporter-linked polymorphic region.

the socially evaluative condition than the condition without the audience (Fig. 3) ($F(1,168) = 0.45$, $p = .5$). The 5-HTTLPR and A118G polymorphisms may also act in concert to affect sensitivity to social support, as both the serotonin transporter and the μ-opioid receptor have their highest cortical concentrations in the anterior cingulate gyrus (45–47), which has been found to be an important site where social support reduces responses to social stress (48).

Clinical Implications of Social Sensitivity Effects of the Serotonin System

In spite of the robust effects of social support on health, interventions designed to capitalize on these effects have yielded mixed results (49–51). To some extent, this variability in the efficacy of social support is influenced by individual differences (52), and 5-HTTLPR-related differences in social sensitivity could be an important contributor to such differences. Consistent with this notion, a training program in parenting that fostered the development of emotional support and monitoring skills significantly reduced the risk of adolescents with the short allele engaging in risky health behaviors (e.g., substance abuse, unsafe sex). The program had little effect on the risk behavior of long/long individuals (53). As this was a randomized control trial that eliminates concerns over gene-environment correlation, it provides particularly compelling evidence that the short allele is associated with greater sensitivity to positive social influences and suggests that studies of social support interventions might profit from controlling for genotype in assessments of efficacy.

CONCLUSION

Based on this selective review of initial forays into social neurochemistry, there is accumulating evidence that the 5-HTTLPR specifically, and the serotonin system more generally, affects sensitivity to both positive and negative social environments. Establishing the serotonin system as a critical mediator of social influences on health is likely to facilitate future endeavors into identifying the specific pathways by which the social realm influences mental and physical health. The genetic approach should facilitate this process, as it allows integration across studies in animal models, the laboratory, the clinic, and the community. Contrary to many fears, genetic research is serving to only underscore the importance of the social environment, not diminish it.

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