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# Long story short: the serotonin transporter in emotion regulation and social cognition

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**The gene encoding the serotonin transporter (5-HTT) contains a regulatory variation that has been associated with anxiety-related traits and susceptibility for depression. Here we highlight recent discoveries related to allelic variation of 5-HTT function with respect to emotion regulation and social behavior, drawing from an interdisciplinary perspective of behavioral genetics and cognitive neuroscience. Following a reductionistic path that leads from gene-behavior association studies to neuroimaging and epigenetic studies, we compare two models of 5-HTT-dependent modulation of brain activity and discuss the role of life stress experience in modifying 5-HTT function in the brain. Integration of these findings suggests that the impact of the 5-HTT gene on behavior is much broader than is commonly appreciated and may have a role in social cognition.**

Serotonergic neurotransmission affects a wide range of behaviors, from food intake and reproductive activity, to sensory processing and motor activity, to cognition and emotion. One key regulator is the serotonin transporter (5-HTT), which removes serotonin released into the synaptic cleft. The 5-HTT protein is encoded by a single gene, *SLC6A4*. Transcriptional activity of the human *SLC6A4* is modulated by several variations, including a repetitive sequence, the *SLC6A4*-linked polymorphic region (*5-HTTLPR*), which is composed of a short and a long version, which result in differential 5-HTT expression and function (**Fig. 1**).

In this review, we begin with association studies linking *SLC6A4* variation to personality traits that are risk factors for affective spectrum disorders. We then discuss neuroimaging studies of intermediate or endophenotypes aimed at identifying the underlying neurobiological mechanisms. We speculate that interactions between gene and environment involving *SLC6A4* may modulate the mirror neuron system and Von Economo neurons within neural circuits involved in social cognition. We conclude with a view toward a social neuroscience of 5-HTT function.

## Serotonin transporter and neuroticism

The contribution of *SLC6A4* to individual differences in personality traits was initially explored in a population and family-based genetic study[1] showing a significant association between the low-expressing *5-HTTLPR* short variant and neuroticism. This trait is related to anxiety, stress reactivity and depression. Individuals with either one or two copies of the *5-HTTLPR* short variant had significantly higher scores of neuroticism than those who were homozygous for the *5-HTTLPR* long variant. This association was replicated in an independent family-based sample[2]. Combined data from the two studies[2], which were corrected for ethnicity and age, gave a highly significant association between the short variant and anxiety-related traits both across individuals and within families, suggesting a genuine genetic influence rather than an artifact of ethnic admixture.

Two adequately powered replication studies using a within-family design[2,3] supported the initial report. On the other hand, one large population study that did not use a within-family design[4] did not replicate the findings. Another large study based on extreme scorers[5] also found no significant association between *5-HTTLPR* genotype and neuroticism. The authors suggested that 5-HTT function may contribute less to an anxious phenotype in extreme scorers. Indeed, reanalysis of the data that included only extreme scorers from the initial report did not show the association[1,6]. Smaller population-based studies produced inconsistent results[7]. These nonreplications may be attributable to small sample sizes, heterogeneous subject populations, differing methods of personality assessment, or selection of extreme scorers[6–9]. However, others have argued that the inconsistent effects suggest a statistical artifact due to the inherent problem of relating gene variations of small effect size to complex traits[10].

Given the diversity of individual study findings, meta-analytic approaches might have helped clarify the data. However, these efforts also produced ambiguous outcomes. Two meta-analyses[11,12] found that *5-HTTLPR* genotype is associated with neuroticism but not with harm avoidance, whereas another group reported the opposite pattern[13]. These discrepancies may reflect the selection of different study samples, based on differing inclusion-exclusion criteria, or choice of genotype comparisons. The largest contributor to these varying findings, however, may be differences in the approach to statistical analysis: when the third meta-analysis was reanalyzed[14] using the approaches of the others, *5-HTTLPR* was significantly associated with neuroticism (and had a recessive effect on harm avoidance).

## Imaging neural correlates of serotonin transporter gene variation

In part, the inconsistent association between *5-HTTLPR* genotype and personality traits may be attributed to modest effect sizes. More than

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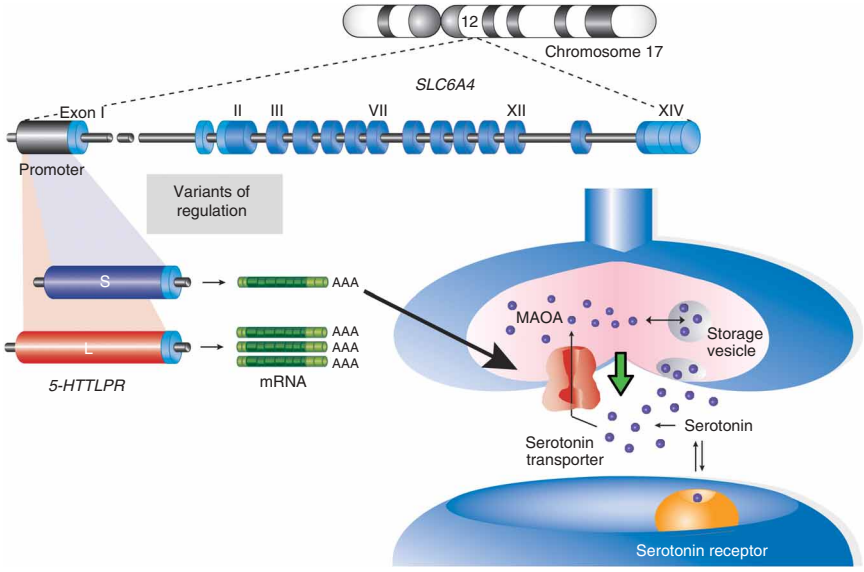


**Figure 1** Allelic variation of serotonin transporter (5-HTT) function in anxiety-related personality disorders, depression and other disorders of emotion regulation. The short (S) *5-HTTLPR* variant (purple) of the 5-HTT gene (*SLC6A4*) produces significantly less 5-HTT mRNA and protein, as indicated by the green arrow, than the long (L) variant (red), leading to higher concentrations of serotonin in the synaptic cleft. The short variant is associated with anxiety-related personality traits such as neuroticism, which are risk factors for affective spectrum disorders. MAOA, monoamine oxidase A; SSRI, selective serotonin reuptake inhibitor.

100 gene polymorphisms may contribute to complex traits[1,2]. Thus, for phenotypes such as self-reported behavioral traits, the influence of a single, common polymorphism on continuously distributed traits is likely to be modest, if not minimal[15].

A promising approach in bridging the gap between gene variants with small effects and complex behavior is the use of endophenotypes[16], such as measures of neural activation or structure. This concept has catalyzed seminal work integrating neuroimaging and molecular genetics in psychiatric research[17,18]. It could be advantageous to the detection of gene effects, because endophenotypes are hypothesized to convey simpler genetic architecture[18] and may be closer to the level at which a gene operates than a more remote phenotype such as self-report[19–21], although this view has been contested[22]. If true, studies using neuropsychological and functional neuroimaging approaches should be more sensitive to the effects of genetic variation. This notion was supported, in part, by the demonstration that *5-HTTLPR* influences 5-HTT availability *in vivo*[23], but other studies have produced a more complex and contradictory picture of the *in vivo* effects of *5-HTTLPR*[24–27].

The first neurophysiological imaging study of genetic variation[28] to take advantage of this endophenotypic approach used event-related potentials and reported an association between *5-HTTLPR* genotype and prefrontal cortex–limbic excitability using a cognitive response control (Go-NoGo) task. This group subsequently reported that individuals who carry at least one copy of the 5-HTTPLR short variant show higher activity of the anterior cingulate cortex (ACC) than noncarriers (that is, homozygous carriers of the long variant)[29], suggesting a relationship between cognitive processing and 5-HTT function. Given the role of 5-HTT in emotionality, these authors anticipated that further "studies of the genetics of complex brain functions may be particularly useful in refining concepts of the heritable components of behavior such as emotion, perception and motor activity"[28].

Such a link between *SLC6A4* variation and emotion-related brain processes was finally confirmed in a functional magnetic resonance imaging (fMRI) study[30] that focused on the amygdala, a brain system central to emotional behavior. *5-HTTLPR* short variant carriers, compared with noncarriers, showed significantly greater amygdala activation during an emotion-related task (matching of emotional facial expressions of anger and fear), relative to a neutral control task.

The neurophysiological imaging study[28] and this fMRI study were based on samples of 23 and 28 individuals, respectively, suggesting that imaging studies may have greater sensitivity for detecting genetic effects on endophenotypes. (A follow-up study replicated the finding with a larger sample[31].) Indeed, unlike association studies based on self-report, imaging studies have consistently shown that *5-HTTLPR* affects brain function across research groups and tasks. *5-HTTLPR* short-variant carriers, compared with noncarriers, show greater amygdala activation during passive viewing of negative (relative to neutral) pictures[32], implicit processing of negative (relative to neutral) words[33], visuospatial matching of fearful and angry faces (relative to simple geometric shapes) in healthy[30,31,34] and in phobia-prone individuals[35], and in patients with social phobia after a public speaking task (relative to a private speaking task)[36]. On the one hand, such convergent evidence from across tasks, stimulus types and subject categories suggests that increased amygdala activation in response to emotional stimuli, compared with neutral stimuli, is a robust effect. On the other, the variety of tasks, stimulus types and subject categories makes it difficult to assess the replicability of these studies, as hardly any two are alike.

The diversity of imaging approaches has two more drawbacks. First, it is difficult to pool data across studies and research groups to increase power, as was done in a genome-wide association study on breast cancer[37], although a meta-analysis would be helpful in approaching these data. Second, it is difficult to understand the source of variation in observed laterality differences. Specifically, many studies reported right-lateralized activation for short variant carriers[30,31,33,35,36], whereas several reported bilateral activation[32,38,39]. To some extent, this inconsistency may reflect differences in statistical robustness for clusters located in the left and right amygdala. For example, one study reported right-lateralized amygdala activation that was significant after statistical correction[33]. The same study reported left amygdala activation based on a whole-brain approach with an uncorrected activation threshold (but a more stringent cluster size threshold). To another extent, this inconsistency may reflect methodological differences across studies that affect laterality, such as verbal versus nonverbal processing, elaborate representation, sex, or local versus global processing. However, a recent meta-analysis[40] of 54 amygdala imaging papers found no support for any of these models of amygdala laterality, although it noted that overall amygdala activation was left-lateralized, which contradicts studies reporting right-lateralized or bilateral activation in carriers of the *5-HTTLPR* short variant. *5-HTTLPR* imaging studies were not included in the meta-analysis, and therefore the variables that predict amygdala lateralization as a function of *5-HTTLPR* genotype remain to be defined.

Given that the *5-HTTLPR* short variant is associated with neuroticism, and that neuroticism is a risk factor for affective spectrum disorders[41], a subsequent imaging study[34] focused on the modifying impact of the amygdala in the context of 5-HTT's role in depression risk. At issue was whether brain structural and functional features associated with depression (specifically, decreased volume in the subgenual division of the ACC, together with altered activity of the limbic circuit components involving ACC and amygdala) reflect abnormalities that precede the disease, and therefore represent biological vulnerability markers, or whether these features represent a consequence of depression. To address this question, healthy individuals with no history of psychiatric disorders were scanned using structural and functional MRI. Carriers of the *5-HTTLPR* short variant had reduced gray matter volume of both the subgenual ACC and the amygdala. In addition, short-variant carriers, compared with noncarriers, showed decreased functional connectivity between the amygdala and ACC, which leads to dysregulation of the amygdala in response to negative stimuli. Thus, the authors proposed[34] that *5-HTTLPR*-associated vulnerability to depression reflects developmental mechanisms that affect the structural connectivity, and consequently functional interactions, within a neural circuit that regulates emotional reactivity and fear extinction. They further proposed that these functional deficits could be exacerbated by environmental adverse experiences, possibly through impaired fear extinction, and thus give rise to interactions between gene and environment that render individuals vulnerable to depression. This hypothesis is further supported by impaired fear extinction recall in mice with a targeted inactivation of 5-Htt[42].

## Two models of serotonin transporter function

The functional imaging studies of *5-HTTLPR* genotype reviewed above converged on what we refer to as the 'standard' or 'phasic' activation model (**Fig. 2**). This model posits that presence of the *5-HTTLPR* short variant is associated with increased amygdala reactivity to briefly presented (phasic) negative stimuli. The model is intuitive and has substantial face validity, given the association between the short variant and negative emotionality-related personality traits and affective spectrum disorders[41,43]. Because all fMRI studies contrasted negative versus neutral task conditions, the model rests on the assumption that any activation differences associated with the short variant should be attributable to the negative, and not the neutral, condition. However, the choice of baseline can critically affect one's conclusion about the activation state of a brain region[44], as regions, including the amygdala, show decreased activation during cognitive processes when compared with a passive control condition[45].

We explicitly tested whether *5-HTTLPR* genotype was associated with differential response to neutral stimuli, by introducing a second neutral baseline condition during which a fixation cross was presented and participants rested (fixation rest)[33]. We replicated earlier reports that the *5-HTTLPR* short variant is associated with greater amygdala response to negative relative to neutral stimuli, but showed that this differential activation is driven by decreased activation to neutral stimuli (when compared with the fixation rest baseline), instead of increased activation to negative stimuli. We interpreted the data in light of a model of default brain state function[45,46], which proposes that many brain regions show elevated levels of activation in the absence of cognitive constraints (such as when participants are at rest), which are revealed by decreased activation levels during cognitive processing. Indeed, a reanalysis of nine PET studies[45] reported consistent activation decreases in the amygdala (and elsewhere) across several active (emotionally neutral), relative to passive, tasks. The authors speculated that increased activation during the passive condition could reflect ongoing thought processes or monitoring of the environment or body. In a similar manner, participants in our study who were carriers of the *5-HTTLPR* short variant showed elevated levels of amygdala activation during rest, which was revealed by decreased activation during processing of neutral stimuli, and may reflect ongoing thought processes or monitoring activity. However, a definitive interpretation of the data remains unachievable, because fMRI results are based on the relative activation difference between two task conditions, rather than on absolute activation values.

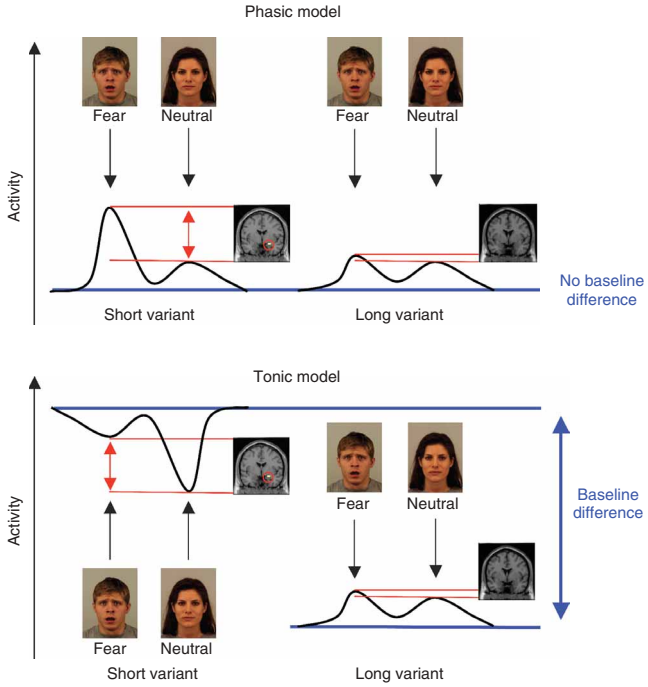


**Figure 2** The standard 'phasic' versus the 'tonic' model of 5-HTT-dependent modulation of brain activity. The phasic model explains greater negative emotionality in carriers of the *5-HTTLPR* short variant, compared with noncarriers, in terms of greater amygdala reactivity to negative stimuli. The tonic model explains greater negative emotionality in carriers of the *5-HTTLPR* short variant, compared with noncarriers, in terms of greater baseline activation of the amygdala.

In light of this notion, an earlier fMRI study was reanalyzed[32,47] to investigate the relation between amygdala activation to negative and neutral pictures, relative to a fixation rest condition, as a function of *5-HTTLPR* genotype. This reanalysis confirmed that individuals who carry the *5-HTTLPR* short variant show decreased activation to neutral, relative to fixation, stimuli. The results were interpreted as indicating elevated amygdala activation during the processing of emotionally undefined stimuli in short variant carriers, and it was suggested that such individuals may experience unconstrained viewing of an undefined stimulus in the scanner as more stressful, aversive or anxiogenic than noncarriers.

Because fMRI is based on relative activation differences across two conditions, one cannot substantiate that the *5-HTTLPR* short variant is associated with elevated activation during the fixation rest condition. To address this limitation, we conducted a perfusion imaging study[38] to measure absolute levels of blood flow at rest as a function of *5-HTTLPR* genotype. We proposed a 'tonic activation' model[38], which posits that carriers of the short variant have elevated levels of amygdala activation at rest, compared with noncarriers (**Fig. 2**). As predicted, carriers of the *5-HTTLPR* short variant had significantly higher absolute resting blood

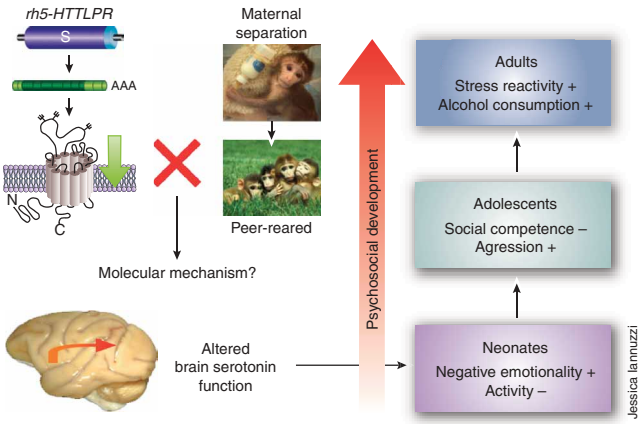


**Figure 3** Effect of interaction between maternal separation and *rh5-HTTLPR* short variant (S), which results in lower 5-HTT mRNA and protein (green arrow; also see **Fig. 1**), on psychosocial development, including brain serotonin function (orange/red arrow), emotion regulation, social competence, stress reactivity, behavior and psychopathology, across the lifespan of rhesus macaques. Plus sign, increase; minus sign, decrease.

flow in the amygdala (and also the hippocampus, another region of relevance for depression[48]) than noncarriers. This result was independently confirmed by another investigation using perfusion imaging that compared resting amygdala activation in homozygous short variant carriers with that of noncarriers[39].

On the one hand, these perfusion data are consistent with the tonic activation model. Tonic activation of the amygdala (and possibly other regions) could have multidimensional effects, such as alteration in arousal state, enhanced acquisition of emotional memories, reduced extinction of such memories, heightened vigilance, or alteration of network functions through projections to or from other regions, all of which could contribute to a depression-vulnerable phenotype, perhaps in interaction with environmental influences (see below). On the other hand, the perfusion data cannot dispel an alternative interpretation: that short-variant carriers are not characterized by tonic activation *per se* (in the sense that the amygdala is intrinsically active at elevated levels), but rather, that they experience scanning as emotionally arousing, which keeps the amygdala active throughout the session. According to this alternative model, tonic activation may be better regarded as a summed activation of repeated phasic responses to an emotionally arousing environment. Thus, the tonic model is not definitive, but rather serves as a useful working model that contrasts with the standard phasic model of 5-HTT function, both of which deserve further experimental evaluation. The tonic model does not deny that the amygdala can respond with a strong phasic response to stress signals[49,50]. Future studies therefore have to address, for example, whether in *5-HTTLPR* short carriers, such phasic response could ride on top of a baseline level of high tonic activation.

If the tonic model is correct, what neural mechanism could account for it? Given the complexity of the serotonergic system, many answers are conceivable that are beyond the scope of this review. One potential mechanism could involve an interaction with the 5- $HT_{1A}$ autoreceptor system in the raphe nuclei. Carriers of the *5-HTTLPR* short variant have lower 5-$HT_{1A}$ receptor binding potential than noncarriers in several brain regions, including the raphe[51], and lower 5-$HT_{1A}$ autoreceptor binding potential in the raphe is associated with greater amygdala activation[52], presumably through negative feedback inhibition. Like most imaging studies, these included relatively small numbers of subjects and thus await further evaluation and extension with larger samples.

## Gene-environment interactions

Several lines of evidence demonstrate that *5-HTTLPR* genotype moderates the effect of environmental variables, particularly developmental and life experience stressors, on later emotional and social behavior. At the behavioral level, there are compelling data from both nonhuman primates and from clinical populations. In rhesus monkeys (*Macaca mulatta*), maternal separation during the first months of life results in deficient social adaptation and peer interaction[53]. These deficiencies are related to serotonergic system function, based on rhesus monkey cohorts that were tested for associations between early life stress, serotonin function, and *rh5-HTTLPR* (a repeat length variation in the transcriptional control region of the rhesus *SLC6A4* gene orthologous to the human *5-HTTLPR*) genotype: in addition to main effects of *rh5-HTTLPR* and early stress to variation in serotonergic function in later life[54], *rh5-HTTLPR* genotype also interacts with deleterious early rearing experience to influence attentional and emotional resources, stress reactivity, and alcohol preference and dependence[55–57] (**Fig. 3**).

Behavioral analysis has also shown similar gene-environment interactions in humans[58]. Carriers of the *5-HTTLPR* short variant are up to twice as likely to get depressed after stressful events such as bereavement, romantic disasters, illnesses or job loss, and childhood maltreatment significantly increases this probability[58]. These associations are supported by two replication studies[59,60], although the literature is inconsistent, with partial replications suggesting further moderation by gender[61,62] or social support[60]. Two studies[63,64] failed to replicate this gene-environment interaction effect altogether, but also used older subject populations than the other studies, indicating that age might be an important variable. As we suggested for earlier association studies, inconsistent replications may be attributable to a small effect size, which could potentially be addressed with endophenotype measures, such as those obtained through neuroimaging.

To investigate gene-environment interactions at the brain systems level, we conducted an fMRI study of healthy volunteers who were genotyped for *5-HTTLPR* and had completed self-report measures of life stress history and levels of rumination[38]. In addition to the amygdala, the hippocampus was included as an a priori region of interest, given its role in depression and stress[65–70]. Both regions showed a gene-environment interaction effect: activation at rest (compared with an active face processing condition) correlated positively with life stress in short variant carriers, but correlated negatively with life stress in noncarriers. Perfusion data further confirmed this gene-environment interaction for resting activation in amygdala and hippocampus. Life events also differentially, as a function of *5-HTTLPR* genotype, affected changes in functional connectivity of the amygdala and hippocampus with a wide network of other regions in response to emotional stimuli, as well as affecting gray matter structural features. These interactions may constitute a neural mechanism for epigenetic vulnerability to depression in carriers of the short variant, by upregulating resting activation in key regions associated with affect and stress, and either directly or indirectly affecting structural features (possibly by modulating neurogenesis[71,72]) within a circuitry that modulates emotional behavior. These interactions are behaviorally relevant because short variant carriers show increased rumination associated with life stress, whereas noncarriers show decreased rumination[38].

Taken together, these investigations are beginning to identify specific neural correlates of gene-environment interactions that affect emotional behavior and render individuals vulnerable to depression and

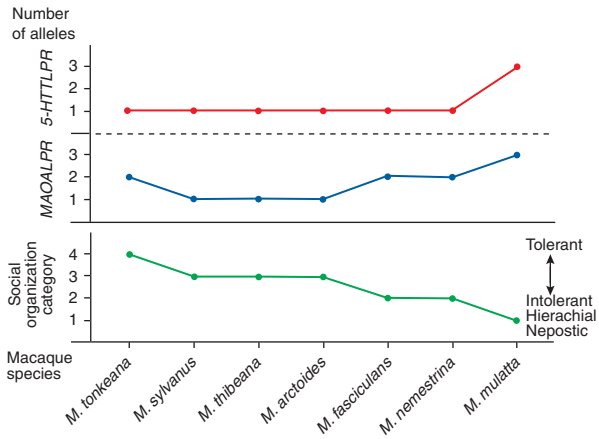


**Figure 4** Degree of variation in two genes of the serotonin signaling pathway (serotonin transporter, *5-HTTLPR*; monoamine oxidase A, *MAOALPR*), aggression and social organization in seven macaque species. This four-grade classification of social organization across several species of the genus *Macaca* is based on the extent and asymmetry of aggression-related behavior within specific macaque species[76]. Grade 1 species show highly hierarchical and nepotistic societies as well as low levels of conciliatory behaviors, whereas grade 4 species can be considered as more tolerant, showing relaxed dominance, open relationships and high levels of conciliatory behaviors. For example, the risk of a retaliatory attack from a subordinate is much higher in grade 4 species than in grade 1 after an initial attack by a dominant, but the retaliatory attack is likely to be much less severe, and the probability of reconciliation much higher, in grade 4 than grade 1 macaques.

comorbid disorders. In a search for the mechanisms underlying these gene-environment interactions, both bottom-up and top-down perspectives will be useful in guiding future work. Bottom-up analyses will investigate whether environmental stressors (for example, early maternal separation, neglect or other life stress experiences) alter epigenetic programming of *SLC6A4* transcription[73], as occurs for other genes[74], and whether these molecular events have consequences at the neural level, such as leading to alterations in resting activation or in structural features of networks that regulate emotional behavior. Top-down analyses will have to address how coping skills or other behavioral interventions may mitigate the vulnerability that may be conferred from genetic predispositions or exposure to unfavorable gene-environment interactions[60].

## A broader role in social cognition and behavior

Beyond emotion and depression, 5-HTT also seems to be involved in social behavior. For example, studies of macaques indicate a link between social behavior and phylogeny that implicates *SLC6A4* variation[75–77] (**Fig. 4**). Macaque species having tolerant societies, with relaxed dominance and high levels of conciliatory behavior, are monomorphic for the *5-HTTLPR* (and a similar repeat length polymorphism, *MAOALPR*, upstream of the monoamine oxidase A gene (*MAOA*), whereas species that show intolerant, hierarchical and nepotistic societies are polymorphic at one or more of these loci[78]. Rhesus monkeys, the most intolerant and hierarchical species of macaque, show the greatest degree of allelic variation in both genes. These findings suggest that genetic variation of serotonin neurotransmission affects the degree of interspecies variation in aggression-related behavior of macaques.

In humans, two association studies[1,2] reported a significant negative correlation between the *5-HTTLPR* short variant and the personality trait 'agreeableness'. Such social traits may derive from 5-HTT-linked anxiety that regulates an individual's response to actual or threatened exclusion from social groups[79], and may have cultural ramifications as a possible population-typical adaptation to prevent social exclusion[80].

There is no direct evidence that *5-HTTLPR* genotype moderates neural circuits in the context of social interaction. Nevertheless, suggestive evidence may be derived from our studies[33,38] that found several brain regions associated with social behavior to show differential effects on activation or gray matter structure as a function of *5-HTTLPR* genotype (**Fig. 5**). For example, we observed significant gene-environment interactions in the superior parietal lobule, superior temporal gyrus, inferior frontal gyrus, precentral gyrus, striatum, insula and anterior cingulate, which collectively comprise a network believed to be involved in imitation, imitative learning, social cognition and communication[81,82]. Although the tasks we used were not specifically designed to assess social cognition, the stimuli used in our study were facial emotional expressions, which carry considerable social information. These indirect data therefore lead to the intriguing hypothesis that social behavior may be subject to an interaction between psychosocial stress and *5-HTTLPR* genotype.

We speculate that the cellular substrate by which such a gene-environment interaction could modulate social behavior involves cell types located in some of the above-mentioned regions that are proposed to be important in social communication (**Fig. 5**). One cell type belongs to the mirror neuron system, which is activated during goal-directed behavior or the observation of such behavior in others[83,84]. The other cell type is the Von Economo neuron, which is believed to be involved in social bonding and fast assessment of complex situations[85]. Dysfunction of these cell types may cause social and communication disabilities associated with autistic syndromes[85,86]. Therefore, one putative mechanism by which the gene-environment interaction would alter processing in these regions could be epigenetic targeting of the neural circuit of imitation and bonding. If this were the case, these cell types should either be innervated by and/or be sensitive to the actions of serotonin, linking *SLC6A4* variation to individual differences in the function of these systems, although there is currently no empirical support for this conjecture.

## Future directions and conclusions

Here, we have highlighted recent work on the role of *5-HTTLPR* genotype in emotion and social cognition and identified a number of

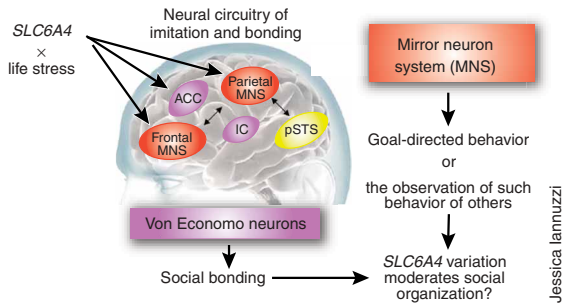


**Figure 5** Influence of interaction between *SLC6A4* and environment on neural networks of social cognition and emotion regulation. These interactions are documented in brain regions that comprise the frontal and parietal mirror neuron system (MNS; orange) or that contain Von Economo neurons (purple), both of which have a role in social cognition and bonding. ACC, anterior cingulate cortex; IC, insular cortex; pSTS, posterior superior temporal sulcus (visual input to MNS).

rich topic areas for future work. For example, the tonic and phasic models of 5-HTT function need more empirical testing in both healthy and patient populations and need to be complemented by electrophysiological measures from animal studies. Future studies will also have to evaluate whether gene-environment interactions involving *5-HTTLPR* modulate neural activation during imitation or social processing tasks, and whether such modulation is specific to the mirror neuron system or Von Economo neurons.

Epigenetic mechanisms and functional proteomics are another rich domain for future work. At the behavioral level, researchers need to dissociate the effects of early-life versus recently experienced stressors on neural correlates of gene-environment interactions, given that the onset of major depressive episodes is associated with recent life stressors[87]. At the molecular level of analysis, life-stress studies should incorporate genome-wide screening for DNA methylation and histone acetylation (as well as other epigenetic processes) in determining gene expression[74,88], and apply this work to human subjects. Finally, genetic studies of individual differences in personality, psychopathology and social function will need to investigate post-translational modification of proteins and construct transcriptome and proteome maps of molecules implicated in the brain circuits mediating these behaviors[89].

Epistatic (gene-gene interaction) mechanisms and large-scale genomics represent another future challenge. More than a hundred gene polymorphisms may contribute to individual differences in complex traits. Therefore, more physiologically relevant polymorphisms in genes within a single neurotransmitter system, or in genes that act in concert and thus comprise a functional unit, need to be identified in both large population and family-based association studies that carefully minimize stratification artifacts. Existing data already show additive effects in pairs of serotonergic genes[90], but the assessment of larger groups of interacting polymorphisms, or of large-scale data from whole-genome scans, will require the development of new biostatistical tools and sophisticated computational models[91,92].

We conclude that the impact of 5-HTT on behavior is likely to be much broader than previously thought. We hope that this review will motivate investigators to study the role of *5-HTTLPR* genotype, and gene-environment interactions, in disorders related to social behavior. Beyond clinical applications, we anticipate advances in social neuroscience toward the development of testable, predictive models of complex human behavior that successfully integrate both genetic and psychological data.

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**COMPETING INTERESTS STATEMENT**

The authors declare no competing financial interests.

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