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The Effect of the Serotonin Transporter Polymorphism (5-HTTLPR) on Empathic and Self-Conscious Emotional Reactivity

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We examined the relationship between a functional polymorphism of the serotonin transporter gene (5-HTTLPR) and individual differences in emotional reactivity in two laboratory studies. In Study 1, empathic responding and physiological reactivity to viewing films of others in distress were assessed in healthy adults in three age groups. In Study 2, emotional responding to watching oneself in an embarrassing situation was assessed in healthy adults and in patients with neurodegenerative diseases. In Study 1, participants with two short alleles of 5-HTTLPR reported more personal distress and showed higher levels of physiological responses in response to the films than participants with long alleles. In Study 2, participants with two short alleles reported more anger and amusement and displayed more emotional expressive behaviors in response to the embarrassing situation than participants with long alleles. These two findings from diverse samples of participants converge to indicate that individuals who are homozygous for the short allele variant of 5-HTTLPR have greater levels of emotional reactivity in two quite different socially embedded contexts.

Keywords: 5-HTTLPR, empathy, self-conscious emotions, physiology, reactivity

The 5-HTTLPR is a polymorphic region of the SLC6A4 gene that codes for regulating the transcription of serotonin (5-HTT; Heils et al., 1996). The polymorphism is based in the promoter region of the gene. There are two variants commonly distinguished in research, the long or L allele and the short or S allele. In the central nervous system the S allele is associated with lower levels of serotonin uptake and lower transcriptional efficiency of the serotonin transporter protein in *in vitro* and postmortem human cells (Heils et al., 1996; Lesch et al., 1996; Little et al., 1998). Early influential studies of the consequences of these variants adopted gene by environment designs to examine negative outcomes associated with carrying these alleles and being exposed to difficult environmental conditions over relatively long periods of time. These studies in general suggested a link between carrying at least one S allele and developing distal negative outcomes such as depression and anxiety after being exposed to challenging environments (Caspi et al., 2003; Lesch et al., 1996).

The robustness of these distal effects were questioned in several meta-analyses (e.g., Munafò, Durrant, Lewis, & Flint, 2009; Risch et al., 2009; but see Caspi, Hariri, Holmes, Uher & Moffitt, 2010 for a different conclusion). Importantly, the most inclusive meta-analysis to date recently strongly reaffirmed the associations reported earlier (Karg, Burmeister, Shedden, & Sen, 2011). In addition to these distal correlational effects, there is accumulating evidence from controlled experimental paradigms supporting a link between the S allele and heightened reactivity in general on a number of relatively proximal behavioral, neural, and immune responses. In terms of individual differences in the emotional realm, a number of studies have demonstrated a link between the S allele of 5-HTTLPR and heightened emotional reactivity (especially negative emotion). Healthy participants with S alleles have

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been shown to process emotional pictures and faces in negatively biased ways (Beevers et al., 2011; Beevers, Wells, Ellis, & McGeary, 2009; Fox, Ridgewell, & Ashwin, 2009; Hayden et al., 2008; Osinsky et al., 2008), react to loud and unpleasant noises with increased startle response (Brocke et al., 2006), and learn to associate stimuli with startle noises more readily because of their noxious nature (Lonsdorf et al., 2009). Individuals with the S allele also evidence heightened immune reactivity, such as elevated inflammatory cytokine responses (Fredericks et al., 2010) and higher cortisol responses in response to social evaluative stress (Way & Taylor, 2010a), and show slower recovery of cortisol responses after a stressful math task (Gotlib, Joormann, Minor, & Hallmayer, 2008). Furthermore, on stressful days, individuals with the short allele report experiencing more anxious mood (Gunthert et al., 2007). Neuroimaging studies have provided insights into possible mechanisms underlying heightened emotional reactivity among individuals with the S allele, demonstrating that S carriers have increased amygdala activation to negative faces (Hariri et al., 2005) and decreased coupling between amygdala and the ventral anterior cingulate cortex (vACC/pgACC). These findings suggest that there are variations in circuitry critical for regulating negative emotion in individuals with the short allele (Pezawas et al., 2005). The emerging understanding from these studies is that elevated baseline negative affectivity associated with the S allele underlies biased information processing and the excitability of emotional circuits. These mechanisms may ultimately provide a basis for connecting findings that involve proximal effects of the S allele with those that involve more distal effects. For example, higher negative emotional reactivity and compromised emotion regulatory circuitry, combined with other vulnerability factors and difficult environments might be most conducive to the development of full-blown clinical psychopathology (Carver, Johnson, & Joormann, 2008; Caspi et al., 2010).

As noted earlier, most studies have used simple auditory (e.g., noxious noises) or visual (e.g., static images of fearful or angry faces) stimuli to study differences in emotional reactivity linked to 5-HTTLPR. These approaches have the advantage of affording tight experimental control, but beg the question of whether similar gene–behavior relationships would be found in more complex, socially embedded situations. Extending work to these more social domains is particularly critical because impairments in socioemotional functioning are precursors to many forms of psychopathology such as depression and social anxiety (Rottenberg & Johnson, 2007). To pursue this further, the present studies investigated the effect of 5-HTTLPR on proximal measures of emotional reactivity in two contexts that are arguably more socially embedded than those used in many previous studies: (a) empathic responding to the distress of others and (b) self-conscious emotional responding.

The Present Studies

We report findings from two laboratory studies using independent samples of participants that assess the relationship between 5-HTTLPR and proximal measures of two aspects of emotional reactivity (empathy and self-conscious emotional responding). Study 1 investigated the effect of 5-HTTLPR on self-reported and physiological aspects of empathic responding to the distress of others in a sample of healthy adults in three age groups (young, middle-aged, old). The self-report measures of primary interest were related to two fundamental aspects of empathy (Batson, Coke, & Darley, 1978; Eisenberg, 2003; Eisenberg & Miller, 1987): empathic concern (feelings of warmth and concern) and personal distress (feelings of discomfort and distress). The physiological responses of primary interest were electrodermal and cardiovascular, which reflects the existing literature on empathic responding. For example, a number of studies have found elevated electrodermal responding during empathic responding (Blair, 1999; Craig & Lowery, 1969; Lanzetta & Englis, 1989). Cardiovascular measures have also been frequently used; however, the pattern of findings has been less consistent (Craig & Lowery, 1969; Eisenberg et al., 1989; Eisenberg & Fabes, 1990; Hastings, Zahn-Waxler, Robinson, Usher, & Bridges, 2000; Krebs, 1975).

We hypothesized that S carriers would show heightened personal distress, indicating that they internalize, react more intensely, and have difficulty in differentiating between their own distress and that of others. We did not expect to find differences in empathic concern, because this does not involve one's own distress, but rather is an other-directed component of empathic responding. In addition, we expected that participants with the S allele would show elevated physiological responding.

Study 2 investigated the effect of 5-HTTLPR on self-reported and behavioral indicators of self-conscious emotional responding in an embarrassing situation. Embarrassment is an inherently social emotion, which arises when we perceive ourselves to have violated social norms (Keltner, 1996). In this study, both healthy adults and patients with neurodegenerative disease were included. Previous studies have shown that S carriers respond to social-evaluative situations with heightened cortisol responses (Way & Taylor, 2010a) and that these responses are slower to return to baseline levels (Gotlib et al., 2008). Furthermore, among socially anxious individuals, those with the S allele show more severe symptoms and heightened amygdala responses to negative faces (Furmark et al., 2004). Recently, we have found that deficits in self-conscious emotional responding have a close association with neural loss in the pregenual anterior cingulate cortex (pgACC; Sturm et al., 2012). Other studies have found that individuals with the S allele have reduced neural connectivity between pgACC and the amygdala (Pezawas et al., 2005). This suggests a possible deficit in connectivity between important emotion generation and emotion regulation regions.

On the basis of these findings, we hypothesized that participants with the S allele would show heightened emotional responding in an embarrassing situation designed to direct attention to the self.

Study 1

Participants

One hundred sixty-three participants were recruited using fliers and online ads in the local community and from a research participant database administered by the University of California, Berkeley. Participants signed consent forms approved by the University of California, Berkeley. Participants were recruited in three age groups: 50 participants in the young age group (age range, 20–30 years, $M = 22.71$, $SD = 2.56$), 48 middle-aged participants (age range, 40–50 years, $M = 44.29$, $SD = 2.84$), and 65 older participants (age range, 60–80 years, $M = 66.01$, $SD = 5.56$). In terms of gender, 66.88% of the participants were female (gender at birth). Reflecting the racial/ethnic composition of the greater San

Francisco Bay Area, the sample was 70.63% Caucasian/White, 13.75% Asian, 6.75% Latino/a, 3.13% African American, and 6.25% other. Participants were selected such that gender and minority status were distributed evenly across the three groups. Participants had to be sufficiently healthy to be able to travel to the laboratory alone and participate in a laboratory assessment of emotional functioning. Data from this sample have been reported previously in a study of age differences in empathic responding (Sze, Gyurak, Goodkind, & Levenson, 2011). Table 1 displays demographics for the sample broken down by 5-HTTLPR status. There were no differences in gender, $\chi^2 = .49$, $p = .77$, as a function of 5-HTTLPR status. Groups did differ in race/ethnicity, $\chi^2 = 27.69$, $p = .005$; however, this difference was not significant when race/ethnicity was coded as White versus Other (the coding used in our main analyses), $\chi^2 = 3.44$, $p = .17$.

Measures

Emotional experience. Upon arriving at the laboratory and again immediately after viewing each of two empathy inducing films (described below), participants completed an emotional response questionnaire on which they indicated the degree to which they were feeling each of 18 emotion items using a 5-point Likert scale (1 = *not at all*; 5 = *extremely*). Based on previous empathy research (Batson et al., 1987; Eisenberg, 2003), three of the items measured empathic concern (EC; sympathetic, moved, compassionate) and three items measured personal distress (PD; disturbed, upset, worried). These items were averaged to compute mean scores for EC and PD separately for each film. Alpha reliabilities among the EC and PD items were high (alphas averaged across films: empathic concern = .89; personal distress = .89). Finally, to ensure that the two films differed thematically, two other items (enthusiastic, proud) were used to compute an "uplifting" score that was used as a manipulation check (see below).

Table 1
Descriptive Statistics for Study 1 and Study 2

	Study 1		Study 2[a]	
	n or *M*	*SD*	*n* or *M*	*SD*
	LL genotype			
Race/ethnicity				
White/Caucasian	24		34	
Asian	1		0	
Hispanic/Latino	0		1	
African American	7		0	
Multiple race/ethnicity	3		0	
Depressive symptoms	.72	.68	n/a	n/a
Age	52.31	19.35	64.05	9.12
Males	23		26	
	SL genotype			
Race/ethnicity				
White/Caucasian	63		44	
Asian	10		1	
Hispanic/Latino	3		1	
African American	3		1	
Multiple race/ethnicity	5		0	
Depressive symptoms	.61	.60	n/a	n/a
Age	45.08	18.90	62.47	9.27
Males	54		29	
	SS genotype			
Race/ethnicity				
White/Caucasian	26		15	
Asian	13		1	
Hispanic/Latino	2		1	
Multiple race/ethnicity	3		0	
Depressive symptoms	.65	.60	n/a	n/a
Age	43.95	16.65	61.61	11.05
Males	31		12	

Note. For Study 1, there are no differences in depressive symptoms, $F < 1$, sex, $\chi^2 = .49$, $p = .77$, as a function of 5-HTTLPR status but groups differ in race/ethnicity, $\chi^2 = 27.69$, $p = .005$. though this difference did not hold when race/ethnicity was coded as white versus minority, $\chi^2 = 3.44$, $p = .17$. For Study 2, there were no differences in gender, $\chi^2 = 3.31$, $p = .50$, or race/ethnicity, $\chi^2 = 3.44$, $p = .90$, as a function of 5-HTTLPR status.
[a] Depression scores were not available (n/a) in Study 2.

Physiology. Continuous recordings of seven physiological measurements of autonomic nervous system activity were measured using a system consisting of either a Grass Model 7 or a Biopac MP-150 (Biopac, U.S.A., Goleta, CA) polygraph. Physiological responses were monitored and averaged on a second-by-second basis for each of the following measures using a computer program written by one of the authors (R.W.L.): (1) interbeat interval (interval, in milliseconds, between successive R waves [using Beckman miniature electrodes with Redux paste or Vermed SilveRest EKG pregelled electrodes] placed on opposite sides of the participant's chest); (2) finger pulse amplitude (a photoplethysmograph attached to the ring finger of the nondominant hand recorded the volume of blood in the finger and the trough-to-peak amplitude of the finger pulse); (3) finger pulse transmission time (the time interval in milliseconds was measured between the R wave of the EKG signal and the upstroke of the peripheral pulse at the finger site, recorded from the distal phalanx of the ring finger of the nondominant hand); (4) ear pulse transmission time (a photoplethysmograph attached to the right earlobe recorded the volume of blood in the ear, and the time interval in milliseconds was measured between the R wave of the EKG and the upstroke of peripheral pulse at the ear site); (5) systolic blood pressure, and (6) diastolic blood pressure (an occluding cuff was placed on the middle phalange of the middle finger of the nondominant hand, and blood pressure was measured on each heartbeat using an Ohmeda Finapress 2300), and (7) skin conductance (a constant-voltage device was used between two Beckman or BIOPAC electrodes [filled with an electrolyte of sodium chloride in Unibase] attached to the palmar surface of the middle phalanges of the ring and index fingers of the nondominant hand).

Three other physiological responses were also monitored (i.e., finger temperature, respiration period, and general somatic activity); however, as explained above, based on prior empathy research (e.g., Eisenberg & Fabes, 1990; Eisenberg et al., 1989; Krebs, 1975), cardiovascular and electrodermal measures were chosen as the focus of the present study. As with our previous study using these data (Sze et al., 2011), we created a composite measure using the standardized mean of the above described variables (with each variable adjusted for baseline physiological levels by subtracting the average for the 30-s prefilm baseline period and rescaled so that higher values indicated greater levels of sympathetic nervous system activation).

Depressive symptoms. The depression subscale from the Brief Symptom Inventory (BSI-18; Derogatis, 2001) was used to assess symptoms of depression. Participants reported on their

symptoms using a 5-point Likert scale (0 = *not at all*; 4 = *extremely*). The BSI-18 has been extensively validated and shows good psychometric properties of reliability and validity. Mean depression score for this sample was .65, $SD = .62$, which is below the level associated with clinical depression.

5-HTTLPR genotyping. DNA was collected and extracted from saliva using Oragene kits (OG-250; DNA Genotek, Kanata, Ontario, Canada) according to manufacturer's protocol. All DNA samples were labeled with an anonymous code and were extracted and purified by an external lab (Abbott-UCSF Viral Diagnostics and Discovery Center, San Francisco, CA). The extracted DNA was then genotyped using the procedure described in Assal et al. (2004), with slight modifications. Briefly, a PCR product was amplified with primers (5′-GGCGTTGCCGCTCTGAATGC-3′ and 5′-GAGGGACTGAGCTGGACAACCA-3′) flanking the region containing the gene variation. The PCR conditions consisted of a 2-min denaturation step at 94 °C, 35 cycles of 30-s denaturation at 95 °C, 30-s annealing at 60 °C, and 30-s extension at 72 °C, and a final 7-min extension step at 72 °C. The genotyping yielded three groups, individuals with two short alleles (SS; $n = 44$), one long and one short allele (SL; $n = 84$), or two long alleles (LL; $n = 35$). This genotype distribution was consistent with previous studies and did not deviate from Hardy-Weinberg equilibrium, $p = .74$.

Procedure

On arrival, participants were greeted by a female experimenter and seated in a comfortable chair in a sound-attenuated experimental room. A 17-inch monitor was placed in front of the participants, Participants were told that they were in a study of emotion and that their behavior and physiological reactions would be recorded. After signing the consent form, a female assistant began attaching the physiological sensors. While these were being attached, participants completed the questionnaire assessing self-reported emotional experience. The experimental protocol consisted of a series of tasks measuring emotional functioning. Here we focus on the tasks in which participants viewed two empathy-inducing films (described below). After the laboratory session, participants either provided genetic samples on site, or, if time did not permit, were mailed the collection device and were given instructions via telephone as to how to collect the genetic samples and mail them back. Participants were paid $60 for completing a questionnaire package, participating in the 2.5hr our laboratory session, and providing the genetic sample.

Each participant viewed two emotional films, both designed to elicit empathic responding. The first film was entitled "Surfers," and it had an uplifting theme, beginning with a brief introduction to childhood autism followed by images of children with autism learning how to surf at a nonprofit camp called Surfers Healing (1 min 56 s). The second film was entitled "Darfur," and it had a distressing theme, beginning with a brief introduction to the Darfur crisis and then presenting images of men, women, and children who are wounded, starving, and dying (1 min 57 s). Manipulation checks indicated that, consistent with the hypothesis, the Surfers film was rated as more uplifting than the Darfur film, $t(159) = 19.04$, $p < .0001$, $M_{\text{Darfur}} = 1.15$, $SD = .49$; $M_{\text{Surfers}} = 2.98$, $SD = 1.22$. Additionally, responses to the two films differed on empathic concern, $M_{\text{Darfur}} = 4.19$, $SD = 1.02$; $M_{\text{Surfers}} = 3.56$, $SD = 1.04$, $t(159) = -8.93$, $p < .0001$, and personal distress, $M_{\text{Darfur}} = 3.62$, $SD = 1.20$; $M_{\text{Surfers}} = 1.26$, $SD = .66$, $t(159) = -23.06$, $p < .0001$, with the Darfur movie eliciting higher levels of empathic concern and personal distress than the Surfers movie.

Both films were preceded by a 1-min resting period during which participants were asked to clear their mind, relax, and focus on an "X" in the center of the screen. Fifty-three seconds into the rest period, a written message appeared above the "X" indicating that the film was about to start. Presentation of the films was randomized across participants. Following each clip, participants filled out the same emotional response questionnaire as they did at the beginning of the study.

Data Analysis

There are several ways to structure statistical comparisons when dealing with the three 5-HTTLPR groupings (i.e., two short alleles, one short and one long allele, two long alleles). In a recent review of studies of 5-HTTLPR × environment interactions by Caspi et al. (2010), 10 studies found effects of the SS variant when compared with SL and LL, 9 studies found effects of the LL variant when compared with SS and SL, and 14 studies found a linear additive effect across the three variants. On the basis of this review, we chose a model that used a "thermometer" coding (Kendler, Kuhn, Vittum, Prescott, & Riley, 2005) to allow simultaneous examination of both S and L effects. The 5-HTTLPR genotype was coded using two dummy variables (H1 and H2), where participants with two S alleles were coded as 1 on both variables, participants with one S and one L alleles were coded as 1 on one variable and 0 on the other, and participants with two L alleles were coded as 0 on both variables. This approach is well suited for the 5-HTTLPR genotype because it anchors the analyses at the most vulnerable SS genotype (coded as 1, 1), extends all the way to the least-vulnerable LL genotype (coded as 0, 0), and assigns intermediate levels to the SL genotype (coded as 1, 0). Accordingly, a significant effect of H1 indicates a difference of the LL genotype from SS/SL and a significant effect of H2 indicates a difference of the SS genotype from SL/LL.

Data in Study 1 were analyzed in an omnibus general linear model using the GLM syntax in SAS (Version 9.2; SAS Institute, Cary, NC). The structure of the analysis was 2 × 2 × 2: 5-HTTLPR effect [H1 and H2] × Film [Surfers or Darfur] × Empathic response [empathic concern or personal distress] with Film and Empathic response treated as within-subject repeated-measures factors for self-reported responses. The analysis structure was identical for the physiological reactivity except there was no within-subject Empathic response factor, which resulted in a 2 × 2: 5-HTTLPR effect [H1 and H2] × Film [Surfers or Darfur] structure. In the self-report analyses, covariates were depressive symptoms (included because of prior studies linking 5-HTTLPR polymorphisms with depression; e.g., Caspi et al., 2003), age in years (included because participants were recruited in age-brackets of young, middle, and older participants resulting in a discontinuous distribution), and averages of the initial levels of empathic concern and personal distress. In the physiological analyses, covariates were depressive symptoms and age. Significant interactions were decomposed using least-squares means t tests. The results of primary interest were those main effects and interactions that involved the 5-HTTLPR factors [H1 and H2]. Significant

main effects and interactions involving 5-HTTLPR were also followed up with additional analyses conducted with gender (0 = *female*; 1 = *male*) and race/ethnicity (0 = *Other*; 1 = *White*) as between-subjects factors to examine whether 5-HTTLPR findings were moderated by these factors.

Results: Study 1

5-HTTLPR and emotional experience. Using the 5-HTTLPR [H1 and H2] × Film [Surfers or Darfur] × Empathic response [empathic concern or personal distress] model, we found a significant 5-HTTLPR × Empathic response effect, $F(1, 155) = 3.77$, $p = .05$. No other terms involving our main variables of interest were significant. Because the 5-HTTLPR × Film effects were not significant, both Fs(1,155) < 1, we decomposed the significant two-way interaction by collapsing across films. In this new model, 5-HTTLPR [H2] showed a main effect on personal distress indicating the effect of the S allele, $F(1, 155) = 7.35$, $p = .01$, whereas there were no 5-HTTLPR effects on empathic concern, Fs(1,155) < 1. No other interactions were significant. Importantly, least-squares means t tests revealed that participants with the SS genotype reported the highest level of personal distress, which was significantly higher than those of participants with the SL/LL genotypes, $t(155) = -2.40$, $p = .01$. These results are depicted in Figure 1. In follow-up analyses these results did not differ by age $F(1, 155) = 1.42$, $p = .23$, *ns*, race/ethnicity coded as White/Other,[1] $F(1, 154) < 1$, *ns*, or gender, $F(1, 154) = 1.39$, $p = .24$.

5-HTTLPR and physiological responses. Using the 5-HTTLPR effect [H1 and H2] × Film [Surfers or Darfur] model, we found no Film × 5-HTTLPR interaction, $F(1, 155) = .56$ and 1.14, *ns,* respectively; thus we collapsed physiological responding across the two films. In this new model, there was a significant main effect of 5-HTTLPR genotype [H2], $F(1, 155) = 7.66$, $p = .001$ with no other terms being significant. Least-squares means t tests revealed that participants with the SS genotype showed the highest level of physiological responding, which was significantly higher than those of participants with the SL/LL genotypes, $t(155) = -2.77$, $p = .001$. These results are depicted in Figure 2. In follow-up analyses of the interaction effects, these results did not differ by age $F(1, 154) = 1.17$, $p = .28$, race/ethnicity coded as White/Other,[1] $F(1, 154) < 1$, *ns*, or gender, $F(1, 154) < 1$, *ns*.

Preliminary Discussion: Study 1

Participants with the SS genotype reported greater levels of personal distress in response to films depicting others in distress than participants with either the SL or LL variant but did not differ in levels of empathic concern. This suggests some specificity in the greater emotional reactivity associated with the SS genotype. SS individuals may be more inclined to internalize the negative feelings of others and have greater difficulty distancing themselves from others' distress. Participants with the SS genotype also showed elevated physiological reactivity in a composite measure of cardiac and electrodermal response. These self-report and physiological results parallel previous findings of heightened reactivity in hormonal and neural correlates of emotions among participants with the SS genotype (e.g., Lonsdorf et al., 2009; Way & Taylor, 2010a).

Study 2

The finding that participants in Study 1 with the SS 5-HTTLPR genotype experienced greater levels of personal distress raised the question of whether other aspects of self-related emotional reactivity might be elevated in these individuals as well. Thus, in Study 2, we focused on embarrassment, an emotion that arises when aspects of the self are evaluated as failing to measure up to social norms (Keltner, 1996), utilizing procedures for studying self-conscious emotional reactivity that we have used in previous studies (Sturm, Ascher, Miller, & Levenson, 2008; Sturm, Rosen, Allison, Miller, & Levenson, 2006).

Participants

We enrolled both normal healthy adults and patients with neurodegenerative diseases. Our rationale for including the latter was our interest in studying possible influences of 5-HTTLPR variants on emotional reactivity in syndromes that impact emotion centers in the brain. The sample consisted of 106 participants (no overlap with Study 1) including 82 (77.4%) patients with suspected neurodegenerative disease and 24 (22.6%) age-matched healthy controls. All participants were recruited through the Memory and Aging Center at the University of California, San Francisco. Participants signed consent forms approved by the University of California, Berkeley. Patients and healthy participants were evaluated by a multidisciplinary team including neurologists, neuropsychologists, psychiatrists, and nurses, using neurological testing, neuropsychological testing, and structural MRI. Thirty-two patients met criteria for Alzheimer's disease based on NINDS-ADRDA criteria (McKhann et al., 1984); 27 patients met criteria for frontotemporal lobar degeneration (FTLD; Neary et al., 1998); six for corticobasal syndrome (Boxer et al., 2006); four for amyotrophic lateral sclerosis (Ince, Lowe, & Shaw, 1998); three for progressive supranuclear palsy (Litvan et al., 1996); two for mild cognitive impairment (Ritchie, Artero, & Touchon, 2001); and one for primary progressive aphasia (Gorno-Tempini et al., 2011). The remaining seven patients could not be diagnosed according to these criteria but showed symptoms of neurodegeneration and thus received a diagnosis of neurodegeneration not otherwise specified (NOS). None of the 24 healthy participants had a previous history of neurological or psychiatric disorder.

Participants were on average 62.89 years old ($SD = 9.70$, range: 28–85). Sixty-seven percent were male (Missing: .9%). The sample was predominantly Caucasian (White/Caucasian, 87.7%, African American, .9%; Asian American, 1.9%; Latino/a, 2.8%;

[1] Given recent evidence that the effects of 5-HTTLPR might differ as a function of race/ethnicity (Chiao & Blizinsky, 2010) in Study 1 where we had some variability on race/ethnicity, we also tested the effects of race/ethnicity as a categorical variable coding for White/Caucasian, Asian, Hispanic, African-American, and Multiracial background separately. These analyses showed that 5-HTTLPR genotype did not interact with race/ethnicity on any of the outcome variables, all $F(1,106)$s < 2. Furthermore, when restricting our analyses only to White/Caucasian race/ethnicity, the findings remained significant such that participants with the SS genotype reported more personal distress in response to the films than those with SL/LL genotypes, $F(1,111) = 5.77$, $p = .02$. For physiological reactivity the effect of 5-HTTLPR was attenuated but remained in the same direction, $F(1,111) = 3.67$, $p = .06$.

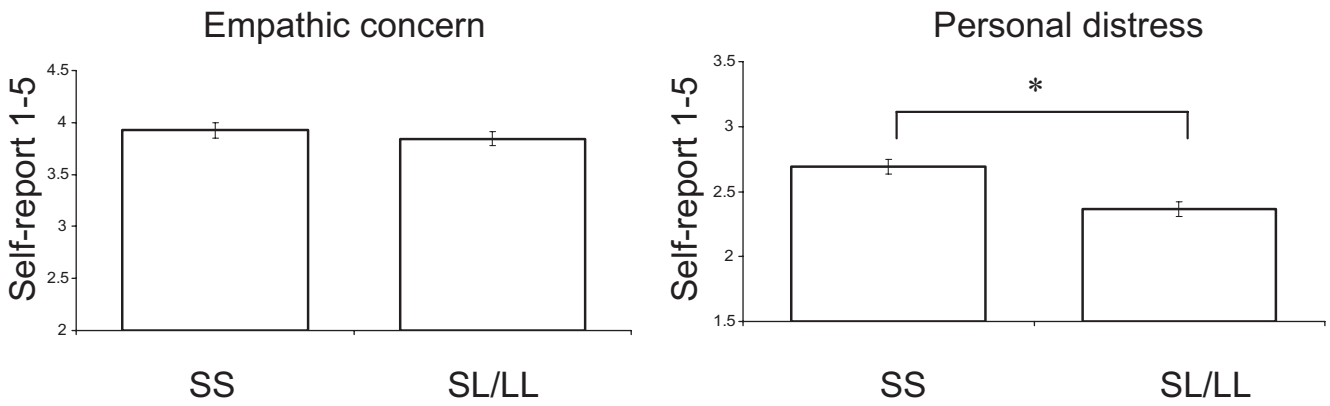

Figure 1. Study 1: 5-HTTLPR and self-reported empathic concern and personal distress in response to films of others in distress. There are no differences in empathic concern, but the SS variant differs from the SL/LL variant on personal distress. *Note*. Estimated marginal means (controlled for covariates). Error bars represent standard errors of the mean. * $p < .05$.

Missing, 6.6%). Table 1 displays demographics information broken down by 5-HTTLPR status.

Procedure

Self-conscious emotional reactivity was assessed with a self-sing "Karaoke" task that reliably elicits self-conscious emotions (Shearn, Bergman, Hill, Abel, & Hinds, 1990; Sturm et al., 2008). Participants were asked to relax during a 60-s pretrial baseline during which an "X" appeared on the monitor. A song title ("My Girl") was then displayed on the monitor for 9 s, followed by presenting the song "My Girl" by the Temptations for 2 min, 33 s (lyrics appeared on the monitor and sound was presented over headphones). Participants were asked to sing along with the song but were not told that they would later be viewing the tape of their performance. When the song ended, the experimenter returned to the room and removed the headphones. The only instruction given for this part of the task was to watch the monitor. After the experimenter left the room, the videotape that had just been recorded of the participant sitting through the baseline and then singing was played on the monitor (participants heard and saw themselves singing without hearing the original version of the song in the background). After watching the videotape, participants rated the emotions they experienced (see below) while watching themselves sing.

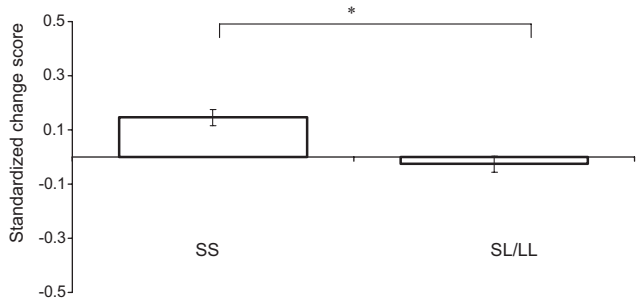

Figure 2. Study 1: 5-HTTLPR and physiological responding to films of others in distress. The SS variant differs from the SL/LL variants and shows the highest levels of reactivity. *Note*. Estimated marginal means (controlled for covariates). Error bars represent standard errors of the mean. * $p < .05$.

Measures

Emotional experience. Participants indicated their subjective emotional experience after watching themselves sing by rating the intensity of a number of emotions (affection, amusement, anger, calm, disgust, embarrassment, enthusiasm, fear, pride, shame, sadness, and surprise) they experienced (0 = *not at all*, 1 = *a little*, 2 = *a lot*). We created a composite score for total emotional experience by averaging all of the codes and also analyzed the individual emotions. Emotional experience data were available for 96 participants (missing data generally resulted from video or other technical problems).

Emotional expressive behavior. For Study 2, we were able to also include a measure of emotional expressive behavior. Behavioral measures are particularly useful when studying emotional reactivity in patient populations because their ability to provide emotional self-reports can be compromised. Participants were videotaped (upper torso and face) using partially hidden cameras throughout the experiment. Emotional expressive behavior was coded by trained raters who were unaware of participant's diagnosis, nature of the trial, or study hypotheses. Raters viewed the video recordings without sound and coded the first 30 s of the period during which participants watched themselves singing. Using a modified version of the Emotional Expressive Behavior coding system (Gross & Levenson, 1993), 10 emotion codes were used (amusement/happiness, anger, confusion, contempt, disgust, embarrassment, fear, interest, sadness, and surprise), with emotions rated on an intensity scale ranging from 0 to 3. Intercoder reliability was high; the intraclass correlation coefficient was .76. For each emotional code, we summed the intensity scores for each occurrence of each emotion during the task and created a composite score for total emotional expressive behavior by summing all of the codes. In follow-up exploratory analyses, we also analyzed the individual emotion codes.

5-HTTLPR. The same collection and assaying procedures were used as in Study 1. The genotyping yielded three groups: individuals with two short alleles (n = 18, 17.0%), one long allele (n = 50, 47.2%), or two long alleles (n = 38, 35.8%). Again, this genotype distribution was consistent with previous studies and did not deviate from Hardy-Weinberg equilibrium, p = .82.

Data Analysis

Emotional experience and expressive behavior data were analyzed in separate omnibus general linear models using the GLM program in SPSS (12.0, SPSS, Chicago, IL). As in Study 1, 5-HTTLPR was coded using two dummy variables (H1 and H2, where SS participants were coded as 1 on both variables, SL participants as 1 on one variable and 0 on the other variable, and LL participants as 0 on both variables). The structure of the analysis was 2 × 2: 5-HTTLPR effect [H1 and H2] × Patient status [Patient or Nonpatient] with all factors treated as between-subjects factors. We used the following covariates[2]: age (in years) because the sample was primarily old and thus nonrepresentative in terms of age), gender (0 = *female*; 1 = *male*) because the sample was primarily male due to gender differences in neurodegenerative disease presentation, and ethnicity/race (*White/Caucasian* = 1; *Other* = 0 to preserve degrees of freedom) because the sample was primarily White/Caucasian and there were several missing data points on race/ethnicity. The results of interest for the present study were the main effects of the 5-HTTLPR factors as well as interaction effects between the 5-HTTLPR factors and patient status. As in Study 1, significant main effects involving 5-HTTLPR were followed up with additional analyses conducted with age (in years) and gender (0 = *male*; 1 = *female*) as between-subjects factors to examine whether 5-HTTLPR findings were moderated by these variables. We did not analyze race/ethnicity effects in Study 2 with the same level of detail used in Study 1 because participants in Study 2 were primarily Caucasian, and thus we had low statistical power in the non-Caucasian group (n = 6).

Results: Study 2

5-HTTLPR and emotional experience. In the analysis of the composite score representing participants' total emotional experience using the 5-HTTLPR [H1 and H2] × Patient status [Patient or Nonpatient] model and controlling for age, gender, and race/ethnicity, none of the main effects of 5-HTTLPR or interaction terms with patient status were significant, all Fs(1,84) < 1, *ns*. We next analyzed the specific emotions, finding that 5-HTTLPR genotype [H2] had a significant effect on anger, $F(1, 77) = 6.85$, p = .01, such that participants with the SS genotype reported higher anger than participants with the SL/LL genotypes, $t(82) = 2.56$, p = .01; see Figure 3A. In addition, 5-HTTLPR [H1] had a significant effect on amusement, $F(1, 77) = 4.15$, p = .04, such that participants with the SL/SS genotypes reported higher amusement than participants with the LL genotype, $t(77) = 2.22$, p = .03; see Figure 3B. These results generalized across patient status, gender, and age, as indicated by nonsignificant interaction terms, H2 × patient status (anger), $F(1, 77) = 1.12$, p = .29; H2 × gender (anger), $F(1, 77) = 2.10$, p = .15, H2 × age (anger), $F(1, 77) = .58$, p = .45, H1 × patient status (amusement), $F(1, 77) = 2.58$, p = .11, H1 × gender (amusement), $F(1, 77) = .78$, p = .38, H1 × age (amusement), $F(1, 77) = .00$, p = .96.[3]

5-HTTLPR and emotional expressive behavior. In the analysis of the composite score representing participants' total emotional expressive behavior, there was a significant main effect for 5-HTTLPR genotype [H2] $F(1, 82) = 5.04$, p = .03, such that participants with the SS genotype showed higher total emotional expressive behavior (see Figure 4) than participants with the SL/LL genotypes, $t(82) = 2.37$, p = .02.[4] These results generalized across patient status and age, as indicated by nonsignificant interaction terms, H2 × patient status, $F(1, 82) = .03$, p = .87; H2 × age, $F(1, 82) = 2.82$, p = .10. There was a significant interaction with gender, $F(1, 82) = 7.20$, p = .01, such that among men, participants with the SS genotype showed higher total emotional expressive behavior than those with the SL/LL genotypes, $t(82) = 4.01$, p = .001, whereas for women there was no significant difference, $t(82) = .21$, p = .83.[3]

Preliminary Discussion: Study 2

Participants with the SS variant of 5-HTTLPR had greater emotional reactivity when watching themselves sing in a Karaoke task than those with the SL or LL variants. This was found for both emotional self-report (i.e., greater reported anger and amusement) and for emotional expressive behavior (i.e., greater total expressive behavior). These findings of greater emotional reactivity in a situation known to elicit self-conscious emotional responding were quite robust, not differing as a function of neurological status or age.

General Discussion

In two studies with independent subject samples and different emotion-eliciting procedures, we examined the effect of the 5-HTTLPR polymorphism on emotional reactivity. Whereas prior

[2] Depression scores were not available for Study 2. Study 1 results were unchanged without using depressive symptoms as a covariate.

[3] When restricting the analyses to White/Caucasian participants in Study 2, the main pattern of results was the same. Specifically, 5-HTTLPR effects were unchanged for self-reported amusement, $F(1, 71) = 6.47$, p = .01, and somewhat attenuated for anger, $F(1, 71) = 2.12$, p = .10. Similarly, the main effect of 5-HTTLPR [H2] was attenuated for total emotional behavior, $F(1, 71) = 1.92$, p = .16, but remained in the same direction.

[4] Even though total emotional expressive behavior was related to 5-HTTLPR genotype in the predicted direction, we also examined the relationship between 5-HTTLPR and individually coded emotional expressive behavior. However, first, we conducted a repeated-measures GLM analysis where we entered the 10 coded emotion scores as within-subject factor [Emotion: amusement/happiness, anger, confusion, contempt, disgust, embarrassment, fear, interest, sadness, and surprise] and 5-HTTLPR effect [H1 and H2] × Patient status [Patient or Nonpatient] as between-subjects factors. We used the following covariates: age, gender, and ethnicity/race. We found no evidence of interaction between 5-HTTLPR and our within-subject Emotion code, $F(1, 77)$s = .25 and 2.96, p = .61 and .1 for H1 or H2, respectively. When the individual emotion codes were analyzed separately, we found a trend level effect for the amusement emotion code, $F(1, 84) = 2.52$, p = .11, where participants with the SS variant showed the highest level of amusement (M = 22.02), followed by participants of the LL and SL variant (Ms = 16.90 and 15.01, respectively). Overall examination of the pattern of individually coded emotions indicated that participants with the SS variant tended to show higher levels of emotions, but in general no coded emotion reached conventional level of significance; thus, we opted to report the overall emotion composite in the main text.

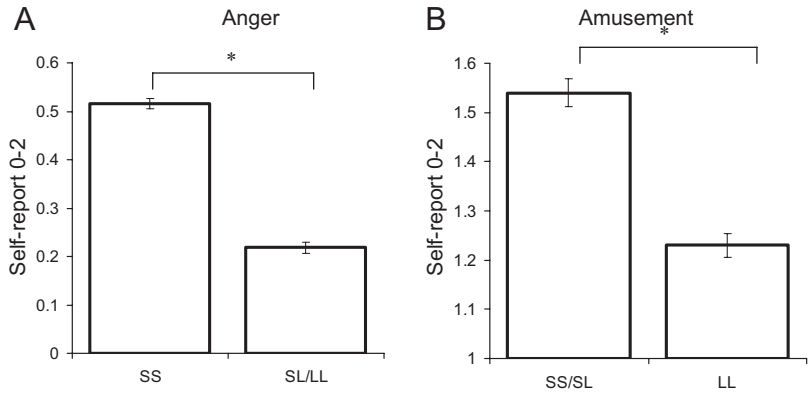

Figure 3. Study 2: 5-HTTLPR and specific emotional experiences of anger and amusement when watching oneself in an embarrassing situation. The SS variant differs from the SL/LL variants on anger and from the LL variant on amusement. *Note*. Estimated marginal means (controlled for covariates). Error bars represent standard errors of the mean. * $p < .05$.

studies of proximal effects of 5-HTTLPR had found greater emotional reactivity associated with the short allele using simple auditory and visual stimuli, we replicated and extended these findings using stimuli that were more socially embedded and more psychologically complex (i.e., viewing others in distress in Study 1, being in an embarrassing situation in Study 2). In both of our studies, differences emerged between participants with the SS genotype in comparison to those who had either the SL or LL genotypes. In Study 1, participants with two short alleles reported greater personal distress and evidenced greater physiological reactivity when viewing a film that depicted the suffering of others. In Study 2, participants with two short alleles reported more anger and more amusement and displayed more emotional expressive behavior when viewing an embarrassing videotape of themselves singing. Taken together these results provide converging evidence that the SS genotype of the 5-HTTLPR polymorphism is associated with greater emotional reactivity. Viewed in this manner, these findings are consistent with those of prior studies using stimuli that were more psychologically simple (e.g., viewing emotional faces on a computer screen) and less socially embedded (i.e., looking at stimuli on a computer screen) (e.g., Beevers et al., 2009, 2011; Fox et al., 2009; Hayden et al., 2008; Osinsky et al., 2008).

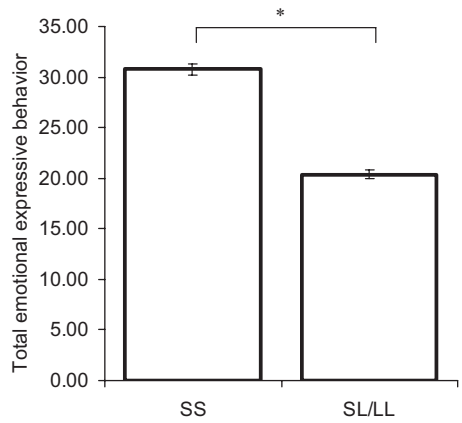

Figure 4. Study 2: 5-HTTLPR and total emotional expressive behavior (sum of all emotions across the coded 30 s weighted by intensity) when watching oneself in an embarrassing situation. The SS variant differs from the SL/LL variants. *Note*. Estimated marginal means (controlled for covariates). Error bars represent standard errors of the mean. * $p < .05$.

The findings from our studies help refine our understanding of the nature of the heightened emotional reactivity associated with the SS genotype. In Study 1, participants with two short alleles experienced greater personal distress when watching the plight of others, but did not experience elevated empathic concern. This suggests that the greater reactivity may not result from having a greater social concern (as would be evidenced by elevated empathic concern), but rather from experiencing the suffering of others to be more personally distressing. This kind of difficulty in distancing oneself from others is consistent with recent theories that propose that the short allele is linked to heightened sensitivity to social influences (Way & Taylor, 2010b). The finding that individuals with the SS genotype also evidenced greater physiological reactivity provides additional confidence in the robustness of the effect, indicating that the elevated reactivity extends beyond the realm of self-reported emotion and into biological systems that are critical for helping prepare the organism for dealing effectively with environmental challenges and opportunities (Levenson, 1999).

In Study 2, participants with two short alleles reported feeling more emotion (anger and amusement) and expressed more emotional behavior when placed in a situation that provokes self-conscious emotional responses (Sturm et al., 2006, 2008). Watching oneself singing in the absence of an accompanying musical background typically invokes a process of self-evaluation that leads to the realization that one's behavior falls short of social norms. This results in emotions such as amusement (focusing on the humorous nature of the situation) or anger (focusing on the resentment for being placed in this kind of situation). Our findings indicate that these kinds of emotional responses to this kind of situation are greater in individuals with two short alleles.

Our inclusion of patients with dementia and other neurodegenerative diseases in Study 2 was motivated by previous findings that FTLD patients showed diminished self-conscious emotional re-

sponding in these kinds of situations (Sturm et al., 2006, 2008). We wondered whether the 5-HTTLPR status of patients might moderate these losses in some way. However, our findings generalized across patient status. This suggests that elevated responses among SS carriers do not change as a function of having a neurodegenerative disorder, thus providing additional support for the robustness and potential generalizability of the findings.

Our results largely supported differences between the SS variant and the SL/LL variants (with one exception pertaining to reported amusement in Study 2). We did not find evidence for a systematic additive effect across the three 5-HTTLPR variants (i.e., SS > SL > LL) that others have found (e.g., Caspi et al., 2003; Pezawas et al., 2005). Of course, with greater power these kinds of additive effects might have been more likely to emerge.[5]

Generalizability of Findings

Our findings were quite robust, with evidence of greater emotional reactivity associated with the SS genotype in two studies with independent subject samples that examined different aspects of emotional reactivity (empathy and self-conscious emotional reactivity). Findings of greater reactivity were found for self-report measures (both studies), expressive behavior (Study 2), and autonomic nervous system physiology (Study 1). Moreover, in Study 1, findings generalized across three age groups (young, middle-aged, old), and in Study 2 they generalized across age and health status (with and without neurodegenerative disease). Of course, we must consider this evidence of within-study generalizability with some caution because small sample sizes work against our ability to detect group differences. In addition, there was one finding that suggested generalizability did not extend across genders. In Study 2, SS men showed more emotional expressive behaviors than LS/LL men, but no differences were found for women. However, it must be noted that the majority of the sample in Study 2 was men, and thus, this study was not optimal for studying gender differences.

Plasticity Versus Risk

Although early studies tended to view the SS genotype as a "risk" or "vulnerability" factor (e.g., Caspi et al., 2003), an increasing body of research has described the short allele as a "plasticity" factor, rendering individuals more reactive to both negative as well as positive experiences (Belsky & Pluess, 2009; Pluess, Belsky, Way, & Taylor, 2010a). Applied in the context of empathy, findings from our group have shown that higher emotional and physiological reactivity in response to distress of others are associated with greater pro-social behavior (Sze et al., 2011). Similarly, greater self-conscious emotional responding (e.g., embarrassment) may provide the individual with more powerful visceral and cognitive cues that social norms have been violated, and, thus, more strongly motivate corrective behavior (Sturm et al., 2008). Viewed within a gene × environment interaction framework, whether greater reactivity in these situations associated with the SS genotype translates into positive or negative distal outcomes would be largely determined by the kind of environment the individual experiences and the opportunities and challenges it presents.

Although the patient samples we studied suffered from neuropathologies, the findings may also have implications for psychopathology. Empathy and self-conscious emotions are thought to play important roles in psychopathology (e.g., empathy in autism; self-conscious emotions such as shame and guilt in depression). The role of premorbid individual differences in emotional functioning as risk and resiliency factors in the development of psychopathology is becoming an increasingly active area of research (Rottenberg & Johnson, 2007). Emotional functioning that is socially embedded, such as is the case with the aspects of empathy and self-conscious emotional responding we have studied, could be particularly important in this regard given the intimate connections between psychopathology and socioemotional functioning (Keltner & Kring, 1998; Rottenberg & Johnson, 2007).

Limitations

As with any research, there are limitations to be highlighted. There is increasing evidence that the effects of genetic polymorphisms may differ as a function of gender and ethnicity (Chiao & Blizinsky, 2010). Our failure to find evidence for moderation of findings by ethnicity may reflect the fact that our samples were not recruited so as to optimize sensitivity to these variables. In addition, we did not analyze the minor allele rs25531 within the L polymorphism that makes the L allele functionally similar to the S variant (Hu et al., 2005; Wendland, Martin, Kruse, Lesch, & Murphy, 2006). It will be important to consider this variant in future research on empathic and self-conscious emotional responding.

Finally, recent studies have suggested that 5-HTTLPR polymorphisms not only affect the magnitude of emotional responses but also their time course (e.g., Beevers et al., 2009, 2011). In the present study, we focused on the amplitude of response and were not able to address questions related to duration. Further exploration of this important question is called for using designs that allow for careful examination of the time course of emotional responses.

Summary

The findings from these two studies add to our understanding of differences in emotional reactivity related to genetic variations in the promoter region of the serotonin transporter gene 5-HTTLPR. Early studies of the influence of 5-HTTLPR (e.g., Caspi et al., 2003; Lesch et al., 1996) utilized outcome variables that were relatively distal (e.g., subsequent psychopathology) and sometimes categorical (e.g., have a given diagnosis or do not). More recent studies (e.g., Beevers et al., 2011) have focused on outcomes that are more proximal (e.g., emotional responses to simple laboratory stimuli) and continuous (e.g., magnitude of response). The present study used a variant of the latter approach in which stimuli were more psychologically complex and more socially embedded and the assessment of emotional response was more comprehensive and multimodal (self-report, facial expressive behavior, and physiology) than had been the case in previous studies.

Using this approach in two studies with independent subject samples, we found evidence that the SS variant of 5-HTTLPR is associated with higher levels of emotional reactivity than the SL/LL variants. The findings were quite robust, generalizing across different kinds of emotional reactivity (empathy and self-

[5] A reviewer pointed out that the unavailability of the rs25531 SNP in these data might have also contributed to the observed differences not being additive.

conscious emotions), subject age, neurological status (with and without neurodegenerative disease), and emotional response system (subjective experience, expressive behavior, and autonomic physiology).

Emotional reactivity is critical to our ability to function effectively in complex social environments and is intimately linked with processes underlying mental and physical health and illness. For this reason, understanding genetic contributions to individual differences has an important position in the current research agenda for both basic and applied affective science.

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