Emotion
2018, Vol. 18, No. 2, 229–236

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1528-3542/18/$12.00 http://dx.doi.org/10.1037/emo0000336

Variation in the Serotonin Transporter Polymorphism (5-HTTLPR) and Inertia of Negative and Positive Emotions in Daily Life

Eeske van Roekel
Tilburg University

Maaike Verhagen
Radboud University Nijmegen

Rutger C. M. E. Engels
Radboud University Nijmegen and Trimbos Institute, Utrecht, the Netherlands

Peter Kuppens
KULeuven-University of Leuven

An important element of understanding the genotype–phenotype link in psychiatric disorders lies in identifying the psychological mechanisms through which genetic variation impacts mental health. Here we examined whether emotional inertia, the tendency for a person's emotions to carry over from 1 moment to the next and a prospective predictor of the development of depression, is associated with a known genetic risk factor for emotional dysregulation, a polymorphism in the serotonin transporter gene (5-HTTLPR). Two hundred thirty-six adolescents recorded their positive and negative emotions in daily life 9 times a day for 6 consecutive days using smartphones, completed a depression questionnaire, and were genotyped for the 5-HTTLPR polymorphism. Carriers of the short 5-HTTLPR were characterized by higher inertia for negative emotions, even after controlling for depressive symptoms. These findings suggest a possible psychological pathway how the serotonin transporter gene contributes to risk for depression.

Keywords: emotional inertia, 5-HTTLPR, depression, experience sampling method, endophenotype

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Identifying the psychological mechanisms through which genetic factors confer risk for psychiatric illness is an important task. This holds particularly for depression, a mood disorder considered to be the single most burdensome disease in the world in terms of total disability-adjusted life years (Kessler & Wang, 2009; Murray & Lopez, 1996). In the present article, we examine whether emotional inertia, a known psychological precursor of depression, is related to genetic variation associated with emotional (dys)functioning in adolescents.

This article was published Online First June 1, 2017.

Eeske van Roekel, Department of Developmental Psychology, Tilburg University; Maaike Verhagen, Behavioural Science Institute, Radboud University Nijmegen; Rutger C. M. E. Engels, Behavioural Science Institute, Radboud University Nijmegen, and Trimbos Institute, Utrecht, the Netherlands; Peter Kuppens, Research Group of Quantitative Psychology and Individual Differences, KULeuven-University of Leuven.

This research was supported by the KULeuven Research Council (GOA/15/003) and by the Interuniversity Attraction Poles program financed by the Belgian government (IAP/P7/06); data collection was supported by a grant from the Behavioural Science Institute, Radboud University Nijmegen. We especially thank Marlies Naber and Angelien Heister for setting up and performing genotyping and the research group for Multifactorial Diseases, department of Human Genetics, Nijmegen.

Correspondence concerning this article should be addressed to Eeske van Roekel, Department of Developmental Psychology, Tilburg University, P.O. Box 90153, 5000 LE Tilburg, the Netherlands. E-mail: g.h.vanroekel@uvt.nl

Emotional Inertia

How people's emotions change across time reflects how they respond to and cope with events. Researchers are learning a great deal about people's well-being from studying the patterns and regularities underlying these changes (Bylsma & Rottenberg, 2011; Hollenstein, Lichtwarck-Aschoff, & Potworowski, 2013; Kashdan & Rottenberg, 2010; Kuppens, Oravecz, & Tuerlinckx, 2010). One such pattern that holds particular promise is emotional inertia. *Emotional inertia* refers to the degree to which a person's current emotional state can be predicted by his or her prior emotional state, and reflects how much it carries over from one moment to the next (Kuppens, Allen, & Sheeber, 2010; Suls, Green, & Hillis, 1998). Emotional inertia should be distinguished from emotional variability (Jahng, Wood, & Trull, 2008), which expresses how much a person's emotional experiences deviate from that person's mean across time. In a way, emotional variability reflects how much someone's emotions change, emotional inertia how slow they change.

The adaptive function of emotions is assumed to lie in their capability to quickly and flexibly respond to environmental threats and opportunities. Consequently, when emotions become inert, this is hypothesized to reflect dysfunctional emotional responding (Kuppens, Allen, et al., 2010). Higher levels of inertia might signify that emotional states have become decoupled from their adaptive function to respond flexibly to significant events and regulation efforts to make disruptive emotions return to baseline. Indeed, depression for instance is characterized by emotional context insensitivity or blunted reactivity to emotional stimuli (e.g., Bylsma, Morris, & Rottenberg, 2008; Rottenberg, 2005) and by impaired emotion regulation skills (e.g.,

Gross & Muñoz, 1995). In sum, emotional inertia reflects the inability for emotions to flexibly change according to internal or external demands, something which is considered to be vital for psychological health (Kashdan & Rottenberg, 2010).

A significant body of research is starting to accumulate showing that emotional inertia is indeed related to both intrapersonal indicators of low well-being (e.g., neuroticism: Suls et al., 1998; anorexia nervosa: Stein, 1996; low self-esteem: Kuppens, Allen, et al., 2010; rumination: Koval, Kuppens, Allen, & Sheeber, 2012) and interpersonal maladjustment (e.g., marital dysfunction: Gottman, Murray, Swanson, Tyson, & Swanson, 2005; poor family relationships: Hollenstein, Granic, Stoolmiller, & Snyder, 2004). Among the most consistent findings is that emotional inertia is related to depression, both in terms of differences between clinically depressed and nondepressed groups, as in terms of depression severity in nonclinical samples (Koval & Kuppens, 2012; Koval et al., 2012; Kuppens, Allen, et al., 2010; Wenze, Gunthert, Forand, & Laurenceau, 2009; for an exception, however, see Thompson et al., 2012).

Moreover, recent findings revealed that emotional inertia is not merely a byproduct of depression, but reflects an early form of emotional dysregulation that creates vulnerability for mood disorder. In a longitudinal study, it was found that higher levels of emotional inertia in early adolescence prospectively predict the onset of clinical depression 2 years later, even after controlling for other known risk factors such as gender and depressive symptoms (Kuppens et al., 2012; see also van de Leemput, et al., 2014. In other words, emotional inertia represents an early risk factor for depression.

Emotional Inertia and 5-HTTLPR

The previous findings raise the question whether emotional inertia may be rooted in known genetic risk factors for emotional dysfunction. One of the most intensely studied genetic factors in depression is a polymorphism (5-HTTLPR) in the promoter region of the serotonin transporter gene (*SLC6A4*). Based on pharmacological and neuroendocrine evidence, serotonin is considered to play a key role in emotional responding, regulation, and disorder (Hariri & Holmes, 2006). Because of this, the genetic region that governs the expression and regulation of the serotonin transporter, which is responsible for the uptake of serotonin from the synaptic cleft, has come into the spotlight of research on emotion and affective disorders (Hamann, 2005; for reviews, see, e.g., Anguelova, Benkelfat, & Turecki, 2003; Canli & Lesch, 2007; Clarke, Flint, Attwood, & Munafò, 2010; Hariri & Holmes, 2006; Munafò, Brown, & Hariri, 2008). Although findings on main effects of the genotype on affective disorders are inconclusive, there are indications that individuals carrying at least one short allele of this polymorphism (s/l or s/s genotype) are characterized by altered emotional responding and regulation compared to individuals homozygous for the long allele (l/l genotype).

However, direct relationships with psychiatric illness prove to be elusive. For instance, several recent meta-analyses cast doubt on the existence of a direct relationship between genetic variation in 5-HTTLPR and depression, or underscore that this relationship is very weak at best (Anguelova et al., 2003; Culverhouse et al., 2017; Lasky-Su, Faraone, Glatt, & Tsuang, 2005; Levinson, 2006; Lotrich & Pollock, 2004). A more fruitful approach might lie in examining whether the genetic variation is associated with psychological processes that themselves form a more proximal risk factor or intermediate endophenotype for depression (Hasler et al., 2004).

Canli and Lesch (2007) argued that short allele carriers are characterized by tonic higher levels of specifically negative emotionality caused by elevated amygdala activation during the processing of emotional stimuli. Moreover, Pezawas et al. (2005) showed that the short allele of the 5-HTTLPR polymorphism is related to impairments in regulatory networks modulating emotional reactivity. Short-allele carriers were characterized by a relative decoupling of the brain circuits implicated in the extinction of negative emotion. In other words, the short version of this genetic variant, most likely through reduced transcription, expression, and function of the serotonin transporter (Hariri & Holmes, 2006), creates impaired regulation capacity, particularly of negative emotions. This impaired reactivity and regulation of negative emotions may also be evident in research exploring gene-environment interactions with the 5-HTTLPR genotype, as these studies showed that short allele carriers are more strongly affected by stress (for a meta-analysis, see Karg, Burmeister, Shedden, & Sen, 2011). However, the evidence for these gene–environment interactions have been questioned in other meta-analytic studies that showed no significant effects (Culverhouse et al., 2017; Duncan & Keller, 2011; Munafò, Durrant, Lewis, & Flint, 2009; Risch et al., 2009).

Although previous findings are inconsistent, they might suggest that carrying the short allele of the serotonin transporter gene may constitute a genetic base for the impaired reactivity and regulation of specifically negative emotions captured in high levels of negative emotional inertia. If the 5-HTTLPR genotype would show a relationship with negative emotional inertia, this could suggest an endophenotypical pathway by which it could create vulnerability for the development of depression.

The Present Study

The aim of the current study was to examine whether the 5-HTTLPR genotype is related to higher versus lower levels of emotional inertia in daily life. A sample of early adolescents was genotyped and participated in an experience sampling method study (ESM; Csikszentmihalyi & Larson, 1987) that tracked their experience of negative and positive emotions throughout daily life. The main advantages of this method are (a) the high ecological validity, as participants report on their emotions in real life and (b) the low recall bias as participants report on their current emotions (Myin-Germeys et al., 2009). Each participant's autocorrelation of negative and positive emotional states across time was estimated using multilevel modeling as an index of respectively negative and positive emotional inertia (see, Gottman et al., 2005; Kuppens, Allen, et al., 2010; Suls et al., 1998) and was related to the information on their genotype. We hypothesized that inertia of particularly negative emotions would be related to the 5-HTTLPR genotype. Specifically, we expected adolescents carrying at least one short allele to display higher negative emotional inertia than adolescents carrying the long-long genotype. To rule out the possibility that any found relationship is due to a common association with depression or other background variables, we also examined

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these relationships while controlling for severity of depressive symptoms, age and gender.

This study is among the few to examine how genetic variation is expressed in emotional phenomena in daily life (see also, e.g., Gunthert, Conner, Armeli, Tennen, Covault, & Kranzler, 2007). It goes beyond much previous research on the genetics of emotion by studying emotions not in the lab but in their natural habitat, by examining a facet of emotion dynamics instead of solely focusing on state or average levels of emotionality, and by examining this in a sample of adolescents, a life stage particularly vulnerable to the onset of depression (Allen & Sheeber, 2008). As such, we hoped to further our understanding of the factors that underlie the patterns of people's naturally occurring emotional changes and fluctuations, and the forms of psychological well- or ill-being they are associated with.

Method

Participants

An initial sample of 303 second-year high school adolescents took part in the study. Based on compliance to the ESM protocol and missing data, 67 participants were removed for further analyses (see below), resulting in a final sample of 236 participants (M_{age} = 14.2 years, SD = 0.5, 143 or 61% girls). The majority of participants was born in the Netherlands (97.1%), and only 1.3% of adolescents were born in a non-European country. Participants were recruited through secondary schools, representative of the Dutch schooling system: 23.4% of the adolescents attended preparatory secondary school for technical and vocational training, 35.8% attended preparatory school for college, and 40.8% attended preparatory school for university. After receiving school consent, adolescents and their parents were sent information about the study along with an invitation to participate. Upon agreement, parents returned a signed consent form and adolescents a signed assent form, in compliance with the Medical Ethical Committee Arnhem-Nijmegen.

Materials

Genotyping procedure. DNA was isolated from saliva using the Oragene system (DNA Genotek Inc., Kanata, Ontario, Canada). Genotyping of the VNTR polymorphism in the *SLC6A4* (*5-HTT, SERT*) gene was performed by simple sequence length analysis. Polymerase Chain Reaction (PCR) was on 50 ng genomic DNA using 10 pmol of forward primer (5′-GGCGTTGCCGCTCTGAATGC-3′) and 10 pmol reverse primer (5′-GAGGGACTGAGCTGGACAACCAC-3′), 0.25 mM dNTPs, 0.5 U Taq DNA polymerase (Invitrogen, Breda, the Netherlands) in a PCR buffer containing 0.3 M Tris-HCl (pH 8.5), 75 mM ammoniumsulfate and 7.5 mM $MgCl_2$. The cycling conditions for the polymerase chain reaction started with 5 min at 92°C, followed by 35 cycles of 1 min at 92°C, 1 min at the optimized annealing temperature (57.5°C), and 1 min at 72°C, then followed by an extra 5 min at 72°C. PCR products were analyzed on a 2% agarose gel. The amplification yielded distinct bands at 484 bp (short "s" allele) and 528 bp (long "l" allele).

To provide further genotype information, we also genotyped the 5-HTT rs25531 polymorphism, because the G variant of the rs25531 is functionally equivalent to the 5-HTTLPR short allele (Hu et al., 2005). The rs25531 polymorphism was genotyped using Taqman analysis. A custom made Taqman Allelic Discrimination assay was ordered. This assay consisted of two primers (forward: CCCTCGCGGCATCCC, reverse: ATGCTGGAAGGGCTGCA) and 2 fluorescent probes (VIC-CTGCACCCCCAGCAT, FAM-CTGCACCCCCGGCAT, Applied Biosystems, Nieuwerkerk a/d IJssel, the Netherlands). Genotyping was carried out in a volume of 10 μl containing 20 ng of genomic DNA, 5 μl of Taqman Mastermix (2×; Applied Biosytems) and 0.25 μl of the Taqman assay (40×) and 2.75 μl of MilliQ. Each amplification for the custom made Taqman Allelic Discrimination assay for the polymorphism rs25531 was performed by an initial denaturation at 95°C for 12 min, followed by 50 cycles of denaturation at 92°C for 15 s and annealing/extension at 60°C for 90 s, this was carried out on a 7,900 Fast Real-Time PCR System. Genotypes were scored using the algorithm and software supplied by the manufacturer (Applied Biosystems). Genotyping was performed in a CCKL-accredited laboratory at the Department of Human Genetics of the Radboud University Nijmegen Medical Centre in Nijmegen. Generally, 5% blanks as well as duplicates between plates were taken along as quality controls during genotyping. No deviations from Hardy-Weinberg equilibrium were detected for the rs25531 SNP (p = .56) and for the VNTR (p = .92). As the G variant of the rs25531 SNP in the long allele is functionally equivalent to the short allele (Hu et al., 2005), the G variant in the long allele was treated as a short allele, and the A variant as the long allele. This resulted in three possible genotypes: s/s, s/l, and l/l. Because of power constraints, we combined the s/s and s/l genotypes.

Experience sampling. ESM was performed using smartphones installed with the MyExperience software (Froehlich, Chen, Consolvo, Harrison, & Landay, 2007). Smartphones were programmed to randomly beep nine times a day in regular 90-min intervals for 6 consecutive days (yielding a maximum of 54 beeps, which could be surpassed however if the participant kept responding to beeps until the next day when they returned the smartphone). At each beep, participants were prompted to respond to a number of questions about what they were doing, feeling, and thinking at that moment. Of interest here, participants were asked to report to what extent they were experiencing a range of negative and positive emotions. Specifically, participants were asked to rate in random order how anxious, irritated, worried, low, insecure, and guilty, and how joyful, satisfied, happy, energetic, relaxed, and cheerful (each time preceded by the stem "I feel . . .") they were feeling using a 7-point scale that ranged from 1 (*not*) to 7 (*very much*). Responses to the negative, respectively positive emotion terms were averaged at each beep to form one single negative, respectively positive emotion score (average within-person Cronbach alphas for the negative and positive scales equaled .69 and .70).

Depressive Symptoms. Depression was measured with the 20-item Center for Epidemiologic Studies Depression Scale (CES-D; Radloff, 1977). Participants were asked to rate on a 4-point scale how often they felt the way described in the past week (1 = rarely or none of the time, 4 = most or all of the time). Sample items are 'I felt depressed' and 'I thought my life had been a failure.' For each individual, a total depressive symptoms score was calculated by summing the responses. Cronbach's alpha was .91.

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Procedure

Assessment of depressive symptoms and saliva sampling, along with a variety of other measures, occurred two to eight weeks prior to the ESM during school hours. One day (always a Friday) before the start of the ESM study adolescents received the smartphone and were individually briefed on their use. They were instructed to pause their activity immediately after they received a signal, and complete the questionnaire on the smartphone. Data were stored on the smartphones and a text message was sent to the principal investigator after each completed questionnaire, making it possible to check compliance. When no messages were received within 2 consecutive hours, adolescents were sent a text message or called to instruct them to attend to their smartphones and complete the questionnaires. On the final day of the study, adolescents were called to make an appointment for returning the smartphones and completing a debriefing form. Adolescents received a reward of €20 (i.e., about $27) when they completed at least 55% of the beeps.

In terms of compliance, the initial sample of 303 participants responded to an average of 37.10 or 69% of the programmed beeps (SD = 11.12, range = 2–63). Because of the difficulty to obtain inertia estimates for participants with too few (consecutive) data points and concerns about their reliability and validity, 52 participants who responded to less than 50% of the programmed beeps were removed from further analyses. In addition, 15 participants had missing data for depressive symptomatology, genotype, and/or age/gender and were removed from further analyses. The resulting final sample consisted of 236 participants who responded to an average of 40.89 or 76% of the beeps (SD = 7.35, range = 27–63), reflecting good average compliance. We checked whether our final sample (N = 236) differed on demographics and model variables from the adolescents who were not included in the analyses (N = 67). No significant differences were found for gender, age, depression, and mean levels of positive and negative emotions ($p > .05$). A small difference was found between the group for educational level, in that adolescents with low educational levels were slightly underrepresented in the final sample ($\chi = 7.10$, $p < .05$).

Data Analyses

We examined the relationship between presence or absence of the short allele of the 5-HTTLPR genotype and inertia of both negative and positive emotions using multilevel regression modeling. This approach takes into account the nested structure of the data (beeps nested in persons) and the resulting dependencies (Nezlek, 2012; Raudenbush & Bryk, 2002). In the models, the level of negative or positive emotions at sampling time t was predicted by the level of negative or positive emotions at time $t - 1$ (person mean-centered; Enders & Tofighi, 2007). Previous day lagged predictor scores were omitted to avoid between-day effects. The intercept of the model represents the average level of negative or positive emotion experienced over the sampling period, whereas the slope represents the autocorrelation of negative or positive emotion, a direct operationalization of inertia (Kuppens, Allen, et al., 2010). Both the intercept and slope values were allowed to vary across persons, and were further predicted by genotype information (coded as 1 = carrying at least one short allele vs. 0 = no short allele) all or not in combination with depressive symptom severity, age and gender at Level 2 of the model. As educational level was not associated with mean levels of positive and negative emotions, we did not include education as a covariate in our models.

Results

Genotyping revealed that the majority (N = 180; 76%) of participants was carrier of at least one short allele of the 5-HTTPLR polymorphism (N = 62 for s/s genotype, N = 118 s/l genotype, N = 56 l/l genotype), closely matching previously found distributions in Caucasian populations (Hariri & Holmes, 2006). Consistent with meta-analytic findings (Anguelova et al., 2003; Lasky-Su et al., 2005; Levinson, 2006; Lotrich & Pollock, 2004), this distribution was not directly associated with depression symptom severity, $r = -.047$, $p > .47$.

In a first model, we tested the simple relationship between negative emotional inertia and 5-HTTLPR genotype by including the latter as a Level 2 predictor of both the intercept and slope. The results are presented in Table 1 and showed that short allele carriers were not characterized by significantly higher levels of average negative emotionality in daily life (intercept), but, crucially, were characterized by significantly higher levels of negative emotional inertia (slope).[1] The proportion of explained variance by the 5-HTTLPR genotype was 3.85%. In a second model, we tested whether this relationship remained after controlling for baseline depressive symptom severity, as measured with the CES-D Scale. The results showed that depressive symptoms were significantly related to average levels of negative emotions in daily life and marginally significantly to higher levels of negative inertia, consistent with previous research (e.g., Kuppens, Allen, et al., 2010). Most importantly, however, they showed that carriers of the short allele still showed higher levels of negative emotional inertia, independent of their level of depressive symptoms (see Table 1). Finally, this remained when additionally controlling for age and gender in a third model (see Table 1).

Next, we also examined these relationships for positive emotions (see Table 1). The results showed that depression related to lower levels of average positive emotions. Yet, genotype was not related to average levels of positive emotion in daily life, nor to positive emotional inertia, both in a simple model or when controlling for depressive symptoms and age and gender.

Discussion

We present preliminary evidence that negative emotional inertia, which has been documented as a risk factor for depression, is related to variation in the 5-HTTLPR gene. This finding might suggest a possible pathway through which genetic factors contribute to risk for depression or affective disorder in general. The 5-HTTLPR genotype putatively regulates the activity and function of the serotonin transporter which is considered to play a role in

[1] We have also tested an additive model, in which we compared the three genotypes by including dummy variables. These analyses showed that the l/l group (reference group, inertia: B = .18) significantly differed in inertia from the s/l group (inertia: B = .26, difference with l/l group: B = .08, $p <$ 05), but not from the s/s group (inertia: B = .24, difference with l/l group: B = .06, p = .23). The s/l group did not differ significantly from the s/s group (difference between groups: B = .03, p = .64).

Table 1
Results of Multilevel Analyses Predicting Negative and Positive Emotion Intercept (Average Emotion) and Autocorrelation Slope (Emotional Inertia) by Genotype (Model 1), Genotype and Depressive Symptom Severity (Model 2), and Genotype, Depressive Symptom Severity, Age and Gender (Model 3)

Model	*B*	*SE*	*p*
Negative Emotion Model 1			
Intercept negative emotion			
Value	1.559	.062	<.001
Genotype	−.072	.071	.312
Slope negative emotion			
Value	.161	.033	<.001
Genotype	.077	.039	.048
Negative Emotion Model 2			
Intercept negative emotion			
Value	1.540	.055	<.001
Genotype	−.048	.064	.453
Depressive symptoms	.025	.005	<.001
Slope negative emotion			
Value	.158	.034	<.001
Genotype	.080	.038	.041
Depressive symptoms	.003	.002	.079
Negative Emotion Model 3			
Intercept negative emotion			
Value	1.511	.072	<.001
Genotype	−.054	.065	.398
Depressive symptoms	.025	.005	<.001
Age	.050	.053	.346
Gender	.057	.054	.295
Slope negative emotion			
Value	.189	.040	<.001
Genotype	.088	.038	.023
Depressive symptoms	.003	.002	.051
Age	−.028	.035	.430
Gender	-.057	.035	.107
Positive Emotion Model 1			
Intercept positive emotion			
Value	5.163	.078	<.001
Genotype	.050	.097	.603
Slope positive emotion			
Value	.234	.031	<.001
Genotype	.039	.037	.299
Positive Emotion Model 2			
Intercept positive emotion			
Value	5.185	.069	<.001
Genotype	.021	.088	.808
Depressive symptoms	−.032	.005	<.001
Slope positive emotion			
Value	.233	.032	<.001
Genotype	.040	.037	.286
Depressive symptoms	.001	.002	.572
Positive Emotion Model 3			
Intercept positive emotion			
Value	5.150	.086	<.001
Genotype	.023	.090	.796
Depressive symptoms	−.032	.005	<.001
Age	−.009	.084	.911
Gender	.055	.094	.556
Slope positive emotion			
Value	.212	.039	<.001
Genotype	.034	.037	.354
Depressive symptoms	.001	.002	.621
Age	.036	.030	.239
Gender	.038	.035	.282

the regulation and extinction of negative emotions (Hariri & Holmes, 2006). Carriers of a short allele of this region show altered serotonin transporter and hence serotonin functioning, which negatively impacts their ability to down-regulate negative emotions by a relative decoupling of the regulation and extinction circuits of negative emotion in the brain (Pezawas et al., 2005). We hypothesized, and found preliminary evidence, that the genetic makeup underlying such mechanisms in the form of the 5-HTTLPR genotype would translate into heightened levels of inertia for particularly negative emotions. Although previous studies examining gene–environment interactions with stress are inconclusive (see, e.g., Culverhouse et al., 2017), there is some evidence that short allele carriers might be more sensitive to stress (e.g., Karg et al., 2011). These findings, combined with the results of the present study, may indicate that short allele carriers are not only more reactive to stressful events, they are also less able to recover in NA after stress, which has been found to be particularly related to increased NA inertia (Koval et al., 2015).

Importantly, this finding was not due to a common association with depression, which suggests that the 5-HTTLPR genotype may be directly implicated in creating higher or lower levels of emotional inertia independent of its impact on depressive symptoms. The finding also held independent of age and gender, which is not unimportant given the gender gap occurring for depression in adolescence. Also, the obtained relationship between 5-HTTLPR genotype and emotional inertia was found to be specific for negative emotions. Although depression involves alterations in both negative and positive affect (e.g., Clark & Watson, 1991), this corroborates previous research linking variation in the 5-HTTLPR genotype to alterations in primarily negative emotionality.

Although the 5-HTTLPR genotype may not be directly associated with depression (see both our results and those from previous meta-analyses), our results may identify a mechanism through which it can indirectly increase risk for depression. Previous work has indeed indicated that it may be more promising to examine endophenotypes for psychiatric problems, which may act to fill the gap between genes and outcomes (Hasler et al., 2004). This approach has also been questioned by some researchers, as endophenotypes based on brain or physiological measures did not show stronger associations with genetic factors (e.g., Franke et al., 2016; Iacono, Malone, Vaidyanathan, & Vrieze, 2014). However, we used real-life reports of emotions, and because only a few studies have used real-life data in exploring genetic associations, more research is needed to determine whether real-life endophenotypes based on experience sampling data may be a promising future direction to explore genetic associations.

It is important to underscore that the higher levels of emotional inertia among short allele carriers were observed in early adolescence. This developmental period is marked by significant cognitive, social, and biological changes that are associated with a steep rise in the incidence of depression (Allen & Sheeber, 2008; Lewinsohn, Rohde, & Seeley, 1998), the onset of which can be predicted by the level of emotional inertia during this period (Kuppens et al., 2012). Our finding that 5-HTTLPR variation is related to higher inertia early in adolescent development is therefore important to establish the potential mechanisms through which this genotype may be related to the onset of depression. Additional, longitudinal evidence is needed (involving multiple assessment waves of depression and inertia across longer periods of time), however, to

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firmly establish that 5-HTTLPR variation increases risk for depression by increasing the likelihood to develop higher levels of inertia during the course of adolescence.

Despite several strengths, such as the use of experience sampling and the use of adolescents as participants, this study is not without limitations. First, we had a relatively small sample size of 236 adolescents. However, by measuring our outcome variable multiple times, we obtained a more reliable measure than in typical single measurement studies. In addition, our sample size is comparable to other studies examining genetic effects using ESM designs (e.g., Gunthert et al., 2007; Wichers et al., 2007). Nevertheless, our effect was small and we did not control for multiple testing. In light of the controversial results of previous studies and a recent large meta-analysis finding no main effects or GxE interactions with the 5-HTTLPR gene (Culverhouse et al., 2017) we cannot exclude the possibility that our finding is a false positive, and we emphasize the need for independent replication. Also, our data were based on a community sample, and did not involve psychiatric diagnosis. In addition to following up samples longitudinally, there is need for clinical data to replicate our findings.

Clearly, more research is needed to identify psychological mechanisms through which genetic factors exert an influence on well-being and ill mental health. The current findings suggesting a potential pathway through which the serotonin gene impacts emotion dysfunction as observed in depression is but a first step. Most evidently, research is needed to identify environmental factors that interact with the serotonin transporter gene to exacerbate or dampen its association with emotional inertia. Genetic factors interact with environmental ones to create risk for psychiatric illness (see, e.g., Caspi et al., 2003; Eley et al., 2004). In the present context, we know that emotional inertia is susceptible to stress (Koval & Kuppens, 2012; Kuppens, Allen, et al., 2010), and it is not unlikely that this may hold particularly for those who are genetically predisposed to develop signs of emotional dysregulation. In addition, as the family environment is considered to play a large role in the development of depression during adolescence (Sheeber, Hops, & Davis, 2001), it may be expected that it or other social support groups (peers, class mates) may act as a protective factor in the development of risk factors for depression in individuals genetically at risk for mood disorder. More research is needed to pinpoint these gene–environment interactions, along with longitudinal data to establish how these processes unfold during development.

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Received May 21, 2014
Revision received April 24, 2017
Accepted April 26, 2017 ■

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