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The interplay of genetic and environmental factors in shaping well-being across the lifespan: Evidence from the serotonin transporter gene

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ABSTRACT

Background: Converging evidence suggests that well-being plays an important role in promoting and maintaining mental health across the life span. It has been shown that well-being has a considerable heritable component, but little is known about the specific genes involved.

Methods: In this study, we investigated a healthy sample ($N = 298$) that was genotyped for the serotonin transporter-linked polymorphic region (5-HTTLPR). We hypothesized that 5-HTTLPR gene variation would influence well-being, and additionally investigated interaction effects with age and the environmental influence of early life stress (ELS).

Results: Using multiple regression, our results showed a significant three-way interaction between genotype, ELS, and age. Exploration of this interaction showed that young subjects had decreased levels of well-being if they were exposed to ELS and homozygous for the short variant of 5-HTTLPR. This relationship was reversed in old age: subjects that were exposed to ELS and carried the long variant of 5-HTTLPR had decreased levels of well-being.

Conclusion: Our results indicate that genetic and environmental factors have joint effects on well-being that are susceptible to profound changes across the life span.

Introduction

There is now accumulating evidence suggesting that mental and physical health are closely linked to subjective well-being (Steptoe, Deaton, & Stone, 2015). Consistently, the WHO recommendation for national mental health policies is to actively promote mental health and well-being in addition to the treatment of mental disorders (WHO – mental health action plan 2013 – 2020; Saxena, Funk, & Chisholm, 2013). While it is clear that mental disorders, such as depression, strongly interfere with well-being, it is not sufficient merely to define well-being as the absence of disease or infirmity. Especially at old age, it has been found that well-being is closely linked to general health and even predictive for survival. In a longitudinal study, Steptoe et al. (2015) found that after an initial assessment the chance of survival in old aged individuals across a follow-up period of 8.5 years was significantly higher if levels of well-being were high. Given this impact of well-being on health and survival, and in view of a rapidly aging population (United Nations, 2015), it is of utmost importance to understand the mechanisms that preserve and promote well-being across the lifespan and especially in old age.

A recent meta-analysis of 10 independent twin studies (Bartels, 2015) suggests that well-being has a significant heritable, genetic component (about 36%), and one study including older individuals suggested that the genetic influence on well-being even increases with age (up to 48%; Harris, Pedersen, Stacey, McClearn, & Nesselroade, 1992). However, until now little is known about the molecular genetics of well-being. It remains unclear which genes are involved, and what mechanisms in the process of aging modulate the genetic influence.

The serotonergic system is of particular interest when studying the molecular basis of well-being, mood, and affect. It is the main target for many antidepressant drugs, and genetic variation in serotonin-related genes has been linked to disruptions in mood. One of the most studied serotonin-related genetic variations is the serotonin transporter-linked polymorphic region (5-HTTLPR). It has been extensively investigated with respect to affective disorders, such as depression (Oliveira et al., 2000; Pezawas et al., 2005), and anxiety (Lesch et al., 1996; Sen, Burmeister, & Ghosh, 2004). Furthermore, the 5-HTTLPR polymorphism is one of the very few specific genetic variations that have been studied with respect to well-being. De Neve (2011) reported a relationship between 5-HTTLPR and life satisfaction in a US nationally representative sample. They found higher levels of well-being in subjects that carried the long allele of this genotype; a finding that had been replicated in one further study investigating a Japanese sample (Matsunaga, Isowa, Yamakawa, & Ohira, 2013).

Hence, the finding of De Neve (2011) is consistent with the common conception from patient studies that the short allele is a vulnerable – and the long allele a protective genotype. A related line of evidence suggests that short allele carriers are especially vulnerable in the presence of life stress, such as early life adversity (Caspi et al., 2003). However, it is still an ongoing debate whether the short allele of the 5-HTTLPR polymorphism and its interaction with life stress are associated with an increased risk to develop affective disorders. There are meta-analyses supporting this hypothesis (Karg, Burmeister, & Shedden, 2011), and others that reject it (Risch et al., 2009). Whether the interaction between 5-HTTLPR

genotype and life stress also influences well-being has not yet been investigated.

A few studies have investigated the 5-HTTLPR polymorphism with respect to aging. In one study, it was hypothesized that successful aging is related to the 5-HTTLPR genotype (O'Hara et al., 2012). Because short allele carriers show reduced resilience to stress, and successful aging is closely linked to resilience, the authors predicted that short allele carriers would be less resilient during the aging process. However, since the hypothesis was not supported by the data, the authors concluded that effects of carrying the short allele might attenuate with age. More recently, the conception of the short allele being purely a vulnerable genotype has been challenged. In their review article, Homberg and Lesch (2011) argue that genetically driven deficient serotonin transporter function would not have been maintained throughout evolution if it only exerted negative effects without conveying any gain of function. In line with this argument, it has been shown that carriers of the short allele show stronger reactions to both negative and positive emotions (Perez-Edgar et al., 2010), and respond better to psychological treatment (Eley et al., 2012). However, it has to be noted that research on 5-HTTLPR genotype with respect to treatment outcome has revealed heterogeneous findings (for a recent review, see Lueken et al., 2016). With respect to the positive findings regarding the short allele, it has been suggested that this allele could function as a genetic plasticity factor that might promote adaptability of the neural system (Kuepper et al., 2012). Furthermore, it has been suggested that short allele carriers are more receptive to social supports, and display higher levels of social conformity (Homberg & Lesch, 2011; Kaufman et al., 2004). These recent findings indicate that carrying the short allele might be advantageous under specific circumstances. Indeed, stronger social conformity and emotionality, as well as increased plasticity might be especially advantageous in the aging process.

Thus, the aim of this study was to further investigate the effects of 5-HTTLPR genotype on well-being, and to test whether genetic effects remain stable across the lifespan. Furthermore, we tested whether exposure to ELS modulates the effects of 5-HTTLPR genotype on well-being. Based on previous findings from patient populations, we expected stronger effects of 5-HTTLPR genotype in subjects exposed to ELS. Because well-being is a multi-faceted construct, comprising evaluative and affective components (Eid & Larsen, 2008), we investigated evaluative well-being (measured by overall life satisfaction) and affective well-being (measured by a positive affect scale) separately. Since well-being in old age has been closely linked to the social environment (Pinquart & Sorensen, 2000), we included the amount of perceived social support as an additional outcome measure.

Methods

Participants

All subjects were recruited from responses to advertising in local newspapers and mailing lists. Subjects were screened for psychiatric disorders using the short version of the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (DSM-IV, SCID). Inclusion criteria were age 18–90 years, absence of present and past diagnosis of psychiatric or neurologic disease, absence of major or unstable

Table 1. Sample characteristics divided by 5-HTTLPR genotype.

	5-HTTLPR genotype				
	LL	LS	SS	Test statistic	p
Age, Mean (SD)	41.8 (18.2)	39.8 (16.6)	37.0 (15.3)	$F = 1.22$	0.3
N (female)	104 (60)	146 (79)	50 (28)	$\chi^2 = 0.32$	0.85
CTQ score, Mean (SD)	38.7 (14.9)	38.9 (14.5)	38.4 (12.0)	$F = 0.01$	0.99

Note: CTQ = Childhood Trauma Questionnaire, LL = long allele homozygotes, LS = long/short allele heterozygotes, SS = short allele homozygotes.

general medical conditions, and ability to participate in study procedures. After applying these criteria, the initial sample of $N = 1402$ was reduced to a sample size of $N = 541$. A subsample of $N = 307$ participated in a second survey in which common aspects of well-being were assessed. Genetic, and questionnaire data was complete for $N = 298$ participants, which was the final sample size for the analysis. Sample characteristics of the final sample are described in Table 1. The study was carried out in accordance with the latest version of the Declaration of Helsinki and approved by the Institutional Review Board of the Charité. All subjects gave written informed consent before screening and were reimbursed for participation.

Psychometric measures

History of ELS experience was assessed using the Childhood Trauma Questionnaire (CTQ; Bernstein & Fink, 1998; Klinitzke, Romppel et al., 2012). Evaluative well-being was assessed using a one-item life satisfaction question ('How satisfied are you with your life as a whole?') on a 9-point Likert scale. This one-item assessment is an adaptation of the Cantril ladder (Cantril, 1965) which is frequently used to assess evaluative well-being. Affective well-being was assessed using the German version of the positive and negative affect schedule (Krohne, Egloff, Kohlmann, & Tausch, 1996). The amount of perceived social support was assessed using the Perceived Social Support Questionnaire (Fydrich, Geyer, Hessel, Sommer, & Brähler, 1999).

Genotyping

Genotyping was performed at the Department of Psychiatry and Psychotherapy, Ludwig-Maximilians-University, Munich, Germany. DNA was extracted from mononuclear cells from peripheral blood. 5-HTTLPR (rs4795541) genotypes (LL-homozygotes, LS-heterozygotes, and SS-homozygotes) were investigated by conventional polymerase chain reaction (PCR). The primer sequences used for the 5-HTTLPR were 5k-CAACTCCCTGTACCCCTCCTA-3k (forward primer) and 5k-GGTTGCAGGGGAGATCCTG-3k (reverse primer), resulting in a 147 base pair (bp) PCR product for S alleles, and a 190 bp PCR product for L alleles.

Statistical analysis

Statistical analysis was performed using the statistics toolbox (Version 7.4) in MATLAB (Version R2010b, The Mathworks Inc., MA, USA). The effect of age, 5-HTTLPR genotype, ELS, and interactions among these factors on evaluative and affective well-being, and social support was assessed using a weighted least squares robust multiple regression model that is less

affected by violations of normality and by the potential presence of outliers (Aiken, West, & Remo, 1991; Prentice & Anderson, 1978). To avoid multicollinearity, all variables were centered before entering the model. Besides the main predictors, the participants' sex was entered as a covariate into the analysis. Significant interaction terms were investigated using simple slope analyses (Caspi et al., 2003; Dawson & Richter, 2006). All regression analyses were performed on continuous variables to avoid biased results, and because of the relatively small sample size. Genotypes were transformed into continuous numbers regarding the amount of L alleles present (SS = 0, LS = 1, LL = 2). However, in order to explore and visualize the effects of the regression analyses, the continuous factor *age* was categorized into the following three age groups: young (18–30 years, $n = 127$), middle-aged (31–60 years, $n = 112$), and old (61–87 years, $n = 59$) and the continuous factor *ELS* was categorized into two groups using median split: low ELS (CTQ score < 34, $n = 161$), and high ELS (CTQ score ≥ 34, $n = 137$).

Results

Participants

The age range of the final sample ($N = 298$, 166 females) included in the analysis was between 18 and 87 years (Mean = 40.0/SD = 17.0). The genotypes did not differ in age ($F_{2,295}$) = 1.22, $p = 0.3$), and gender distribution ($\chi^2(2, N = 298) = 0.32$, $p = 0.85$). Furthermore, genotypes did not differ in CTQ scores ($F_{2,295} = 0.01$, $p = 0.99$). For summary, see Table 1.

Evaluative well-being

The multiple regression model that was calculated to predict evaluative well-being based on genotype, age, ELS, and the interaction between these terms revealed a significant regression equation ($F_{7,290} = 2.1$, $p = 0.04$).

The main factor age ($p = 0.046$), and importantly the three-way interaction term between genotype, age, and ELS ($p = 0.023$) were significant predictors of evaluative well-being. The main factors of genotype ($p = 0.052$) and ELS ($p = 0.06$) were marginally significant predictors of evaluative well-being. All other interaction terms and the covariate sex are not significant (all $p > 0.1$).

Post hoc comparisons for the effect of age showed that evaluative well-being increased from young age to old age ($t_{297} = 2.34$, $p = 0.016$), and increased marginally from young age to middle age ($t_{297} = 1.79$, $p = 0.074$). The effect of genotype showed marginally higher evaluative well-being in LL-homozygotes compared to LS-heterozygotes ($t = 1.84$, $p = 0.067$). *Post hoc* comparisons for the effect of ELS showed higher levels of evaluative well-being in the low ELS group compared to the high ELS group ($t_{297} = 2.67$, $p = 0.007$, see Figure 1).

Single slope analysis performed to explore the three-way interaction between genotype, age, and ELS on evaluative well-being showed that in the young group the presence of ELS reduced evaluative well-being in SS-homozygotes ($p = 0.006$), and not in the other two genotypes (both $p > 0.6$). In the middle-aged group, no effects of ELS and genotype on evaluative well-being were observed (all $p > 0.3$), and in the old group, the presence of ELS reduced evaluative well-being in LL-homozygotes ($p = 0.0001$) and in LS-heterozygotes ($p = 0.009$). For SS-homozygotes, a trend towards an increase of evaluative well-being in the presence of ELS was observed ($p = 0.052$, see Figure 2).

Affective well-being

The multiple regression model that was calculated to predict affective well-being based on genotype, age, ELS, and the interaction between these terms did not reveal a significant regression equation ($F_{7,290} = 1.31$, $p = 0.25$).

However, the main factor age ($p = 0.01$), and the main factor ELS (0.038) were significant predictors of affective well-being. All other predictors were not significant (all $p > 0.6$).

Post hoc comparisons for the effect of age showed that affective well-being increased from young age to old age ($t_{297} = 3.13$, $p = 0.002$), and from middle age to old age ($t_{297} = 2.49$, $p = 0.013$). *Post hoc* comparisons for the effect of ELS on affective well-being showed higher levels of positive affect in the low ELS group compared to the high ELS group ($t_{297} = 2.55$, $p = 0.01$, see Figure 3).

Social support

The multiple regression model that was calculated to predict the amount of perceived social support based on genotype, age, ELS, and the interaction between these terms revealed a significant regression equation ($F_{7,290} = 4.42$, $p = 0.0001$).

The main factor genotype ($p = 0.037$), the main factor ELS (0.001), the two-way interaction between genotype and age ($p = 0.001$), and the three-way interaction term between genotype, age, and ELS ($p = 0.018$) were significant predictors of perceived social support. Sex ($p = 0.09$) and the interaction
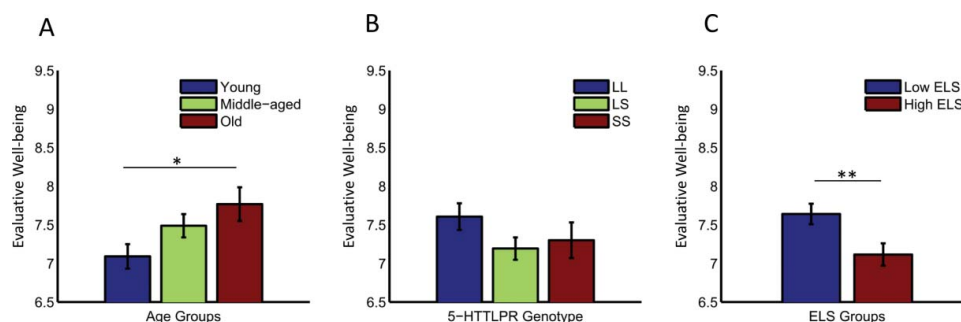

Figure 1. Main effects of age, genotype, and ELS on evaluative well-being. (A) Effects of age group (young, middle-aged, old) on evaluative well-being. (B) Effects of 5-HTTLPR genotype (LL-homozygotes, LS-heterozygotes, SS-homozygotes) on evaluative well-being. (C) Effects of ELS group (low ELS, high ELS) on evaluative well-being. Significant differences between groups are marked with stars. *$p < 0.05$; **$p < 0.01$.
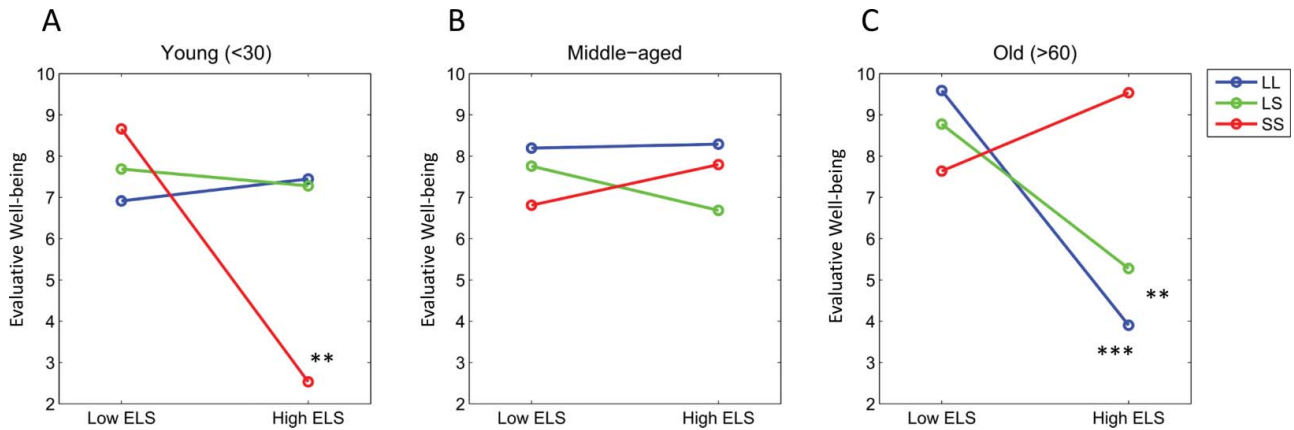
Figure 2. Interaction effects between age, genotype, and ELS on evaluative well-being. Exploration of the significant three-way interaction ($p = 0.023$) between age, 5-HTTLPR genotype, and ELS on evaluative well-being by single slope analysis. In young subjects (A), a significant decrease in evaluative well-being was observed in the presence of ELS in SS-homozygotes, and not in LS-heterozygotes and LL-homozygotes. In middle-aged subjects (B), no significant differences were observed, and in old subjects (C), a decrease in evaluative well-being was observed in LL-homozygotes and LS-heterozygotes, and not in SS-homozygotes. Significant slopes are marked with stars. *$p < 0.05$; **$p < 0.01$.
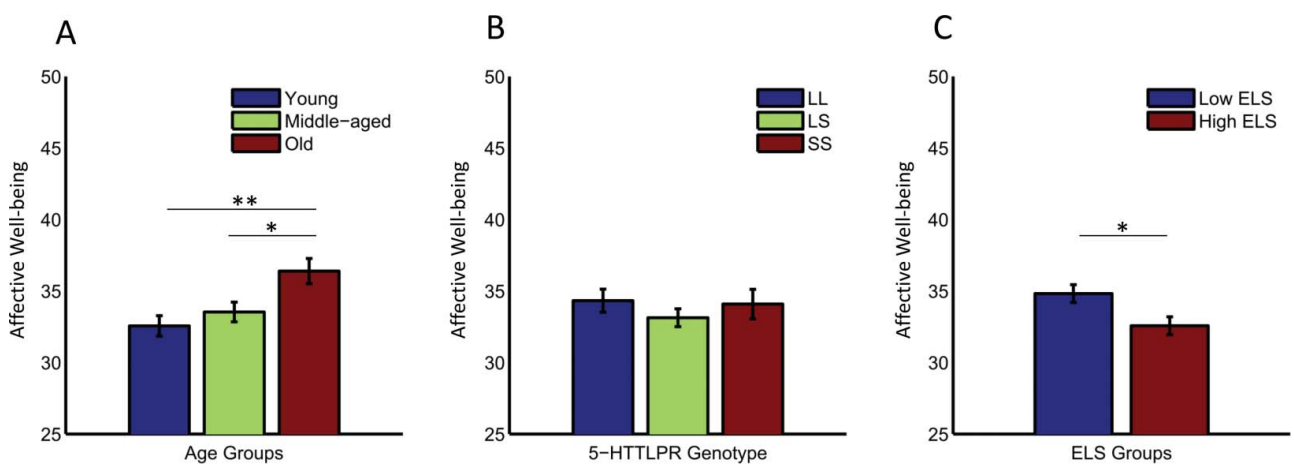

Figure 3. Main effects of age, genotype, and ELS on affective well-being. (A) Effects of age group (young, middle-aged, old) on affective well-being. (B) Effects of 5-HTTLPR genotype (LL-homozygotes, LS-heterozygotes, SS-homozygotes) on affective well-being. (C) Effects of ELS group (low ELS, high ELS) on affective well-being. Significant differences between groups are marked with stars. *$p < 0.05$; **$p < 0.01$.

between genotype and ELS ($p = 0.074$) were marginally significant predictors. All other predictors were not significant (all $p > 0.1$).

Post hoc comparisons for the main effect of genotype showed that perceived social support was marginally higher in LL-homozygotes compared to LS-heterozygotes ($t_{297} = 1.75$, $p = 0.08$). *Post hoc* comparisons for the effect of ELS showed higher levels of perceived social support in the low ELS group compared to the high ELS group ($t_{297} = 3.51$, $p = 0.0005$, see Figure 4).
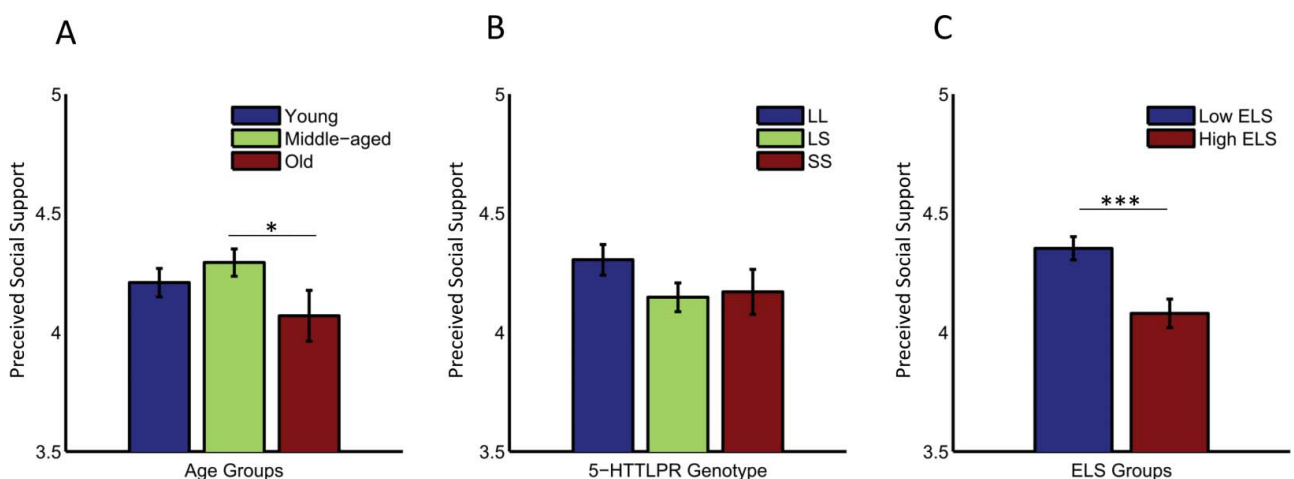

Figure 4. Main effects of age, genotype, and ELS on perceived social support. (A) Effects of age group (young, middle-aged, old) on perceived social support. (B) Effects of 5-HTTLPR genotype (LL-homozygotes, LS-heterozygotes, SS-homozygotes) on perceived social support. (C) Effects of ELS group (low ELS, high ELS) on perceived social support. Significant differences between groups are marked with stars. *$p < 0.05$; **$p < 0.01$.
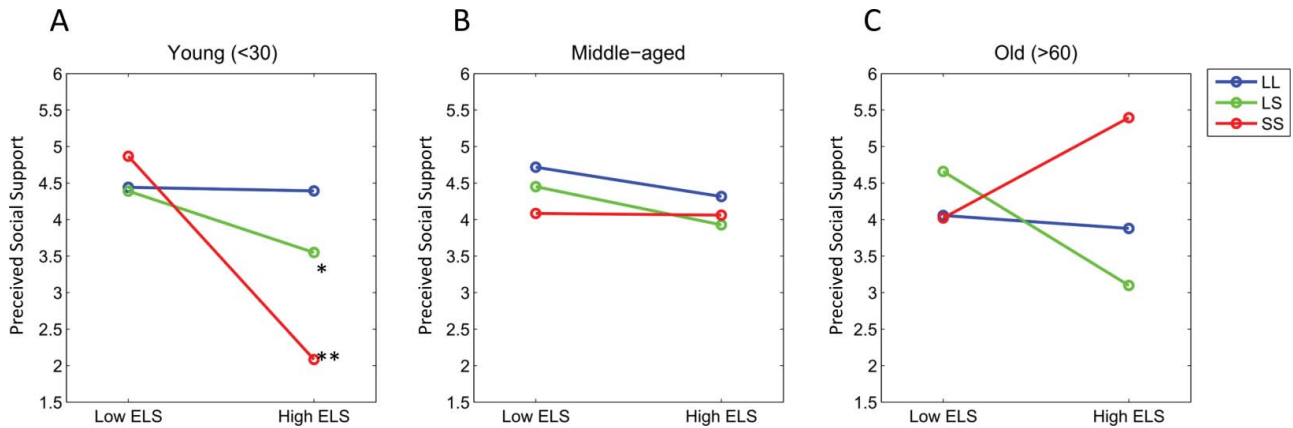
Figure 5. Interaction effects between age, genotype, and ELS on perceived social support. Exploration of the significant three-way interaction ($p = 0.018$) between age, 5-HTTLPR genotype, and ELS on perceived social support by single slope analysis. In young subjects (A), a significant decrease in perceived social support was observed in the presence of ELS in SS-homozygotes and LS-heterozygotes, and not in LL-homozygotes. In middle-aged subjects (B) and in old subjects (C), no significant differences were observed. Significant slopes are marked with stars. *$p < 0.05$; **$p < 0.01$.

Single slope analysis performed to explore the three-way interaction between genotype, age, and ELS showed that in the young group the presence of ELS reduced perceived social support in SS-homozygotes ($p = 0.002$) and in LS-heterozygotes ($p = 0.041$), and not in LL-homozygotes ($p = 0.9$). In the middle-aged and old group, no effects of ELS and genotype were observed (all $p > 0.1$, see Figure 5).

Discussion

In the present study, we investigated joint effects of 5-HTTLPR genotype and early life stress (ELS) on evaluative and affective well-being across the lifespan. Key results from previous studies, such as higher well-being with increasing age (Blanchflower & Oswald, 2008) or reduced well-being in individuals exposed to ELS (Zielinski, 2009), were confirmed by our data. Most importantly, our results showed effects of 5-HTTLPR genotype on evaluative well-being in the presence of ELS that were additionally modulated by age. Interestingly, these interrelations observed for evaluative well-being were tightly linked to the observations for perceived social support, but not to affective well-being.

In the young age group, our results showed a gene–environment interaction between 5-HTTLPR genotype and ELS on evaluative well-being similar to earlier findings from studies in which depression vulnerability was the primary outcome measure. These studies suggest that genetic vulnerability to develop depression only takes effect if it occurs in conjunction with exposure to stressful life events (e.g. Caspi et al., 2003). In the presence of ELS, young SS-homozygotes showed lower levels of evaluative well-being than the two subject groups carrying at least one long allele. Interestingly, this relationship disappeared in middle-aged subjects and was even reversed in old age. Old long allele carriers reported lower levels of evaluative well-being in the presence of ELS than SS-homozygotes that have often been described as the vulnerable genotype before. This novel finding can be interpreted in light of recent studies suggesting the short allele to be a genetic factor promoting neural plasticity. Neural plasticity is very important for processes of adaptation, which, in turn, have been reported to be a key component of successful aging (Jeste, Depp, & Vahia, 2010). Decreasing physical and cognitive capacities force older adults to continuously adapt to new circumstances. Therefore, higher levels of functional

plasticity might contribute substantially to successful adaptation processes (Greenwood, 2007), which then promote evaluative well-being in the elderly.

In addition to increased neural plasticity and successful adaptation, individual levels of social conformity might also contribute to higher well-being in old age. As demonstrated in a recent study by Herrmann and colleagues (2015), short allele carriers showed increased inferior parietal lobe activation in a joint-action paradigm reflecting higher social conformity, challenging the previous deficit oriented connotation of the 5-HTTLPR short allele. Social conformity is defined as the act of matching attitudes, behaviors, and beliefs to the norms of a group one belongs to (Cialdini & Goldstein, 2004). Thus, social conform behavior might increase an individual's chance to become a part of a social network which is one of the main predictors for well-being in late life, and has been shown to be protective against the development of late life depression (Fiske, Wetherell, & Gatz, 2009). Moreover, these findings can be connected to our results showing that there is an effect of the different 5-HTTLPR genotypes on the amount of perceived social support, which is modulated by age and ELS. Short allele carriers who experienced ELS showed reduced levels of perceived social support in the young age group, a pattern that was not observed in middle-aged and old age group. Given the influence of ELS on social functioning (Pechtel & Pizzagalli, 2011), it is not unlikely that short allele carriers might have been successful in developing and adapting their social skills in a way that led them to build a well-functioning social support system in old age. Here, increased social conformity might have played a role that needs to be clarified by future investigations.

It remains unclear which biological mechanisms related to 5-HTTLPR genotype bring about such profound phenotypic changes at different ages. There is evidence that due to receptor loss and changes in serotonin transporter availability, the serotonergic system undergoes marked changes in the aging process that have been linked to age-related psychopathology such as Alzheimer's disease or late life depression (Meltzer et al., 1998; van Dyck et al., 2000). It is likely that these neurobiological changes interact with 5-HTTLPR genotype. A possible explanation could be that long allele carriers have optimal serotonin availability in young age, which decreases to deficient levels in old age. Whereas, in short allele carriers, the aging process reduces serotonin availability from

excessive to optimal levels in old age. However, this assumption is clearly speculative at the current stage of research and needs to be verified empirically.

The interaction effects between genotype, age, and ELS we reported were observed for evaluative well-being and perceived social support. No such interaction effects were observed for affective well-being. However, the main effects of age and ELS were similar for evaluative and affective well-being. It has been suggested that evaluative well-being can be conceptualized as people's subjective evaluation of their global life circumstances, whereas affective well-being can be conceptualized as people's subjective evaluation of recent activities and events (Luhmann, Hawkley, Eid, & Cacioppo, 2012). Since interaction effects with 5-HTTLPR genotype were only observed for evaluative well-being, it could be speculated whether such genetic influences are more likely observed in such a global measure of well-being instead of a measure that is susceptible to transient changes of mood state. While this assumption is speculative and in need of empirical support, the differential effects we report for evaluative and affective well-being clearly indicate that well-being is a multifaceted construct with different sub-domains that need to be distinguished (Kahneman & Riis, 2005).

The main limitation of our study is the sample size ($N = 298$). Thus, it is necessary to replicate our findings using larger samples. However, despite the relatively small sample, we believe that the theoretical background of our study, and the statistical model we applied allow us to draw first conclusions and encourage upcoming studies to further investigate age-related changes in well-being under consideration of genetic and environmental factors.

In summary, our results indicate that the evaluative component of well-being is affected by genetic and environmental factors, and that these effects differ substantially across the lifespan. Short allele carriers of the 5-HTTLPR genotype that additionally experienced ELS might have advantages in adaptation processes that become increasingly important in old age, and are possibly more receptive to social supports. Alterations in serotonergic signaling across the life span pose a putative neurobiological mechanism that might interact with 5-HTTLPR genotype and bring about the observed phenotypic changes.

Disclosure statement

All authors declare that they have no conflicts of interest.

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