



The Molecular Genetics of Life Satisfaction: Extending Findings from a Recent Genome-Wide Association Study and Examining the Role of the Serotonin Transporter

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Abstract

In a recent genome-wide association study (GWAS), three polymorphisms (rs3756290, RAPGEF6; rs2075677, CSE1L; rs4958581, NMUR2) were suggested as potentially being related to subjective-well-being and life satisfaction. Additionally, associations between the 5-HTTLPR polymorphism (serotonin transporter) and subjective well-being have been reported in other previous studies. In the current study, we therefore sought to further investigate the findings of the GWAS and examine the association between 5-HTTLPR and subjective well-being. A total of 1174 participants (821 females) were recruited and asked to provide information on their demographics, life satisfaction, and positive affect. All participants provided a genetic sample. We found associations between one SNP derived from the GWAS (rs4958581, NMUR2) and life satisfaction. We also replicated findings involving 5-HTTLPR and life satisfaction, but only for the housing, leisure and family life satisfaction variables, and not for overall life satisfaction or positive affect. Our study underlines that research investigating complex traits in the field of behavioral genetics is challenging due to their (a) pleiotropic and (b) polygenic effects, resulting in tiny effect sizes of each marker investigated. The current study also highlights the importance of investigating genetic markers of distinct areas of life satisfaction.

Keywords Subjective well-being · 5-HTTLPR · Polymorphism · rs4958581, NMUR2 · Happiness

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1 Introduction

Over the last several decades, the constructs of life satisfaction and subjective well-being (SWB) (Diener 1984) have been examined using many different theoretical and methodological approaches, and in relation to a host of demographic, psychological and environmental variables. For example, previous studies have focused on demographic variables like gender (Batz-Barbarich et al. 2018) and age (e.g. Moksnes and Espnes 2013; Ulloa et al. 2013) in relation to life satisfaction. Here, the findings for age have been inconsistent: In a review of the literature, (Ulloa et al. 2013) suggested that the observed relationship between age and SWB was either U-shaped, inverted U-shaped, or linear. The results for gender have also been mixed; for example, a meta-analysis reported differences for job satisfaction, with women showing lower job satisfaction than men, but no gender differences for overall life satisfaction (Batz-Barbarich et al. 2018). Cultural influences on life satisfaction have also attracted broad interest, particularly focusing on the differences between collectivistic and individualistic cultures (e.g. Kim et al. 2018; Park et al. 2004; Schimmack et al. 2002; Tov and Diener 2013), and highlighting differences in levels of life satisfaction across nations (Diener and Suh 2000).

Many studies have focused on the role that environmental and life variables play in relation to SWB, for example, the role of specific life events (Luhmann et al. 2012b), the impact of life style (Burrell et al. 2006), the effects of marital status (Shapiro and Keyes 2008), to name just a few. This previous research has also examined SWB in relation to behaviors and experiences that are typical of modern industrial societies, including, for example, commuting (Lachmann et al. 2017) and the use of digital technologies (Samaha and Hawi 2016). Internet use disorder and smartphone use disorder have been examined in conjunction with life satisfaction: Some studies have examined the personality characteristics underpinning these two disorders (Lachmann et al. 2019; Montag et al. 2015; Peterka-Bonetta et al. 2019), while others have sought to examine more specific constructs like empathy or optimism (Lachmann et al. 2018b; Renaud et al. 2018).

Previous research has also focused on individual differences in life satisfaction and SWB; for example, the association between overall life satisfaction and personality (e.g. Fowler et al. 2018; Kim et al. 2018; Zalewska et al. 2018), as well as the association between specific variables of life satisfaction (e.g. family, leisure, income) and overall life satisfaction (e.g. Heller et al. 2004; Kahneman and Deaton 2010; Kuykendall et al. 2015). These approaches can be described as, respectively, top-down (i.e. personality is associated with overall life satisfaction) and bottom-up approaches (i.e. specific life satisfaction variables are related to overall life satisfaction). In some cases, both approaches have been combined into what might be called an integrative approach, postulating the simultaneous applicability of both top-down and bottom-up approaches (e.g. Brief et al. 1993; David et al. 1997; Feist et al. 1995; Headey et al. 1991; Lachmann et al. 2018a).

As part of the effort to better understand individual differences in life satisfaction, research has also increasingly sought to utilize newer methods and techniques to help understand the genetic influences on life satisfaction. The study of the influence of nature versus nurture on individual differences in SWB usually begins with estimating the heritability of the given phenotype (Plomin and Colledge 2001). The research approach used to answer this type of question is the twin/family study design, mostly utilizing an ACE [i.e. additive genetic variance (A), shared environmental factors (C), non-shared environmental factors (E) or ACED (i.e. the same as ACE, plus non-additive genetic variance (D)] model to discriminate between genetic and environmental influences (Polderman et al. 2015; e.g.

Sauce and Matzel 2018). Bartels (2015) summarized 25 years of research on the heritability of life satisfaction and SWB in a meta-analysis, making a distinction between SWB and life satisfaction, although these two terms are often used interchangeably in the literature (Layard 2010). For SWB, they found an estimated heritability of 36% based on a total sample size of $n=55,974$. The lowest estimated heritability was 23% (Weiss et al. 2008), and the highest was 59% (Tellegen et al. 1988). Similar results were found for life satisfaction, with an estimated heritability of 32% based on a sample size of $n=47,750$ participants, with the lowest estimated heritability at 18% (Nes et al. 2008) and the highest at 47% (Bartels and Boomsma 2009). In sum, these findings demonstrate that genetic factors contribute to the characteristics of life satisfaction and SWB by explaining approximately 34% of the variance (Bartels 2015).

Beyond exploring the heritability of life satisfaction, several studies have investigated whether specific genetic variants are associated with life satisfaction and SWB. The focus in these studies has been largely, but not solely, on gene loci associated with neurotransmitters like dopamine, oxytocin, and serotonin (Farhud et al. 2014). These studies use what can be termed the candidate gene approach (Montag and Reuter 2014), typically where pharmacological studies have suggested a particular neurotransmitter may play a role in relation to a defined phenotype. This knowledge is then used to search for genetic variants on genes linked to this neurotransmitter. For example, Chen et al. (2013) established a link between monoamine oxidase A (MAOA) and happiness in women, but not men. MAOA deaminates, among other things, serotonin and dopamine, but the efficiency of the polymorphism is dependent upon a variable number of tandem repeats (VNTR), resulting in genotypes with low activity of MAOA (MAOA-L) and high-activity of MAOA (MAOA-H) (Sabol et al. 1998). Female carriers of the MAOA-L genotype showed significantly higher happiness compared to carriers of the MAOA-H genotype (Chen et al. 2013). Another study investigated the association between SWB and the catechol-*O*-methyltransferase (COMT) Val158Met polymorphism (Liu et al. 2017). COMT Val158Met is a Single Nucleotide Polymorphism (SNP) on the Catechol-*O*-Methyltransferase gene involved in the inactivation of catecholamines (e.g. dopamine), in which the VAL/VAL genotype shows a 40% increase in enzyme activity compared to the MET/MET genotype (Lachman et al. 1996). Liu et al. (2017) reported greater SWB for individuals with a higher number of VAL alleles.

A review of the literature by IsHak et al. (2011) investigated the relationship between the neuropeptide oxytocin and SWB (IsHak et al. 2011). Oxytocin is involved in a wide spectrum of positive social behaviors (e.g. intimacy and bonding), facilitates social interaction, and is therefore assumed to be related to SWB (Farhud et al. 2014). IsHak et al. concluded that oxytocin would be of potential use in enhancing SWB. On the other hand, a recent genetic study by Conner et al. (2018) reported a null finding on the association between SWB and an oxytocin-related genetic variation (rs53576), suggesting that this locus might not be as widely involved in SWB as initially thought (Conner et al. 2018).

In addition to the above, the effect of the serotonergic system on SWB has also been investigated, since serotonin is associated with, among other things, emotional behavior, pain, and depression (Haase et al. 2013). The functional polymorphism focused on here is a various number tandem repeat (VNTR) variation in the promoter region of the serotonin transporter gene (5-HTTLPR), consisting of a short and a long variant. The long variant of 5-HTTLPR shows an approximately three times higher expression rate than the shorter version, resulting in the release of more serotonin transporters in the synaptic cleft (Canli and Lesch 2007). Additionally, the effect of 5-HTTLPR can be further influenced by a SNP in the promotor region (rs25531), as demonstrated in

a recent study (Hooten et al. 2017). De Neve (2011) reported in a case-control study significantly higher levels of SWB for carriers of the longer variant of the serotonin transporter gene (De Neve 2011). However, the replication of these initial findings in independent samples could be only partially accomplished (De Neve et al. 2012).

To identify further promising candidate genes in the context of SWB/life satisfaction, neuroticism, and depressive symptoms (Okbay et al. 2016), a genome wide association study (GWAS) was conducted recently. These traits are commonly also referred to as the well-being spectrum (Baselmans et al. 2019), and they show a high genetic overlap which suggests the presence of a specific interaction between those traits. Okbay et al. (2016) detected three polymorphisms that were possibly associated with SWB, namely RAPGEF6 (rs3756290), CSE1L (rs2075677), and NMUR2 (rs4958581), although not much is currently known about their mode of operation. In this regard, it is important to mention that the phenotype measure they used in this study was either life satisfaction or positive affect, and in some cohorts a mixture of both, so they could utilize as large a sample as possible (Okbay et al. 2016). However, with this course of action the effects of these polymorphisms might be difficult to interpret (Røysamb and Nes 2018). This also influences further research because both life satisfaction and positive affect must then be included prospectively when investigating the associations between the polymorphisms detected in the GWAS and SWB/life satisfaction.

Given the state of the literature summarized above, the findings examining the genetics of life satisfaction/SWB are obviously mixed and difficult to interpret. It is clear that the replication and further examination of previously shown and assumed associations between specific gene loci and life satisfaction/SWB is warranted (Conner et al. 2018).

The present study seeks to add more clarity to the literature by re-examining the relationship between specific polymorphisms and SWB. We will focus on the *5-HTTLPR* polymorphism since several studies have suggested it could play an important role relating to mental well-being (e.g. Canli and Lesch 2007; De Neve 2011; De Neve et al. 2012; Murakami et al. 1999; Risch et al. 2009). Further to this, we seek to extend the findings from the GWAS of Okbay et al. (2016) by conceptually replicating their findings in relation to SWB. In contrast to the classic pharmacologically based candidate gene approach, we stress that the approach to the research used in the present study might be termed the *genome wide scan-based candidate gene* approach. This approach might be helpful in addressing the replication crisis in psychology (and in the field of molecular genetic association studies, more specifically). Furthermore, we were interested in examining the extent to which demographic variables might influence the results. Therefore, all analyses were conducted in both the complete original sample (controlling for demographic variables) and alternatively in a balanced sample, matching all male participants from the original sample with females, considering age and education. So the use of statistical control measures can be placed at a minimum. From a methodological point of view, it might be beneficial to further analyze the potential interaction of those demographic variables (i.e. gender, age, and education) and SWB (Hutchison et al. 2004) using this alternative design. The results from the balanced sample are reported in the supplement. For all analyses, positive affect and overall life satisfaction were included, given both measures were used to represent life satisfaction in the GWAS referred to above (Okbay et al. 2016). We also followed the approach of the German Socio-Economic Panel (SOEP) by including specific life satisfaction variables in our analyses, in addition to overall life satisfaction (Siedler et al. 2008).

2 Materials and Methods

2.1 Participants

A total of $n=1174$ participants (821 females) completed an online survey and gave socio-demographic information, including age, gender, and education. The mean age in this sample was $M=23.48$ ($SD=7.11$), ranging from 18 to 82 years, with 93.1 percent of the participants in the age range between 18 and 29 years. Overall, 6.6% had a secondary school leaving certificate, 72.9% held a Baccalaureate-Diploma, and 20.5% had a university degree. The participants were recruited from Ulm University in Germany so most of the participants were university students. All participants are part of the Ulm Gene Brain Behavior project, from which other studies have been published (e.g. Montag et al. 2017; Sindermann et al. 2018). The local ethics committee of Ulm University approved the study, and every participant had to provide their electronic and written consent to participate.

2.2 Measures

The items used to measure life satisfaction were retrieved from a specific section of the German Socio-Economic Panel (SOEP) which covers one's current life situation. Individuals were asked to report on their degree of life satisfaction in the areas of health, job, income, housing, leisure time, family, and their overall satisfaction with life. Furthermore, data on mood were collected (also derived from SOEP) to use this information in the analyses as covariate. A Likert-scale was used to answer this item, ranging from 0 ("altogether bad") to 10 ("altogether good"). The SOEP recommends administering the item concerning overall life satisfaction as the final item to avoid possible interference with the specific life satisfaction variables (Siedler et al. 2008). It should be noted that overall life satisfaction is not a simple composite of the specific life satisfaction variables (Erdogan et al. 2012); all life satisfaction variables are distinct, but they also overlap to some extent (e.g. a person more satisfied with their leisure is also more likely to have a higher score on overall satisfaction). The items of life satisfaction were answered using a Likert-scale, ranging from 0 ("completely dissatisfied") to 10 ("completely satisfied").

The Positive and Negative Affect Scale (PANAS) was administered to collect data on positive affect (Watson et al. 1988) taking into account the last 6 month. Ten adjectives describing either negative affect (e.g. upset, ashamed, distressed) or positive affect (e.g. strong, inspired, active) formed the two-dimensional questionnaire, with items rated on a 5-point Likert scale ranging from 1 = 'very slightly or not at all' to 5 = 'extremely'. The items from each dimension add up to one summed score for both positive affect and negative affect. Watson et al. (1988) provided comprehensive information concerning the psychometric properties of this scale. It has been used very widely in previous research. Cronbach's alpha in the current sample was $\alpha = .86$ for positive affect ($\alpha = .87$ for the balanced sample), and $\alpha = .85$ for negative affect ($\alpha = .86$ for the balanced sample). In the current study we only used the positive affect scale, together with the variables of life satisfaction, to stay close to the original approach of the Okbay et al. (2016) study. It should be noted that the association between negative affect and the polymorphisms of interest in this study yielded no significant results. The findings concerning negative affect and the correlations between negative affect and the variables of life satisfaction as well as positive affect can be found in the supplement.

2.3 Procedure

The participants were asked to complete the online survey. After indicating their willingness to take part in the study and the provision of a valid email address, they received a personalized link to access the online survey. Upon receipt of the link, participants could complete the survey using the digital device of their choice. Completed surveys were transmitted via an SSL encrypted link to our secure data server for further processing and analyses. After this, an appointment in our laboratory was scheduled so the participants could provide a genetic sample. Genetic samples were collected using a non-invasive method, (i.e. extraction of buccal cells using cotton swabs) to safeguard the participants from any harm.

2.4 Genotyping

DNA was automatically extracted from buccal cells using a MagNA Pure 96 instrument and commercial extraction kits (MagNA Pure 96 DNA and Viral NA Small Volume Kit; Roche Diagnostics, Mannheim, Germany) in our own laboratory (Department of Molecular Psychology, Ulm University, Ulm, Germany).

Genotypes for the Single Nucleotide Polymorphisms (SNPs) rs3756290 (RAPGEF6), rs2075677 (CSE1L), and rs4958581 (NMUR2) were identified using the MALDI-TOFF Mass Spectrometer technique on a MassARRAY and iPLEX system (Sequenom, San Diego, California, USA) by the Varionostic GmbH (Ulm, Germany).

Genotyping the 5-HTTLPR 44-bp variable-number tandem repeat (VNTR) polymorphism including SNP rs25531 was undertaken in the laboratory of the Department of Molecular Psychology, Ulm University, Ulm, Germany. We included SNP rs25531 in the analyses (triallelic approach) since it has been shown that carriers of the long version of 5-HTTLPR showed a similar low expression rate to carriers of the short version if a base exchange from A to G occurred in SNP rs25531 (Hu et al. 2006). To indicate the triallelic approach in the analyses a dash was attached (S', L'). The 5-HTTLPR was amplified by polymerase chain reaction (PCR) using a peqSTAR (VWR (Avantor), Darmstadt, Germany). The protocol consisted of a 5-min denaturation phase at 95 °C. Thereafter, 35 cycles of 30 s denaturation (95 °C), 30 s annealing (64.9 °C), and 60 s extension (72 °C) were undertaken. The final elongation was performed for 5 min (72 °C). For the PCR the following primer sequences (TIB MOLBIOL, Berlin, Germany) were used:

Forward: 5'-TCCTCCgCTTTggCgCCTCTTCC-3';

Backward: 5'-TgggggTTgCAggggAgATCCTg-3'.

The PCR-product of rs25531 SNP was genotyped using MSP1 (restriction enzyme; New England Biolabs) for digestion and incubated at 37 °C for 90 min. Thereafter, samples were loaded for 2 h at 175 V on to a 1.8% agarose gel in a TBE solution. After completion of the gel electrophoresis, the results were documented by means of a gel documentation system and classified by two independent raters.

2.5 Statistical Analysis

SPSS version 22.0 for Windows (IBM SPSS Statistics, IBM, New York, NY, USA) was used to conduct the statistical analyses. All analyses were performed for the complete original sample, as well as the balanced sample (as described above) to assess any potential

influences of these demographic variables on the results using two different approaches. Normality of the distribution for all variables was inspected visually and using the procedure described by Miles and Shevlin (2001). Gender differences across life satisfaction/positive affect were examined using ANOVAs. The association of age and mood on life satisfaction and positive affect variables were examined using Pearson correlations. The associations between overall life satisfaction and the specific life satisfaction variables with the respective genetic variants were examined using ANCOVAs, with gender as a second fixed factor, and age and mood as covariates (please see the results section for further details). The level of significance (Bonferroni correction) for all analyses was set at $.05/8 = .00625$ (life satisfaction variables plus positive affect).

3 Results

The inspection of the data revealed no outliers and a minimal amount of missing data where some participants did not provide information for all variables of interest (please see Table 1 for the exact numbers of participants). A normal distribution for all variables in the complete sample ($n = 1174$) and the balanced sample ($n = 524$) was observed (results concerning the balanced sample can be found in the supplement).

3.1 Analyses in the Complete Sample

The life satisfaction variables and the positive affect variables were analyzed for gender specific effects. Significant differences were found for the variables health ($F_{(1, 1172)} = 9.83$, $p = .002$) and family ($F_{(1, 1171)} = 10.32$, $p = .001$), with females showing lower scores for health ($M_{\text{Female}} = 7.37$, $SD = 2.11$; $M_{\text{Male}} = 7.78$, $SD = 1.75$) and higher scores for family ($M_{\text{Female}} = 7.59$, $SD = 2.41$; $M_{\text{Male}} = 7.09$, $SD = 2.47$). No significant differences across gender were found for mood ($t_{(1, 1170)} = 1.84$, $p = .066$), however mood was significantly and positively associated with overall life satisfaction ($r = .41$, $p < .001$), all specific life satisfaction variables [ranging between $r = .18$, $p < .001$ (income) and $r = .41$, $p < .001$ (leisure)], and positive affect ($r = .31$, $p < .001$). Age was correlated with the life satisfaction variables job ($r = .10$, $p = .001$) and income ($r = .18$, $p < .001$). Given the observed associations between mood, gender, and age with the life satisfaction variables and positive affect, further analyses were conducted using gender as a second fixed factor (besides genotype), and with age and mood as covariates. The descriptive statistics for the life satisfaction variables and positive affect (complete sample) are summarized in Table 1.

The genotype frequencies and Hardy–Weinberg equilibria for the SNPs under investigation were as follows: for RAPGEF6 (CC: $n = 583$, CT: $n = 410$, TT: $n = 56$; HWE: $X^2 = 2.18$, $df = 1$, $p = .140$), NMUR2 (CC: $n = 132$, CT: $n = 479$, TT: $n = 438$; HWE: $X^2 = .01$, $df = 1$, $p = .953$), CSE1L (AA: $n = 613$, AG: $n = 375$, GG: $n = 59$; HWE: $X^2 = .03$, $df = 1$, $p = .868$), and 5-HTTLPR including rs25531 (trialelic approach) (L'L': $n = 253$, L'S': $n = 435$, S'S': $n = 193$; HWE: $X^2 = .05$, $df = 1$, $p = .815$). Due to different reasons (e.g. genotyping failure, MALDI TOF dropout) we have varying genotype frequencies. In the following paragraphs we will use the name of the genes which includes the respective SNP.

We should note here that our analyses of the association between genes and life satisfaction/positive affect showed few statistically significant results, but for the sake of completeness we have reported all of our findings without regard to their significance. For clarity, however, the statistically significant findings have been highlighted in Figs. 1, 2, 3 and 4.

Table 1 Descriptive statistics for all life satisfaction (LS) variables, positive affect (PA), and mood in the complete sample ($N=1174$)

Variables	N	Mean	SD	Min (scale)	Max (scale)	Skew
LS-Health	1173	7.50	2.02	0	10	-1.16
LS-Job	1173	5.11	3.69	0	10	-.39
LS-Income	1173	4.41	3.11	0	10	.02
LS-Housing	1168	7.23	2.45	0	10	-1.03
LS-Leisure	1173	7.16	2.06	0	10	-.95
LS-Family	1172	7.44	2.44	0	10	-1.14
OLS	1168	7.92	1.80	0	10	-1.42
PA	1170	34.61	5.92	10	50	-.40
Mood	1172	6.52	1.71	0	10	-.67

OLS overall life satisfaction

3.2 Associations for RAPGEF6, NMUR2, CSE1L and Life Satisfaction/Positive Affect in the Complete Sample

For RAPGEF6, there was no significant association with the life satisfaction variables (overall life satisfaction ($F_{(2, 1035)}=.44, p=.642$; health: $F_{(2, 1035)}=.55, p=.577$; job: $F_{(2, 1035)}=.84, p=.432$; income: $F_{(2, 1035)}=1.56, p=.211$; housing: $F_{(2, 1035)}=1.68, p=.188$; leisure: $F_{(2, 1035)}=.60, p=.548$; family: $F_{(2, 1035)}=3.57, p=.028$); nor with *positive affect* ($F_{(2, 1035)}=.45, p=.640$) on genotype level (CC vs. CT vs. TT).

Testing the same variables when combining participants carrying at least one T-allele (T+: TT, TC) against participants who were homozygous for the C-allele (T-: CC) also yielded no significant results (overall life satisfaction ($F_{(1, 1037)}=.46, p=.498$; health: $F_{(1, 1037)}=1.10, p=.295$; job: $F_{(1, 1037)}=.67, p=.413$; income: $F_{(1, 1037)}=.20, p=.656$; housing: $F_{(1, 1037)}=.03, p=.955$; leisure: $F_{(1, 1037)}=.19, p=.666$; family: $F_{(1, 1037)}=4.04, p=.045$; positive affect: $F_{(1, 1037)}=.54, p=.465$). Doing the same analyses for participants carrying at least one C-allele (C+: CC, TC) against participants who were homozygous for the T-allele (C-: TT) provided again no significant results.

The interaction between gender and RAPGEF6 was not significant, independent of genotype grouping.

For NMUR2, the results were as follows: overall life satisfaction $F_{(2, 1035)}=4.96, p=.007$; health: $F_{(2, 1035)}=1.13, p=.325$; job: $F_{(2, 1035)}=.63, p=.533$; income: $F_{(2, 1035)}=.89, p=.413$; housing: $F_{(2, 1035)}=.75, p=.473$; leisure: $F_{(2, 1035)}=.21, p=.808$; family: $F_{(2, 1035)}=7.68, p<.001$; positive affect: $F_{(2, 1035)}=.52, p=.594$ (tested on genotype level CC vs. CT vs. TT). After a Bonferroni correction ($.05/8=.00625$), the variable family showed a significant association with NMUR2. Post-hoc analyses (Games-Howell) revealed a significant difference between the TT and CT genotypes ($p=.003$; $-.53, 95\% \text{ CI} [-.91, -.14]$) relating to the variable family, showing lower scores for the TT genotype ($M=7.24, SD=2.61$) compared to the CT genotype ($M=7.76, SD=2.20$). For details, please see Fig. 1.

On allele level (C+: CC, TC vs. C-: TT carriers), the following results were observed: overall life satisfaction: $F_{(1, 1037)}=3.98, p=.046$; health: $F_{(1, 1037)}=2.26, p=.133$; job: $F_{(1, 1037)}=.32, p=.571$; income: $F_{(1, 1037)}=.63, p=.428$; housing: $F_{(1, 1037)}=.73, p=.393$; leisure: $F_{(1, 1037)}=.40, p=.528$; family: $F_{(1, 1037)}=11.48, p=.001$; positive affect: $F_{(1, 1037)}=.01, p=.968$. Again, the variables family and NMUR2 (Bonferroni corrected) were significantly associated with the C- group ($M=7.23, SD=2.63$), showing lower scores compared to the C+ group ($M=7.64, SD=2.28$). Please refer to Fig. 2 for an

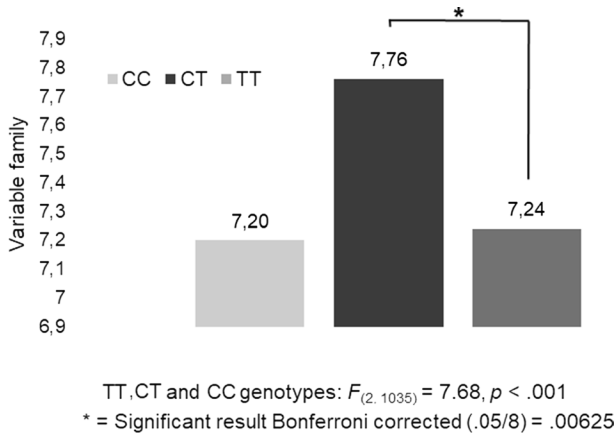


Fig. 1 Significant findings for NMUR2 (genotype level) and the variable family

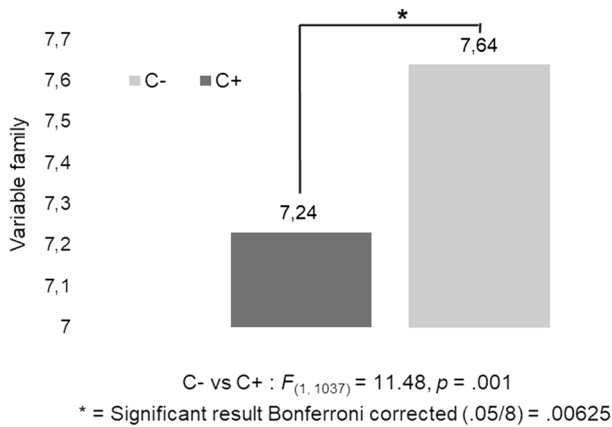


Fig. 2 Significant findings for NMUR2 (allele level) and the variable family

illustration of this. The analyses for T+ carriers versus T- carriers yielded no significant result.

The interaction between gender and NMUR2 was not significant, independent of genotype grouping.

For CSE1L, there were no significant results in relation to the life satisfaction variables and positive affect: overall life satisfaction $F_{(2, 1034)} = .55, p = .576$; health: $F_{(2, 1034)} = .44, p = .641$; job: $F_{(2, 1034)} = 1.02, p = .360$; income: $F_{(2, 1034)} = .73, p = .482$; housing: $F_{(2, 1034)} = 1.64, p = .195$; leisure: $F_{(2, 1034)} = .66, p = .518$; family: $F_{(2, 1034)} = .11, p = .892$; positive affect: $F_{(2, 1034)} = 2.22, p = .109$ (tested on genotype level AA vs. AG vs. GG).

Comparing the G+ group with the G- group also showed no significant results (after Bonferroni correction): overall life satisfaction: $F_{(1, 1036)} = 1.08, p = .298$; health: $F_{(1, 1036)} = .59, p = .441$; job: $F_{(1, 1036)} = .01, p = .954$; income: $F_{(1, 1036)} = .40, p = .527$; housing: $F_{(1, 1036)} = 3.34, p = .068$; leisure: $F_{(1, 1036)} = 1.11, p = .292$; family: $F_{(1, 1036)} = .03,$

$p = .868$; positive affect: $F_{(1, 1036)} = 4.28$, $p = .039$. Also, no significant results have been found when comparing A+ carriers with A- carriers.

The interaction between gender and CSEIL was not significant, independent of genotype grouping.

3.3 Associations Between 5-HTTLPR and Life Satisfaction/Positive Affect in the Complete Sample

The findings for the association between 5-HTTLPR (including rs25531) and life satisfaction and positive affect were as follows (tested on genotype level: L'L' vs. L'S' vs. S'S'): overall life satisfaction: $F_{(2, 870)} = 2.65$, $p = .071$; health: $F_{(2, 870)} = .01$, $p = .991$; job: $F_{(2, 870)} = .37$, $p = .692$; income: $F_{(2, 870)} = .33$, $p = .719$; housing: $F_{(2, 870)} = 4.36$, $p = .013$; leisure: $F_{(2, 870)} = 3.39$, $p = .034$; family: $F_{(2, 870)} = 5.04$, $p = .007$; positive affect: $F_{(2, 870)} = .18$, $p = .839$.

Testing these associations for S'+ carriers (S'S', S'L') versus S'- carriers (L'L') showed the following results: overall life satisfaction: $F_{(1, 872)} = .33$, $p = .568$; health: $F_{(1, 872)} = .02$, $p = .903$; job: $F_{(1, 872)} = .70$, $p = .404$; income: $F_{(1, 872)} = .01$, $p = .917$; housing: $F_{(1, 872)} = 8.71$, $p = .003$; leisure: $F_{(1, 872)} = 5.09$, $p = .024$; family: $F_{(1, 872)} = 3.42$, $p = .065$; positive affect: $F_{(1, 872)} = .21$, $p = .645$. This time the variable housing and 5-HTTLPR (Bonferroni corrected) were significantly associated, with the S'+ group ($M = 7.19$, $SD = 2.42$) showing lower scores compared to the S'- group ($M = 7.63$, $SD = 2.28$). The result is illustrated in Fig. 3.

When comparing S'S' carriers with L'L' carriers (extreme groups), the following results were observed: overall life satisfaction: $F_{(1, 439)} = 2.99$, $p = .084$; health: $F_{(1, 439)} = .02$, $p = .892$; job: $F_{(1, 439)} = .27$, $p = .606$; income: $F_{(1, 439)} = .33$, $p = .568$; housing: $F_{(1, 439)} = 5.60$, $p = .018$; leisure: $F_{(1, 439)} = 6.35$, $p = .012$; family: $F_{(1, 439)} = 8.80$, $p = .003$; positive affect: $F_{(1, 439)} = .36$, $p = .551$. The variable family and 5-HTTLPR (Bonferroni corrected) were associated, with the S'S' group ($M = 7.10$, $SD = 2.60$) showing lower scores compared to the L'L'- group ($M = 7.67$, $SD = 2.27$).

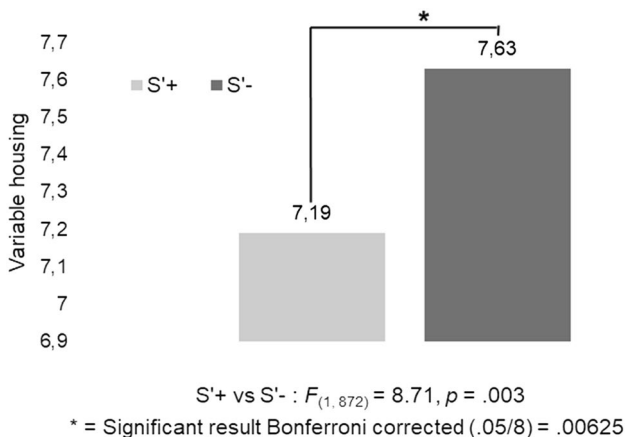


Fig. 3 Significant findings for 5-HTTLPR (allele level) and the variable housing

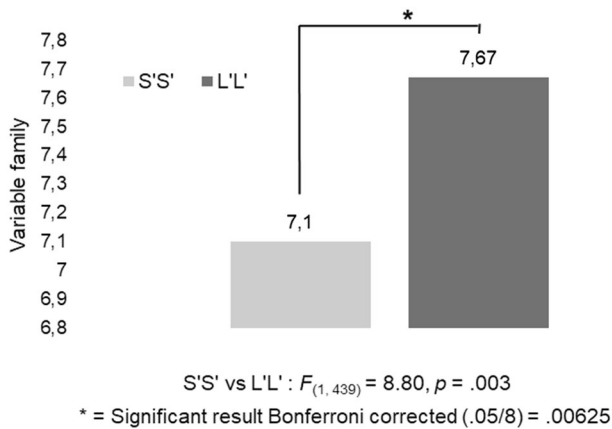


Fig. 4 Significant findings for 5-HTTLPR (S'S' vs. L'L') and the variable family

The interaction between gender and 5-HTTLPR was not significant, independent of genotype grouping. The results are depicted in Fig. 4.

4 Discussion

The present study investigated the association between three genetic variants (rs3756290, RAPGEF6; rs2075677, CSE1L; rs4958581, NMUR2) and life satisfaction derived from a recent GWAS (Okbay et al. 2016). The study also re-examined the association between 5-HTTLPR and life satisfaction (De Neve 2011; De Neve et al. 2012). Further to this, for methodological reasons, all analyses were replicated in a sample balanced for gender, age, and education, following a different methodological approach since there is some evidence in the literature of interactions between those three demographic variables and genetics (e.g. Belsky et al. 2016; Jiang et al. 2017; Miettinen et al. 2018; Wu et al. 2016). The results for the balanced sample are summarized in the supplement.

Our findings in this study showed that the only significant association detected in the complete sample for the SNPs found in the GWAS (Okbay et al. 2016) was between rs4958581, NMUR2 and the life satisfaction variable family. For the same analyses in the balanced sample, no significant associations were shown at all. The results for 5-HTTLPR were mixed: In the complete sample, the life satisfaction variables housing [S'+ (S'S', S'L') vs. S'– (L'L')] and family (S'S' vs. L'L') were associated with 5-HTTLPR, with L'L' carriers showing higher scores on life satisfaction. In the balanced sample, we found associations between the life satisfaction variables housing and leisure with 5-HTTLPR [S'+ (S'S', S'L') vs. S'– (L'L')], with L'L' carriers showing higher scores on life satisfaction.

In line with the previous literature, in the present study carriers of the L'L' genotype showed higher scores on life satisfaction compared to those carrying at least one S' (S'+) allele (De Neve 2011; De Neve et al. 2012), but only for some specific life satisfaction variables, and not for overall life satisfaction or positive affect. A positive influence of the long variant of 5-HTTLPR on various phenotypical characteristics is reported in the literature (e.g. Fox et al. 2009), while also showing the potential role of the short variant of

5-HTTLPR as a risk allele, for example, regarding depression (Caspi et al. 2003) or anxiety (Lesch et al. 1996). Moreover, in several studies and meta-analyses, the moderating role of 5-HTTLPR is highlighted, for example, in terms of moderating emotional behavior and changes in marital satisfaction (Haase et al. 2013), stress and depression (Karg et al. 2011), or coping strategies and emotion regulation (Plieger et al. 2017). A recent meta-analysis, however, concluded that the 5-HTTLPR by stress interaction on depression must be of a modest effect size and only observable in limited situations (Culverhouse et al. 2018). In other cases, the following relationship has been reported, in which the short variant of 5-HTTLPR was associated with positive emotional expressions (Haase et al. 2015), or with nostalgia proneness (Luo et al. 2019). The previous research seems to suggest 5-HTTLPR plays an important role in both the positive and negative regulation of behavior; further attention on its role seems warranted at this point. Taking this into account, our findings showing that only some of the specific life satisfaction variables were associated with 5-HTTLPR are in line with the current state of research.

It cannot be ruled out that inclusion of SNP rs25531 in our analyses (triallelic approach) had some influence on potentially replicating the findings of de Neve (2011; De Neve et al. 2012), the latter of which were undertaken without consideration of SNP rs25531. It is now widely agreed, however, that it is best to use a triallelic approach, since it is known that the expression rates of 5-HTTLPR change depending on SNP rs25531, thus altering the functional effect (Hooten et al. 2017; Hu et al. 2006).

Of note, given the mixed findings shown in the previous literature, in addition to the analyses reported in the results, although not the focus of the current study, we also explored associations between overall life satisfaction and several polymorphisms with theoretical associations with life satisfaction (the data used for the analyses were derived from the Ulm Gene Brain Behavior project; please see the method section for further information). We report these (non-) findings for the reason of completeness without further discussion. No significant results for overall life satisfaction were found in relation to either OXTR (rs53576), COMT Val158Met or MAOA (VNTR). In other words, only the null findings from Conner et al. (2018) were replicated. Also, we did not find any significant results for BDNF VAL66 MET (Brain-derived neurotrophic factor; i.e. playing a role in neuronal growth and long-term memory), DRD2/ANKK1 Taq Ia and DRD4 (VNTR) (both dopamine receptors) in relation to overall life satisfaction (please see Table S4).

Analyzing the SNPs derived from the GWAS (Okbay et al. 2016) showed one significant result in the complete sample, relating to SNP rs4958581 (NMUR2). The only significant association was found between rs4958581 and the life satisfaction variable family; in this case, carriers of the TT genotype showed lower scores compared to C+ carriers. It should be noted that our analyses on genotype level showed a significant difference between the CT and TT genotypes, but not between CT and CC genotypes which could be because of the smaller sample size of the CC ($n=132$) group compared to the CT and TT groups (CT: $n=479$, TT: $n=438$). A GWAS is a method used to detect potential correlations between a specific trait and SNP. To accomplish this goal, millions of genetic markers are tested, with typically a large number of participants included in this type of study (Røysamb and Nes 2018). The GWAS approach is not hypothesis-driven and is assumption-free, relying solely on the discovery of statistically highly significant associations between a trait and a specific gene locus. Since there is typically no theoretical basis underpinning the findings of a GWAS, the findings from these studies need to be further investigated in studies such as that reported here. The findings from a GWAS can form a useful starting point for further studies (we have termed this the *genome wide scan-based candidate gene* approach further above). Over the last few years, the GWAS methodology has produced many promising

discoveries in the field of behavioral genetics, of relevance for the understanding of various diseases, and potentially helping the development of new treatments and therapeutic approaches (Visscher et al. 2017). Nevertheless, it can often be difficult to interpret the results of a GWAS since the detected effects of specific SNPs are very small, and because of the influence of pleiotropic and polygenic effects (Reimers et al. 2019; Røysamb and Nes 2018).

In relation to the GWAS by Okbay et al. (2016), it should be noted that the phenotype measures used were life satisfaction, positive affect, and in some cases a mixture of both measures. Life satisfaction and positive affect were used to measure SWB, but these measures potentially reflect different constructs, namely cognitive and affective SWB (e.g. Luhmann et al. 2012a). Even though both constructs overlap, they are also somewhat distinct (Weiss et al. 2016). The combination of both measures to gather data on SWB complicates the interpretation of the findings from this GWAS (Okbay et al. 2016), and could have affected our findings as well. We used separate measures for life satisfaction and positive affect.

The analyses in the current study were conducted separately across two samples; firstly, on the complete sample, and secondly, on a balanced sample to attempt to control for stratification effects (Hutchison et al. 2004). Given the findings from these analyses, it remains unclear if this strategy was successful or not. Conducting the analyses in a balanced sample in this study allowed stronger statistical control of some of the variables, but at the same time it led to a loss of power in the sample. This may have led to an inability to find specific effects in the balanced sample; this was the case for the findings from the analyses of the SNPs derived from the GWAS, and for all but one finding in relation to 5-HTTLPR. In one case, we observed a novel association in the balanced sample concerning the life satisfaction variable leisure and 5-HTTLPR, and in a further case one finding was present in both samples (that between the life satisfaction variable housing and 5-HTTLPR). In general, however, the associations found in the complete sample were not observed in the balanced sample, which could point to a statistical power problem when using the balanced sample.

4.1 Strength and Limitations

One limitation of the present study is the sample size, especially when conducting the analyses in the balanced sample. Even though the complete sample consisted of more than 1000 participants, the balanced sample was only about half that size, which led to a loss of statistical power. Furthermore, there was an imbalance in the distribution of females and males in the complete sample. The strategy to counteract this imbalance by conducting a second set of analyses in a balanced sample was only partially successful given the loss of statistical power described above. On the other hand, we should note that the findings for the life satisfaction variable housing and 5-HTTLPR were replicated in the balanced sample, despite the decrease in statistical power. This suggests that the association between 5-HTTLPR and the life satisfaction variable housing might be particularly robust.

We should also note that 93,1 percent of the participants were between 18 and 29 years old and students. This should be kept in mind when considering the degree to which the results in this study generalize to other samples in future studies.

We were able to replicate previously established findings with respect to 5-HTTLPR and SWB in our sample. Moreover, we found support for the association between rs4958581 (NMUR2) and SWB. Finally, the inclusion of various life satisfaction variables provides additional insights into the structure and functioning of life satisfaction generally

(Schimmack et al. 2004) and, more specifically, may be also useful for future studies examining cross-cultural aspects of life satisfaction.

5 Conclusion

In the current study, we found significant associations between rs4958581 (NMUR2), a relevant SNP identified in a previous GWAS, and the life satisfaction variable family. We also found associations between 5-HTTLPR and the specific life satisfaction variables of housing, leisure, and family, but not for overall life satisfaction or positive affect. Our findings reflect the somewhat heterogeneous pattern of previous research findings regarding the link between 5-HTTLPR and SWB, in which for most of the studies the L' allele was associated with higher life satisfaction, but not in all cases (e.g. De Neve et al. 2012). For the findings from the GWAS (Okbay et al. 2016), our analyses show a first independent evidence of potential associations with SWB, in addition to those noted in the GWAS. In more general terms, it is very challenging to find and validate significant effects in the field of behavioral genetics because of pleiotropic and polygenic effects, epistasis effects, and gene by environment interactions. Therefore, much more work is needed to further consolidate our understanding of the genetic basis of SWB.

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Author Contributions BL and CM designed the study. BL, CS, HH, and RS performed the genetical analyses. BL performed the statistical analyses and wrote the manuscript. BL, CM, RS, CS, HH, AC, and AD critically worked on the manuscript. AC checked the manuscript for usage errors. All authors contributed substantially to the final version of the paper.

Compliance with Ethical Standards

Conflict of interest There are no actual or potential conflict of interest.

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