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ORIGINAL ARTICLE

Functional polymorphism (*5-HTTLPR*) in the serotonin transporter gene is associated with subjective well-being: evidence from a US nationally representative sample

Jan-Emmanuel De Neve

Variation in the promotor region of the serotonin transporter gene (*5-HTTLPR*) is a promising candidate for better understanding individual heterogeneity in subjective well-being or happiness, as measured by life satisfaction. This functional polymorphism has previously been associated with mental health and selective processing of positive and negative emotional stimuli. A case–control association study on a representative sample of Americans (*N*=2574) finds that individuals with the transcriptionally more efficient version of the serotonin transporter gene, report significantly higher levels of life satisfaction (*P*=0.01). This new finding may help explain the important genetic component of the individual baseline levels of happiness.
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INTRODUCTION

Research on subjective well-being has produced valuable insights into the sources of individual happiness. An important finding from this literature is that people tend to have a 'baseline' or 'set point' happiness level[1] that shows persistent strength over time, and twin studies indicate that up to 50% of the variance in happiness between individuals can be attributed to genetic influences.[2,3] However, twin studies do not identify which genes might be involved. Functional variation in the promotor region of the serotonin transporter gene (*5-HTTLPR*) is a promising candidate for better understanding the individual heterogeneity in subjective well-being.

The *5-HTT* gene (locus symbol SLC6A4) codes for the serotonin transporters (5-HTT or SERT) that are placed in the cell wall and reabsorb the neurotransmitter serotonin from the synaptic cleft. Most serotonin is recycled after use and the serotonin transporter allows serotonergic neurons to restock. The serotonin transporter gene has been studied extensively, and much is known about the way different versions of this gene influence serotonergic neurotransmission which, in turn, is found to influence personality and mental health.[4–6]

The *5-HTT* gene contains a 44-bp variable-number tandem repeat polymorphism in the promoter region (5-HTTLPR); that is believed to be responsible for variation in transcriptional efficiency. The 'long' (528 bp) and 'short' (484 bp) polymorphism produces the same protein, but the long allele is associated with an approximately three times higher basal activity than the shorter allele. Consequently, the long variant produces significantly more *5-HTT* mRNA and protein.[6–9] The long polymorphism thus results in increased gene expression and more serotonin transporters in the cell membrane. In turn, more serotonin is reintroduced into the pre-synaptic cell. This process is shown in Figure 1.

Functional variation in the serotonin transporter gene is increasingly understood to exert strong influence on parts of the brain regulated by serotonergic neurotransmission. In particular—with remarkable consistency—a body of neuroscientific research shows increased amygdala activation to negative emotional stimuli among carriers of short alleles.[4,10–13] A morphometrical study of this genetic association reports reduced gray matter volume in short-allele carriers in limbic regions critical for processing of negative emotion, particularly perigenual cingulate and amygdala.[12] These authors conclude that 5-HTT induced variation in anatomy and function of an amygdala-cingulate feedback circuit that is critical for emotional states and implied a genetic susceptibility for depression.[12] Another morphometrical study corroborates the finding that short-allele carriers show decreased volume in the affective division of the anterior cingulate and decreased gray matter density in its pre-genual region.[13] The same study also finds that the *5-HTTLPR* polymorphism is associated with activation changes to positive stimuli, suggesting a general role in emotional processing, rather than negative valence specifically.[13]

Myriad genetic association studies also suggest that serotonin and 5-HTT has an important role in mental health.[4,5,14,15] Specifically, the short *5-HTTLPR* allele was found to be a risk allele for depression,[7,12]

Department of Government, London School of Economics and Political Science, London, UK
Correspondence: Dr J-E De Neve, Department of Government, London School of Economics and Political Science, Houghton Street, London WC2A 2AE, UK.
E-mail: j.c.de-neve@lse.ac.uk or jdeneve@post.harvard.edu
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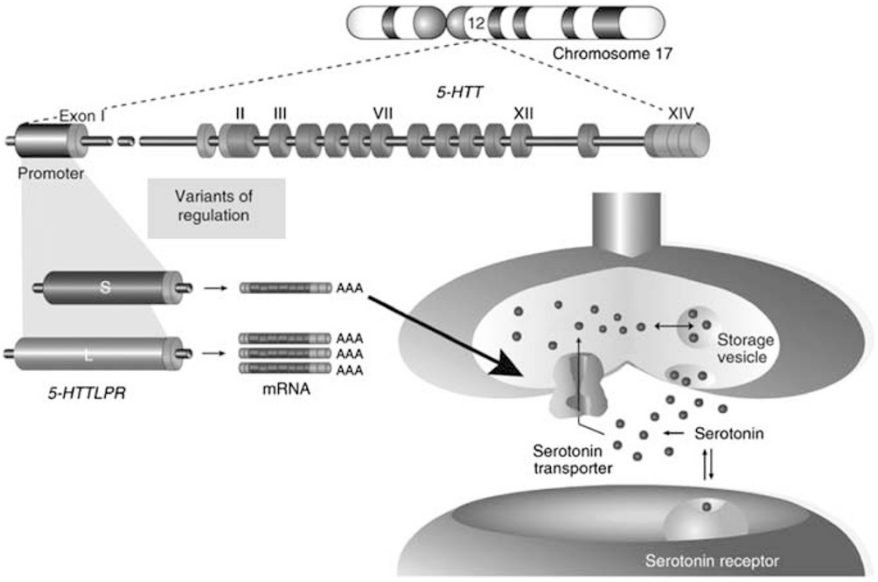

Figure 1 Representation of the long/short polymorphism of the *5-HTT* gene and the release, reception and recycling of serotonin in neurons. Adapted from Canli and Lesch,[6] with permission from the Nature Publishing Group.

and subsequent studies report that about 10% of variance in anxiety-related traits is contingent upon serotonin transporters.[16,17] However, the role of 5-HTT in mental health remains disputed with the meta-analysis by Risch *et al.*[18] yielding no evidence that the serotonin transporter is associated with an elevated risk of depression. Other recent work shows either mixed results[19] or a positive association between the short *5-HTTLPR* allele and anxiety-related traits and suicide.[20,21]

A recent study by Fox *et al.*[22] suggests that long *5-HTTLPR* allele may influence optimism. The authors obtained DNA from about 100 participants and compared reaction times to pictures with positive, negative and neutral emotional valence, in line with a common experiment in psychopathology research. The results show that individuals with the transcriptionally more-efficient long *5-HTTLPR* alleles display a significant bias toward processing positive information and selectively avoiding negative information. This emotionally self-protective pattern does not obtain in individuals carrying one or both short alleles.

Not all studies show a direct relationship between a gene variant and a phenotype. Instead, developmental or concurrent environments may moderate an association between genes and phenotypes. A well-known study identifies a gene–environment (GxE) interaction for the influence of life stress on depression.[23] The authors find that individuals with short 5-HTTLPR alleles gene are more vulnerable to stress-induced depression. Among those individuals that had experienced a relatively large number of stressful life events, about 33% of the carriers of the less-efficient short allele were cases of diagnosed depression as compared with only 17% of the individuals that carried both long alleles. Thus, in the Caspi *et al.*[23] study the gene itself is not associated with depression. Rather, it is the combination of both gene and environment that yields a significant association. This study does not report on a gene–environment interaction, but the direct association between the number of long 5-HTTLPR alleles and life satisfaction. Future research may produce new insights from exploring how environmental factors moderate the association between 5-HTTLPR and happiness.

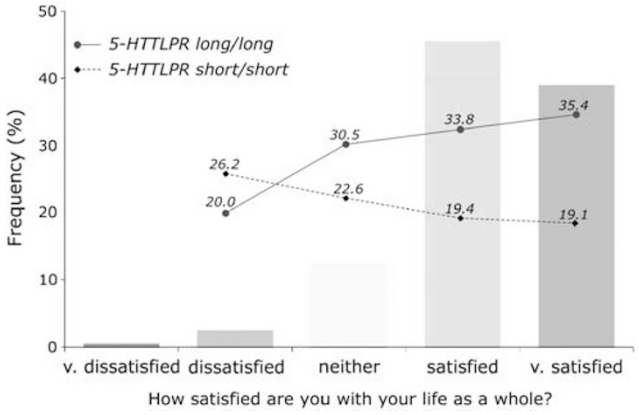

Figure 2 Percentage distribution of life satisfaction in Add Health (N=2574) and the *5-HTTLPR* genotype frequency for each category. No allelic frequency is reported for the 'very dissatisfied' category because of the small N.

MATERIALS AND METHODS

Sample

Data are from the National Longitudinal Study of Adolescent Health (Add Health) that explores health-related behavior of adolescents.[24] By now, four waves (1995, 1996, 2001 and 2008) of data collection have taken place and participating individuals are around 30-years old. In Wave III, subjects were asked 'How satisfied are you with your life as a whole?' Answer categories ranged from very dissatisfied, dissatisfied, neither satisfied nor dissatisfied, satisfied, to very satisfied. Alternative answers were 'refused' or 'don't know', and these were discarded for the purpose of this study (less than 1% of interviewees gave such a response). Figure 2 gives the distribution of life satisfaction. Allelic information for seven genetic markers is available for 2574 individuals as part of Wave III, including markers that identify alleles of *5-HTTLPR*. A subset of individuals is nested in the same family, and these sibling relationships are accounted for in the statistical model. Allele frequency for the transcriptionally more efficient long allele is 57%, and 43% for the short

allele. Supplementary Tables 1–4 available in the online Supplementary Information provide detailed descriptive statistics. This secondary analysis on the data collected by the National Longitudinal Study of Adolescent Health[24] was reviewed and granted human subjects approval by the Human Research Protections Program (IRB) of the University of California, San Diego, USA (PI James H. Fowler).

Genotyping

Details of the Add Health DNA collection and genotyping process are available at the Add Health website[25] and reproduced here. The *5-HTT* gene maps to 17q11.1-17q12 and contains the 44-bp variable-number tandem repeat in the 5′ regulatory region of the gene. The assay used is similar to Lesch *et al.*[7] The primer sequences are: forward, 5′-GGCGTTGCCGCTCTGAATGC-3′, and reverse, 5′-GAGGGACTGAGCTGGACAACCAC-3.′ These primer sequences yield products of 484 or 528 bp.

Statistical analyses

To test for genetic association, a regression model with robust cluster variance estimator is employed to account for sibling relationships in the data:

$$Y_{ij} = \beta_0 + \beta_G G_{ij} + \beta_k Z_{kij} + U_j + \varepsilon_{ij}$$

where i and j index subject and family, respectively. For *5-HTTLPR*, $G=2$ if the subject's genotype is LL, $G=1$ for genotypes LS or SL, and $G=0$ if the subject's genotype is SS (where L represents having a copy of a 528-bp long allele, and S represents having a copy of a 484-bp short allele). Z is a matrix of variables to control for the underlying population structure of the Add Health sample. Finally, the variable U is a family random effect that controls for potential genetic and environmental correlation among family members, and ε is an individual-specific error. To control for the effects of the underlying population structure, we include indicator variables for whether a subject is self-reported as Black, Hispanic or Asian (base category is White). Following the policy of the United States Census, Add Health allows respondents to mark more than one race. As this complicates the ability to control for stratification, we exclude these individuals ($N=117$), but a supplementary analysis including them yields substantively equal results. The introduction of a cluster variance estimator for the sibling relationships makes the model specification robust to within-cluster correlation.

RESULTS

Figure 2 illustrates the descriptive breakdown of the answer to 'How satisfied are you with your life as a whole?' and the *5-HTTLPR* genotype frequency for each answer category. With increasing life satisfaction levels, we find that the proportion of individuals that carry both long alleles rises from 20 to about 35%. In contrast, the frequency of individuals that carry both short alleles is highest in the lower life satisfaction categories. Carriers of the long-short or short-long alleles are evenly distributed across the latter, most populated, answer categories.

Supplementary Table 5 (available in the online Supplementary Information) presents the results of several specifications of the model to test the hypothesis that *5-HTTLPR* is associated with subjective well-being. Each of these specifications includes variables for age, gender and race to control for population stratification. Model 1 shows that the long allele of *5-HTTLPR* is significantly associated with increased life satisfaction ($P=0.013$). Figure 1 in Supplementary Information summarizes these results for *5-HTTLPR* by simulating first differences from the coefficient covariance matrix of this basic model. Holding all else constant and changing the *5-HTTLPR* genotype of all subjects from zero to one long allele would increase the reporting of being very satisfied with one's life in this population by about 8.5%. Similarly, changing the genotype from zero to two long alleles would increase the reporting of being very satisfied by about 17.3%.

As a robustness test for population stratification, we also include Model 2; that is a case–control model for those subjects that uniquely identified themselves as being white ($N=1456$). The coefficient on *5-HTTLPR* and its *P*-value ($P=0.043$) suggests that population stratification between self-reported racial categories is not driving the association between *5-HTTLPR* and life satisfaction.

Supplementary Table 6 details and specifies a family-based test through a variance-components based association analysis for the available sibling pairs.[26,27] By decomposing genotype scores into between-family (b) and within-family (w) components, it is possible to control for spurious results due to population stratification, because only the coefficient on the between-family variance (β_b) will be affected. The coefficient is not significant ($P=0.548$), indicating that population stratification is not driving this analysis. For the family-based test, the association result is determined by the coefficient on the within-family variance (β_w). The resulting coefficient in this study is positive but not significant ($P=0.188$). It is important to note that many observations are lost in the family-based test, because it only includes individuals who have a different genotype than their sibling ($N=708$). As a result, this method suffers from much lower power in detecting a true association and is thus prone to false negatives.[28]

DISCUSSION

The single-item life satisfaction measure used in Add Health is standard in the psychology and happiness economics literatures.[29–32] Generally, multi-item scales are preferred because a single-item measure is more vulnerable to question specification and statistical noise in the data. Still, the life satisfaction scale has adequate convergent validity. A recent overview of the measurement of subjective well-being is given in Lewis *et al.*[33] where the authors conclude that 'The evidence to date indicates that such self-reports of happiness are reliable and valid: most instruments show impressive internal consistency, temporal stability, convergence with non-self-report measures of well-being, and acceptable levels of criterion validity.' The life satisfaction question has also been cross-validated with alternative measures that gauge subjective well-being,[3,31] and Oswald and Wu[34] provide objective confirmation of life satisfaction as a measure of subjective well-being. Still, the life satisfaction question has been criticized for inducing a focusing illusion by drawing attention to people's relative standing rather than moment-to-moment hedonic experience.[35]

In line with the happiness literature, a large majority of respondents report being satisfied or very satisfied. That most people, in fact, report a positive level of subjective well-being is the object of a paper by Diener and Diener,[30] where the authors find this distribution to be representative in a wide cross-national analysis.

Although these data give us a valuable opportunity to explore genetic influences on subjective well-being, two limitations of the data need to be emphasized. First, the Add Health sample is restricted to individuals who are 18–26 years old during Wave III. Still, the distribution of answers is typical of other life satisfaction surveys and may suggest some degree of generalizability. As such, the age limits are not likely to gravely distort our results. Second, because we employ a case–control design our association results remain vulnerable to population stratification. We limit this potential threat to the validity of our results by including controls for race and restricting the analysis to a specific racial or ethnic group, as well as by specifying a family-based test. A family-based design eliminates population stratification, but provides much lower power in detecting a true association (false negatives). Xu and Shete[28] show, based on simulation work, that a case–control association study using a mixed-effects regression

outperforms family-based designs in detecting an association while at the same time effectively limiting type I error (false positives).

This analysis suggests that genetic factors significantly influence individual subjective well-being and a particular genotype—5-HTTLPR 'long'—is identified as having a sizeable positive association with self-reported life satisfaction. The 5-HTTLPR 'short' genotype has been thoroughly studied as a risk allele for depression and anxiety-related disorders. This research, however, presents the first evidence of the influence of this functional polymorphism on subjective well-being or happiness. As such, this research addresses the 'set point' of subjective well-being that previous research has identified to be of great importance.[1,2,3]

Future work should attempt to identify other genes or gene–environment interactions that are associated with subjective well-being. Finding out which genes they are and what physical function they have will improve our understanding of the biological processes that underlie well-being and may also shed light on their evolutionary origin.[36] It is important to emphasize that there is no single 'happiness gene.' Instead, there is likely to be a set of genes whose expression, in combination with environmental factors, influences subjective well-being.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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