Twenty candidate genes predicting neuroticism and sensation seeking personality traits: A multivariate analysis association approach

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The official citation that should be used for this material is:

Aluja, A., Balada, F., Blanco, E., Fibla, J., & Blanch, A. (2019). Twenty candidate genes predicting neuroticism and sensation seeking personality traits: A multivariate analysis association approach. *Personality and Individual Differences*, *140*, 90-102. https://doi.org/10.1016/j.paid.2018.03.041

Abstract: Neuroticism and Sensation Seeking are part of temperament that contribute to later personality. Both traits are related with internalizing and externalizing behavioral problems and psychiatric disorders. Neuroticism and Sensation Seeking are also associate with different genetic polymorphisms in several studies. In this research, we evaluated the involvement of 153 tagged single-nucleotide polymorphisms (tagSNPs) from 20 candidate-genes in a sample of 290 healthy Caucasian volunteers (147 males and 143 females). We explored the contribution of each single-nucleotide polymorphism (SNP) combination scores to predict Neuroticism and Sensation Seeking, with a score codification according to dominant, codominant and recessive models for common, rare allele and negative heterosis. We performed a multivariate analysis of associations (MAA) technique to explore and identify SNPs on the candidate genes. The 4 tagSNPs related to GABBR2, GNAS-AS1, DRD4 and FKBP5 candidate genes that explained the 13.8% of the Neuroticism variance, and the 4 tagSNPs related to AR, SLC6A3, DRD2 and DRD4 that explained the 14.5% of the Sensation Seeking variance. GABAergic, dopaminergic, glutamatergic and glucocorticoid receptors were associated with Neuroticism, whereas serotonin carrier, dopaminergic and androgenetic receptors associated with Sensation Seeking. These findings account for 24.87% and 29.78% of the heritable variance in base of the 4 tagSNPs for each personality variable.

Keywords: Neuroticism, Sensation Seeking, candidate genes, biological personality models, Alternative five-factor Zuckerman's personality model, ZKA-PQ.

1. INTRODUCTION

Neuroticism is characterized by a tendency for emotional instability, psychological distress, low self-esteem and negative emotions such as anxiety and depression. Sensation Seeking personality trait is defined as the search for experiences and feelings, that are varied, novel, complex and intense, and by the readiness to take physical, social, legal, and financial risks for the sake of such experiences (Zuckerman, 1994; Zuckerman & Aluja, 2014). Neuroticism has a strong with sensitivity to punishment, and Sensation Seeking correlates with extraversion, aggressiveness, psychoticism, impulsiveness, venturesomeness and sensitivity to reward (Aluja et al., 2013). Neuroticism and Sensation Seeking are non-correlated factors similar to sensitivity to punishment and sensitivity to reward concerning the Gray's Behavioral Inhibition System and Behavioral Approach System (Aluja, Kuhlman, & Zuckerman, 2010). Neuroticism and Sensation Seeking traits are associated with several cognitive, emotional and behavioral inhibition and disinhibition systems related to internalizing and externalizing behaviors and psychiatric disorders. Thus, the etiology of personality traits such as Neuroticism and Sensation Seeking, especially the genetic basis, should be studied because they can have profound effects on mental health outcomes, as described in the sections to follow.

1.1. Neuroticism, Sensation Seeking and internalizing/externalizing behaviors

A primary classification of behavioral problems must distinguish among internalizing and externalizing behavior manifestations. Internalizing behavior problems are characterized by social withdrawal, feelings of inferiority, loneliness, demand for attention, and feelings of worthlessness, guilt, irritability, nervousness, and concentration difficulties. Externalizing behavior problems are characterized by fighting, cursing, irritability, belligerence stealing under control of emotions, difficulties with interpersonal relationships and rule breaking (Achenbach &

Edelbrock, 1978; Guttmannova, Szanyi, & Cali, 2008; Hinshaw, 1992; McCulloch, Wiggins, Joshi, & Sachdev, 2000). Longitudinal investigations have described the stability of internalizing and externalizing behaviors even at early ages (Briggs-Gowan, Carter, Bosson-Heenan, Guyer, & Horwitz, 2006).

In the personality domain, internalized behavior might be linked with *emotionality* (a tendency to experience anxiety, anger, and alienation), and externalized behavior with a *lack of constraint* (a tendency to engage in risk behavior, to act on impulses, and to endorse non-conventional values) (Krueger, McGue, & Iacono, 2001). In the structure of mental disorders, neuroticism/negative emotionality appears to provide the personological basis for internalizing psychopathology, and negative emotionality paired with disinhibition appears to provide the personological basis for externalizing psychopathology. The connections between personality and psychopathology make psychological sense (Krueger, 2005).

The biological-factorial personality models consider that anxiety (internalizing) and impulsiveness (externalizing) are basic components of human personality. Anxiety is associated with Neuroticism (emotionality) and sensitivity to punishment, and impulsiveness is associated with psychoticism, aggressiveness, sensitivity to reinforcement and Sensation Seeking (Eysenck, 1967; Zuckerman, 1994).

1.2. Neuroticism, Sensation Seeking and mental health disorders

Neuroticism is a potential underlying vulnerability factor of various mental health disorders and accounts for 26% of the comorbidity among psychiatric disorders (Khan, Jacobson, Gardner, Prescott, & Kendler, 2005). Elevated Neuroticism is associated with mood disorders, such as depression and bipolar disorder, anxiety, personality disorders, anorexia/bulimia nervosa, substance abuse, schizophrenia and schizoaffective disorder, dissociative identity disorder, and

hypochondriasis (Ormel et al., 2013). Sensation Seeking/Novelty seeking accounts for 11.9% proportion of the variance of externalizing disorders (Khan et al., 2005). Sensation Seeking is associated with substance abuse, pathological gambling, attention deficit hyperactivity disorder (ADHD), and antisocial and borderline personality disorder (Aluja, Garcia, Blanch, De Lorenzo, & Fibla, 2009; Archer, Oscar-Berman, Blum, & Gold, 2012; Laplana et al., 2014). The etiology of personality traits such as Neuroticism and Sensation Seeking, especially the genetic basis, should be studied because they can have profound effects on mental health outcomes.

1.3. Neuroticism, Sensation Seeking and genetics

The heritability of Neuroticism has been estimated in the range from 30% to 50% based on twin studies (Calboli et al., 2010), whereas the heritability for Sensation Seeking ranges was from 40% to 60% (Fulker, Eysenck, & Zuckerman, 1980; Hur & Bouchard, 1997; Koopmans, Boomsma, Heath, & van Doornen, 1995). Personality data were analyzed in with more than 160,000 individuals from 23 cohorts across Europe, USA and Australia in which Neuroticism and extraversion were assessed by nine different personality inventories (van den Berg et al., 2014). Common genetic variants explain 15% of the variance in Neuroticism. Based on the meta-analysis polygenic scores significantly predicted Neuroticism in two independent cohorts (de Moor et al., 2015). Aleksandrova et al. (2009) reported that several genome-wide single-nucleotide polymorphism (SNP) were associated with high Neuroticism scores (CNR1, GABRA2, GABRA6 and MAMDC1). SNP is a variation in a single nucleotide that occurs at a specific position in the genome, where each variation is present to some appreciable frequency within a population. Vinkhuyzen et al. (2012) informed that the proportion of the Neuroticism phenotypic variance explained by all common single nucleotide polymorphisms (SNPs) and estimated using all ‘unrelated’ individuals was the 6% (n=12,000).

Fulker et al. (1980) analyzed genetic and environmental contributions to Sensation Seeking in twins (442 pairs) and the results showed that 58% of the Sensation Seeking trait is heritable. If the unreliability component is taken into account, the heritability of Sensation Seeking increase to 69%. Tellegen, Lykken, Bouchard, Wilcox, Segal and Rich (1988) studied separate twins, identical and fraternal reared in different environments. The means of heritability was of 64% for identical and 54% for fraternal twins. The average between both was of the 59%. Derringer et al. (2010) presented a genetic association analysis of Sensation Seeking using 273 SNPs from eight dopamine genes in a sample of 635 unrelated individuals. The authors found that 12 SNPs in four dopamine genes accounted for 3.9% of Sensation Seeking, indicating that aggregation of multiple SNPs within genes relevant to a specific neurobiological system into a "genetic risk score" might explain a nontrivial proportion of the variance in human personality.

The genetic evidence from personality traits is far from being conclusive (Munafo et al., 2003; Munafo & Gage, 2013). As for other complex traits, only an association with SNPs can explain a small percentage of the heritability of personality traits. In contrast to single-locus analysis, some authors propose that the evaluation of multiple genetic markers might be translated into a significant enhancement of the predictive value due to the epistatic interaction (2003).

1.4. Purposes of the present study

We used an adaptation of a multivariate analysis of associations (MAA) technique (Comings et al., 2000) to analyze the genetic contribution to explain the Neuroticism and Sensation Seeking traits. The MAA provides information about the genes involved: 1) which genes are included in the equation; 2) the fraction of the variance attributed to each included gene; 3) the level of significance for each included gene; 4) the relative involvement of the

different genotypes of each involved gene for each trait; and 5) the sum of the variance of functional groups of genes for each trait. Several association studies of psychopathology show that heterosis models would be relevant for their interpretation (for a review see Comings and MacMurray, 2000). Nevertheless, few genetic studies of personality include these models, and these effects are neglected. In the current study, we used different codification scores according to dominant, codominant and recessive models for common and rare alleles, as well as heterosis. Heterosis, hybrid vigor, or outbreeding enhancement, is the improved or increased function of any biological quality in a hybrid offspring. We studied the distribution of 153 tagSNPs in a total series of healthy volunteers that fulfilled a self-report of Neuroticism and Sensation Seeking.

In the current study, candidate genes were selected based on text, phenotype and pathway mining search by using public available databases. Candidate genes covered the four main neurological pathways potentially involved on personality: dopaminergic, serotonergic, glutaminergic and GABAergic. In addition, key processes in the nervous system such as ligand-receptor, signaling, synaptic vesicle and circadian rhythm control were also covered. We selected 20 genes whose haplotypic diversity was captured using tagged single-nucleotide polymorphisms (tagSNPs). A tagSNP is a representative single nucleotide polymorphism (SNP) in a region of the genome that represents a group of SNPs called a haplotype. It is possible to identify genetic variation and association to phenotypes without genotyping every SNP in a chromosomal region.

The objective of this study was to identify the SNPs of the 20 candidate genes associated with Neuroticism and Sensation Seeking to predict the individual contribution of a set of independent genetic markers previously associated with human personality. A multilocus analysis would create a better predictive panel, allowing us to explore the proportion of the variance explained to the genetic component of the Neuroticism and Sensation Seeking starting from the genes selected candidates and the corresponded tagSNPs.

METHOD

2.1. Sample

The sample was composed by 290 healthy Caucasian volunteers (147 males and 143 females) with a mean age of 21.31 years (*SD*: 2.79; age range: 17-30). All participants were informed of the purpose of the project and the experimental procedures. All subjects provided written informed consent before entering the study, according to the Declaration of Helsinki. Ethic Committee of the university approved the experiment.

2.2 Procedure

The subjects were collectively invited to participate in the study by an email addressed to the students of the university. All participants completed twice (test-retest) the on-line personality questionnaire approximately between one and three months. The variability percentage was obtained from the difference between the first and second trait measure, divided by the mean of the two values. We accepted only subjects with personality test-retest variability below 20%. Note that human biochemistry laboratories accept the results if a coefficient of variability (CV) inter-assay as steroid hormones lower than 15% (Potischman, Falk, Laiming, Siiteri, & Hoover, 1994). Sensation Seeking was negatively correlated with the age (Zuckerman, 1994). We discarded 35 subjects with variability above 20% and 4 subjects aged more than 30 years. All subjects were explored by an open psychiatric interview and we only considered those individuals who had not suffered any psychopathological disorders according to DSM-IV-TR (axis I and II) criteria. Two subjects were rejected for having depressive symptoms and taking antidepressant medication. For the analysis, we used the average of the first and second scores

on the personality test. Genomic DNA was obtained from buccal swaps using the BuccalAmp DNA extraction kit (Epicentre, Madison, USA).

2.3. Personality variables

The Zuckerman-Kuhlman-Aluja Personality Questionnaire (ZKA-PQ; Aluja et al., 2010) is composed of 200 items and 5 factors: a) Aggressiveness, b) Activity, c) Extraversion, d) Neuroticism, and e) Sensation Seeking. Four facets of 10 items compose each factor. Neuroticism facets are integrated by anxiety, depression, dependency, and low self-esteem, and Sensation Seeking facets are integrated by thrill and adventure seeking, experience seeking, disinhibition, and boredom susceptibility. The ZKA-PQ has 4-point Likert-type response format (1, Strongly Disagree; 2, Somewhat Disagree; 3, Somewhat Agree; 4, Strongly Agree). Alpha reliabilities for the five factors ranged between 0.85 and 0.92 for the Spanish sample and between 0.88 and 0.93 for the American sample (Aluja et al., 2010). The average alpha for the twenty facets of the ZKA-PQ in the Spanish validation sample was 0.75 with a minimum and a maximum of 0.65 and 0.90 respectively. In this study, we used only the Neuroticism and Sensation Seeking factors and their corresponding facets.

2.4. Candidate gene selection and genotyping

Candidate genes were selected from public databases based on three criteria: text, phenotype, and pathway mining search (Table 1). Text mining is the process of deriving high-quality information from text. Text mining search was performed with the SNPs3D Disease Candidate Gene[1] platform by using a selected list of keywords. Phenotype mining search was performed by HuGE Navigator (version 2.0) Gene Prospector and Phenopedia platforms using a

[1] http://www.snps3d.org

selected list of phenotype terms[2]. Pathway-mining search was performed by choosing all genes included in selected KEGG pathways database[3]. A Venn diagram (Figure 1) showed common genes among the three selection criteria.

Among all the genes considered, we selected as the candidate genes those that were coincident in at least two of the three selection criteria. After an accurate inspection, 20 genes were selected as candidates (Table 2). Ten genes were selected from those common in all tree selection strategies (10/20), 3 genes were selected from those common in pathway and phenotype strategies (4/40), one gene was selected from those common in pathway and text strategies (1/2), and 6 genes were selected from those common in text and phenotype strategies (6/17). With this procedure the most important candidate genes were selected, but it is possible that there are other genes related to personality that are not included in our selection.

In order to capture the sequence variability of each *locus* for each candidate gene, tagSNPs were identified by using Haploview's V4.2 software tagger option[4], with minor allele frequency (MAF)>1% according to the CEU population (Utah residents with ancestry from northern and western Europe) in the HapMap[5]. From the initially selected 159 tagSNPs, a final set of 153 tagSNPs were considered for the association analysis. All markers selected were in Hardy-Weinberg equilibrium (Appendix).

Genotyping is the process of determining differences in the genetic make-up (genotype) of an individual by examining the individual's deoxyribonucleic acid (DNA) sequence using biological assays and comparing it to another individual's sequence or a reference sequence.

[2] http://www.hugenavigator.net/HuGENavigator/geneProspectorStartPage.do
[3] http://www.genome.jp/kegg/pathway.html
[4] http://www.broad.mit.edu/mpg/haploview
[5] International HapMap Project: http://hapmap.ncbi.nlm.nih.gov, Ensemble 36, dbSNP b126, phase III

Genotyping was conducted by the CEGEN (Spanish National Genotyping Center[6]) using the Sequenom iPlex® MassARRAY platform, according to manufacturer's instructions (Sequenom, San Diego, CA). Genotyping assays were designed using the Sequenom MassARRAY Assay Designer 4.0 software. All assays were performed in 384-well plates, including negative controls and a trio of Coriell samples (NA1083, NA10831 & NA12147) for quality control. A 95% SNP genotyping success rate was imposed on the analysis. A 100% concordance was observed for 15 samples tested in duplicate (5%). The cost of genotyping was 15.234 euros.

2.5. Codification of genetic models

A phenotype is the composite of an organism's observable characteristics or traits, such as behavior, and products of behavior. A phenotype results from the expression of an organism's genetic code, its genotype, as well as the influence of environmental factors and the interactions between both, genes and environment. In this study, the phenotype refers to personality.

In order to evaluate genotype association with phenotype by linear regression analysis, all potential genotype models were coded with the multivariate analysis of associations (MAA) technique (Comings et al., 2000). Each polymorphic marker was assigned a genotype value ranging from 0 to 2. According to their phenotype value, carriers of two copies of common allele (homozygote common), one copy (heterozygote) or zero copies (homozygote rare) could be coded as 012, if these genotypes had, the lower, the intermediate and the higher phenotype values, respectively. This 012 genotype code, which corresponds to a codominant model for rare allele increasing phenotype value (positive-codominant, pC), had a mirror negative-codominant (nC) model for rare allele decreasing phenotype value, which should be coded as 210. In that case, the highest phenotype value corresponded to carriers of two copies of the common allele,

[6] http://www.usc.es/cegen/

intermediate values for those carrying one copy and the lowest phenotype value for those with zero copies. In a similar way, a positive-recessive (pR) model for a rare allele was coded as 002 indicating that rare allele homozygotes had the highest phenotype value while common allele homozygote and heterozygotes had the lowest phenotype. This had a mirror negative-dominant (nD) model for rare allele coded as 200 indicating that rare allele homozygote and heterozygotes had the lowest phenotype value while common allele homozygotes had the highest phenotype. Therefore, a total of 6 pairs of mirrored genotype value models could be assigned to each marker (Figure 2). To avoid redundancy, only one member of each of the six pairs was considered for every marker in the multiple regression analysis.

2.6. Statistical analysis

Descriptive statistics, distribution frequency values, sex differences in personality and alpha internal consistency, stability reliability (test-retest) of scales were performed. A Confirmatory Factor Analysis with Neuroticism and Sensation Seeking scales was carried out with the two personality factors, including the facets, to verify that Neuroticism and Sensation Seeking are two uncorrelated constructs. Confirming the non-relationship between the two traits is important because since they are independent the SNPs must also be different.

Box Plot graph was drawn by BoxPlotR online plotting tool (http://boxplot.tyerslab.com). Cross-tabulation and Venn diagrams were performed with Venny 2.0 (Oliveros, 2007-2015). The genetic contribution to the phenotypic personality factors were explored by a multiple regression analysis (MRA) with the stepwise method. Akaike's information criterion analysis was used to find the best-fitting model for each case. For each marker we introduced all six genotype coding scores with a probability of inclusion (PIN) of $p < 0.005$ and a probability of exclusion (POUT) of $p > 0.10$. Standardized coefficients were assigned

to each subject according to MRA equation scores to analyze the contribution of the "genetic risk score" to the phenotypic variables. The multiple regression analysis results were replicated using an Univariate Analysis of Variance (UNIANOVA). Statistical analyses were performed with SPSS and AMOS computer software.

3. RESULTS

3.1. Descriptive statistics, sex differences and alpha reliability

Table 3 shows descriptive statistics, sex differences in Neuroticism and Sensation Seeking, kurtosis and skewness, and alpha reliabilities. Frequency distributions for the facets were normal as indicated by kurtosis and skewness values ($\pm$1) for males and females except for age. Males were older than females. Males scored higher than females in all the Sensation Seeking facets, but only SS1 was significant. On the other hand, females scored significantly higher than males in all the Neuroticism facets. Alpha reliabilities were satisfactory in eight facets and two dimensions, ranging from 0.82 to 0.95. Test-retest reliability was 0.85 and 0.82 for Neuroticism and Sensation Seeking scales. The inter-correlations between the 4 facets of Neuroticism obtain an average of 0.59. The correlations of Sensation Seeking facets have an average of 0.63. The factors of Neuroticism and Sensation Seeking obtain a correlation of -0.06.

3.2. Neuroticism and Sensation Seeking personality factors

A Confirmatory Factor Analysis (CFA) of Neuroticism and Sensation Seeking facets as observed variables and Neuroticism and Sensation Seeking as latent variables was carried out over the variance-covariance matrix, with the Maximum Likelihood estimation method. In order to achieve model identification, regression coefficients of the error terms over the endogenous

variables were fixed at 1. The χ^2 to degrees of freedom ratio was $\chi^2/df = 4.78$ ($p < 0.001$), with additional satisfactory goodness-of-fit indices (GFI= 0.93; TLI= 0.92; CFI= 0.96; RMSEA= 0.11 [.09-.12] and SRMR= 0.07) (Bentler, 1980; Bollen, 1989). While the GFI, TLI and CFI indicate a good fit, the value of the RMSEA exceeds the cut-off point (0.08). According to Garrido, Abad and Ponsola (2016), the size of the factor loadings has been found to strongly impact the power of fit indices to detect model misfit. Indices that appear to be most affected by this variable are the RMSEA and SRMR, sometimes indicating a poor fit to the data when the factor loadings are high. Figure 3 show the path analysis and the standardized weights.

3.3. Multiple regression analysis (MRA) and genotype marks

Considering Neuroticism as the dependent variable MRA included as predictor variables rs7847080 (GABBR2), rs2057291 (GNAS-AS1), rs3758653 (DRD4), rs3798346 (FKBP5) markers under negative-codominant (nC210), negative-heterosis (nH202), negative-heterosis (nH201), and positive-recessive (pR002) models, respectively (total variance accounted 15.2%; adjusted: 13.8%). Considering Sensation Seeking as dependent variable the MRA included as predictor variables rs4370673 (AR), rs7122454 (DRD2), rs12516758 (SLC6A3), rs752306 (DRD4) markers under negative-dominant (nD200), negative-recessive (nR220), negative heterosis (nH102), and negative-recessive (nR220) models, respectively (total variance accounted 15.9%; adjusted: 14.5%) (Table 4).

According to the nominal variables nature of the SNPs, we replicated our results re-analyzing the data using univariate analysis of variance (UNIANOVA) and the results were similar (Neuroticism: *R* squared = 0.16, adjusted = 0.14; Sensation Seeking: *R* squared = 0.16, adjusted = 0.14). A genotype score was assigned to each subject based on standardized coefficients according to the four SNPs included in the equation for the Neuroticism and

Sensation Seeking factors respectively. Figure 4 shows Neuroticism and Sensation Seeking *z*-values plotted against percentile groups (quintiles), showing that an enhancement in the "genetic risk score" was associated with higher Neuroticism and Sensation Seeking phenotype.

4. DISCUSSION

The purpose of the present study was to estimate the proportion of phenotypic variance in Neuroticism and Sensation Seeking personality traits explained by all SNPs simultaneously detected in genome-wide association studies (GWAS). Neuroticism and Sensation Seeking are non-correlated traits with a strong biological and genetic basis and related with internalizing and externalizing behaviors. Internalizing and externalizing behaviors are a part of the temperament, a more biologically based set of predispositions that contribute to later personality (Nigg, 2000) and mental disorders (Khan et al., 2005). Neuroticism and Sensation Seeking were related with the internalizing and externalizing constructs and represent the personality traits more associated with genetic studies (Krueger, Markon, Patrick, Benning, & Kramer, 2007). Behavior-genetic research supports a genetic basis for these connections, indicating that personality and psychopathology are linked at an etiological level (Krueger, 2005).

Twin studies in personality reported that approximately half of the variance could be attributed to genetic effects (Eaves, Eysenck, & Martin, 1989; Eaves, Heath, Neale, Hewitt, & Martin, 1998; Loehlin, 1992). To date, several individual loci have been associated with different dimensions of human personality in GWAS. However, as expected for a polygenic phenotype, the amount of explained variance for each individual locus is scarce (Munafo et al., 2003; Munafo, Yalcin, Willis-Owen, & Flint, 2008). Simultaneous analysis of multiple loci data may provide a better understanding on the genetic pathways involved with the phenotype. Following the argument of Derringer et al., (2010), given a heritability of Sensation Seeking of 58.3%

(Fulker et al., 1980), we were able to account for 24.87% compared with the 6.5% of Derringer et al. (2010) of the heritable variance in Sensation Seeking. Considering that the heritability for Neuroticism measured by the Eysenck Personality Questionnaire revised 23-item scale was of 46.5% (Birley et al., 2006), we are able to explain a 29.68% of the heritable variance of Birley finding for Sensation Seeking.

The comparison of the effects of multiple genes on a phenotypic variable taps into the major characteristics of polygenic inheritance –the additive, epistatic and heterotic effect of multiple genes. We found that eight SNPs associated with genes of GABAergic, glutamatergic, serotonergic, dopaminergic systems, estrogen signaling pathways and androgen receptor, predicted an important proportion of variance for Neuroticism and Sensation Seeking. The genes associated with personality traits in the current study have already been reported in previous studies. The GABBR2 (Mombereau et al., 2004), GNAS_AS (McDonald, MacMullen, Liu, Leal, & Davis, 2012), DRD4 (Tochigi et al., 2006), FKBP5 (Boscarino, Erlich, Hoffman, Rukstalis, & Stewart, 2011) were genes associated with Neuroticism and anxiety disorders (internalizing behaviors). The AR (Aluja, Garcia, Blanch, & Fibla, 2011), SLC6A3 (Kasparbauer et al., 2015), DRD2 (Hamidovic, Dlugos, Skol, Palmer, & de Wit, 2009) and DRD4 (Campbell et al., 2010; Munafo et al., 2008) were associated with Sensation Seeking and impulsivity (externalizing behaviors).

Our results support the relationship between Sensation Seeking and dopaminergic activity and modulating the action of androgens. Three of the four SNPs associated with Sensation Seeking are related to dopamine. The two SNPs associated with DRD receptors showed significant association with gene methylation levels (Docherty et al., 2012). The third SNP corresponds to SLC6A3 gene that encodes the dopamine transporter. Many studies indicate the relationship between dopaminergic activity with Sensation Seeking (Norbury & Husain, 2015).

The last SNP belongs to the androgen receptor. Studies have shown sex differences in Sensation Seeking (Cross, Cyrenne, & Brown, 2013). In this regard, a recent study shows that androgens modify dopaminergic response in the nigrostriatal pathway (Purves-Tyson et al., 2014).

Three of the four Neuroticism SNPs were related to specific receptors: such as DRD4, GABA and glucocorticoids, while the other belongs to a gene that encodes an alpha subunit of G protein. The expression of the gene FKBP5 results in an immunophilin called FKBP51 that has been linked to the regulation of glucocorticoid response to stress-related disorders (Galigniana et al., 2012). The gene GABBR2 that encodes the receptor GABAb coupled to protein G that inhibits neuronal activity through a system of second messengers. Alterations in the GNAS_AS1 result in a pseudo hypoparathyroidism type 1b and a decrease in plasma calcium levels. Unlike Sensation Seeking data, which showed relevance of dopaminergic pathways, Neuroticism data did not suggest any significant effect of a specific neurotransmitter system; it could suggest a multifactorial mechanism for inhibition trait.

A recent meta-analysis has detected variants related to Neuroticism (Smith et al., 2016) considered in the design of this study. Common to all of these studies is the finding that the strongest evidence for association is found at a locus on chromosome 8. Other associated loci included interesting candidate genes on chromosome 1 (GRIK3 *glutamate receptor ionotropic kainate 3*), chromosome 4 (KLHL2 *Kelch-like protein 2*), chromosome 17 (CRHR1 (*corticotropin-releasing hormone receptor 1*) and MAPT (*microtubule-associated protein Tau*), and on chromosome 18 CELF4 (CUGBP *elav-like family member 4*). Okbay et al. (2016) conducted GWAS studies an identified eleven variants associated with Neuroticism (N = 170,910). Also Lo et al. (2017) identified six genetic loci, including five novel loci, significantly associated with personality traits in a meta-analysis of genome-wide association studies (N =

123,132–260,861). Of these genome-wide significant loci, neuroticism was associated with variants on chromosome 8p23.1 and in L3MBTL*2*.

As reflecting the complex genetic component of the studied phenotypes, an association was found under several genetic models to each marker including codominant, dominant, recessive and heterosis models. The codominant model reflects the additive/subtractive component of each allele in the final phenotypic value. Dominant and recessive models reflect the effect of alleles on the phenotype in subjects is carrying one or two allele copies. Finally, heterosis is defined when heterozygous subjects for a polymorphism show a higher (positive heterosis) or lower (negative heterosis) effect for a quantitative or dichotomous trait than for homozygous subjects for either allele (Comings & MacMurray, 2000). These authors reviewed evidence indicating that heterosis is common in humans and, at least in their study, was involved in 50% of the all gene associations. Several studies suggest heterosis in neurological pathways, potentially involved on personality as dopamine receptor genes (Comings & MacMurray, 2000; Guo, Roettger, & Shih, 2007; Lee et al., 2011; Pecina et al., 2013), serotonin transporter gene (Comings & MacMurray, 2000; Sonuga-Barke et al., 2011) or norepinehrine transporter gene (Hohmann et al., 2015). Our results suggest that the negative heterosis for GNAS, AS and DRD4 SNPs plays a role in Neuroticism dimension and for SLC6A3 SNP for Sensation Seeking dimension.

Our approach revealed a significant improvement on the determination of the genetic components of human personality. The results showed that the use of a MAA approach increased the explained variance and improved model fit (Comings et al., 2000). The use of the standardized regression individual score for grouping the subjects in quintiles improved the data visualization of the genetic association with the personality traits. Using a univariate analysis of variance according to the nominal nature of the genetic variables, the regression analysis results

were replicated. The identification of SNPs explained significant variance in Neuroticism (13.8%) and Sensation Seeking (14.5%). Notice that recent studies using different SNPs informed only of the 6% and 3.9% of Neuroticism and Sensation Seeking variance respectively (Derringer et al., 2010; Vinkhuyzen et al., 2012). Later, harm avoidance and novelty seeking, which are equivalent constructs to Neuroticism and Sensation Seeking, were explained by the 7% and 10% of variance accounted for all autosomal SNP's on a sample of 12.859 individuals and 269.616 SNPs (Verweij et al., 2012). In our study, we used the Neuroticism and Sensation Seeking measures of the ZKA-PQ (Aluja et al., 2010). This is the first genetic study conducted with Neuroticism and Sensation Seeking factors of the ZKA-PQ and their corresponding facets.

The current study also has limitations and strengths. The main weakness was the small sample size. Nevertheless, this sample was accurately selected according to phenotypic variables. We did not replicate the results with an independent sample, but it is necessary to consider that the relationship between SNPs and personality has been extensively examined by other studies. On the other hand, the strength of this study was the use of a relatively wide number of SNPs previously related with candidate-genes associated with Neuroticism and Sensation Seeking constructs. We used different codes of the SNPs (negative-codominant, negative-dominant, negative-recessive, positive-recessive, negative-heterosis, heterozygote and homozygote rare), which allowed capturing a higher amount of the genetic variance in the phenotype. The results indicated the possible existence of negative molecular heterosis mechanisms to explain part of the genetic variance in the genotype. These data support the need to take into account the molecular heterosis in studies about the hereditary basis of personality together with the additive models. Neuroticism and Sensation Seeking are formed by four facets each one. This study was designed to explore the genes that are associated with each factor (40 items per factor), but no attempt has been made to find out which SNPs are related to the facets of depression,

disinhibition and aspects of adventure seeking, etc., because these measures have a lower phenotypic variability (10 items per facet).

In summary, a significant proportion of the phenotypic variance of Neuroticism and Sensation Seeking was explained by eight SNP's. The findings indicated that GABAergic synapse, GNAS complex locus, dopaminergic receptor synapse and estrogen signaling pathway genes were associated with Neuroticism, whereas androgen receptor, dopamine receptor and dopamine-related genes were associated with Sensation Seeking. This approach accounted for a higher percentage of variance than in other studies. The use of dominant, codominant and recessive models for common and rare alleles, and negative heterosis can be a strategy that contributes to capture a wider part of the Neuroticism and Sensation Seeking genetic variance.

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Tables and figures

Table 1.

Followed criteria used for candidate gene selection.

Selection criteria	Selected terms		Source
Text	Aggression	Impulsivity	SNPs3D http://www.snps3d.org
	Aggressive behavior	Inhibition	
	Antisocial personality	Inhibitory control	
	Anxiety	Introversion	
	Attention	Introverts	
	Depression	Major depressive	
	Disinhibition	disorder	
	Emotion	Neuroticism	
	Emotional state	Novelty seeking	
	Empathy	Psychoticism	
	Extraversion	Sensation-seeking	
	Hostility	Sensitivity to	
	Impulsiveness	punishment	
	Impulsive behavior	Sensitivity to reward	
Phenotype	Antisocial personality		Gene Prospector http://www.hugenavigator.net/
	Extraversion		HuGENavigator/geneProspectorStartPage.do
	Impulsivity/impulsive behavior		
	Neuroticism/psychoticism		
	Novelty-seeking/Sensation-Seeking		
	Dependence/addiction		
Pathway	04721 Synaptic vesicle cycle		KEGG Pathway database
	04724 Glutamatergic synapse		http://www.genome.jp/
	04726 Serotonergic synapse		kegg/pathway.html
	04727 GABAergic synapse		
	04728 Dopaminergic synapse		
	04020 Calcium signaling pathway		

Table 2
Candidate genes selected.

Gene	ID	chr	Start ($)	Stop ($)	Strand	Map	OMIM (#)	Description	KEGG Pathway (&)
ADRA2A	150	10	112836789	112840662	+	10q25.2	104210	adrenoceptor alpha 2A	04080 Neuroactive ligand-receptor
ADRA2B	151	2	96778622	96781984	+	2q11.1	104260	adrenoceptor alpha 2B	04080 Neuroactive ligand-receptor
ADRB1	153	10	115803805	115806667	+	10q25.3	109630	adrenoceptor beta 1	04020 Calcium signaling pathway
AP2B1	163	17	33914281	34053436	+	17q11.2-q12	601025	adaptor-related protein complex 2, beta 1 subunit	04721 Synaptic vesicle cycle
AR	367	X	66763873	66950461	+	Xq12	313700	RAS-like, family 10, member B androgen receptor	04114 Oocyte meiosis
COMT	1312	22	19929262	19957498	-	22q11.21	116790	catechol-O-methyltransferase	04728 Dopaminergic synapse
CRHR1	1394	17	43861645	43913194	+	17q21.31	122561	corticotropin releasing hormone receptor 1	04730 Long-term depression
CRY2	1408	11	45868668	45904799	+	11p11.2	603732	cryptochrome circadian clock 2	04710 Circadian rhythm
DRD2	1813	11	113280316	113346001	-	11q23	126450	dopamine receptor D2	04728 Dopaminergic synapse
DRD4	1815	11	637304	640705	+	11p15.5	126452	dopamine receptor D4	04728 Dopaminergic synapse
FKBP5	2289	6	35541361	35696360	-	6p21.31	602623	FK506 binding protein 5	04915 Estrogen signaling pathway
GABBR2	9568	9	101050363	101471479	-	9q22.1-q22.3	607340	gamma-aminobutyric acid (GABA) B receptor, 2	04727 GABAergic synapse
GABRA6	2559	5	161112657	161129598	+	5q34	137143	gamma-aminobutyric acid (GABA) A receptor, alpha 6	04727 GABAergic synapse 04724 Glutamatergic synapse 04726 Serotonergic synapse 04728 Dopaminergic synapse
GNAS-AS1	2778	20	57466425	57486250	-	20q13.3	139320	GNAS complex locus	04020 Calcium signaling pathway 04724 Glutamatergic synapse 04726 Serotonergic synapse
GNB3	2784	12	6950017	6956559	+	12p13	139130	guanine nucleotide binding protein (G protein), beta polypeptide 3	04727 GABAergic synapse 04728 Dopaminergic synapse 04726 Serotonergic synapse
MAOB	4129	X	43625856	43741721	-	Xp11.23	309860	monoamine oxidase B	04728 Dopaminergic synapse
OXTR	5021	3	8792094	8811300	-	3p25	167055	oxytocin receptor	04020 Calcium signaling pathway
SIRPB1	10326	20	1545028	1600689	-	20p13	603889	signal-regulatory protein beta 1	04380 Osteoclast differentiation
SLC6A3	6531	5	1392904	1445543	-	5p15.3	126455	solute carrier family 6 (neurotransmitter transporter), member 3	04728 Dopaminergic synapse
SLC6A4	6532	17	28521336	28562986	-	17q11.2	182138	solute carrier family 6 (neurotransmitter transporter), member 4	04726 Serotonergic synapse

($) Gene coordinates were assigned according to Human Feb. 2009 (GRCh37/hg19)
(#) OMIM, Online-Mendelian Inheritance on Men data base (http://www.ncbi.nlm.nih.gov/omim)
(&) KEGG Pathway database (http://www.genome.jp/kegg/pathway.html)

Table 3.

Descriptive statistics, sex differences and alpha reliability of Neuroticism and Sensation Seeking facets.

	Males (*N*=147)		Females (*N*=143)		All						
	M	*SD*	*M*	*SD*	*M*	*SD*	*K*	*S*	α	*t*-test	*p* <
Age	22.23	4.25	20.81	2.58	21.31	2.79	0.74	1.10	--	3.49	0.001
SS1 Thrill & adventure seeking	26.93	6.35	24.12	5.91	25.54	6.29	-0.78	-0.22	0.86	3.90	0.001
SS2 Experience seeking	27.15	5.95	27.53	5.29	27.34	5.63	0.00	-0.39	0.86	-0.58	0.56
SS3 Disinhibition	25.50	5.19	25.65	4.44	25.57	4.83	0.20	-0.44	0.84	-0.27	0.79
SS4 Bore. Suscept./Impulsivity	20.06	4.11	20.21	3.68	20.13	3.90	0.24	0.21	0.86	-0.32	0.75
Sensation Seeking Total	99.63	17.50	97.51	15.88	98.59	16.73	0.27	-0.39	0.95	1.08	0.28
NE1 Anxiety	24.24	5.75	25.98	5.22	25.10	5.55	-0.36	-0.07	0.85	-2.68	0.008
NE2 Depression	22.27	5.59	23.82	5.62	23.03	5.65	-0.59	0.15	0.83	-2.35	0.02
NE3 Dependence	24.11	5.21	26.29	5.40	25.19	5.41	-0.61	-0.14	0.82	-3.50	0.001
NE4 Low self-esteem	21.73	7.02	23.49	7.26	22.60	7.18	-0.86	0.09	0.93	-2.10	0.04
Neuroticism Total	92.35	21.00	99.58	21.01	95.92	21.28	-0.69	-0.05	0.95	-2.93	0.004

Note: *M*: Mean; S*D*: Standard deviation; *K*: Kurtosis*; S*: Skewness; α: Cronbach alpha reliability.

Table 4.

Linear regression analysis predicting Neuroticism and Sensation Seeking personality factors starting from selected SNPs.

Dependent variable: Neuroticism factor										
Locus	rs code	Model[1]	*R*	$R^{2(a)}$	Adjusted R^2 % variance	Standardized Coefficients β	*t*	*p*	95% Confidence Interval for β Lower	Upper
GABBR2	rs7847080	nC[2]-210 (Hr) [3]	0.22	0.05	0.044 (4.4%)	0.222	3.703	<0.001	0.138	0.450
GNAS-AS1	rs2057291	nH202 (Ht)	0.29	0.09	0.078 (3.4%)	0.209	3.518	<0.001	0.088	0.311
DRD4	rs3758653	nH201 (Ht)	0.35	0.12	0.108 (3.0%)	0.189	3.165	0.002	0.078	0.335
FKBP5	rs3798346	pR002 (Hc ∨ Ht)	0.39[b]	0.15	0.138 (3.0%)	0.184	3.085	0.001	0.153	0.692
		Total variance explained 15.2% (adjusted: 13.8%).								
Dependent variable: Sensation Seeking factor										
Locus	rs code	Model[1]	*R*	R^2	Adjusted R^2 % variance	Standardized Coefficients β	*t*	*p*	95% Confidence Interval for β Lower	Upper
AR	rs4370673	nD[2]200 (Ht ∨ Hr) [3]	0.23	0.05	0.047 (4.7%)	0.210	3.519	<0.001	0.087	0.309
SLC6A3	rs12516758	nH102 (Ht)	0.30	0.09	0.083 (3.6%)	0.202	3.402	<0.001	0.143	0.537
DRD2	rs7122454	nR220 (Hr)	0.36	0.13	0.120 (3.7%)	0.204	3.421	<0.001	0.278	1.032
DRD4	rs752306	nR220 (Hr)	0.40[b]	0.16	0.145 (2.5%)	0.168	2.837	0.005	0.212	1.177
		Total variance explained 15.9% (adjusted: 14.5%).								

Note: [a] R^2= R Square. [b]The multiple correlation for Neuroticism and Sensation Seeking scale (not factor) and genotype score were 0.378 and 0.390 respectively.

1. Models are referred to the association with increased values of dependent variable.
2. Genotype models: nC, negative-codominant; nD, negative-dominant; nR, negative-recessive; pR, positive-recessive; nH, negative-heterosis.
3. Numbers are referred to the weighted contribution of each genotype ordered as homozygote common (Hc), heterozygote (Ht) and homozygote rare (Hr).

AR: androgen receptor; DRD2: dopamine receptor D2; DRD4: dopamine receptor D4; FKBP5: FK506 binding protein 5; GABBR2: gamma-aminobutyric acid (GABA) B receptor, 2; GNAS-AS1: GNAS complex locus; SLC6A3: solute carrier family 6 (neurotransmitter transporter), member 3.

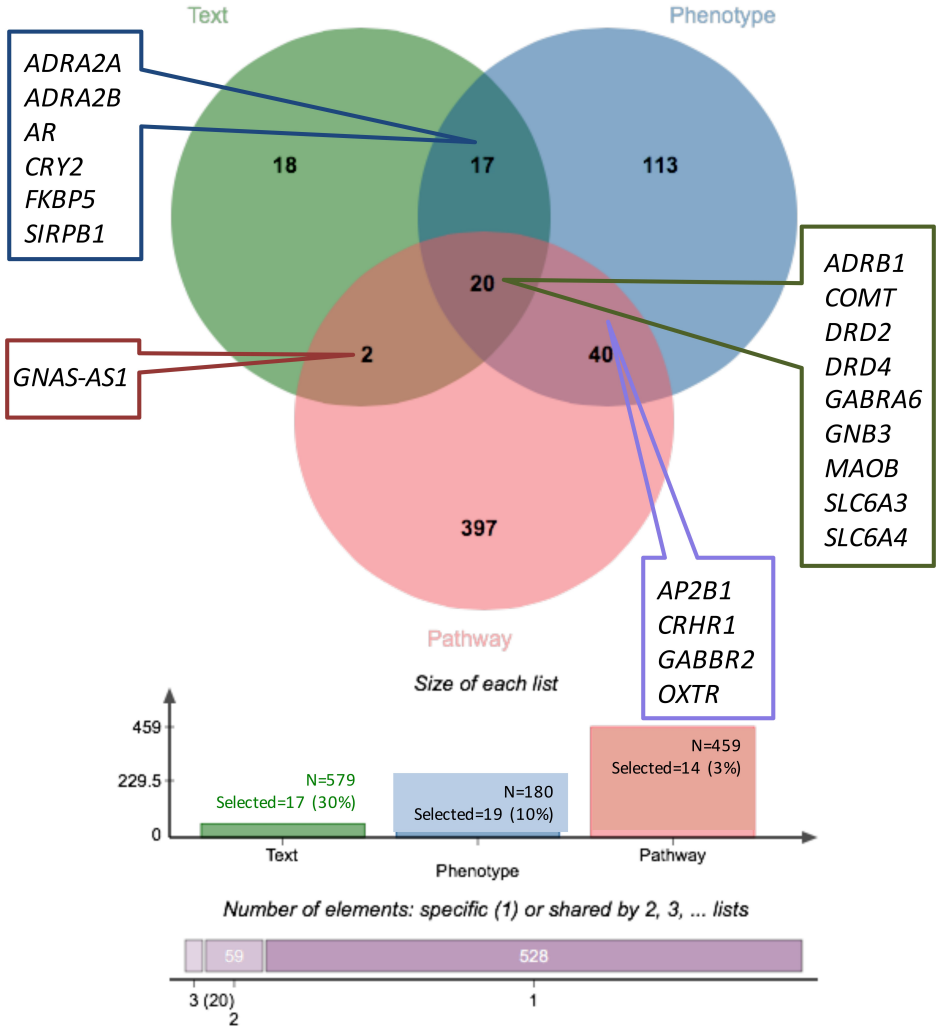


Figure 1

Note: Venn diagram distribution of selected twenty-candidate genes based on text, phenotype and pathway mining search. (*ADRA2A: adrenoceptor alpha 2A; ADRA2B: adrenoceptor alpha 2B; ADRB1: adrenoceptor beta 1; AP2B1: adaptor-related protein complex 2, beta 1 subunit RAS-like, family 10, member B; AR: androgen receptor; COMT: catechol-O- Methyltransferase; CRHR1: corticotrophin releasing hormone receptor 1; CRY2: cryptochrome circadian clock 2; DRD2: dopamine receptor D2; DRD4: dopamine receptor D4; FKBP5: FK506 binding protein 5; GABBR2: gamma-aminobutyric acid (GABA) B receptor, 2; GABRA6: gamma-aminobutyric acid (GABA) A receptor, alpha 6; GNAS-AS1: GNAS complex locus; GNB3: guanine nucleotide binding protein (G protein), beta polypeptide 3; MAOB: monoamine oxidase B; OXTR: oxytocin receptor; SIRPB1: signal-regulatory protein beta 1; SLC6A3: solute carrier family 6 (neurotransmitter transporter), member 3; SLC6A4: solute carrier family 6 (neurotransmitter transporter), member 4*).

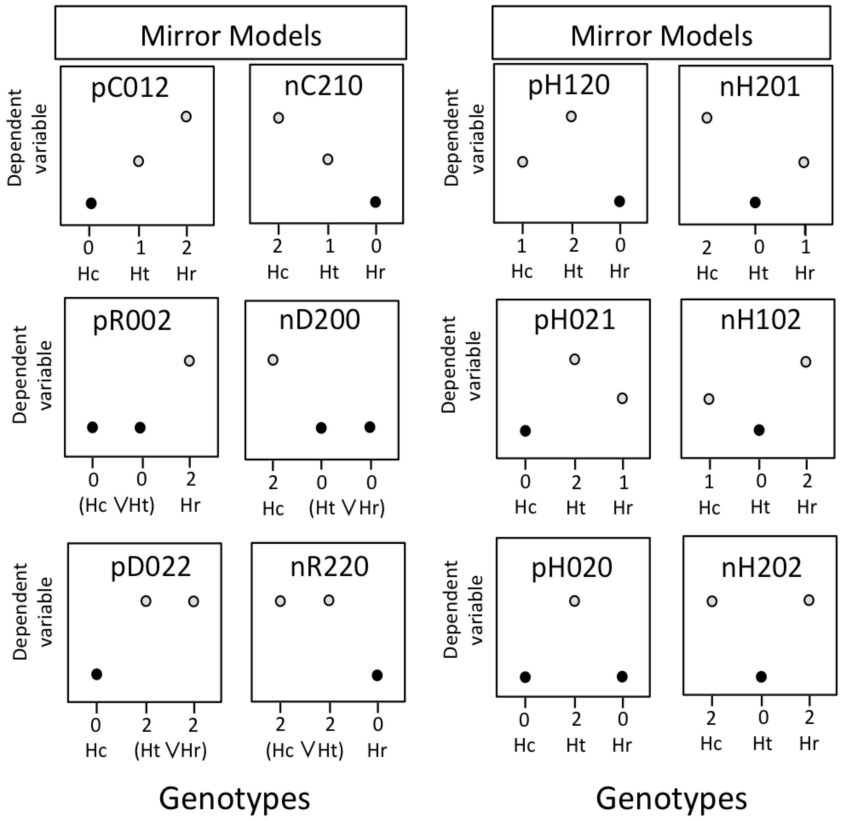
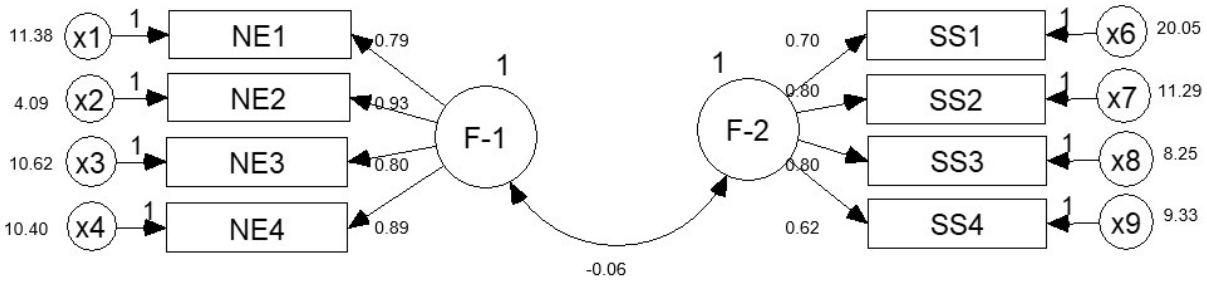


Figure 2.

Genetic model coding scheme.

Genotype models: nC, negative-codominant; nD, negative-dominant; nR, negative-recessive; pR, positive-recessive; nH, negative-heterosis. Numbers are referred to the weighted contribution of each genotype ordered as homozygote common (Hc), heterozygote (Ht) and homozygote rare (Hr).



Confirmatory Factor Analysis (CFA) of Neuroticism (F-1) and Sensation Seeking (F-2). $\chi^2/f.d$: 4.78, $p < 0.001$; GFI: 0.93;TLI: 0.92; CFI: 0.96; SRMR: 0.07; RMSEA: 0.11 (.09-.12)

Figure 3.

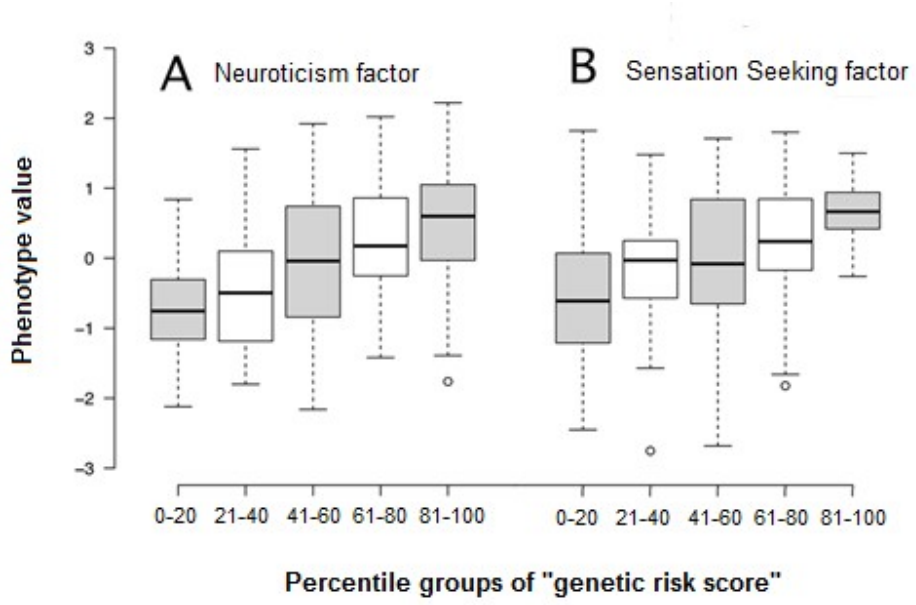


Figure 4.

"Genetic risk score" distributed by percentile groups plotted against Neuroticism and Sensation Seeking scores (factorial loadings).