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Serotonin transporter gene (*SLC6A4*) variation and sensory processing sensitivity—Comparison with other anxiety-related temperamental dimensions

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Abstract

Background: The short (*s*) allele of the 5-HTTLPR polymorphism in the promoter region of the human serotonin transporter (5-HTT) gene *SLC6A4* has previously been associated with anxiety-related personality dimensions. However, this relationship has not been confirmed in all studies and may be modified by environmental circumstances and/or psychiatric illness. This study examined whether the temperamental trait sensory processing sensitivity (SPS), characterized by increased responsivity to environmental stimuli, is related to 5-HTTLPR/rs25531 genotype.

Methods: 5-HTTLPR and rs25531 genotypes, level of SPS, self-reported Revised NEO Personality Inventory (NEO-PI-R) and Temperament and Character Inventory (TCI) personality profiles, and symptoms of psychological distress (SCL-90R Global Severity Index) were determined for 405 healthy volunteers.

Results: Sensory processing sensitivity was highly correlated with the anxiety-related dimensions of the NEO-PI-R and the TCI models of personality, Neuroticism, and Harm Avoidance, respectively. However, the level of SPS was not associated with the combined 5-HTTLPR and rs25531 *s′/s′* genotype. Neuroticism and Harm Avoidance were also not associated with 5-HTTLPR/rs25531 *s′/s′* genotype. Correcting for symptoms of psychological distress had no effect on the relationships between personality and genotype.

Conclusion: The level of SPS was not associated with serotonin transporter gene variation. Further, combined 5-HTTLPR and rs25531 genotype was not associated with other anxiety-related dimensions.

KEYWORDS
Harm Avoidance, Neuroticism, personality, serotonin, temperament

1 | INTRODUCTION

In response to environmental adversity a functional polymorphism in the serotonin (5-hydroxy-tryptamine, 5-HT) transporter (5-HTT) gene *SLC6A4*, the 5-HTT linked polymorphic region (5-HTTLPR), may predispose to mental illness (Uher & McGuffin, 2008, 2010). The 5-HTTLPR gives rise to short (*s*) and long (*l*) alleles, which have been associated with distinct psychiatric disorders, including depression in the context of adverse life events (Caspi et al., 2003) and obsessive-compulsive disorder (Hu et al., 2006), respectively. Since the initial report of an association between the 5-HTTLPR *s* allele and the personality dimension Neuroticism (Lesch et al., 1996), many studies have reported associations of the *s* allele with anxiety-related personality dimensions. However, several studies including large-scale population studies of Neuroticism (Terracciano et al., 2009) and Harm Avoidance (Munafo et al., 2009), as well as a large meta-analysis (Minelli, Bonvicini, Scassellati, Sartori, & Gennarelli, 2011), have not been able to confirm the association. Since the initial discoveries, focus has shifted toward interpreting the 5-HTTLPR and other polymorphisms, which may confer risk to mood disorders, as underlying individual differences in susceptibility to both beneficial and detrimental environmental circumstances (Belsky et al., 2009; Homberg & Lesch, 2011). Carriers of the 5-HTTLPR *s* allele show increased environmental reactivity in the form of enhanced positive and negative emotional processing (Canli et al., 2005), stronger seasonal effects of daylight time on brain 5-HTT levels (Kalbitzer et al., 2010), and a stronger acoustic startle response (Brocke et al., 2006). 5-HTTLPR *s*/*s* homozygotes, which constitute 18%–29% of the European population (Noskova et al., 2008), display phenotypic differences compared to both *s*/*l* and *l*/*l* genotypes, including stronger cortisol reactivity to social threat (Way & Taylor, 2010b). Among 5-HTTLPR genotypes, *s*/*s* homozygosity is associated with the lowest 5-HTT mRNA expression while, when including the rs25531 (A/G) single nucleotide polymorphism (SNP) in the *l* allele, l_A/l_A homozygotes have the highest expression (Hu et al., 2006). These differences are reflected in higher brain 5-HTT binding in l_A/l_A homozygotes (Willeit & Praschak-Rieder, 2010). In genetic mouse models abolished 5-HTT expression leads to many-fold increased brain extracellular 5-HT levels (Shen et al., 2004), while 2–3-fold 5-HTT overexpression leads to 50%–60% reduced extracellular 5-HT levels (Jennings et al., 2006).

The temperamental trait sensory processing sensitivity (SPS) is defined by increased social, emotional, and physical sensitivity (Aron & Aron, 1997; Aron, Aron, & Jagiellowicz, 2012). In particular, SPS has in fMRI studies been associated with enhanced neural processing of detailed visual stimuli (Jagiellowicz et al., 2011) and increased neural activation in response to pictures of happy and sad faces (Acevedo et al., 2014). Among personality dimensions of the Five Factor Model of personality, SPS was correlated with Neuroticism and Openness to Experience (Smolewska, McCabe, & Woody, 2006), and the three SPS facets Aesthetic Sensitivity (AES), Ease of Excitation (EOE), and Low Sensory Threshold (LST) (Liss, Mailloux, & Erchull, 2008; Smolewska et al., 2006) showed differential correlations with Neuroticism, Extraversion, and Openness to Experience (Smolewska et al., 2006). The level of SPS is also correlated with symptoms of depression and trait anxiety (Liss, Timmel, Baxley, & Killingsworth, 2005), as well as current levels of stress (Benham, 2006), and is higher among individuals with seasonal affective disorder (Hjordt & Stenbæk, 2019). Notably, individuals high in SPS had higher levels of negative affectivity in the context of low parenting quality during childhood, and in response to a recent experimental stressful event, than those with lower levels of SPS (Aron, Aron, & Davies, 2005). Only one study has examined the biological bases of SPS, reporting associations between polymorphisms in genes encoding factors in the dopaminergic system and SPS (Chen et al., 2011).

The purpose of the present study was to investigate a possible association between SPS and the combined 5-HTTLPR/rs25531 *s′*/*s′* genotype in healthy volunteers. In addition, relationships between SPS and the personality dimensions of the Five Factor Model (the Revised NEO Personality Inventory [NEO-PI-R]) and the Temperament and Character Inventory (TCI) were evaluated. To allow comparison with putative associations between SPS and 5-HTTLPR/rs25531 *s′*/*s′* genotype, associations between Neuroticism and Harm Avoidance and 5-HTTLPR/rs25531 genotype were also determined.

Based on the literature, we hypothesized that the 5-HTTLPR/rs25531 *s′*/*s′* genotype would be associated with higher levels of SPS. Also, we hypothesized that SPS would be associated with the anxiety-related personality traits of Neuroticism and Harm Avoidance.

2 | METHODS

2.1 | Editorial policies and ethical compliance

All individual projects were approved by the regional Ethics Committee, and permission to collect and store data was obtained from the Danish Data Protection Agency. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Written informed consent was obtained from all participants before individual project enrollment and subsequent inclusion in the Cimbi database. When contacted again in 2010, all participants provided new informed consent and received

a financial compensation for the time spent completing the questionnaires.

2.2 | Participants

Participants were recruited from an established database at the Center for Integrated Molecular Brain Imaging (Cimbi) at the Copenhagen University Hospital Rigshospitalet. In October 2018, the Cimbi database contained biological and psychometric datasets (including the Highly Sensitive Person [HSP] Scale) from 405 healthy volunteers (18–87 years old), who were initially recruited through departmental websites and had gone through a screening process, which included a general evaluation of mental health (based on anamnesis and completion of the Revised Hopkins Symptom Checklist-90R (SCL-90R)), a medical and neurological examination, and blood biochemistry analyses. The 405 healthy volunteers were included in the Cimbi database between 2000 and 2015, at which time they completed NEO-PI-R and TCI personality batteries, and blood and/or saliva samples for genotyping were collected. In the summer of 2010, the cohort was asked to complete nine additional questionnaires, including the HSP Scale and the SCL-90R, through an online survey application (LimeSurvey®, www.limesurvey.org). Of the 204 database participants, contact was established with 188, of which 169 completed the HSP Scale and the SCL-90R (i.e., a response rate of 90%). The group of 169 participants plus additionally 236 participants included in the Cimbi database between 2010 and 2015 were included in this study. The individuals included after the summer of 2010 completed all relevant questionnaires at the time of inclusion. The participants were between 18 and 87 years old (mean ± *SD* = 34 ± 17 years), and 50.1% were female.

2.3 | Measures

2.3.1 | Highly Sensitive Person Scale

The temperamental trait SPS was assessed with the HSP Scale, a 27-item self-report questionnaire developed by Elaine N. Aron and Arthur Aron (Aron & Aron, 1997), which provides a measure of SPS and of the three facets AES (sensitivity to the aesthetic quality of the environment, 7 items), EOE (sensitivity to overstimulation, 12 items), and LST (sensitivity to sensory stimuli, 6 items) (Smolewska et al., 2006 and Lionetti et al., 2018). Examples of questions include "Do other people's moods affect you?"; "Do you startle easily?"; and "Does being very hungry create a strong reaction in you, disrupting your concentration or mood?". Items are rated on a 1–7 Likert scale (1 = "not at all" to 7 = "extremely"), giving total SPS scores in the range of 27–189. The HSP Scale was translated from English to Danish by the investigators, Danish–English bilinguals, and native English speakers, checked by independent back-translation, and approved by E. N. Aron.

2.3.2 | NEO-PI-R—the Revised NEO Personality Inventory

Personality profile was assessed with the Danish version of the NEO-PI-R (Hansen & Mortensen, 2003), a 240-item self-report questionnaire providing a measure of the Five Factor Model of personality encompassing the dimensions Neuroticism, Extraversion, Openness to Experience, Agreeableness, and Conscientiousness (Costa & McCrae, 1992). A total of 398 participants completed the NEO-PI-R questionnaire.

2.3.3 | Temperament and Character Inventory

Personality profile was also assessed with the Danish version of the TCI (Kristensen, Mortensen, & Mors, 2009), a 240-item questionnaire providing a measure of four dimensions of temperament (Harm Avoidance, Novelty Seeking, Reward Dependence, and Persistence) and three of character (Self-directedness, Cooperativeness, and Self-transcendence) (Cloninger, Przybeck, Svrakic, & Wetzel, 1994). A total of 395 participants completed the TCI.

2.3.4 | Revised Hopkins Symptom Checklist (SCL-90R)

Symptoms of psychological distress and psychopathology during the past week was assessed with the Danish version of the SCL-90R (Olsen, Mortensen, & Bech, 2004), a 90-item self-report questionnaire rated on a five-point Likert scale (0 = "not at all" to 4 = "extremely"). The SCL-90R provides a total score, the Global Severity Index (GSI), and scores for nine subscales of psychopathology: Somatization, Obsessive-Compulsive, Interpersonal Sensitivity, Depression, Anxiety, Anger-Hostility, Phobic Anxiety, Paranoid Ideation, and Psychoticism (Derogatis, 1994). A total of 400 participants completed the SCL-90R.

2.4 | Genotyping

Blood samples for DNA analysis were stored at −20°C. DNA was extracted using an automated Maxwell® 16 Blood DNA Purification System according to the manufacturer's guidelines (Promega), or DNA was extracted from blood using

the Qiagen DNA mini kit (Qiagen) (Kalbitzer et al., 2010) or from saliva using either the prepIT-L2P kit or the Oragene DNA self-collection kit OG-500 (both from DNA Genotek), as described previously (Mc Mahon et al., 2016). DNA was stored at −20°C (long-term) or 5°C until genotyping. Genotyping of the 44-bp insertion/deletion polymorphism of the 5-HTT gene (*SLC6A4*; 17q11.1-q12,; NG_011747.2), the 5-HTTLPR (rs4795541), was performed with a TaqMan 5′-exonuclease allelic discrimination assay according to the manufacturer's instructions (Assay-on-Demand, Applied Biosystems) and ABI 7500 multiplex polymerase chain reaction (PCR) machine (Applied Biosystems) with the forward primer: 5′-GCA ACC TCC CAG CAA CTC CCT GTA-3′, reverse primer: 5′-GAG GTG CAG GGG GAT GCT GGA A-3′, and FAM- and VIC-labeled probes. A subset of seven samples were genotyped for 5-HTTLPR by the following method: PCR amplification using the primers F: FAM-5′-GGC GTT GCC GCT CTG AAT GC-3′ and R: 5′-CTG ACC CCT GAA AAC TGT GC-3′. The resulting PCR fragments were run on an ABI 3130 XL genetic analyzer using the internal size standard GeneScan 500 Rox, and data were analyzed using the GeneMapper Software (Applied Biosystems).

The rs25531 (A/G) SNP in the 5-HTTLPR long allele was determined as previously described (Kalbitzer et al., 2010; Mc Mahon et al., 2016). A subset of samples was genotyped for rs25531 by another method consisting of PCR amplification with the following primers: forward 5′-GGC GTT GCC GCT CTG AAT GC-3′ and reverse 5′-CTG ACC CCT GAA AAC TGT GC-3′, followed by MspI digestion and fragment analysis by electrophoresis, either in an agarose gel or on an ABI using a FAM-labeled forward primer. When using the fluorescence labeling and MspI digestion the following three alleles can be demonstrated: 5-HTTLPR *l* + rs25531/A (l_A, 341 bp), 5-HTTLPR *s* + rs25531/A (s_A, 298 bp), and rs25531/G (167 bp). In order to distinguish the 5-HTTLPR *l* + rs25531/G (l_G) from the rare 5-HTTLPR *s* + rs25531/G (s_G) allele, all samples showing a G allele were subsequently analyzed for 5-HTTLPR *s* or *l* allele by PCR amplification with the same primers followed by electrophoresis of the undigested product (*l* allele: 571 bp, *s* allele: 528 bp).

In 2012–2013, another subset of samples was genotyped for 5-HTTLPR and rs25531 by another method, as previously described (Jensen et al., 2015; Wendland, Martin, Kruse, Lesch, & Murphy, 2006).

Due to insufficient DNA, the rs25531 A/G SNP could only be determined for 398 participants.

2.5 | Statistical analysis

One main model of 5-HTTLPR/rs25531 genotype was used with coding of genotypes as binary variables: 5-HTTLPR/rs25531 *s′/s′* homozygotes: 5-HTTLPR/rs25531 *s′/s′* genotype (*s/s*, *s*/l_G, and l_G/l_G) versus l_A allele carriers (*s*/l_A, l_A/l_G, and l_A/l_A). Also, we analyzed the effects of 5-HTTLPR genotype alone: 5-HTTLPR *s/s* homozygotes: 5-HTTLPR *s/s* genotype versus *l* allele carriers (*s/l* and *l/l*) (see supplementary material for results).

In order to independently assess whether sex or age should be included as covariates in the personality genotype analysis, we first examined these relationships in our own sample. Relationships between SPS (total and facets) and sex were analyzed by ANCOVA, including age at HSP as covariate (Estimated Marginal Means ± SE), and relationships between SPS (total and facets) and age at HSP were determined as partial correlations controlling for sex, as males were older than females (mean ± *SD*: 34 ± 16 vs. 33 ± 17 years; Mann–Whitney test: $p = .026$, $n = 405$) in our sample.

Relationships between SPS and its facets and personality dimensions of NEO-PI-R and TCI were evaluated by bivariate Spearman's correlations, as the personality dimensions were not normally distributed (except for Conscientiousness), and as partial correlations controlling for age at HSP Scale completion and sex. The level of SPS of 5-HTTLPR *s′/s′* genotypes and l_A-allele carriers were compared by ANCOVA analysis to control for age and sex. Associations between 5-HTTLPR/rs25531 genotype and SPS were also tested by ANCOVA analyses taking SCL-90R GSI into account to control for psychological distress at the time of HSP Scale completion. Comparable analyses of associations between 5-HTTLPR/rs25531 genotype and Neuroticism and Harm Avoidance were performed. To evaluate eventual effects of time interval between NEO-PI-R and SPS assessment, the sample was subdivided in those with time intervals of more than 6 months and those with intervals equal to 6 months or less. Inclusion of this parameter in an ANCOVA analysis of the relationship between SPS and Neuroticism had no significant effect (data not shown). Also, including the time interval between acquisition of NEO-PI-R and SPS measures in linear regression analyses of the relationship between SPS and NEO-PI-R dimensions had no significant effects (data not shown). The statistical analyses are not corrected for multiple testing. The statistical analyses were performed in IBM SPSS Statistics 25.

3 | RESULTS

3.1 | Reliability and characteristics of the HSP Scale

The Danish version of the HSP Scale showed good reliability (internal consistency) with a Cronbach's α coefficient of 0.87 and a mean inter-item correlation of 0.19 (Table 1). SPS was significantly higher among females (103.0 ± 1.2, $n = 203$) compared to males (88.8 ± 1.2, $n = 202$, $p < .001$) and

TABLE 1 Reliability and intercorrelations of the HSP Scale and its facets

Aesthetic Sensitivity		Ease of Excitation	Low Sensory Threshold	Cronbach's α	Item-total correlation	Inter-item correlation
SPS (27)	0.61***	0.87***	0.81***	0.87	0.11–0.59	0.19
AES (7)	—	0.30***	0.32***	0.63	0.17–0.47	0.20
EOE (12)	0.30***	—	0.61***	0.78	0.13–0.62	0.23
LST (6)	0.32***	0.61***	—	0.75	0.26–0.71	0.35

Note: Values are Spearman's correlations between SPS (HSP Scale total score) and the facets AES (Aesthetic Sensitivity), EOE (Ease of Excitation), and LST (Low Sensory Threshold), and reliability estimates for each construct. The number of items included in each facet is indicated in parenthesis. $n = 405$.

Abbreviations: HSP Scale, Highly Sensitive Person Scale; SPS, sensory processing sensitivity.

***$p < .001$.

was negatively correlated with age (pr = −0.16, $p = .001$, $n = 405$). SPS was correlated with SCL-90R GSI, a global measure of symptoms of psychological distress within the past week (Spearman: $r = .41$, $p < .001$, $n = 400$). The three SPS facets AES, EOE, and LST showed good internal consistency and acceptable to high item-total correlations (Table 1). The facets were moderately intercorrelated ($r = .30$–$.61$, $n = 405$) and moderately to highly correlated with SPS total score ($r = .61$–$.87$, $n = 405$) (Table 1). All SPS facets were higher among females compared to males (AES: 31.6 ± 0.4 vs. 29.6 ± 0.4, $p < .001$, $n = 405$; EOE: 46.1 ± 0.6 vs. 39.7 ± 0.6, $p < .001$, $n = 405$; and LST: 18.3 ± 0.4 vs. 14.0 ± 0.4, $p < .001$, $n = 405$). Both AES and EOE were negatively correlated with age (AES: pr = −0.22, $p < .001$, $n = 405$; EOE: pr = −0.22, $p < .001$, $n = 405$), while LST was positively correlated with age (pr = 0.10, $p = .041$, $n = 405$).

3.2 | Relationship of SPS to personality dimensions

Among the five personality dimensions assessed by the NEO-PI-R, SPS was positively correlated with Neuroticism, Openness to Experience, and Agreeableness, and negatively correlated with Extraversion (Table 2). Similar to the full SPS measure, all facets were positively correlated with Neuroticism. EOE and LST were negatively correlated with Extraversion, while AES was positively correlated with Openness to Experience and Extraversion (Table 2). Agreeableness was positively correlated with all three SPS facets, while EOE was negatively correlated with Conscientiousness. Correcting for age and sex had some effects on the correlations between SPS facets and NEO-PI-R dimensions (Table S1). In particular, AES was no longer significantly correlated with Neuroticism, EOE no longer significantly negatively correlated with Cooperativeness, and LST no longer significantly correlated with Agreeableness. Due to the collection in 2010 of HSPS data for a subset of the sample, who had completed NEO-PI-R and other questionnaires years earlier, 39.4% of the sample had more than 6 months between their NEO-PI-R and HSPS exam. On average the NEO-PI-R data was collected 1.9 ± 3.1 (*SD*) years before the HSPS data. However, time between NEO-PI-R and HSPS exam had no significant effect on the relationships between SPS and NEO-PI-R dimensions (data not shown).

Among the personality dimensions assessed by the TCI, SPS was positively correlated with Harm Avoidance, Reward Dependence, Persistence, and Self-transcendence but negatively correlated with Novelty Seeking and Self-directedness (Table 2). Analyses of the SPS facets showed a positive correlation of both EOE and LST with Harm Avoidance, of EOE and AES with Reward Dependence, and of AES and LST with Self-transcendence. EOE and LST were negatively correlated with Novelty Seeking and Self-directedness, while AES was positively correlated with Novelty Seeking, Persistence, and Cooperativeness. Correction for age and sex affected the correlation between SPS and Persistence, which was no longer significant (Table S1). Also, when correcting for age and sex the correlation between AES and Novelty Seeking lost significance, as did the correlations between EOE and Reward Dependence, and LST and Self-transcendence. Interestingly, the negative correlation between EOE and Cooperativeness became significant.

3.3 | Relationships between SPS and 5-HTTLPR/rs25531 genotype

As the rs25531 (A/G) SNP G allele is extremely rare on chromosomes carrying the *s* allele, we only included this SNP in haplotypes on chromosomes carrying the *l* allele, leading to the 5-HTTLPR/rs25531 genotypes of *s*/*s* ($n = 74$, 18.3%), s/l_G ($n = 21$, 5.2%), s/l_A ($n = 148$, 36.5%), l_G/l_G ($n = 1$, 0.2%), l_A/l_G ($n = 28$, 6.9%), and l_A/l_A ($n = 126$, 31.1%). These genotypes were in Hardy–Weinberg equilibrium: l_G allele frequency = 6%, *s* allele frequency = 40%, and l_A allele frequency = 54%, $X^2 = 6.152$, ($df = 3$), $p > .05$. However, the 5-HTTLPR genotypes alone (without rs25531) of *s*/*s* ($n = 74$, 18.3%), *s*/*l* ($n = 172$, 42.5%), and *l*/*l* ($n = 159$, 39.3%) were not

TABLE 2 Correlations between SPS and personality dimensions of the NEO-PI-R and TCI

SPS		AES	EOE	LST
NEO-PI-R				
Neuroticism	0.48***	0.18***	0.51***	0.34***
Extraversion	−0.17**	0.16**	−0.20***	−0.28***
Openness	0.22***	0.52***	0.05	0.07
Conscientiousness	−0.08	−0.01	−0.11*	−0.04
Agreeableness	0.14**	0.10*	0.11*	0.13*
TCI				
Harm Avoidance	0.47***	0.03	0.55***	0.43***
Reward Dependence	0.24***	0.28***	0.18***	0.08
Novelty Seeking	−0.12*	0.12*	−0.17***	−0.16**
Persistence	0.11*	0.21***	0.03	0.04
Self-directedness	−0.26***	−0.04	−0.34***	−0.13**
Cooperativeness	0.02	0.19***	−0.06	−0.01
Self-transcendence	0.26***	0.40***	0.10	0.13*

Note: Values are Spearman's correlation coefficients. HSP Scale and NEO-PI-R: $n = 398$; HSP Scale and TCI: $n = 395$.

Abbreviations: AES, Aesthetic Sensitivity; EOE, Ease of Excitation; HSP Scale, Highly Sensitive Person Scale; LST, Low Sensory Threshold; NEO-PI-R, Revised NEO Personality Inventory; SPS, sensory processing sensitivity; TCI, Temperament and Character Inventory.

*$p < .05$. **$p < .01$. ***$p < .001$.

TABLE 3 Personality dimensions and 5-HTTLPR/rs25531 genotype: s'/s' versus l_A allele carrier

	s'/s'[a]	l_A allele carrier
SPS	96.0 ± 1.8	95.8 ± 1.0
Neuroticism	74.6 ± 2.1	76.9 ± 1.2
Harm Avoidance	10.5 ± 0.6	11.6 ± 0.3

Note: Values are estimated marginal means ± standard error (ANCOVA) of each personality dimension for the given 5-HTTLPR/rs25531 genotype group, taking age (at HSP Scale completion) and sex into account. s'/s': s/s, s/l_G, and l_G/l_G. $n = 388–398$.

Abbreviations: HSP Scale, Highly Sensitive Person Scale; SPS, sensory processing sensitivity.

[a]5-HTT gene (*SCL6A4*): NG_011747.2.

in Hardy–Weinberg equilibrium: s allele frequency = 40%, $X^2 = 5.033$, ($df = 1$), $p < .05$.

There was no significant association between the combined low expressing 5-HTTLPR/rs25531 genotypes (s/s, s/l_G, and l_G/l_G), referred to as 5-HTTLPR/rs25531 s'/s' genotype, and SPS when taking age at HSP completion and sex into account (Table 3). Inclusion of psychological distress (SCL-90R GSI) as a covariate had no significant effects on the results (Table S2). Also, controlling for Neuroticism had no significant effect on the results (data not shown). We also analyzed relationships between 5-HTTLPR s/s genotype alone and level of SPS but found no significant association when taking age at HSP completion and sex into account (Table S3). Inclusion of psychological distress (SCL-90R GSI) as a covariate had no significant effects on the results (Table S4). Also, controlling for Neuroticism had no significant effect on the results (data not shown). There were no significant associations between 5-HTTLPR/rs25531 status in s' or s allele dominant model and SPS: s' allele $p = .25$, s allele $p = .52$).

3.4 | Neuroticism and Harm Avoidance versus 5-HTTLPR/rs25531 genotype

We also examined, if we could replicate previous reports on 5-HTTLPR genotype association with other measures of personality. Self-reported psychological distress (SCL-90R GSI) was positively correlated with both Neuroticism (Spearman: $r = .49$, $p < .001$, $n = 394$) and Harm Avoidance (Spearman: $r = .40$, $p < .001$, $n = 391$). There were no significant associations between 5-HTTLPR/rs25531 s'/s' genotype (or s/s genotype) and Neuroticism, when controlling for age at HSP completion and sex (Table 3 and Table S3). Including SCL-90R GSI as a covariate had no effect on the relationships between 5-HTTLPR/rs25531 s'/s' genotype and Neuroticism (Table S2) or between 5-HTTLPR s/s genotype and Neuroticism (Table S4). There were also no significant associations between 5-HTTLPR/rs25531 s'/s' genotype and Harm Avoidance, when controlling for age at HSP completion and sex (Table 3). Including SCL-90R GSI as a covariate had no effect on the relationship (Table S2). However, there

was a significant relationship between 5-HTTLPR genotype and Harm Avoidance in that Harm Avoidance was significantly higher among *l* allele carriers, when taking age at HSP completion and sex into account (Table S3). This remained significant when controlling for SCL-90R GSI (Table S4). 5-HTTLPR/rs25531 *s′* allele carrier (or *s* allele carrier) status was not associated with Neuroticism or Harm Avoidance (N: *s′* allele $p = .74$, *s* allele $p = .81$; HA: *s′* allele $p = .77$, *s* allele $p = .41$).

4 | DISCUSSION

We found no associations between common polymorphisms in the human 5-HTT gene (*SLC6A4)*, 5-HTTLPR, and rs25531, and the temperamental trait SPS in our group of healthy adults. The 5-HTTLPR/rs25531 *s′*/*s′* genotype was not associated with SPS, when taking sex and age at HSP Scale completion into account. Also, including psychological distress (SCL-90R GSI) as a covariate had no significant effect on the relationship. The 5-HTTLPR/rs25531 *s′*/*s′* genotype was also not significantly associated with the anxiety-related personality dimensions of Neuroticism and Harm Avoidance.

The reliability estimates of the Danish version of the HSP Scale were in accordance with studies using the original English version (Aron & Aron, 1997; Aron et al., 2005; Smolewska et al., 2006), and reliability indices of the SPS facets were similar to those found in Canadian, Dutch, and US samples (Evers, Rasche, & Schabracq, 2008; Liss et al., 2008; Smolewska et al., 2006). In agreement with previous studies we found higher levels of SPS among females than among males (Aron & Aron, 1997; Benham, 2006). This sex difference has been proposed to reflect underreporting of sensitivity among males due to Western gender roles (Aron & Aron, 1997). SPS was correlated with psychological distress within the past week (SCL-90R GSI), suggesting that level of SPS in part reflects psychological state among healthy adults. This is in agreement with SPS being correlated with perceived stress within the past month (Benham, 2006) and with symptoms of depression (Liss et al., 2005) in nonclinical samples. We found similar correlations between psychological distress and both Neuroticism and Harm Avoidance, indicating that this is a general characteristic of anxiety-related personality dimensions.

Two studies have related SPS to personality dimensions of the Five Factor Model of personality using the Big Five Inventory (Aron & Aron, 1997) and the NEO-FFI (Smolewska et al., 2006). In agreement with previous studies, SPS total score (Aron & Aron, 1997) and all three facets were correlated with Neuroticism (Smolewska et al., 2006). However, the moderate size of the correlation coefficient ($r = .48$) indicates that the SPS construct may be distinct from negative emotionality, as assessed by Neuroticism. A negative correlation of −0.29 between SPS and Extraversion was found using Eysenck's Personality Inventory (Aron & Aron, 1997) but not with the NEO-FFI (Smolewska et al., 2006). In our sample, SPS was also negatively correlated with Extraversion ($r = -.17$; suggestive of a positive correlation with introversion), reflecting negative correlations with the facets EOE and LST but a positive correlation with AES. The relationship is in line with SPS incorporating physiological aspects, which differ between introverts and extraverts (Aron & Aron, 1997), while the rather small coefficient underscores the difference between the constructs. Finally, in agreement with the study by Smolewska et al. (2006), SPS was positively correlated with Openness to Experience. Overall, EOE and LST were similarly correlated with NEO-PI-R personality dimensions, while AES showed a distinct pattern. Notably, AES was most strongly correlated with Openness to Experience ($r = .52$), which has been associated with genetic variation in the dopamine system (Deyoung et al., 2011).

With respect to Cloninger's psychobiological model of temperament and character, in our sample of healthy adults, SPS was correlated with Harm Avoidance, Reward Dependence, Persistence, and Self-transcendence. This is in partial agreement with results obtained with the Tridimensional Personality Questionnaire (TPQ) in a smaller sample ($n = 89$) of outpatients with social anxiety disorder, where SPS was correlated with Harm Avoidance only (Hofmann & Bitran, 2007).

The distribution of 5-HTTLPR/rs25531 allele and genotype frequencies among the Danish participants in our study was in accordance with those of a large group ($n = 771$) of Finnish whites (Hu et al., 2006). We hypothesized that 5-HTTLPR/rs25531 *s′*/*s′* genotype would be associated with SPS but found no significant relationship when taking sex and age at HSP Scale completion into account. Also, including psychological distress (SCL-90R GSI) as a covariate had no effect. Furthermore, analyses of the SPS facets revealed no significant relationships with 5-HTTLPR/rs25531 *s′*/*s′* genotype (data not shown).

Individuals with at least one short allele of the 5-HTTLPR have increased sensitivity to pictures of emotional faces (Homberg & Lesch, 2011), increased sensitivity to social experiences including psychosocial stress (Way & Taylor, 2010a), more depressive symptoms in response to early life or recent stress (Caspi et al., 2003), increased effects of an academic examination on negative mood (Verschoor & Markus, 2011), increased acoustic startle response (Brocke et al., 2006), and differences in pain regulation (Lindstedt et al., 2011). As the HSP Scale was originally developed by interviews with individuals who identified themselves as highly sensitive (Aron et al., 2012), and include descriptors of increased

sensitivity to other people's mood, pain, and hunger; being upset by many simultaneous demands, time pressure, and major life changes; as well as being easily startled, SPS could have represented a general description of the subjective experience of physiological consequences of plasticity genotypes such as the 5-HTTLPR/rs25531 *s′/s′* genotype or related 5-HTTLPR genotypes. However, this hypothesis was not supported in our sample.

Studies using fMRI to assess psychobiological changes associated with high SPS have obtained the clearest results when controlling for Neuroticism (Acevedo, Aron, & Aron, 2010, Acevedo et al., 2014; Jagiellowicz et al., 2011). However, controlling for Neuroticism had no effect on our results. Also, 5-HTTLPR/rs25531 *s′* allele carrier status and the 5-HTTLPR genotypic categories *s/s* and *s* allele carrier, not taking variation at the rs25531 SNP into account, were not related to SPS.

Similar to SPS, 5-HTTLPR/rs25531 *s′/s′* genotype was not significantly associated with Neuroticism or Harm Avoidance. The lack of associations between Neuroticism and 5-HTTLPR *s* allele carrier status is in agreement with large population studies of Neuroticism (Terracciano et al., 2009) and with a meta-analysis from 2011 (Minelli et al., 2011). In their meta-analysis, Minelli et al. (2011) detected a significant association between the 5-HTTLPR *s/s* genotype and studies of Harm Avoidance and Neuroticism combined but when studies without structured psychiatric screening were excluded, the association was no longer significant. The discrepancy between studies may be explained by reports showing that association between the 5-HTTLPR *s* allele and Neuroticism is dependent on adverse environmental circumstances (Pluess, Belsky, Way, & Taylor, 2010; Vinberg, Mellerup, Andersen, Bennike, & Kessing, 2010). Also, many of the previous studies have not included the rs25531 SNP in their analyses of relationships between serotonin transporter gene (*SLC6A4*) variation and anxiety-related traits.

A potential weakness of the present study pertains to the fact that the NEO-PI-R and the TCI personality data of a subset of participants were not collected at the same time as the SPS data. While longitudinal studies have shown very high stability of NEO-PI-R scores on an individual basis with 6- to 15-year retest correlations of 0.78–0.85 (Terracciano, Costa, & McCrae, 2006), among 5-HTTLPR *s* allele carriers the level of Neuroticism to some extent reflect environmental circumstances (Pluess et al., 2010; Vinberg et al., 2010). We therefore compared the effect of time interval between collection of SPS and NEO-PI-R data on the relationships between SPS and NEO-PI-R dimensions but found no significant differences.

In conclusion, the 5-HTTLPR/rs25531 *s′/s′* genotype was not associated with the temperamental trait SPS, when controlling for age and sex. Taking psychological distress into account had no significant effect. There were also no associations between any categorization of 5-HTTLPR/rs25531 genotypes and Neuroticism or between 5-HTTLPR/rs25531 *s′/s′* genotype and Harm Avoidance. Given the relatively large sample size, the present results may be considered robust evidence of non-significant associations between 5-HTTLPR/rs25531 genotype and anxiety-related temperamental dimensions but the results still require independent confirmation.

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AUTHOR CONTRIBUTION

CLL, ELM, and GMK designed the study. CLL collected questionnaire data for the database, analyzed the data, and wrote the manuscript. ELM supervised the data analysis. TEA and AN performed genotyping analyses. LVH and DSS contributed to data management and data analysis. All authors contributed to writing of the manuscript and approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

Due to the General Data Protection Regulation (GDPR), the data that support the findings of this study are not readily available. However, data in the Cimbi database can be accessed by application (www.cimbi.dk).

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REFERENCES

Acevedo, B., Aron, A., & Aron, E. (2010). Sensory Processing Sensitivity and Neural Response to Stranger´s Emotional States. Presented at American Psychological Association Annual Convention 2010, Symposium 2273, San Diego, CA.

Acevedo, B. P., Aron, E. N., Aron, A., Sangster, M. D., Collins, N., & Brown, L. L. (2014). The highly sensitive brain: An fMRI study of sensory processing sensitivity and response to other´s emotions. *Brain and Behavior*, *4*, 580–594. https://doi.org/10.1002/brb3.242

Aron, E. N., & Aron, A. (1997). Sensory-processing sensitivity and its relation to introversion and emotionality. *Journal of*

Personality and Social Psychology, *73*, 345–368. https://doi.org/10.1037/0022-3514.73.2.345

Aron, E. N., Aron, A., & Davies, K. M. (2005). Adult shyness: The interaction of temperamental sensitivity and an adverse childhood environment. *Personality and Social Psychology Bulletin*, *31*, 181–197. https://doi.org/10.1177/0146167204271419

Aron, E. N., Aron, A., & Jagiellowicz, J. (2012). Sensory processing sensitivity: A review in the light of the evolution of biological responsivity. *Personality and Social Psychology Review*, *16*, 262–282. https://doi.org/10.1177/1088868311434213

Belsky, J., Jonassaint, C., Pluess, M., Stanton, M., Brummett, B., & Williams, R. (2009). Vulnerability genes or plasticity genes? *Molecular Psychiatry*, *14*, 746–754. https://doi.org/10.1038/mp.2009.44

Benham, G. (2006). The Highly Sensitive Person: Stress and physical symptom reports. *Personality and Individual Differences*, *40*, 1433–1440. https://doi.org/10.1016/j.paid.2005.11.021

Brocke, B., Armbruster, D., Muller, J., Hensch, T., Jacob, C. P., Lesch, K.-P., … Strobel, A. (2006). Serotonin transporter gene variation impacts innate fear processing: Acoustic startle response and emotional startle. *Molecular Psychiatry*, *11*, 1106–1112. https://doi.org/10.1038/sj.mp.4001908

Canli, T., Omura, K., Haas, B. W., Fallgatter, A., Constable, R. T., & Lesch, K. P. (2005). Beyond affect: A role for genetic variation of the serotonin transporter in neural activation during a cognitive attention task. *Proceedings of the National Academy of Science of the United States of America*, *102*, 12224–12229. https://doi.org/10.1073/pnas.0503880102

Caspi, A., Sugden, K., Moffitt, T. E., Taylor, A., Craig, I. W., Harrington, H., … Poulton, R. (2003). Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene. *Science*, *301*, 386–389. https://doi.org/10.1126/science.1083968

Chen, C., Chen, C., Moyzis, R., Stern, H., He, Q., Li, H. E., … Dong, Q. I. (2011). Contributions of dopamine-related genes and environmental factors to highly sensitive personality: A multi-step neuronal system-level approach. *PLoS One*, *6*, e21636. https://doi.org/10.1371/journal.pone.0021636

Cloninger, C. R., Przybeck, T. R., Svrakic, D. M., & Wetzel, R. D. (1994). *The temperament and character inventory (TCI): Guide to its development and use*. St. Louis, MO: Center for Psychobiology of Personality, Washington University. ISBN 978-0-9642917-1-3.

Costa, P. T., & McCrae, R. R. (1992). *Professional manual for revised NEO personality inventory*. Odessa, FL: Psychological Assessment Resources.

Derogatis, L. R. (1994). *SCL-90-R: Administration, scoring, and procedures for the Brief Symptom Inventory* (3rd ed.). Minneapolis, MN: National Computer Systems.

Deyoung, C. G., Cicchetti, D., Rogosch, F. A., Gray, J. R., Eastman, M., & Grigorenko, E. L. (2011). Sources of cognitive exploration: Genetic variation in the prefrontal dopamine system predicts openness/intellect. *Journal of Research in Personality*, *45*, 364–371. https://doi.org/10.1016/j.jrp.2011.04.002

Evers, A., Rasche, J., & Schabracq, M. J. (2008). High sensory-processing sensitivity at work. *International Journal of Stress Management*, *15*, 189–198. https://doi.org/10.1037/1072-5245.15.2.189

Hansen, H. S., & Mortensen, E. L. (2003). *NEO PI-R manual*. Virum, Denmark: PsykologiErhverv A/S.

Hjordt, L. V., & Stenbæk, D. S. (2019). Sensory processing sensitivity and its association with seasonal affective disorder. *Psychiatry Research*, *272*, 359–364. https://doi.org/10.1016/j.psychres.2018.12.112

Hofmann, S. G., & Bitran, S. (2007). Sensory-processing sensitivity in social anxiety disorder: Relationship to harm avoidance and diagnostic subtypes. *Journal of Anxiety Disorders*, *21*, 944–954. https://doi.org/10.1016/j.janxdis.2006.12.003

Homberg, J. R., & Lesch, K. P. (2011). Looking on the bright side of serotonin transporter gene variation. *Biological Psychiatry*, *69*, 513–519. https://doi.org/10.1016/j.biopsych.2010.09.024

Hu, X.-Z., Lipsky, R. H., Zhu, G., Akhtar, L. A., Taubman, J., Greenberg, B. D., … Goldman, D. (2006). Serotonin transporter promoter gain-of-function genotypes are linked to obsessive-compulsive disorder. *The American Journal of Human Genetics*, *78*, 815–826. https://doi.org/10.1086/503850

Jagiellowicz, J., Xu, X., Aron, A., Aron, E., Cao, G., Feng, T., & Weng, X. (2011). The trait of sensory processing sensitivity and neural responses to changes in visual scenes. *Social Cognitive and Affective Neuroscience*, *6*, 38–47. https://doi.org/10.1093/scan/nsq001

Jennings, K. A., Loder, M. K., Sheward, W. J., Pei, Q., Deacon, R. M., Benson, M. A., … Sharp, T. (2006). Increased expression of the 5-HT transporter confers a low-anxiety phenotype linked to decreased 5-HT transmission. *The Journal of Neuroscience*, *26*, 8955–8964. https://doi.org/10.1523/JNEUROSCI.5356-05.2006

Jensen, C. G., Lansner, J., Petersen, A., Vangkilde, S. A., Ringkøbing, S. P., Frokjaer, V. G., … Hasselbalch, S. G. (2015). Open and Calm–a randomized controlled trial evaluating a public stress reduction program in Denmark. *BMC Public Health*, *15*, 1245. https://doi.org/10.1186/s12889-015-2588-2

Kalbitzer, J., Erritzoe, D., Holst, K. K., Nielsen, F. Å., Marner, L., Lehel, S., … Knudsen, G. M. (2010). Seasonal changes in brain serotonin transporter binding in short serotonin transporter linked polymorphic region-allele carriers but not in long-allele homozygotes. *Biological Psychiatry*, *67*, 1033–1039. https://doi.org/10.1016/j.biopsych.2009.11.027

Kristensen, A. S., Mortensen, E. L., & Mors, O. (2009). The association between bodily anxiety symptom dimensions and the scales of the Revised NEO Personality Inventory and the Temperament and Character Inventory. *Comprehensive Psychiatry*, *50*, 38–47. https://doi.org/10.1016/j.comppsych.2008.06.005

Lesch, K.-P., Bengel, D., Heils, A., Sabol, S. Z., Greenberg, B. D., Petri, S., … Murphy, D. L. (1996). Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science*, *274*, 1527–1531. https://doi.org/10.1126/science.274.5292.1527

Lindstedt, F., Berrebi, J., Greayer, E., Lonsdorf, T. B., Schalling, M., Ingvar, M., & Kosek, E. (2011). Conditioned pain modulation is associated with common polymorphisms in the serotonin transporter gene. *PLoS One*, *6*, e18252. https://doi.org/10.1371/journal.pone.0018252

Lionetti, F., Aron, A., Aron, E. N., Burns, G. L., Jagiellowicz, J., & Pluess, M. (2018). Dandelions, tulips and orchids: Evidence for the existence of low-sensitive, medium-sensitive and high-sensitive individuals. *Translational Psychiatry*, *8*, 24. https://doi.org/10.1038/s41398-017-0090-6

Liss, M., Mailloux, J., & Erchull, M. J. (2008). The relationships between sensory processing sensitivity, alexithymia, autism, depression, and anxiety. *Personality and Individual Differences*, *45*, 255–259. https://doi.org/10.1016/j.paid.2008.04.009

Liss, M., Timmel, L., Baxley, K., & Killingsworth, P. (2005). Sensory processing sensitivity and its relation to parental bonding, anxiety, and depression. *Personality and Individual Differences*, *39*, 1429–1439. https://doi.org/10.1016/j.paid.2005.05.007

Mc Mahon, B., Andersen, S. B., Madsen, M. K., Hjordt, L. V., Hageman, I., Dam, H., … Knudsen, G. M. (2016). Seasonal difference in brain serotonin transporter binding predicts symptom severity in patients with seasonal affective disorder. *Brain*, *139*, 1605–1614. https://doi.org/10.1093/brain/aww043

Minelli, A., Bonvicini, C., Scassellati, C., Sartori, R., & Gennarelli, M. (2011). The influence of psychiatric screening in healthy populations selection: A new study and meta-analysis of functional 5-HTTLPR and rs25531 polymorphisms and anxiety-related personality traits. *BMC Psychiatry*, *11*, 50. https://doi.org/10.1186/1471-244X-11-50

Munafò, M. R., Freimer, N. B., Ng, W., Ophoff, R., Veijola, J., Miettunen, J., … Flint, J. (2009). 5-HTTLPR genotype and anxiety-related personality traits: A meta-analysis and new data. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *150B*, 271–281. https://doi.org/10.1002/ajmg.b.30808

Noskova, T., Pivac, N., Nedic, G., Kazantseva, A., Gaysina, D., Faskhutdinova, G., … Seler, D. M. (2008). Ethnic differences in the serotonin transporter polymorphism (5-HTTLPR) in several European populations. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *32*, 1735–1739. https://doi.org/10.1016/j.pnpbp.2008.07.012

Olsen, L. R., Mortensen, E. L., & Bech, P. (2004). The SCL-90 and SCL-90R versions validated by item response models in a Danish community sample. *Acta Psychiatrica Scandinavica*, *110*, 225–229. https://doi.org/10.1111/j.1600-0447.2004.00399.x

Pluess, M., Belsky, J., Way, B. M., & Taylor, S. E. (2010). 5-HTTLPR moderates effects of current life events on neuroticism: Differential susceptibility to environmental influences. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *34*, 1070–1074. https://doi.org/10.1016/j.pnpbp.2010.05.028

Shen, H.-W., Hagino, Y., Kobayashi, H., Shinohara-Tanaka, K., Ikeda, K., Yamamoto, H., … Sora, I. (2004). Regional differences in extracellular dopamine and serotonin assessed by in vivo microdialysis in mice lacking dopamine and/or serotonin transporters. *Neuropsychopharmacology*, *29*, 1790–1799. https://doi.org/10.1038/sj.npp.1300476

Smolewska, K. A., McCabe, S. B., & Woody, E. Z. (2006). A psychometric evaluation of the Highly Sensitive Person Scale: The components of sensory-processing sensitivity and their relation to the BIS/BAS and "Big Five". *Personality and Individual Differences*, *40*, 1269–1279. https://doi.org/10.1016/j.paid.2005.09.022

Terracciano, A., Balaci, L., Thayer, J., Scally, M., Kokinos, S., Ferrucci, L., … Costa, P. T. (2009). Variants of the serotonin transporter gene and NEO-PI-R Neuroticism: No association in the BLSA and SardiNIA samples. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *150B*, 1070–1077. https://doi.org/10.1002/ajmg.b.30932

Terracciano, A., Costa, P. T. Jr, & McCrae, R. R. (2006). Personality plasticity after age 30. *Personality and Social Psychology Bulletin*, *32*, 999–1009. https://doi.org/10.1177/0146167206288599

Uher, R., & McGuffin, P. (2008). The moderation by the serotonin transporter gene of environmental adversity in the aetiology of mental illness: Review and methodological analysis. *Molecular Psychiatry*, *13*, 131–146. https://doi.org/10.1038/sj.mp.4002067

Uher, R., & McGuffin, P. (2010). The moderation by the serotonin transporter gene of environmental adversity in the etiology of depression: 2009 update. *Molecular Psychiatry*, *15*, 18–22. https://doi.org/10.1038/mp.2009.123

Verschoor, E., & Markus, C. R. (2011). Affective and neuroendocrine stress reactivity to an academic examination: Influence of the 5-HTTLPR genotype and trait neuroticism. *Biological Psychology*, *87*, 439–449. https://doi.org/10.1016/j.biopsycho.2011.06.001

Vinberg, M., Mellerup, E., Andersen, P. K., Bennike, B., & Kessing, L. V. (2010). Variations in 5-HTTLPR: Relation to familiar risk of affective disorder, life events, neuroticism and cortisol. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *34*, 86–91. https://doi.org/10.1016/j.pnpbp.2009.10.002

Way, B. M., & Taylor, S. E. (2010a). Social influences on health: Is serotonin a critical mediator? *Psychosomatic Medicine*, *72*, 107–112. https://doi.org/10.1097/PSY.0b013e3181ce6a7d

Way, B. M., & Taylor, S. E. (2010b). The serotonin transporter promoter polymorphism is associated with cortisol response to psychosocial stress. *Biological Psychiatry*, *67*, 487–492. https://doi.org/10.1016/j.biopsych.2009.10.021

Wendland, J. R., Martin, B. J., Kruse, M. R., Lesch, K.-P., & Murphy, D. L. (2006). Simultaneous genotyping of four functional loci of human *SLC6A4*, with a reappraisal of *5-HTTLPR* and rs25531. *Molecular Psychiatry*, *11*, 224–226. https://doi.org/10.1038/sj.mp.4001789

Willeit, M., & Praschak-Rieder, N. (2010). Imaging the effects of genetic polymorphisms on radioligand binding in the living human brain: A review on genetic neuroreceptor imaging of monoaminergic systems in psychiatry. *NeuroImage*, *53*, 878–892. https://doi.org/10.1016/j.neuroimage.2010.04.030

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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