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A neuroeconomic investigation of *5-HTT*/*5-HT1A* gene variation, social anxiety, and risk-taking behavior

Caitlin A. Stamatis[a], **Jan B. Engelmann**[b,c,d], **Christiane Ziegler**[e], **Katharina Domschke**[e,f], **Gregor Hasler**[g], **Kiara R. Timpano**[a]

[a]Department of Psychology, University of Miami, Coral Gables, FL, USA;

[b]Center for research in experimental economics and political decision making (CREED), Faculty of Economics and Business, University of Amsterdam, Amsterdam, Netherlands;

[c]Amsterdam Brain and Cognition (ABC), University of Amsterdam, Amsterdam, Netherlands;

[d]The Tinbergen Institute, Amsterdam, Netherlands;

[e]Department of Psychiatry and Psychotherapy, Medical Center - University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany;

[f]Center for Basics in NeuroModulation, Faculty of Medicine, University of Freiburg, Freiburg, Germany;

[g]Department of Psychiatry, University of Fribourg, Villars-sur-Glâne, Switzerland

Abstract

Background and objectives: Although approaches combining behavioral genetics and neuroeconomics have advanced models of addiction, no study has synthesized these methods to elucidate mechanisms of competing risk-approachand risk-avoidance in social anxiety (SA). Grounded in dual-mode models of serotonergic systems and self-regulation, this study investigated associations between SA, serotonin transporter *5-HTT* (LPR; rs25531) and receptor *5-HT1A* genes, and risk-taking on behavioral and self-report measures.

Design and methods: Young adults ($N = 309$) completed a neuroeconomic task measuring gambling attractiveness (δ), reward probability discrimination (γ), and risk attitudes (α). Risk genotypes included *5-HTT* (LPR; rs25531) low-expression variants (SS/SL_G/L_GL_G), and *5-HT1A* (rs6295) GG.

Results: Path analysis revealed that SA related to increased gambling attractiveness, but only for *5-HT1A* risk groups. Although the *5-HTT* (LPR; rs25531) risk genotypes and self-reported SA predicted lower social risk-taking, high-SA individuals who exhibited more accurate reward probability discrimination (γ) reported taking increased social risks.

Conclusion: In line with dual-mode models, results suggest that SA predicts behavioral risk-approach at the basic decision-making level, along with self-reported social risk-avoidance,

✉**CONTACT** Kiara R. Timpano kiaratimpano@gmail.com.

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modulated by serotonergic genotypes. High-SA individuals with more accurate assessments of reward probabilities may engage in greater social risk-taking, perhaps reflecting an adaptive tendency to approach feared situations.

Keywords

Social anxiety; neuroeconomics; *5-HT1A* ; *5-HTT* (LPR; rs25531); risk-taking; decision-making

1. Introduction

Social anxiety disorder (SAD) is characterized by a persistent fear of negative evaluation by others, which presents as distress and shame in social situations (American Psychiatric Association, 2013). SAD represents one of the most common anxiety disorders, with a lifetime prevalence of 13 percent (Kessler, Petukhova, Sampson, Zaslavsky, & Wittchen, 2012). Debilitating as it is ubiquitous, social anxiety (SA) engenders impairment across domains, impacting occupational, social, and general functioning (American Psychiatric Association, 2013). Impairment is exacerbated by high comorbidity with other affective and substance use disorders (Stewart, Morris, Mellings, & Komar, 2006). SAD marks a significant problem for young adults, with symptoms typically emerging in adolescence or early adulthood. Prevalence estimates reach 42% in normative college samples and 49% in clinical college samples (Stewart & Mandrusiak, 2007).

Dysfunctional appraisals of risk/reward tradeoffs may contribute to the impairment exhibited by individuals with SA symptoms (Maner & Schmidt, 2006), and healthy participants similarly show altered risk preferences and related neural correlates when experiencing incidental anxiety (Cohn, Engelmann, Fehr, & Maréchal, 2015; Engelmann, Meyer, Fehr, & Ruff, 2015). Individuals high in SA are likely to overestimate the distress they will feel in social situations (Hofmann, 2007), which fuels the experiential avoidance central to models of SAD (Kashdan et al., 2014; Lorian & Grisham, 2010). This tendency to overestimate potential negative outcomes has been linked to deficits in decision-making, with socially anxious individuals exhibiting poorer goal-directed decision making in the context of anxiety-related stimuli (Pittig, Alpers, Niles, & Craske, 2015). Consequently, along with behavioral avoidance, individuals high in SA exhibit risk-*seeking* behavior across various domains (Kashdan, Collins, & Elhai, 2006), including alcohol and substance use (Buckner, Eggleston, & Schmidt, 2006), aggression, and risky sexual behavior (Bodinger et al., 2002).

From the perspective of self-regulatory models of psychopathology (Carver, Johnson, & Joormann, 2009), the relevance of both risk avoidance and risk-seeking to SAD may reflect distinct components of the two-mode model of self-regulation. Bottom-up or reflexive processing in SA may take the form of social avoidance, which would reduce negative emotion in an immediate sense, as well as engagement in risk-seeking behaviors such as heavy drinking, which would increase positive emotion in the short term. Conversely, high-SA individuals with greater effortful control capacity may choose to take social risks in spite of the gut feeling to avoid, and to abstain from engagement in maladaptive risk behaviors when faced with negative emotion. In line with self-regulatory models, high-SA college-

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age individuals report using substances to increase positive emotion under social stress (Buckner et al., 2006), cope with negative emotion, and fit in with peers (Stewart et al., 2006). Moreover, individual differences in personality and information processing, including impulsivity (Keough, Badawi, Nitka, O'Connor, & Stewart, 2016), decision-making styles, and reward expectancies (Kashdan et al., 2006), appear to moderate the association between risk-taking and SA, further supporting the role of effortful control in regulating SA-related behaviors. Importantly, however, most previous studies on this topic have relied on self-report measures of risk-taking and impulsivity (e.g., Kashdan et al., 2006; Kashdan, Elhai, & Breen, 2008). There remains a need to integrate experimental, biobehavioral, and self-report measures within the same study to better understand specific mechanisms of distorted decision-making in SA, particularly in contexts of anticipated risks and rewards.

The field of neuroeconomics, which uses experimental economic tasks to investigate risk preferences, has contributed to understanding the neurobiological basis of decision-making, with implications for risk behaviors in anxiety disorders (Hartley & Phelps, 2012; Hasler, 2012). Behavioral economic evidence has long indicated that people deviate from expected utility theory by generally overvaluing small probabilities of a gain or loss, while underemphasizing larger probabilities (Kahneman & Tversky, 1979; Lattimore, Baker, & Witte, 1992). Neuroeconomics has allowed researchers to better understand the individual differences involved in those appraisals of risk-reward tradeoffs (Glimcher & Fehr, 2013). A handful of studies have probed predictors of individual differences in reward valuation, including the influence of personality characteristics on probability distortions (Capra, Jiang, Engelmann, & Berns, 2013). From research at the intersection of personality psychology and neuroeconomics, individuals high in neuroticism and inhibition exhibit greater distortions of reward probabilities (Capra et al., 2013), a finding that has implications for maladaptive decision-making in affective disorders characterized by these personality features (e.g., SAD). Despite the relevance of these methods to characterize effortful and reactive behavior in affective disorders (Engelmann et al., 2015; Engelmann & Tamir, 2009), no studies have employed gambling tasks from neuroeconomic studies to test mechanisms of reward-based decision-making in SAD.

The parameters derived from neuroeconomic tasks may elucidate specific facets of risk approach and avoidance at a basic decision-making level, which could interact with anxiety symptoms to influence the choice to engage in or escape a perceived threat (Charpentier, Aylward, Roiser, & Robinson, 2017). In terms of explaining SA-related risk behavior, it is unknown whether decision-making on neuroeconomic tasks differentially predicts propensities to engage in real-world social and non-social risk behaviors. Conceivably, high SA individuals who display greater willingness to bet on chance outcomes and lower risk aversion on a neuroeconomic task may report significantly greater risk-taking in their day-to-day lives. Alternatively, socially anxious individuals who perceive probabilities more accurately (i.e., more in line with expected utility theory) may exhibit a greater propensity to engage the top-down control processes required to take adaptive social risks, which could fuel a beneficial willingness to expose oneself to distressing situations (Leyro, Zvolensky, & Bernstein, 2010). No studies to date have tested interactions between SA and basic gambling behavior in relationship to self-reported risk taking across social and non-social domains.

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From the perspective of the previously-discussed two-mode model of self-regulation, the relationships between SA and reward-based decision-making are likely moderated by effortful control, suggesting the relevance of the serotonergic system in understanding competing risk-approach/avoidance behaviors in SAD (Carver, Johnson, & Joormann, 2008; Carver et al., 2009). The serotonin transporter and the serotonin receptor 1A have been linked with mood and anxiety pathology (Carver et al., 2009), including SA (Lanzenberger et al., 2007; Mathew & Ho, 2006), as well as decision-making and impulsivity (Cools, Roberts, & Robbins, 2008; McHugh et al., 2015). In particular, behavioral research highlights a link between the *5-HTT* (LPR; rs25531) low-expression genotype and willingness to pay in potential gambles (Millroth, Juslin, Eriksson, & Agren, 2017). Although previous studies suggest variants of the *5-HTT* (LPR; rs25531) gene ($SS/SL_G/L_GL_G$ genotype of the linked polymorphic region (LPR); rs25531) and the *5-HT1A* (*HTR1A*) gene (G allele of the −1019C/G promoter polymorphism; rs6295) may be relevant to risk-taking and SA symptoms individually (Benko et al., 2010; Domschke et al., 2006; Domschke & Dannlowski, 2010; Straube et al., 2014), none have examined the role of these putative risk genotypes in explaining overlapping SA and risk-taking. To explain the relationship of serotonergic genes to these seemingly disparate facets of emotion and behavior, proponents of the two-mode model contend that the serotonergic system influences reflexive responding to strong emotion (Carver et al., 2008, 2009; Carver & Miller, 2006). Individuals with high SA are vulnerable to experiencing strong negative emotion when faced with potential social stimuli. Thus, we propose that in the context of SA, low serotonergic function may contribute to lower availability of effortful control resources to guide adaptive exposure to feared situations, ultimately resulting in greater reactive risk-seeking and greater avoidance. Further, we assert that in line with critiques of previous genetic studies as relying on overly-broad definitions of anxiety and impulsivity (Carver & Miller, 2006), there is a need to utilize specific and multimethod measures of reward-based decision-making to study risk-taking and SA.

The current study expands upon prior research on risk approach and avoidance in SA in several ways. First, we assess risk behavior with both a neuroeconomic task and self-report measures. Second, using a novel application of two-mode models of serotonergic function and self-regulation, we consider the incremental role of *5-HTT* (LPR; rs25531) and *5-HT1A* genotypes as distal contributing factors in the relationship between SA symptoms and risk. Our first aim was to test the association between SA and neuroeconomic task performance. In line with prior research linking SA to risk behaviors (e.g., Buckner et al., 2006; Stewart et al., 2006), we hypothesized that SA would be associated with greater willingness to bet on chance outcomes, as well as poorer discrimination of reward probabilities, on a monetary gambling task (Figure 1). Second, we examined the relationship between SA symptoms and self-reported social and nonsocial risk-taking, hypothesizing that SA symptoms would relate to lower levels of social risk taking (c.f., Kashdan et al., 2006), but higher levels of financial risk taking. Finally, we tested a theoretical model of the joint impact of *5-HTT* (LPR; rs25531) and *5-HT1A* (rs6295) genotypes, SA symptoms, and task parameters on self-reported risk-taking across social and non-social domains (Figure 1). Despite limitations inherent in conducting candidate gene association studies with relatively small sample sizes (Charney & English, 2012), we feel that our integrative approach represents an important

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initial step in understanding contributing factors to social anxiety and risk attitudes from the perspective of a two-mode model. Consequently, we designed this study in adherence to best candidate gene practices, which included taking proximal measurements such as a behavioral economic design, using common polymorphic variants, and focusing on genes that have been empirically shown to have physiological significance in neural systems related to social anxiety (Moffitt, Caspi, & Rutter, 2005). In line with research connecting low serotonergic function to poor effortful control and greater willingness to gamble (Carver et al., 2009; Millroth et al., 2017), we predicted that risk genotype carriers would exhibit greater propensity to gamble and poorer reward discrimination. However, we expected that socially anxious individuals demonstrating greater discrimination of reward probability would report higher levels of social risk-taking (i.e., adaptive, effortful risk-approach), and that this association would be strengthened for the non-risk genotype groups, who may benefit from greater top-down control.

2. Methods

2.1. Participants and procedures

The research protocol for this study was approved by the Institutional Review Board of the University of Miami. A sample of 337 young adults participated in partial fulfillment of an undergraduate research requirement. We excluded 28 participants because they did not survive a relatively conservative test of goodness of fit when attempting to estimate parameters from the neuroeconomic task. The final sample consisted of 309 individuals (57.7% female) with a mean age of 19.86 years ($SD = 2.20$). Roughly half of the sample identified their ethnicity as Caucasian (48.9%), with 14.9% identifying as Asian American, 14.2% Hispanic/Latino, 7.1% African American, 3.6% Mixed, 0.3% Native American, 3.2% other, and 7.8% not reporting their ethnicity.

2.2. Sample collection and DNA isolation

Serotonin transporter 5-HTT (LPR; rs25531) gene.—Genetic variants in the *5-HTT* promoter region (LPR; rs25531) were genotyped according to published protocols (Schiele et al., 2016). Genotypes of *5-HTT* LPR (SS, SL, or LL) and the functionally related single nucleotide polymorphism rs25531 (AA, AG, or GG) were grouped as previously described into low expression “risk genotypes” (SS, SL_G, L_GL_G; $n = 84$), high expression “non-risk genotype” (L_AL_A; $n = 59$) and “intermediate genotypes” (SL_A, L_AL_G; $n = 146$; Hu et al., 2006). The distribution of the combined *5-HTT* (LPR; rs25531) genotype was as follows: SS ($n = 69$); SL_G ($n = 14$); SL_A ($n = 133$); L_GL_G ($N = 1$); L_AL_G ($N = 13$); L_AL_A ($N = 59$). Hardy-Weinberg criteria were fulfilled for *5-HTT* (LPR; rs25531) genotype distribution (SS = 69, SL = 146, LL = 73; $p = .91$) as well as for rs25531 genotype distribution (AA = 118, AG = 13, GG = 15.; $p = .13$) using the program DeFinetti provided as an online source (http://ihg.gsf.de/cgi-bin/hw/hwa1.pl; Wienker TF and Strom TM). There were no significant differences by ethnicity for *5-HTT* LPR, $\chi^2(2) = 3.202$, $p = .20$, or rs25531 genotype distribution, $\chi^2(3) = .870$, $p = .83$.

Serotonin receptor 1A (5-HT1A) gene.—All samples were additionally genotyped for *5-HT1A* rs6265 as described previously (Straube et al., 2014) with minor

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modifications. Briefly, genomic DNA was amplified using oligonucleotide primers (F: 5′-AGTTTTGTTCTTCATTTCGAGAT-3′ and R: 5′-GAAGAAGACCGAGTGTGTCTAC-3′). PCR products were digested with TaiI and separated by gel electrophoresis. Fragments were visualized via ethidium bromide staining under ultraviolet light and genotypes were determined by two independent blinded investigators. *5-HT1A* rs6295 genotype distribution was as follows: CC (N = 86); CG (N = 136); GG (N = 73). Genotypes fulfilled the criterion of Hardy–Weinberg equilibrium (p = .20). There were no significant differences by ethnicity for *5-HT1A* rs6265 genotype distribution, $\chi^2(2) = 5.097$, p = .08.

2.3. Experimental task

2.3.1. Task procedure—Participants made 126 incentivized decisions between probabilistic lotteries and sure payoffs (Figure 2). The lottery always offered one potential payoff that was greater than the sure amount (x_1) at probability p, and one that was smaller (x_2) at probability 1-p. Payoff probabilities were indicated via pie charts, with payoff amounts displayed at the top and bottom of the pie chart. Lottery payoff amounts and probabilities varied on every trial: large amounts were displayed at the top and varied between $10 and $50; small amounts were displayed at the bottom and varied between $0 and $20. Probabilities could take on the following values: 5%, 10%, 20%, 50%, 80%, 90%, and 95%, and sure payoffs varied on each trial between $1.25 and $46.25, always falling between the smallest and largest lottery values. Lottery amounts, probabilities and respective sure payouts, as well as the script implementing the choice task in Ztree, are available upon request from the authors.

Subjects were required to pass a quiz querying their understanding of the probabilities and potential earnings, followed by 10 practice trials, prior to beginning the task. To determine additional winnings, one payout-relevant trial was selected at random at the end of the experiment. If the participant chose the lottery on that trial, the outcome was determined by flipping a biased virtual coin reflecting the probabilities of the lottery. If the subject chose the sure payout, the subject simply received the respective amount.

2.3.2. Econometric choice model—Cumulative Prospect Theory (CPT; e.g., Bruhin, Fehr-Duda, & Epper, 2010; Tversky & Kahneman, 1992) was used to estimate subject-specific prospective utilities U(x) of each lottery x with outcomes x_1 and x_2. The lottery in each trial was formalized as:

$$x = (x_1, p_1; x_2, p_2) \tag{1}$$

where p_i is the probability of obtaining outcome x_i, $i \in \{1, 2\}$, and $p_1 + p_2 = 1$. Subject-specific values of the lottery (and the sure amount) were calculated by fitting prospect theory's value function to determine the value $v(x_i)$ for each outcome x_i:

$$v(x_i) = x_i^{\alpha} \tag{2}$$

where α quantifies risk attitude, with risk aversion reflected by $\alpha < 1$, risk neutrality reflected by $\alpha = 1$ and a risk seeking attitude for $\alpha > 1$. All analyses were restricted to the gain domain, as no potential losses were presented. Subject-specific distortions of

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probabilities were estimated by fitting prospect theory's probability weighting function (w(p)) using the two-parameter specification by Lattimore et al. (1992):

$$W(p) = \frac{\delta p^{\gamma}}{\delta p^{\gamma} + (1-p)^{\gamma}} \quad (3)$$

where the γ parameter primarily controls the curvature and the δ parameter primarily controls the elevation of the probability weighting function (Gonzalez & Wu, 1999; Lattimore et al., 1992). The γ parameter can be interpreted as capturing the rationality of gambling choices, with higher values indicating that subjects are better at discriminating reward probabilities. The δ parameter reflects attractiveness of gambling (Gonzalez & Wu, 1999), with higher values reflecting a greater willingness to bet on chance outcomes. Taking into account the value and probability weighting functions, the prospective utility of a gamble, $U(x)$, is defined as

$$U(x) = [w(p_1) \times v(x_1)] + [w(p_2) \times v(x_2)] \quad (4)$$

To determine the probability p of choosing the lottery (LO) over the sure option (SO), we employed a form of the logit probabilistic choice rule that allows for noise in option selection via the free parameter μ.

$$p(LO, SO) = \frac{1}{1 + e^{-\mu(U(LO) - U(SO))}} \quad (5)$$

Parameters were estimated using Maximum Likelihood implemented in *R* via the stats4 package.

2.4. Self-report measures

2.4.1. Social anxiety symptoms—The Social Interaction Anxiety Scale (SIAS; Mattick & Clarke, 1998) is a 20-item measure of SA symptoms. Items are rated on a 5-point Likert scale with responses ranging from 0 ("Not at all characteristic or true of me") to 4 ("Extremely characteristic or true of me"). The SIAS has demonstrated high reliability, as well as strong convergent and discriminant validity (Osman, Gutierrez, Barrios, Kopper, & Chiros, 1998)

2.4.2. Social and financial risk-taking—Willingness to take risks was measured using the Domain-Specific Risk Taking (DOSPERT) scale (Weber, Blais, & Betz, 2002). The DOSPERT contains 40 items about risks across five domains, including ethical, financial, health/safety, recreational, and social risks. Participants rate how likely they would be to engage in each behavior on a five-point Likert-type scale with responses ranging from 1 ("Very unlikely") to 5 ("Very likely"). Because we were interested in distinguishing the relationship of SA symptoms with both social and non-social risk-taking, the social and financial subscales were selected. The financial risk-taking subscale was selected as the non-social risk taking scale because it tapped the same domain as the gambling task.

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2.5. Statistical analyses

Path models were tested using Mplus with maximum likelihood (ML) estimation; all other analyses were conducted using R and RStudio. Data and analysis scripts are available upon request from the authors. After assessing primary study variables for skew and kurtosis, we computed descriptive statistics and examined bivariate correlations (Table 1). Because prior research indicates significant gender differences across risk-taking domains (Charness & Gneezy, 2012), we employed t-tests of gender differences for all primary study variables and included gender as a covariate if it was significantly related to outcome variables of interest. Predictor variables were centered to facilitate interpretation of beta weights in regression models. For all path models, model fit was evaluated using the following criteria: nonsignificant χ^2 test; RMSEA ≤ .06, CFI ≥ .95, and SRMR ≤ .08 (Kline, 2015).

We employed a model building approach to carry out our analyses, starting with specific regression models and integrating additional components using path analysis, which was chosen as a means of testing our integrative theoretical model. The final path model incorporated effects of genotype along with interactions between genetic risk groups, SA, and neuroeconomic parameters on self-reported risk behavior (Kline, 2015). Variables were centered prior to entering interaction terms. We compared the fit of a saturated model, which contained all originally-hypothesized paths, to a trimmed model, which reflected our hypotheses adjusted by results from the regression analyses. To address the question of specificity, we re-ran models substituting a non-social risk-taking subscale (DOSPERT financial) for the DOSPERT social risk-taking subscale. All reported results from regression and path models are standardized coefficients.

3. Results

3.1. Model building

3.1.1. Covariate analysis—Gender was unassociated with gambling task performance, SA symptoms, or genotype, but it related to both forms of self-reported risk taking, Specifically, female participants reported higher social risk-taking than male participants, t (290) = 1.629, p = .008, whereas the converse was true for financial risk-taking, t (289) = −4.887, p < .001. Consequently, gender was included as a covariate for models where risk taking was the outcome variable.

3.1.2. Basic regression models—As part of our model building approach, we conducted several specific regression analyses. First, we assessed the relationship between SA symptoms and the behavioral gambling task parameters by regressing δ, γ, and α on SA symptoms. SA displayed a significant positive association with willingness to bet on chance outcomes (δ), β = .126, 95% CI [.001, .250], p = .049, but no association with γ, β = −.055, 95% CI [−.180, .073], p = .400, or with α, β = .021, 95% CI [−.107, .149], p = .743.

Second, to test relationships of SA symptoms with social and financial risk taking, we regressed self-reported social and financial risk-taking on SA symptoms, controlling for gender. SA symptoms were significantly negatively related to social risk-taking behavior, β

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= −.210, 95% CI [−.320, −.097], $p < .001$, showing no relation to financial risk taking, $\beta =$ .044, 95% CI [−.063, .150], $p = .420$.

3.1.3. Moderation analyses—We next tested moderation models, where genotypes were considered as moderators of the relationship between SA and the task parameters. First, we regressed δ and γ on SA, genotype, and the interaction of these two variables. The *5-HT1A* non-risk (CC) genotype was marginally associated with greater γ, $\beta = .124$, 95% CI [−.019, .267], $p = .088$, and the *5-HTT* (LPR; rs25531) low-expression (i.e., risk) genotype was marginally linked to poorer discrimination of reward probabilities (γ), $\beta =$ −.119, 95% CI [−.257, .019], $p = .093$. There was a significant interaction between genotype and SA on δ, such that among those high in SA symptoms, having the *5-HT1A* non-risk (CC) genotype was associated with lower willingness to bet on chance outcomes (δ), $\beta =$ −.155, 95% CI [−.295, −.015], $p = .030$. Additionally, there was a significant interaction between SA and *5-HTT* (LPR; rs25531) to predict α, such that those high in SA who also had the risk genotype exhibited higher risk-seeking (α), $\beta = .184$, 95% CI [.015, .353], $p =$ .033.

Subsequently, we tested the interactions between SA symptoms, genetics, and the three neuroeconomic task parameters to predict social and financial risk-taking behavior, controlling for gender.[1] In this model, social risk taking was again negatively associated with SA, $\beta = -.173$, 95% CI [−.303, −.043], $p = .010$, and poor discrimination of reward probabilities (i.e., low γ), $\beta = -.183$, 95% CI [−.315, −.051], $p = .007$, with women reporting greater social risk-taking compared to men, $\beta = .143$, 95% CI [.016, .270], $p =$ .028. Moreover, SIAS and γ significantly interacted, such that individuals with high SA who also exhibited high reward probability discrimination (i.e., high γ) reported greater social risk-taking, $\beta = .133$, 95% CI [.002, .264], $p = .049$. In terms of genetic contributions, the *5-HTT* (LPR; rs25531) risk group reported lower social risk-taking, $\beta = -.142$, 95% CI [−.278, −.005], $p = .043$. No interaction effect was found with regard to financial risk taking, nor with the α or δ parameters.

3.2. Path analysis

Turning to the path models combining all aspects of the theoretical hypothesized relationships, we observed good model fit for both the baseline model, χ^2 (29) = 36.716, $p = 0.154$; RMSEA = 0.028, CFI = 0.987, and SRMR = 0.034, and trimmed model, χ^2 (45) = 51.029, $p = .249$; RMSEA = 0.020, CFI = 0.989, and SRMR = 0.039. The chi square difference test between these models suggested that it was appropriate to retain the more parsimonious model, as removing paths did not significantly worsen fit, χ^2_{diff} (16) = 14.313, $p = .575$. In addition, the AIC and BIC values favored the trimmed model ($AIC_{baseline}$ = 20386.622 vs. $AIC_{trimmed}$ = 20368.935; $BIC_{baseline}$ = 20860.089 vs. $BIC_{trimmed}$ = 20780.813).

Results of the final trimmed model suggested tentative evidence for relationships between serotonin genes, SA symptoms, decision-making behavior, and self-reported social risk-

[1]When models were re-run without controlling for gender, there were no changes to the significance of the effects reported.

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taking (see Figure 3). We observed a negative main effect of the *5-HT1A* risk genotype (GG) on SIAS, $\beta = -.144$, 95% CI [−.254, −.033], $p = .011$. As hypothesized, greater SIAS scores were linked with greater willingness to gamble (δ), $\beta = .251$, 95% CI [.116, .387], $p < .001$ (see Figure 4). The *5-HT1A* non-risk genotype (CC) interacted with SIAS scores to predict lower δ, $\beta = -.200$, 95% CI [−.335, −.065], $p = .004$ (see Figure 5). A similar interaction was found for *5-HTT* (LPR; rs25531), SIAS, and α, $\beta = .169$, 95% CI [.027, .312], $p = .020$. Turning to influences on social risk-taking, we found a negative main effect of SIAS, $\beta = -.196$, 95% CI [−.309, −.084], $p = .001$. In addition, there were marginal main effects of γ, $\beta = -.112$, 95% CI [−.232, .008], $p = .066$, and the *5-HTT* (LPR; rs25531) risk genotype, $\beta = -.117$, 95% CI [−.235, .001], $p = .052$, on social risk-taking. SIAS interacted with γ, $\beta = .134$, 95% CI [.012, .225], $p = .031$, such that at lower levels of SA, having low γ was associated with greater social-risk taking. Conversely, high SA individuals who displayed more accuracy in discriminating reward probabilities reported taking more social risks. The overall model explained 13.3 percent of the variance in social risk-taking.

When the model was re-run with financial risk-taking as the outcome, model fit was again strong for the full model, χ^2 (29) = 37.732, $p = 0.128$; RMSEA = 0.029, CFI = 0.984, and SRMR = 0.034, and trimmed model, χ^2 (45) = 50.379, $p = 0.269$; RMSEA = 0.019, CFI = 0.990, and SRMR = 0.039. The chi square difference test between the baseline and trimmed model suggested that it was again appropriate to retain the more parsimonious model, χ^2_{diff} (16) = 12.647, $p = 0.698$. In addition, the AIC and BIC values favored the trimmed model ($AIC_{baseline}$ = 20539.704 vs. $AIC_{trimmed}$ = 20520.351; $BIC_{baseline}$ = 21013.171 vs. $BIC_{trimmed}$ = 20932.229). There were no main effects or moderation effects of SA and genotype on financial risk-taking. However, we observed a marginal main effect of γ on financial risk-taking, $\beta = -0.114$, 95% CI [−.244, .016], $p = .085$, indicating a potential trend between poorer discrimination of reward probabilities and greater self-reported financial risk-taking. The overall model explained 2.2 percent of the variance in financial risk-taking.

4. Discussion

The present study is the first to integrate clinical self-reports, neuroeconomic measures, and genetic assays to elucidate complex patterns of risk-taking related to SA. Results indicated a dissociation between SA symptoms and self-reported compared to actual financial decisions, as well as a moderating influence of choice rationality in the financial domain in attenuating the relationship between SA and social risk-taking. Specifically, while SA symptoms were unrelated to *self-reported* financial risk-taking, they were associated with greater attractiveness of gambling (δ) on a behavioral economic task. In line with prior research supporting social avoidance in SAD (Maner & Schmidt, 2006), SA symptoms were predictive of lower social risk-taking; however, for those displaying highly rational gambling decisions (γ), the relationship between SA and social risk-taking was attenuated. In support of our hypothesis, the *5-HT1A* CC non-risk genotype modulated the influence of SA on gambling attractiveness (δ).

We found that SA was associated with greater gambling propensity for incentivized economic decisions (δ) on the gambling task, but we did not find support for the hypothesized association between SA and poorer discrimination of reward probabilities (γ).

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Our behavioral results converge with previous findings showing domain-specific increases in risky behaviors in relation to SAD symptoms, such as substance use (Buckner et al., 2006) and sexual behaviors (Bodinger et al., 2002), extending these to the domain of monetary decision-making. In prior research examining personality factors that influence risk behavior, Capra et al. (2013) found *lower* gambling propensity (i.e., lower δ) among individuals high in neuroticism and inhibition. Given the relevance of these personality traits to anxiety disorders broadly and SAD in particular (Kashdan, 2002), our finding that SA instead predicted greater risk optimism may reflect the unique role of SA-related risk behaviors in the context of affective symptoms. Conversely, our results did not support the notion that individuals with higher levels of SA might exhibit poorer discrimination of potential reward values. On the one hand, this is surprising, in that finding this association would have been in line with the notion that SA symptoms may relate to impulsive decision-making (Keough et al., 2016). On the other hand, it may be that these decision-making patterns emerge only in the context of disorder-relevant threat cues (e.g., exposure to a social situation).

As previously noted, results suggested distinct associations of SA with self-reported and behavioral measures of financial willingness to take risks. In considering differential results for behavioral measures and self-reports of financial risk-taking, it is possible that behavior on the gambling task commonly used in neuroeconomics does not map onto self-perceived financial risk-taking behavior in the real world. More concretely, the divergence noted may be due to the fact that the DOSPERT financial subscale items reflect more planned behaviors about investing in risky stock options, as opposed to the split-second, reactive choices that are made in the gambling task. Differences according to reactive versus planned risk-taking behavior would be in line with two-mode models of self-regulation (e.g., Carver et al., 2008), and with the notion that risk-taking in SA reflects a bottom-up, reflexive response to negative emotion (Keough et al., 2016). Alternatively, the differential association of SA with the gambling task and financial risk-taking on the DOSPERT could reflect additional evidence in line with a larger literature indicating discrepancies in self-reported and experimental measures of risk preferences (Mata, Frey, Richter, Schupp, & Hertwig, 2018). Researchers have theorized that one reason for these differences may be that gambling tasks could be measuring cognitive abilities more so than risk preferences (Hertwig, Wulff, & Mata, 2018). While future studies will clarify this discrepancy, the dissociation between self-reported and behaviorally measured financial risk-taking underscores the importance of employing experimental tasks to elucidate patterns of risk-taking in conjunction with SA symptoms.

While our hypothesis of a relationship between SA and financial risk-taking was only partially supported, our results indicated a dissociation of risk behavior across risk-taking domains in relation to SA symptoms. Whereas SA symptoms were positively related to gambling propensity and negatively-related to self-reported social risk-taking, the absence of an association between SA and self-reported financial risk-taking supports the notion of a more domain-specific view of risk-taking in relation to specific experiences and clinical symptoms (c.f., Hanoch, Johnson, & Wilke, 2006), rather than a global notion of risk-taking across domains. Supporting this concept, one study similarly reported that individuals with clinical levels of SA had no significant differences in self-reported risk-taking on the

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DOSPERT financial subscale (Lorian & Grisham, 2011). On the other hand, the findings regarding social risk avoidance adhere nicely to cognitive–behavioral models of anxiety (Maner & Schmidt, 2006), which underscore reactive avoidance of feared situations as a maintaining factor. Notably, however, rationality of gambling decisions (γ) tempered the relationship between SA and social risk-taking, such that individuals with high SA who displayed more accurate reward probability estimates reported taking average levels of social risks, performing more similarly to those without high levels of SA. This pattern of results could reflect an adaptive tendency to approach feared situations or an ability to judge risks with greater accuracy, which may facilitate engagement in effortful social behaviors.

Results of our moderation analyses indicated tentative support for conceptualizing *5-HT1A* as a driver of bottom-up risk-taking in relation to SA symptoms. While low serotonergic activity and reduced *5-HT1A* receptor binding have been related to SA symptoms in isolation (Lanzenberger et al., 2007), this is the first study to consider genetic influences on experimentally measured risk-taking in SA. While we did not find a direct association between *5-HT1A* and irrational gambling, we did observe an interaction effect such that the association between SA and irrational gambling decisions was weaker in *5-HT1A* non-risk allele carriers. Prior research has indicated that the G allele of the *5-HT1A* −1019C/G promoter polymorphism (rs6295) may depress 5-HT1A autoreceptor expression by disrupting an inhibitory transcription factor binding (Lemonde et al., 2003). This may reduce serotonergic neurotransmission, a deficit that empirical research links with poor response selection (Beste, Domschke, Falkenstein, & Konrad, 2010), inhibition (Beste, Domschke, Radenz, Falkenstein, & Konrad, 2011), and performance monitoring (Beste, Domschke, Kolev, et al., 2010), and that has been associated with depression and suicide completion (Lemonde et al., 2003). In the context of these previous studies, our results may reflect the notion that reduced serotonergic function influences diminished effortful control, which would contribute to individuals high in SA relying on bottom-up, reactive processes resulting in maladaptive risk behaviors. In addition, we found that the *5-HTT* (LPR; rs25531) low expression (i.e., risk) genotype group reported marginally higher social risk-taking behavior, and that this risk genotype interacted with SIAS to predict lower risk aversion on the gambling task (i.e., high α). Our findings linking the *5-HTT* (LPR; rs25531) $SS/SL_G/L_GL_G$ group with behavioral risk-taking would dovetail with prior research linking rs25531 to self-reported impulsivity (Carver & Miller, 2006; Cools et al., 2008). However, the lack of a direct association of *5-HTT* (LPR; rs25531) to SA symptoms, specifically, suggests that the tentative contribution of serotonergic function to effortful decision-making may serve as a non-specific risk factor.

4.1. Limitations

Results of this study should be considered in light of its strengths and limitations, pointing to avenues for future research. While a strength of this study involved the use of both behavioral and self-report measures of financial risk-taking, we lacked a behavioral measure of social risk-taking. Future studies should extend this paradigm to include experimental tests of social risk, such as the Trust Game (Berg, Dickhaut, & McCabe, 1995), as well as tests that elicit social or performance pressure, such as the Trier Social Stress Test (Kirschbaum, Pirke, & Hellhammer, 1993). Moreover, the gambling task employed in the

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present study measured risk aversion, but continued research on this topic may consider differential relationships of social anxiety symptoms with risk and loss aversion using mixed gambles. Given the robust literature linking intolerance of uncertainty to SA symptoms (Boelen & Reijntjes, 2009), it will be important to utilize behavioral tasks assessing risk preferences under conditions of ambiguity to further elucidate these risk-taking patterns. In interpreting our findings, it is important to reflect on our use of a candidate gene approach, a technique that has received criticism for having low replicability (e.g., Okbay & Rietveld, 2015), potentially stemming from false positives (Border et al., 2019). In an attempt to protect against these issues, the experiment outlined in our manuscript reflects the careful selection of variables (behavioral tasks, clinical symptoms, and genetic factors) to test our theoretical model in line with recommendations for candidate gene studies (Moffitt et al., 2005). However, it will be important for future studies to attempt to replicate these findings. More broadly, by combining genetic assays, decision-making task behavior, and biological or psychophysiological evidence, future studies may elucidate patterns of risk-taking in SA across levels of analysis. The use of imaging genetics has yielded insights into the role of *5-HT1A* in panic disorder (Domschke et al., 2006) and has strong potential to contribute to models of anxiety disorders more broadly (Domschke & Dannlowski, 2010). These techniques may aid in further dissecting the relationship between SA and financial risk behavior across forms of measurement.

4.2. Conclusions

This study expands on relationships between SA and risk-taking as measured behaviorally and through self-report measures, as well as the unique and synergistic influence of serotoninergic genes on risk behavior and SA, to contribute to models of SA symptom risk and maintenance. Results indicated that individuals high in SA symptoms exhibit greater willingness to gamble, which was not reflected in self-reports of financial risk-taking. Moreover, greater serotonergic activity conferred by the *5-HT1A* non-risk genotype (CC), which attenuated the impaired decision-making relating to SA in our sample, may represent a protective factor with regard to risk-taking behavior in SA, perhaps as it relates to a greater effortful control capacity to drive top-down processing. Further clarification of the roles of serotonin genes on risk-taking, particularly in the context of neuroimaging and psychophysiological measurements, may inform conceptual models of risk-taking in SA, and ultimately, improve early identification of social anxiety disorder.

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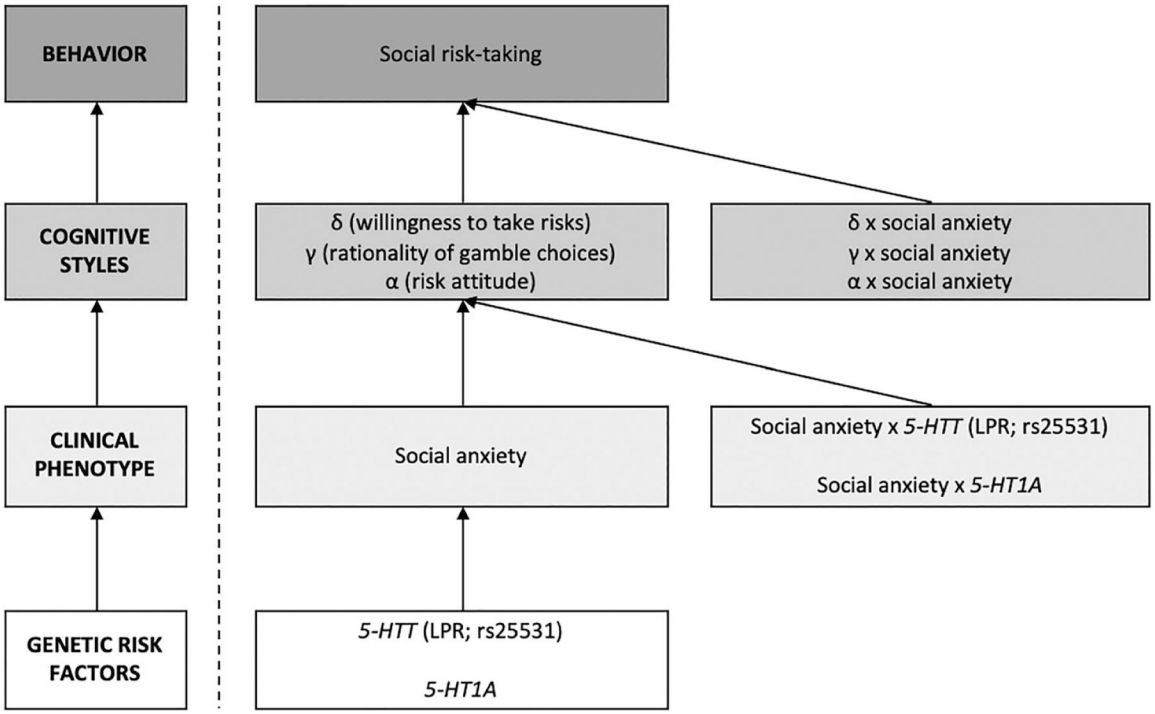

Figure 1.

Theoretical model of genetic factors, clinical symptoms, cognition, and behavior to be tested. Genetic, clinical, and cognitive risk factors are theorized to influence social risk-taking behavior. Genetic risk factors are thought to serve as distal contributing factors that influence and interact with clinical SA symptoms. SA symptoms, in turn, are thought to influence and interact with cognitive styles to predict social risk-taking behavior.

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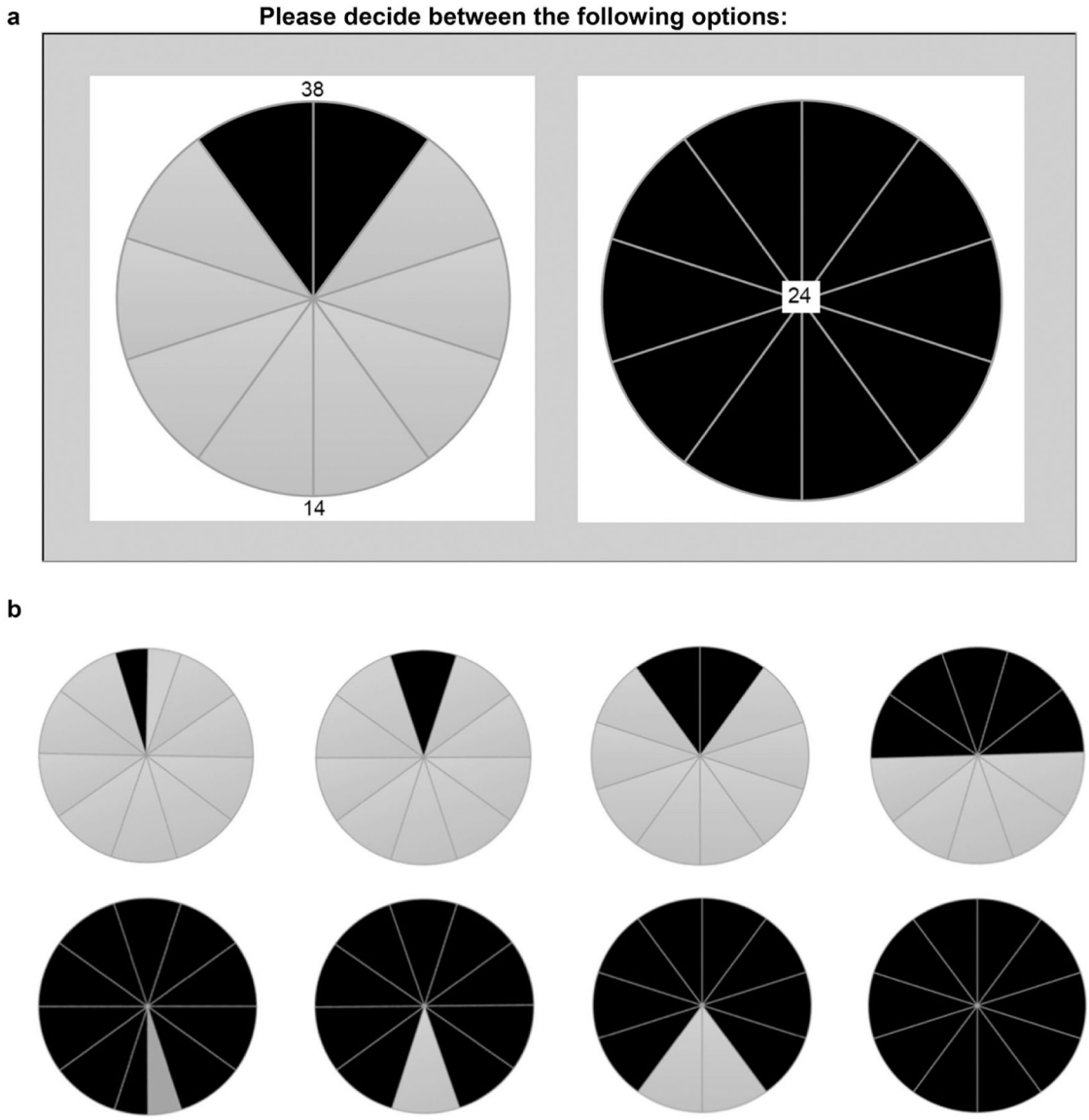

Figure 2.

Sample trial **(a)** and pie charts used across trials **(b)** in the risky decision-making task. The sample trial **(a)** displays a choice between a gamble and a fixed amount. The gamble option (left) involves a 20% probability of receiving $38 or an 80% probability of receiving $14. The fixed amount (right) involves a 100% chance of receiving $24. The pie charts **(b)** indicate the different relative probabilities represented across the trials presented during the decision-making task.

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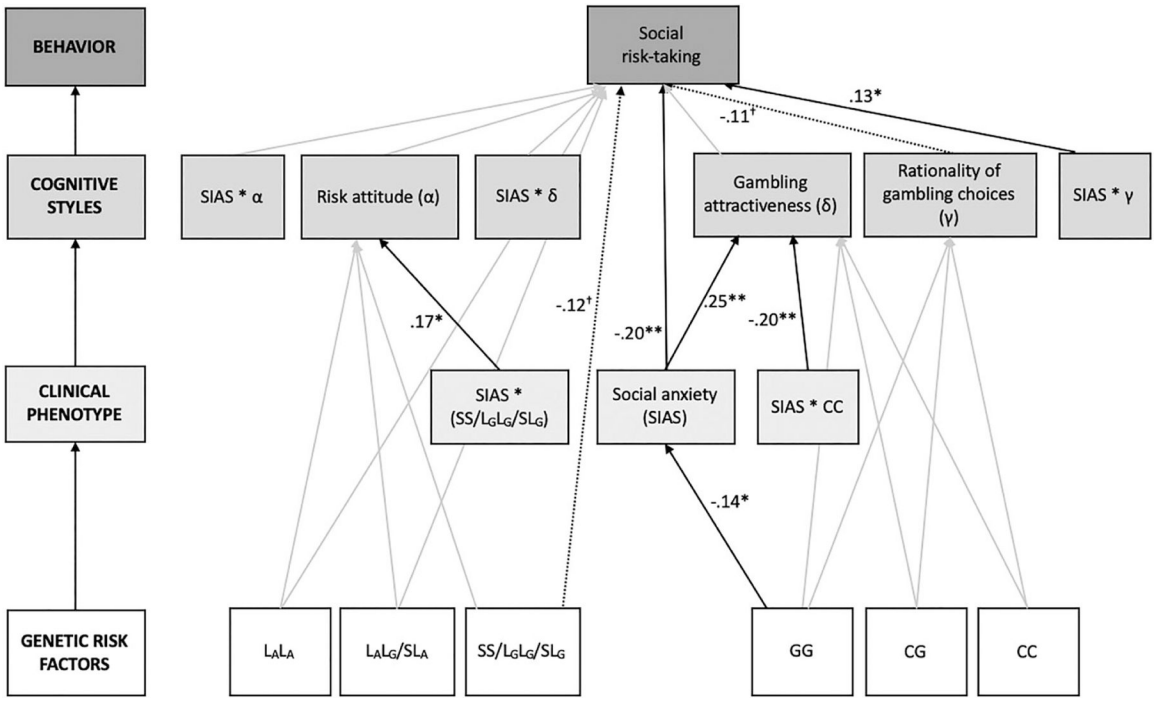

Figure 3.

Path diagram testing theoretical model of genetic risk factors, clinical phenotype, cognitive styles, and social risk-taking. SIAS, Social Anxiety Interaction Scale; DOSPERT_s, Domain Specific Risk Taking Scale – Social; δ, gambling attractiveness; γ, rationality of reward probability discrimination; $L_AL_A/(L_AL_G/SL_A)/(SS/L_GL_G/SL_G)$, Serotonin transporter gene 5-HTT (LPR; rs25531) genotypes; GG/CG/CC, serotonin receptor 1A gene (5-HT1A; HTR1A) rs6295 genotypes. Significance values are represented as $^{**}p < .01$, $^{*}p < .05$, $^{\dagger}p < .10$, and non-significant paths are depicted in grey.

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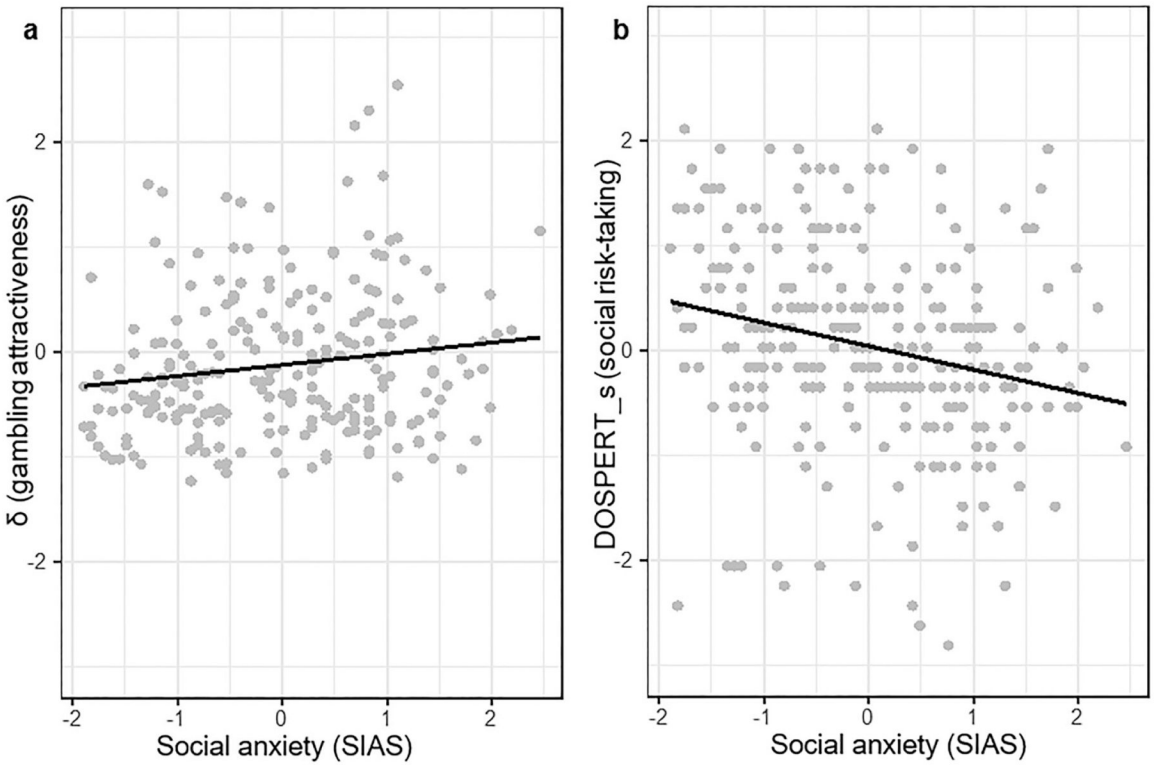

Figure 4.

Dissociation of relationships of social anxiety with incentivized gambling **(a)** and self-reported social risk taking **(b)**. SIAS, Social Anxiety Interaction Scale; DOSPERT_s, Domain Specific Risk Taking Scale – Social; *δ*, gambling attractiveness. In **(a)**, social anxiety symptoms exhibited a significant positive relationship with propensity to gamble *δ* on the neuroeconomic task. In **(b)**, social anxiety symptoms were negatively related to self-reported social risk-taking behavior.

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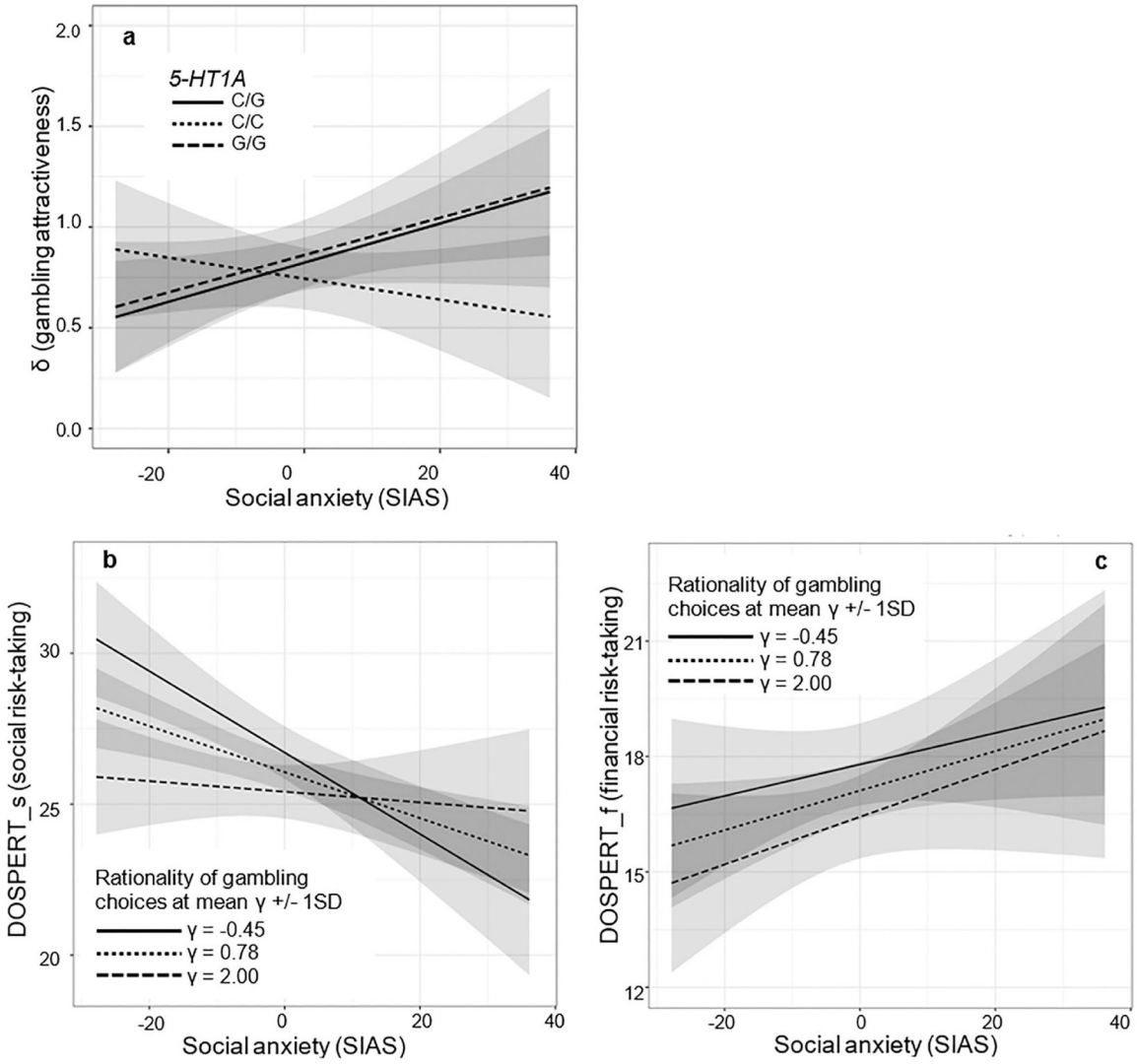

Figure 5.

Moderation hypotheses for gambling attractiveness **(a)**, social risk-taking **(b)** and financial risk-taking **(c)**, with *5-HT1A* as the moderator in **(a)** and γ as the moderator in **(b)** and **(c)**. Moderator values are presented for the mean and 1 standard deviation above and below the mean. Shaded areas indicated 95% confidence intervals for each simple slope. **(a)** depicts the moderation effect whereby social anxiety (SIAS) is overall positively related with propensity to bet on chance outcomes (δ), but this effect is attenuated for individuals with the non-risk (C/C) genotype of 5-HT1A. **(b)** displays the interaction effect of gambling choice rationality (γ) and SIAS on self-reported social risk-taking (DOSPERT_s): while social anxiety predicts lower social risk-taking, individuals who are better able to discriminate reward probabilities are less likely to have social risk-taking behavior influenced by social anxiety. **(c)** displays the non-significant interaction effect of gambling choice rationality (γ) and SIAS on self-reported financial risk-taking (DOSPERT_f).

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Table 1.

Descriptive statistics and zero-order correlations among primary study variables.

Variables	1. SIAS	2. DOSPERT_s	3. DOSPERT_f	4. δ	5. γ	Mean (SD)
1. SIAS	–					27.83 (14.72)
2. DOSPERT_s	−.22**	–				25.83 (5.27)
3. DOSPERT_f	.08	.17**	–			16.93 (6.26)
4. δ	.13*	−.09	.01	–		1.30 (0.68)
5. γ	−.05	−.14*	−.13*	.11†	–	0.61 (0.42)

Notes: SIAS = Social Anxiety Interaction Scale; DOSPERT_s = Domain Specific Risk Taking Scale – Social; DOSPERT_f = Domain Specific Risk Taking Scale – Financial; δ = gambling attractiveness; γ = rationality of reward probability discrimination.

** $p < .01$,

* $p < .05$,

† $p < .10$.