Neuropsychologia 48 (2010) 3926–3933

Contents lists available at ScienceDirect

Neuropsychologia

journal homepage: www.elsevier.com/locate/neuropsychologia

Cognitive and emotional processing associated with the Season of Birth and dopamine D4 receptor gene

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ARTICLE INFO

Article history:
Received 2 June 2010
Received in revised form
14 September 2010
Accepted 17 September 2010
Available online 25 September 2010

Keywords:
Decision making
Season of Birth
Dopamine D4 receptor
Iowa Gambling Task
Novelty seeking

ABSTRACT

The 7-repeats variant of the dopamine D4 receptor (7R) VNTR polymorphism has been associated with higher novelty seeking (NS) and disadvantageous decision making in the Iowa Gambling Task (IGT). Season of Birth (SOB) is a significant determinant of NS. SOB and L-DRD4 genetic polymorphism may independently and interactively influence similar behaviors through their common effects on the dopaminergic system. Two hundred and twenty-seven healthy males grouped in summer-born/4-repeats (4R) ($n=75$), winter-born/4R ($n=90$), summer-born/7R ($n=31$) and winter-born/7R ($n=31$) groups, completed multimodal assessment for personality, planning for problem solving and decision making. Winter-born/7R subjects had significantly worse IGT performance throughout the task compared to 4R individuals, while summer-born 7R subjects had intermediate, although not significantly different performance. Moreover, winter-born/7R subjects had increased behavioral approach to reward without parallel reduction in sensitivity to fear or to social approval cues. The DRD4-by-SOB groups did not differ in planning for problem solving. These results suggest that a DRD4-by-SOB interaction is associated with increased behavioral approach to reward and risk taking but efficient problem solving. In addition, these results further support the hypothesis that SOB modifies the behavioral expression of dopaminergic genetic polymorphism. SOB should be included in future studies of risky behaviors and behavioral genetic studies of the dopamine system.

1. Introduction

The role of genetic and environmental factors and their interaction in the onset and course of psychiatric disorders, has become the focus of intense research efforts in recent years. Season of Birth (SOB) is an environmental factor associated with increased risk for mental illnesses as diverse as eating disorders (Jongbloet, Groenewoud, & Roeleveld, 2005), suicide (Chotai & Renberg, 2002; Chotai, Renberg, & Jacobsson, 1999; Rock, Greenberg, & Hallmayer, 2006; Salib & Cortina-Borja, 2006), schizophrenia (Davies, Welham, Chant, Torrey, & McGrath, 2003; Tochigi, Okazaki, Kato, & Sasaki, 2004), autism (Bolton, Pickles, Harrington, Macdonald, & Rutter, 1992), panic disorder (Castrogiovanni, Iapichino, Pacchierotti, & Pieraccini, 1999) and the personality trait of novelty seeking (NS) (Chotai, Forsgren, Nilsson, & Adolfsson, 2001; Chotai, Jonasson, Hagglof, & Adolfsson, 2002; Chotai, Lundberg, & Adolfsson, 2003). NS refers to a heritable tendency to respond strongly to novelty and cues for reward or relief from punishment, which leads to exploratory activity in pursuit of rewards as well as active avoidance of monotony and punishment (Cloninger, Svrakic, & Pszybeck, 1993). NS is in itself a risk factor for several psychiatric disorders characterized by dysregulated affect and responses to reward including bipolar disorder (Haro et al., 2007; Nery et al., 2008), ADHD (Downey, Pomerleau, & Pomerleau, 1996; Faraone, Kunwar, Adamson, & Biederman, 2009), substance abuse (Acton, 2003; Howard, Kivlahan, & Walker, 1997), addictions and pathological gambling (Forbush et al., 2008; Hollander & Wong, 1995; Kim & Grant, 2001; Shin, Lim, Choi, Kim, & Grant, 2009).

The dopamine D4 receptor (DRD4) is highly distributed in prefrontal and limbic regions such as the amygdala and hippocampus (Meador-Woodruff et al., 1996) and may be important in affective and reward-related behaviors. In Caucasians, the seven repeats (7R) allele of the DRD4 Variable Number Tandem Repeat (VNTR) polymorphism codes for a less efficient gene at the levels of both transcription and translation as well as second messenger generation (Ebstein, 2006). *In vivo* human studies show that it is indeed associated with a less responsive DRD4 (Brody et al., 2006; Hamarman, Fossella, Ulger, Brimacombe, & Dermody, 2004; Hutchison et al., 2003, 2006; McGough et al., 2006). The 7R DRD4 variant is associated with high NS (Benjamin et al., 1996; Ebstein et al., 1996) and increases the risk for the same group of disorders (Comings et al., 1999; Kotler et al., 1997; Lopez Leon et al., 2005;

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doi:10.1016/j.neuropsychologia.2010.09.021

Serretti & Mandelli, 2008; Swanson et al., 2007), suggesting that at least part of the risk conferred by the 7R DRD4 for this group of disorders, is mediated via a 7R DRD4-related increase in NS.

However, the biological basis of NS is not completely understood (Oak, Oldenhof, & Van Tol, 2000), while the evidence for association of the 7R DRD4 variant to high NS is inconsistent (Paterson, Sunohara, & Kennedy, 1999; Savitz & Ramesar, 2004) with meta-analyses not supporting a strong relationship (Munafo, Yalcin, Willis-Owen, & Flint, 2008). One reason for the above may be that NS is in itself a relatively complex phenotype, currently measured by "noise"-prone self reports. We recently demonstrated in healthy males that the 7R allele was associated with high NS and, risky decision making but normal planning and cognitive problem solving ability. We also found reduced physiological startle reactivity and reduced startle modulation by pleasant and aversive affective stimuli, but preserved attentional processing of such stimuli. We concluded that healthy male subjects with the 7R allele present with dysregulation of emotional and reward processes but otherwise apparently intact attention and executive cognition (Roussos, Giakoumaki, & Bitsios, 2009). Such attempts to better operationalise NS associated with the 7R DRD4 VNTR polymorphism, may lead to a better understanding of this personality trait and its association with DRD4, both of which are evidently important risk factors for disorders characterized by impulsivity and affect/reward dysregulation.

Here we conducted a multimodal personality assessment including, besides NS, investigation of sensitivity to punishment/nonreward and approach behaviors in response to reward, and we tested our subjects for their decision-making and planning for problem solving. We then investigated for a possible impact of a genetic (DRD4 VNTR 48 bp polymorphism) by environmental (SOB) interaction on the phenotypic variation. Based on the existing literature, we predicted that compared to four repeats (4R) individuals, winter-born 7R carriers would exhibit higher levels of NS and approach to reward, reduced proclivity to experience anxiety in response to punishment and frustrative nonreward, riskier and potentially maladaptive decision making, but intact cognitive problem solving, while summer-born 7R individuals would be intermediate.

2. Materials and methods

2.1. Subjects

The study has been approved by the Ethics Committee of the University of Crete and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Two hundred and eighty-six unrelated, right-handed Greek/Caucasian healthy males aged 18–35 years were recruited from the pooled volunteer list of the University staff and students. We restricted the sample to men to avoid additional, gender-related variability in the gambling task (Bolla, Eldreth, Matochik, & Cadet, 2004; Overman et al., 2004; Reavis & Overman, 2001). Exclusion criteria were personal history of head trauma, medical and neurological conditions, use of prescribed and recreational drugs and personal or family history of DSM-IV axis I disorders. Following written informed consent, all subjects underwent IQ testing with the Raven's progressive matrices, psychiatric assessment using the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998) and physical assessment including urine toxicology. Family history of psychiatric disorders was assessed using the Family Interview for Genetic Studies (Maxwell, 1992), supplemented by medical notes as necessary. Eleven subjects were excluded because of a psychiatric condition and/or a family history of psychiatric illness and 23 had a positive drug screen. Two hundred and fifty-two subjects (mean age ± SD, 26.0 ± 4.5) entered and completed the study. All subjects were of South-East European ancestry based on self-reported ancestry and further confirmed by STRUCTURE (Pritchard, Stephens, & Donnelly, 2000) analysis used 58 ancestry informative unlinked markers selected for maximal informativeness; none of the subjects deviated from a single population, which makes genetic inhomogeneity of the tested population unlikely.

2.2. Genotyping

Blood DNA was extracted using the Flexigene DNA kit (Qiagen, Valencia, CA). DRD4 exon III genotypes were determined with polymerase chain reaction, as described elsewhere (Roussos et al., 2009).

2.3. Personality Questionnaires

All subjects were administered the Temperament and Character Inventory (TCI), which evaluates NS, and three more personality dimensions of temperament – harm avoidance (HA), reward dependence (RD) and persistence (P). HA is defined as a heritable tendency to respond intensely to signals of aversive stimuli, leading to learned inhibition of behavior to avoid punishment and novelty. RD is defined as a heritable tendency to respond strongly to rewards, particularly social approval, and to maintain behaviors previously associated with reward or relief of punishment. P is a measure of resilience and perseverance despite frustration and fatigue. These temperament factors are hypothesized to be based on distinct neurochemical and genetic substrates (Cloninger et al., 1993) with heritabilities ranging between 50% and 65% (Heath, Cloninger, & Martin, 1994; Stallings, Hewitt, Cloninger, Heath, & Eaves, 1996).

Additionally, all participants completed the Carver and White BIS/BAS scales (Carver & White, 1994), which are based on Gray's behavioral inhibition and behavioral activation systems (Gray, 1973). The BIS is sensitive to signals of punishment and nonreward, as well as novel stimuli and innate fear stimuli. Engagement of the BIS leads to inhibition of behavior, as well as increased arousal and vigilance, and is related to the subjective state of anxiety. Thus, individual differences in the BIS are related to the proclivity to experience anxiety in response to cues for punishment and frustrative nonreward (Carver & White, 1994), as well as traits such as neuroticism and negative affectivity (Heubeck, Wilkinson, & Cologon, 1998; Jorm et al., 1999).

The BAS is thought to facilitate approach behavior in response to signals of reward and nonpunishment (see also Depue & Iacono, 1989; Fowles, 1988). Activation of the BAS is associated with the experience of positive affect, and individual variation in the BAS predicts approach-related behavior and positive emotion in response to reward cues (Carver & White, 1994). BAS is positively correlated with trait positive affectivity and extraversion (Heubeck et al., 1998; Jorm et al., 1999). The BIS/BAS questionnaire has a 7-item BIS and a 13-item BAS scale (Carver & White, 1994), on which respondents indicate the extent to which they agree (i.e. strongly agree, agree, disagree, strongly disagree) with each item. The BAS scale is made up of three subscales: drive (D) (four items, e.g., "When I want something, I usually go all out to get it."), fun-seeking (FS) (four items, e.g., "I will often do things for no other reason than that they might be fun."), and reward responsiveness (RR) (five items, e.g., "When I get something I want, I feel excited and energized.").

2.4. Cognitive assessment

Stockings of Cambridge (*SoC*) (Owen, Downes, Sahakian, Polkey, & Robbins, 1990): Subjects were asked to rearrange in the minimum possible number of moves, "balls" presented in "socks" in the lower half of the screen such that their positions match a target arrangement in the upper half. The test presents the subject with easy 2- and 3-move and harder 4- and 5-move problems. Subjects are asked to plan the complete sequence of moves required to solve the problem prior to their first move. Initial thinking time (ITT) prior to execution of the first move, subsequent thinking time (STT) for the execution of all subsequent moves, and problems solved in minimum moves (MM) are recorded. Poor performance in this test translates into shorter ITT (less time planning), and/or longer STT (more time executing the solution) with less perfect solutions.

Iowa Gambling Task (*IGT*) (Bechara, Damasio, Damasio, & Anderson, 1994; Bechara, Damasio, & Damasio, 2000): Choices in this simulated gambling task are made under conditions of uncertainty. This type of decision-making is motivated by reward, punishment and the uncertainty of outcomes and has been regarded as a type of emotional decision-making (Bechara et al., 1994; Pecchinenda, Dretsch, & Chapman, 2006). Its premises lie in the "somatic marker" hypothesis (Damasio, 1996) which proposes that the body states evoked by the experience of reward or punishment signal the potential occurrence of an outcome, and these emotional signals guide behavior and help bias the choices made in the gambling task, in a manner that is advantageous to the organism in the long-term (Bechara et al., 2000). Participants were instructed to select one card at a time from four decks (A, B, C, D) displayed on the screen in order to win "pretend" money. Unknown to the subjects, decks A and B were associated with high monetary rewards but also high penalties (monetary loses) while decks C and D had lower rewards but also lower penalties. The win or loss associated with the selection of a card appeared visually on the screen. Across 100 trials, more choices from the decks C and D lead to a net gain while choosing from the other two decks resulted in greater loss. Dividing card selections into 5 blocks of 20 allowed us to determine the rate of learning over the course of the task. Scores were (a) total numbers of cards selected from advantageous decks C and D minus total numbers of cards selected from "risky" decks A and B, with a higher score indicating superior performance (b) total money won.

3. Statistical analysis

Data analysis was performed using the statistical software SPSS 17 (SPSS Inc., Chicago, IL). With the exception of NS, BIS and total BAS scores, all other personality and all cognitive and demographic

variables did not follow a normal distribution and log transformation failed to normalize the data. Therefore, one-way ANOVAs (for NS, BIS and total BAS) or the non-parametric Mann–Whitney test were used to examine the effects of genotype group (4R vs. 7R) on demographic, cognitive and personality variables. The χ^2-test was used for the dichotomus variable of smoking status. The same procedures were used to examine the effects of SOB [summer borns (April to September) vs. winter borns (October to March)] on demographic, cognitive and personality variables.

Following these initial analyses, the subjects were divided according to their SOB and DRD4 genotype status into 4 groups (4R summer borns, 4R winter borns, 7R summer borns and 7R winter borns), in preparation for examination of a DRD4 by SOB interaction on phenotypic variance. One-way ANOVAs (NS, BIS and total BAS) or the non-parametric Kruskal–Wallis test were used to examine demographic, personality or cognitive performance differences between the four groups. More detailed analyses of the IGT and SoC data included 2×5 (group-by-block) and 2×4 (group-by-difficulty level) ANOVAs, respectively. The Greenhouse–Geisser correction was used for variables with more than 2 degrees of freedom (i.e. block or level of difficulty for the IGT and SoC data, respectively). The epsilon correction with uncorrected degrees of freedom and corrected p values are reported in this case. Effect sizes (partial η^2 from the ANOVAs) are reported for significant results.

In order to limit the risk for Type II error, we avoided Bonferroni correction of our significance criterion for multiple testing, because these corrections are too conservative and unsuitable for personality traits and cognitive variables, which cannot be assumed to be independent (Bland, 2000; Perneger, 1998). In order to limit the risk for Type I error we set the significance criterion at $p < 0.01$.

Table 1
DRD4 VNTR allele frequencies, genotypes and genotype classifications.

Allele/Genotype	*n*	%
Allele		
2	58	11.5
3	16	3.2
4	347	68.8
5	8	1.6
6	5	1.0
7	70	13.9
Total	504	100.0
Genotype		
2/2 (excluded)	12	4.7
2/3 (excluded)	5	2.0
2/4	29	11.5
3/4	11	4.3
4/4	122	48.5
4/5	5	2.0
4/6 (excluded)	5	2.0
4/7	53	21.0
5/7	3	1.2
7/7	7	2.8
Total	252	100.0
Genotype classification[a]		
4R	167	72.6
7R	63	27.4
Total	230	100.0

[a] 7R subjects have at least one allele 7 repeats (in bold) and 4R subjects have at least one allele 4 repeats and both alleles equal or shorter than 5 repeats (in italics). Individuals with 2/2, 2/3 and 4/6 repeats genotypes were excluded from the study due to inconsistencies in the literature regarding the classification to either the 4R or the 7R group.

4. Results

Subjects were classified as 7R ($n = 63$) if they had at least one allele 7 repeats and 4R ($n = 167$) if they had at least one allele 4 repeats and both alleles equal or shorter than 5 repeats (Table 1). Individuals with 2/2, 2/3 and 4/6 repeats genotypes were excluded from the study due to inconsistencies in the literature regarding the classification to either the 4R or the 7R group. The DRD4 genotypic distribution was consistent with the Hardy–Weinberg expectations ($\chi^2 = 0.73$, df = 1, $p = 0.4$). Three subjects failed to complete all phenotypic assessment, and therefore we present data from 227 subjects. All our subjects were born in Greece, which locates in the northern hemisphere (latitude 35–41). There were no separate genotype or SOB group effects on demographic variables. Table 2 shows the demographic characteristics of the 4 groups and their comparison.

Personality assessment: The initial ANOVAs revealed no effect of SOB (all $p > 0.3$), but significant effects of genotype on personality traits; compared to the 4R, the 7R group showed significantly higher (mean ± SD) BAS RR (7R: 13.98 ± 3.9, 4R: 12.2 ± 3.8; $p < 0.005$) and FS (7R: 10.3 ± 2.3, 4R: 9.55 ± 2.55; $p < 0.008$) and TCI NS (7R: 10.8 ± 3.4, 4R: 9.5 ± 3.6; $p < 0.04$) although the latter did not reach the $p < 0.01$ significance criterion.

Table 3 shows the group mean scores (±SD) for each personality trait for the winter born 4R and 7R and the summer born 4R and 7R groups. The ANOVAs revealed significant group effects in the case of total BAS score, and RR, D and FS subscale scores, although only the total BAS and the RR scores met the $p < 0.01$ significance criterion (Table 4). The results which met the significance criterion were followed up with individual Mann–Whitney comparisons with the level of significance corrected for the six possible between-group post hoc comparisons (0.05/6 = 0.008). These post hoc tests revealed no significant differences among the summer born 7R and the two 4R groups (all $p > 0.3$), but significantly higher total BAS and RR scores for the winter born 7R group compared to both 4R (both $p < 0.001$) or the summer born 7R group ($p < 0.01$). Evidently however, the latter comparison just fell short of significance at the corrected p value ($p < 0.008$).

4.1. Cognitive testing

The initial ANOVAs examining the effects of SOB or genotype on SoC and IGT performance revealed only a significant effect of the DRD4 genotype on IGT performance (all other $p > 0.1$); compared to the 4R, the 7R group showed worse IGT performance in terms of money won (7R: 1392.5 ± 1294.3, 4R: 1766.9 ± 1237.6;

Table 2
Demographic characteristics (mean ± SD) for the winter born 4R and 7R and the summer born 4R and 7R groups.

	Summer born/4R ($n = 75$)	Winter born/4R ($n = 90$)	Summer born/7R ($n = 31$)	Winter born/4R ($n = 31$)	Kruskal–Wallis X^2	p-Value
Age	26.4 (3.7)	26.1 (4.7)	25.4 (4.4)	26.7 (5.3)	2.8	>0.4
Education	17.6 (2.8)	16.6 (2.7)	16.9 (2.5)	17.0 (2.5)	3.1	>0.3
Estimated IQ	107.1 (2.9)	102.9 (2.8)	104.8 (2.6)	105.4 (2.6)	1.5	>0.7
Smokers/Non-smokers[a]	37/38	39/51	16/15	13/18	1.56	>0.6
Cigarettes/Day	18.8 (7.3)	15.4 (7.7)	20.4 (10.0)	21.2 (11.9)	6.5	>0.09

[a] Chi square comparison.

Table 3
Group mean scores (SD) for each personality trait obtained by the BIS/BAS and the TCI questionnaires, for the winter born 4R and 7R and the summer born 4R and 7R groups. Significance was set at $p < 0.01$.

	Summer born/4R ($n = 75$)	Winter born/4R ($n = 90$)	Summer born/7R ($n = 31$)	Winter born/7R ($n = 31$)	Kruskal–Wallis χ^2 or ANOVA F	p-Value
BIS/BAS						
BIS[a]	16.3 (3.2)	17.3 (3.5)	17.8 (3.8)	17.5 (4.1)	1.7	>0.17
Total BAS[a]	32.7 (7.6)	31.0 (7.4)	31.9 (8.6)	37.6 (4.5)	5.4	<0.001*
RR	12.4 (3.8)	11.9 (3.9)	12.8 (4.5)	15.4 (2.5)	16.1	<0.001*
FS	9.8 (2.5)	9.3 (2.5)	9.7 (2.2)	11 (1.9)	9.3	<0.025
D	10.2 (2.6)	9.7 (2.6)	9.9 (2.4)	11.2 (1.7)	8.7	<0.034
TCI						
NS[a]	9.7 (3.3)	9.3 (3.6)	10.6 (3.6)	10.8 (3.4)	1.5	>0.2
HA	8 (4.9)	8.2 (4.4)	8 (4.3)	7.2 (4.6)	0.9	>0.8
RD	9 (2.7)	8.9 (2.5)	8.6 (3.2)	8.4 (2.5)	1.0	>0.8
P	2.3 (1.6)	2.4 (1.4)	1.7 (1.5)	2.4 (1.5)	5.2	>0.16

[a] For this measure, the parametric one-way ANOVA was used; BIS/BAS: Behavioral Inhibition/Behavioral Activation System; TCI: Temperament and Character Inventory; RR: Reward Responsiveness; FS: Fun Seeking; D: Drive; NS: Novelty Seeking; HA: Harm Avoidance; RD: Reward Dependence; P: Persistence.
* $p < 0.001$.

Table 4
Group mean scores (SD) for each SoC and IGT performance variable, for the winter born 4R and 7R and the summer born 4R and 7R groups. Significance was set at $p < 0.01$.

	Summer born/4R ($n = 75$)	Winter born/4R ($n = 90$)	Summer born/7R ($n = 31$)	Winter born/4R ($n = 31$)	Kruskal–Wallis χ^2	p-Value
SoC						
Mean ITT (ms)	8610.7 (6270)	7274.7 (3977.3)	7913.2 (3817.9)	7386.1 (3767.9)	0.9	>0.8
Mean STT (ms)	733.4 (700.5)	629.5 (715.1)	912.8 (919.4)	975.4 (1938)	4.3	>0.2
Mean moves	3.98 (0.45)	3.94 (0.39)	3.98 (0.43)	3.90 (0.43)	1.3	>0.7
Problems solved correctly	9.72 (1.76)	9.90 (1.76)	9.73 (1.64)	10.0 (1.92)	1.5	>0.6
IGT						
Total CD-AB score	19.4 (28.1)	19.6 (25.5)	18.0 (28.0)	−1.1 (17.1)	16.7	<0.001*
Total money won	1726.7 (1329.2)	1765.9 (1121.7)	1754.9 (1393.8)	922.2 (884.1)	13.3	<0.004*

SoC: Stockings of Cambridge; IGT: Iowa Gambling Task; ITT: initial thinking time; STT: subsequent thinking time.
* $p < 0.005$.

Mann–Whitney U: 4131; $p < 0.02$) or total number of picks from advantageous C and D minus total picks from risky A and B decks [CD-AB score (mean ± SD): 7R: 9.4 ± 25.9, 4R: 19.8 ± 26.8; Mann–Whitney U: 3964.5; $p < 0.006$]. The genotype groups were almost identical in SoC performance.

Table 4 shows the group mean scores (±SD) for each SoC and IGT variable for the four SOB by DRD4 groups. The Kruskal–Wallis ANOVAs revealed significant group effects in the case of IGT but not the SoC (Table 4). Post hoc Mann–Whitney comparisons of the IGT data, revealed no significant differences among the summer born 7R and the two 4R groups for any IGT variable (all $p > 0.5$). However, the winter born 7R group had greater CD-AB score suggesting of more picks from the risky decks compared to all other groups (all $p < 0.004$). Moreover, the winter born 7R group won less money compared to both 4R groups ($p < 0.005$) or the summer born 7R group ($p < 0.01$) although the latter comparison failed to reach criterion ($p < 0.008$).

Fig. 1 shows the progressive switch toward more advantageous choices in the IGT in the four groups. A repeated measures ANOVA with block (5 levels) as the within- and group (4 levels) as the between-subject factor revealed significant main effects of group [$F(3,223) = 5.6$, $p < 0.001$; $\eta^2 = 0.07$] and block [$F(4,892) = 51.6$, $p < 0.001$; Greenhouse-Geisser epsilon = 0.864; $\eta^2 = 0.189$] and a significant interaction [$F(12,892) = 2.52$, $p < 0.005$, $\eta^2 = 0.033$]. Post hoc comparisons with the Least Significant Difference test revealed that the winter born 7R individuals selected more cards from the "risky" decks A and B compared to all other groups [winter born 4R ($p < 0.001$), summer born 4R ($p < 0.001$) and summer born 7R ($p < 0.006$)]. No significant differences were revealed amongst the other three groups. Inclusion of smoking status as a between-subject factor showed no main effect of smoking or interactions involving smoking status (all p values >0.1). Furthermore, these results were not altered when IQ was taken as a covariate. Similar 4 × 4 (group × difficulty level) ANOVAs for ITT, STT and MM of the SoC, revealed the expected significant main effect of difficulty level [ITT: $F(3,660) = 95.2$, $p < 0.0001$; STT: $F(3,660) = 19.3$, $p < 0.0001$; MM: $F(3,660) = 1272.2$, $p < 0.0001$] but not group main effects [ITT: $F(3,220) = 1.1$, $p > 0.4$; STT: $F(3,220) = 1.3$, $p > 0.3$; MM: $F(3,220) < 1$] or interactions [ITT: $F(9,660) = 1.7$, $p > 0.1$; STT: $F(9,660) = 1.5$, $p > 0.2$; MM: $F(9,660) < 1$].

5. Discussion

We found as predicted, that the 7R allele of the DRD4 VNTR increases NS and worsens performance in the IGT but not in the

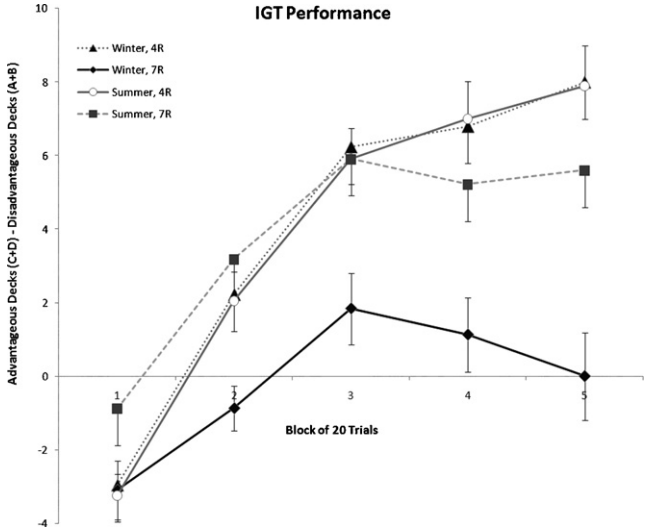

Fig. 1. Number of cards selected from advantageous decks C and D minus the number of cards selected from the "risky" decks A and B (CD – AB) per block of 20 trials, for the four SOB × DRD4 groups in the IGT test. Bars represent SEM.

SoC task replicating our previous findings. It appears that the 7R allele affects planning when the latter depends on emotional processing of incentive information for decision making, but it spares planning for cognitive problem solving (Roussos et al., 2009). We also found as predicted that winter-born 7R subjects had worse IGT performance throughout the task compared to 4R individuals, while summer-born 7R subjects had intermediate performance in the last, exploitation phase of the task, although this was based on visual inspection of the data and did not reach statistical significance (Fig. 1). There were no effects of SOB alone on any of our outcome measures. This is first evidence for a gene (DRD4) by environment (SOB) interaction in decision making. As predicted, the DRD4-by-SOB groups did not differ in planning for problem solving.

In agreement with previous results (Benjamin et al., 1996; Ebstein et al., 1996; Roussos et al., 2009) NS was higher in 7R subjects although this was an effect of marginal significance and given the inconsistencies in the literature, we can only speculate at the moment, that the relationship of NS to the VNTR DRD4 polymorphism is not robust and other factors may also moderate it. Contrary to prediction, NS was not increased in winter-born 7R individuals. The concept of NS taps both on behavioral approach to reward as well as insensitivity to fear, and it appears that only the former component is modified by the SOB × DRD4 interaction. Indeed our healthy winter-born 7R subjects had a specific increase in behavioral approach to reward (BAS score) without parallel reduction in sensitivity to fear (BIS and HA scores) or to social approval cues (RD score). Alternatively, the BAS score may be more sensitive to the effects of this gene by environment interaction or less prone to the "desirable response" bias compared to BIS, HA and RD scores. Clearly, these results need replication but based on the above we can tentatively suggest that the DRD4 by SOB interaction does not affect the entire NS construct as it is measured by the TCI questionnaire; however, it does affect subcomponents of this personality trait, i.e. it increases risky decision making and behavioral approach to rewards. More research is required before safe conclusions can be drawn, not in the least because the observed dissociation of the effects of the DRD4 × SOB interaction on IGT performance and questionnaire data may be due to the influence of other genes and environmental factors.

Importantly, our findings were obtained from a homogeneous cohort of healthy male subjects and cannot be attributed to differences in demographic characteristics or genetic inhomogeneity, since the groups did not differ in that respect. All subjects were South-East European and ancestry was confirmed by typing a panel of informative SNPs. Furthermore, exposure to the specific environmental factor under study did not vary between subjects since they were all born within restricted latitude. The results presented here resonate with previously published studies that have documented SOB interactions with the expression of dopamine system genetic polymorphisms, including SOB by DRD4 interactive effects on psychiatric disorders (Chotai, Serretti, Lattuada, Lorenzi, & Lilli, 2003; Seeger, Schloss, Schmidt, Ruter-Jungfleisch, & Henn, 2004), Body Mass Index in women with seasonal affective disorder (Levitan et al., 2006), novelty seeking (Eisenberg et al., 2007b) and self-reported impulsivity (Eisenberg, Campbell, Mackillop, Lum, & Wilson, 2007a) in healthy individuals. Decision-making is disturbed in psychiatric disorders such as drug addiction, schizophrenia, and obsessive-compulsive disorder (Brand, Labudda, & Markowitsch, 2006). It is therefore conceivable that exploring genetic factors affecting decision-making in healthy subjects could be an approach to identify risk factors for developing psychiatric disorders.

The dopamine system, including the DRD4, has been highly implicated in the process of reward and decision-making based on emotional feedback (Haber & Knutson, 2010; Roussos et al., 2009). The DRD4 is expressed on both postsynaptic striatal neurons and presynaptic corticostriatal excitatory glutamatergic afferents (Jaber, Robinson, Missale, & Caron, 1996; Missale, Nash, Robinson, Jaber, & Caron, 1998; Tarazi, Campbell, Yeghiayan, & Baldessarini, 1998). Based on this localization pattern, the DRD4 can exert both direct and indirect inhibitory effects on striatal neurons. This inhibitory effect would be expected to be diminished in the 7R individuals, as the 7R allele results in a less efficient DRD4 (Ebstein, 2006). Thus, decreased inhibition of striatal neurons through either direct or indirect effects of the DRD4 7R allele, may be associated with increased ventral reactivity which will affect the preference for immediate over delayed reward. Indeed, a recent fMRI study using a delay discounting task revealed higher reward-related ventral striatum reactivity in healthy 7R individuals (Forbes et al., 2009).

Season of Birth on the other hand, and more specifically being born in winter months may be associated with dysregulated central DA neurotransmission as evidenced by indirect observations of the levels of peripheral DA metabolites (Chotai & Adolfsson, 2002; Chotai & Åsberg, 1999; Chotai, Murphy, & Constantino, 2006). There is certainly solid evidence for an excess of winter-births among psychiatric disorders such as schizophrenia (Davies et al., 2003; McGrath & Welham, 1999; Torrey, Miller, Rawlings, & Yolken, 2000) and bipolar disorder (Dalen, 1975; Hare & Price, 1968; Torrey, Rawlings, Ennis, Merrill, & Flores, 1996) where dysregulation of central DA neurotransmission is considered to be important to their pathophysiology.

Although the exact biological mechanism of the SOB by DRD4 interaction is not well understood, one possible explanation includes influence of daylight variation during gestation or perinatally on the circadian and seasonal rhythms through dopamine-melatonin dysregulation which interferes with dopamine release (Chotai & Adolfsson, 2002; Chotai & Åsberg, 1999; Joinson & Nettle, 2005; Natale, Adan, & Chotai, 2002). The cyclic rhythm of secretion of the pineal hormone melatonin is entrained by the length of daylight exposure, and alters the timing of mammalian circadian rhythms (Brzezinski, 1997). More specifically, melatonin production is highest during the night and lowest during the day (Reppert & Weaver, 1995). Maternal melatonin can pass via the placenta to the fetus and entrain the fetus' circadian rhythms (Goldman, 2003). Therefore, for winter month pregnancies, lower maternal daylight exposure would lead to increased melatonin production in pregnant mothers which can pass via the placenta to the fetus. Additionally, melatonin is known to inhibit dopamine release in numerous brain regions such as the hypothalamus, hippocampus, medulla/pons, retina and the striatum (Zisapel, 2001). Of those, the striatum, due to its prominent role in reward related processes may be a priority candidate for speculation on the convergence of melatonin and dopamine interactions relevant to our findings. Taking all the above into account, we propose here that higher maternal/fetal melatonin would inhibit dopamine release in the striatum which would result in reduced stimulation of the inhibitory D4 receptor resulting in greater ventral striatum reactivity during processing of reward stimuli; this effect could be conceivably more exacerbated in 7R allele carriers who already have an inefficient DRD4. Although this explanation is highly speculative, we believe that it makes best use of the available evidence.

An alternative, not mutually exclusive mechanism underlying our findings may be related to prenatal levels of vitamin D, a secosteroid hormone, produced photochemically in the epidermis, its levels decreasing in winter months and with higher latitude (Webb, Kline, & Holick, 1988). Vitamin D deficiency in pregnancy, even if it is restricted to late gestation only (O'Loan et al., 2007), alters brain development in rodent models (Eyles, Brown, Mackay-Sim, McGrath, & Feron, 2003; Feron et al., 2005; O'Loan et al., 2007), and it is considered a risk factor for adverse neuropsychiatric outcomes (Fernandes de Abreu, Eyles, & Feron, 2009; McGrath, 1999).

Recent evidence points to alterations in dopamine turnover during development (Kesby et al., 2009) and changes in the striatum (McGrath et al., 2008), where dopamine is known to modulate a range of limbic and cortical functions relevant to the pathophysiology of several neuropsychiatric disorders (Grace, Floresco, Goto, & Lodge, 2007; Joseph, Datla, & Young, 2003; Lauer, Senitz, & Beckmann, 2001; Schlaepfer et al., 2008). The above taken together would predict that dopaminergic/striatal or other neurodevelopmental aberrations due to maternal vitamin D deficiencies in the winter born subjects should result in measurable behavioral differences compared to summer borns. However, we observed a notable absence of SOB effects on any outcome measure in our sample. We tentatively suggest that this could be partially attributed to the counteracting effects of the presumably higher photic levels as a result of the low latitude of Greece, where our sample originated from. Indeed, vitamin D levels in the population also depend on latitude, decreasing with higher and increasing with lower latitude (Webb et al., 1988). To explain our findings we postulate an interaction between the less efficient 7R DRD4 receptor and vitamin D-related changes in the striatum and alteration in the ontogeny of the dopaminergic system in winter-born subjects. However, this remains a phenomenological study, and the exact relationship of DRD4 to SOB cannot be decided. Moreover, given the limited sample size as well as the factorial nature of our statistical models, our results must be considered preliminary. Future research ought to examine DA release in the striatum in subjects stratified for SOB and DRD4 status and the possible interactions of SOB, melatonin, vitamin D and the dopaminergic system.

In conclusion, we report here for the first time a gene by environment interaction on emotional decision making which does not seem to be attributable to differences in executive function or common confounders; this should be taken into account in future genetic association and genetic imaging studies examining the role of the DRD4 VNTR polymorphism in human behavior, personality and brain function in health and disease.

Acknowledgments

This project was supported by the University of Crete Research Funds Account (ELKE 1348). PR was supported by a 'Manasaki' scholarship and SGG was supported by a 'Propondis Foundation' postdoctorate fellowship.

References

Acton, G. S. (2003). Measurement of impulsivity in a hierarchical model of personality traits: Implications for substance use. *Substance Use & Misuse*, *38*, 67–83.
Bechara, A., Damasio, H., & Damasio, A. R. (2000). Emotion, decision making and the orbitofrontal cortex. *Cerebral Cortex*, *10*, 295–307.
Bechara, A., Damasio, A. R., Damasio, H., & Anderson, S. W. (1994). Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition*, *50*, 7–15.
Benjamin, J., Li, L., Patterson, C., Greenberg, B. D., Murphy, D. L., & Hamer, D. H. (1996). Population and familial association between the D4 dopamine receptor gene and measures of Novelty Seeking. *Nature Genetics*, *12*, 81–84.
Bland, M. (2000). *Multiple significance tests and the Bonferroni correction. An introduction to medical statistics*. Oxford: Oxford University Press.
Bolla, K. I., Eldreth, D. A., Matochik, J. A., & Cadet, J. L. (2004). Sex-related differences in a gambling task and its neurological correlates. *Cerebral Cortex*, *14*, 1226–1232.
Bolton, P., Pickles, A., Harrington, R., Macdonald, H., & Rutter, M. (1992). Season of birth-issues, approaches and findings for autism. *Journal of Child Psychology and Psychiatry*, *33*, 509–530.
Brand, M., Labudda, K., & Markowitsch, H. J. (2006). Neuropsychological correlates of decision-making in ambiguous and risky situations. *Neural Networks*, *19*, 1266–1276.
Brody, A. L., Mandelkern, M. A., Olmstead, R. E., Scheibal, D., Hahn, E., Shiraga, S., et al. (2006). Gene variants of brain dopamine pathways and smoking-induced dopamine release in the ventral caudate/nucleus accumbens. *Archives of General Psychiatry*, *63*, 808–816.
Brzezinski, A. (1997). Melatonin in humans. *New England Journal of Medicine*, *336*, 186–195.
Carver, C. S., & White, T. L. (1994). Behavioral inhibition, behavioral activation, and affective responses to impending reward and punishment: The BIS/BAS scales. *Journal of Personality and Social Psychology*, *67*, 319–333.
Castrogiovanni, P, Iapichino, S., Pacchierotti, C., & Pieraccini, F. (1999). Season of birth in panic disorder. *Neuropsychobiology*, *40*, 177–182.
Chotai, J., & Adolfsson, R. (2002). Converging evidence suggests that monoamine neurotransmitter turnover in human adults is associated with their season of birth. *European Archives of Psychiatry and Clinical Neuroscience*, *252*, 130–134.
Chotai, J., & Åsberg, M. (1999). Variations in CSF monoamine metabolites according to the season of birth. *Neuropsychobiology*, *39*, 57–62.
Chotai, J., Forsgren, T., Nilsson, L. G., & Adolfsson, R. (2001). Season of birth variations in the temperament and character inventory of personality in a general population. *Neuropsychobiology*, *44*, 19–26.
Chotai, J., Jonasson, M., Hagglof, B., & Adolfsson, R. (2002). The Temperament Scale of Novelty Seeking in adolescents shows an association with season of birth opposite to that in adults. *Psychiatry Research*, *111*, 45–54.
Chotai, J., Lundberg, M., & Adolfsson, R. (2003). Variations in personality traits among adolescents and adults according to their season of birth in the general population: Further evidence. *Personality and Individual Differences*, *35*, 897–908.
Chotai, J., Murphy, D. L., & Constantino, J. N. (2006). Cerebrospinal fluid monoamine metabolite levels in human newborn infants born in winter differ from those born in summer. *Psychiatry Research*, *145*, 189–197.
Chotai, J., & Renberg, E. S. (2002). Season of birth variations in suicide methods in relation to any history of psychiatric contacts support an independent suicidality trait. *Journal of Affective Disorders*, *69*, 69–81.
Chotai, J., Renberg, E. S., & Jacobsson, L. (1999). Season of birth associated with the age and method of suicide. *Archives of Suicide Research*, *5*, 245–254.
Chotai, J., Serretti, A., Lattuada, E., Lorenzi, C., & Lilli, R. (2003). Gene-environment interaction in psychiatric disorders as indicated by season of birth variations in tryptophan hydroxylase (TPH), serotonin transporter (5-HTTLPR) and dopamine receptor (DRD4) gene polymorphisms. *Psychiatry Research*, *119*, 99–111.
Cloninger, C. R., Svrakic, D. M., & Pszybeck, T. R. (1993). A psychobiological model of temperament and character. *Archives of General Psychiatry*, *50*, 975–990.
Comings, D. E., Gonzalez, N., Wu, S., Gade, R., Muhleman, D., Saucier, G., et al. (1999). Studies of the 48 bp repeat polymorphism of the DRD4 gene in impulsive, compulsive, addictive behaviors: Tourette syndrome, ADHD, pathological gambling, and substance abuse. *American Journal of Medical Genetics*, *88*, 358–368.
Dalen, P. (1975). *Season of birth: A study of schizophrenia and other mental disorders*. North Holland, Amsterdam: Elsevier.
Damasio, A. R. (1996). The somatic marker hypothesis and the possible functions of the prefrontal cortex. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, *351*, 1413–1420.
Davies, G., Welham, J., Chant, D., Torrey, E. F., & McGrath, J. (2003). A systematic review and meta-analysis of Northern Hemisphere season of birth studies in schizophrenia. *Schizophrenia Bulletin*, *29*, 587–593.
Depue, R. A., & Iacono, W. G. (1989). Neurobehavioral aspects of affective disorders. *Annual Review of Psychology*, *40*, 457–492.
Downey, K. K., Pomerleau, C. S., & Pomerleau, O. F. (1996). Personality differences related to smoking and adult attention deficit hyperactivity disorder. *Journal of Substance Abuse*, *8*, 129–135.
Ebstein, R. P. (2006). The molecular genetic architecture of human personality: Beyond self-report questionnaires. *Molecular Psychiatry*, *11*, 427–445.
Ebstein, R. P., Novick, O., Umansky, R., Priel, B., Osher, Y., Blaine, D., et al. (1996). Dopamine D4 receptor (D4DR) exon III polymorphism associated with the human personality trait of Novelty Seeking. *Nature Genetics*, *12*, 78–80.
Eisenberg, D. T. A., MacKillop, J., Modi, M., Beauchemin, J., Dang, D., Lisman, S. A., et al. (2007). Examining impulsivity as an endophenotype using a behavioral approach: A DRD2 TaqI A and DRD4 48-bp VNTR association study. *Behavioral and Brain Functions*, *3*, 2.
Eisenberg, D. T., Campbell, B., Mackillop, J., Lum, J. K., & Wilson, D. S. (2007). Season of birth and dopamine receptor gene associations with impulsivity, sensation seeking and reproductive behaviors. *PLoS One*, *2*, e1216.
Eyles, D., Brown, J., Mackay-Sim, A., McGrath, J., & Feron, F. (2003). Vitamin D3 and brain development. *Neuroscience*, *118*, 641–653.
Faraone, S. V., Kunwar, A., Adamson, J., & Biederman, J. (2009). Personality traits among ADHD adults: Implications of late-onset and subthreshold diagnoses. *Psychological Medicine*, *39*, 685–693.
Feron, F., Burne, T. H., Brown, J., Smith, E., McGrath, J. J., Mackay-Sim, A., et al. (2005). Developmental Vitamin D3 deficiency alters the adult rat brain. *Brain Research Bulletin*, *65*, 141–148.
Fernandes de Abreu, D. A., Eyles, D., & Feron, F. (2009). Vitamin D, a neuro-immunomodulator: Implications for neurodegenerative and autoimmune diseases. *Psychoneuroendocrinology*, *34S*, S265–S277.
Forbes, E. E., Brown, S. M., Kimak, M., Ferrell, R. E., Manuck, S. B., & Hariri, A. R. (2009). Genetic variation in components of dopamine neurotransmission impacts ventral striatal reactivity associated with impulsivity. *Molecular Psychiatry*, *14*, 60–70.
Forbush, K. T., Shaw, M., Graeber, M. A., Hovick, L., Meyer, V. J., Moser, D. J., et al. (2008). Neuropsychological characteristics and personality traits in pathological gambling. *CNS Spectrums*, *13*, 306–315.
Fowles, D. C. (1988). Psychophysiology and psychopathology: A motivational approach. *Psychophysiology*, *25*, 373–391.
Goldman, B. D. (2003). Pattern of melatonin secretion mediates transfer of photoperiod information from mother to fetus in mammals. *Sciences STKE*, *192*, PE29.

Grace, A. A., Floresco, S. B., Goto, Y., & Lodge, D. J. (2007). Regulation of firing of dopaminergic neurons and control of goal-directed behaviors. *Trends in Neurosciences*, *30*, 220–227.
Gray, J. A. (1973). Causal theories of personality and how to test them. In J. R. Royce (Ed.), *Multivariate analysis and psychological theory*. New York: Academic Press.
Haber, S. N., & Knutson, B. (2010). The reward circuit: Linking primate anatomy and human imaging. *Neuropsychopharmacology*, *35*, 4–26.
Hamarman, S., Fossella, J., Ulger, C., Brimacombe, M., & Dermody, J. (2004). Dopamine receptor 4 (DRD4) 7-repeat allele predicts methylphenidate dose response in children with attention deficit hyperactivity disorder: A pharmacogenetic study. *Journal of Child and Adolescent Psychopharmacology*, *14*, 564–574.
Hare, E. H., & Price, J. S. (1968). Mental disorder and season of birth: Comparison of psychoses with neurosis. *British Journal of Psychiatry*, *115*, 533–540.
Haro, G., Calíbrese, J. R., Larsson, C., Shirley, E. R., Martín, E., Leal, C., et al. (2007). The relationship of personality traits to substance abuse in patients with bipolar disorder. *European Psychiatry*, *22*, 305–308.
Heath, A. C., Cloninger, C. R., & Martin, N. G. (1994). Testing a model for the genetic structure of personality: A comparison of the personality systems of Cloninger and Eysenck. *Journal of Personality and Social Psychology*, *66*, 762–775.
Heubeck, B., Wilkinson, R., & Cologon, J. (1998). A second look at Carver and White's (1994) BIS/BAS scales. *Personality and Individual Differences*, *25*, 785–800.
Hollander, E., & Wong, C. M. (1995). Body dysmorphic disorder, pathological gambling, and sexual compulsions. *Journal of Clinical Psychiatry*, *56*(Suppl.), 7–12.
Howard, M. O., Kivlahan, D., & Walker, R. D. (1997). Cloninger's tridimensional theory of personality and psychopathology: Applications to substance use disorders. *Journal of Studies on Alcohol*, *58*, 48–66.
Hutchison, K. E., Ray, L., Sandman, E., Rutter, M. C., Peters, A., Davidson, D., et al. (2006). The effect of olanzapine on craving and alcohol consumption. *Neuropsychopharmacology*, *31*, 1310–1317.
Hutchison, K. E., Wooden, A., Swift, R. M., Smolen, A., McGeary, J., Adler, L., et al. (2003). Olanzapine reduces craving for alcohol: A DRD4 VNTR polymorphism by pharmacotherapy interaction. *Neuropsychopharmacology*, *28*, 1882–1888.
Jaber, M., Robinson, S. W., Missale, C., & Caron, M. G. (1996). Dopamine receptors and brain function. *Neuropharmacology*, *35*, 1503–1519.
Joinson, C., & Nettle, D. (2005). Season of birth variation in sensation seeking in an adult population. *Personality and Individual Differences*, *38*, 859–870.
Jongbloet, P. H., Groenewoud, H. M. M., & Roeleveld, N. (2005). Seasonally bound ovopathy versus "temperature at conception" as cause for anorexia nervosa and other eating disorders. *The International Journal of Eating Disorders*, *38*, 236–243.
Jorm, A. F., Rodgers, B., Jacomb, P. A., Christensen, H., Henderson, S., & Korten, A. E. (1999). Smoking and mental health: Results from a community survey. *Medical Journal of Austria*, *18*, 74–77.
Joseph, M. H., Datla, K., & Young, A. M. (2003). The interpretation of the measurement of nucleus accumbens dopamine by in vivo dialysis: The kick, the craving or the cognition? *Neuroscience and Biobehavioral Reviews*, *27*, 527–541.
Kesby, J. P., Cui, X., Ko, P., McGrath, J. J., Burne, T. H. J., & Eyles, D. W. (2009). Developmental vitamin D deficiency alters dopamine turnover in neonatal rat forebrain. *Neuroscience Letters*, *461*, 155–158.
Kim, S. W., & Grant, J. E. (2001). Personality dimensions in pathological gambling disorder and obsessive-compulsive disorder. *Psychiatry Research*, *104*, 205–212.
Kotler, M., Cohen, H., Segman, R., Gritsenko, I., Nemanov, L., Lerer, B., et al. (1997). Excess dopamine D4 receptor (D4DR) exon III seven repeat allele in opioid-dependent subjects. *Molecular Psychiatry*, *2*, 413–416.
Lauer, M., Senitz, D., & Beckmann, H. (2001). Increased volume of the nucleus accumbens in schizophrenia. *Journal of Neural Transmission*, *108*, 645–660.
Levitan, R. D., Masellis, M., Lam, R. W., Kaplan, A. S., Davis, C., Tharmalingam, S., et al. (2006). A birth-season/DRD4 gene interaction predicts weight gain and obesity in women with seasonal affective disorder: A seasonal thrifty phenotype hypothesis. *Neuropsychopharmacology*, *31*, 2498–24503.
Lopez Leon, S., Croes, E. A., Sayed-Tabatabaei, F. A., Claes, S., Van Broeckhoven, C., & van Duijn, C. M. (2005). The dopamine D4 receptor gene 48-base-pair-repeat polymorphism and mood disorders: A meta-analysis. *Biological Psychiatry*, *57*, 999–1003.
Maxwell, M. E. (1992). *Manual for the FIGS*. Bethesda, MD: National Institute of Mental Health.
McGough, J., McCracken, J., Swanson, J., Riddle, M., Kollins, S., Greenhill, L., et al. (2006). Pharmacogenetics of methylphenidate response in preschoolers with ADHD. *Journal of the American Academy of Child and Adolescent Psychiatry*, *45*, 1314–1322.
McGrath, J. (1999). Hypothesis: Is low prenatal vitamin D a risk-modifying factor for schizophrenia? *Schizophrenia Research*, *40*, 173–177.
McGrath, J., Iwazaki, T., Eyles, D., Burne, T., Cui, X., Ko, P., et al. (2008). Protein expression in the nucleus accumbens of rats exposed to developmental vitamin D deficiency. *PLoS ONE*, *3*, e2383.
McGrath, J. J., & Welham, J. L. (1999). Season of birth and schizophrenia: A systematic review and meta-analysis of data from the Southern Hemisphere. *Schizophrenia Research*, *35*, 237–242.
Missale, C., Nash, S. R., Robinson, S. W., Jaber, M., & Caron, M. J. (1998). Dopamine receptors: From structure to function. *Physiological Reviews*, *78*, 189–225.
Meador-Woodruff, J. H., Damask, S. P., Wang, J., Haroutunian, V., Davis, K. L., & Watson, S. J. (1996). Dopamine receptor mRNA expression in human striatum and neocortex. *Neuropsychopharmacology*, *15*, 17–29.
Munafo, M. R., Yalcin, B., Willis-Owen, S. A., & Flint, J. (2008). Association of the dopamine D4 receptor (DRD4) gene and approach-related personality traits: Meta-analysis and new data. *Biological Psychiatry*, *63*, 197–206.
Natale, V., Adan, A., & Chotai, J. (2002). Further results on the association between morningness-eveningness preference and the season of birth in human adults. *Neuropsychobiology*, *46*, 209–214.
Nery, F. G., Hatch, J. P., Glahn, D. C., Nicoletti, M. A., Monkul, E. S., Najt, P., et al. (2008). Temperament and character traits in patients with bipolar disorder and associations with comorbid alcoholism or anxiety disorders. *Journal of Psychiatric Research*, *42*, 569–577.
Oak, J. N., Oldenhof, J., & Van Tol, H. H. (2000). The dopamine D(4) receptor: One decade of research. *European Journal of Pharmacology*, *405*, 303–327.
O'Loan, J., Eyles, D. W., Kesby, J., Ko, P., McGrath, J. J., & Burne, T. H. J. (2007). Vitamin D deficiency during various stages of pregnancy in the rat; its impact on development and behaviour in adult offspring. *Psychoneuroendocrinology*, *32*, 227–234.
Overman, W. H., Frassrand, K., Ansel, S., Trawalter, S., Bies, B., & Redmond, A. (2004). Performance on the IOWA card task by adolescents and adults. *Neuropsychologia*, *42*, 1838–1851.
Owen, A. M., Downes, J. J., Sahakian, B. J., Polkey, C. E., & Robbins, T. W. (1990). Planning and spatial working memory following frontal lobe lesions in man. *Neuropsychologia*, *28*, 1021–1034.
Paterson, A. D., Sunohara, G. A., & Kennedy, J. L. (1999). Dopamine D4 receptor gene: Novelty or nonsense? *Neuropsychopharmacology*, *21*, 3–16.
Pecchinenda, A., Dretsch, M., & Chapman, P. (2006). Working memory involvement in emotion-based processes underlying choosing advantageously. *Experimental Psychology*, *53*, 191–197.
Perneger, T. V. (1998). What's wrong with Bonferroni adjustments. *BMJ*, *316*, 1236–1238.
Pritchard, J. K., Stephens, M., & Donnelly, P. (2000). Inference of population structure using multilocus genotype data. *Genetics*, *155*, 945–959.
Reavis, R., & Overman, W. H. (2001). Adult sex differences on a decision-making task previously shown to depend on the orbital prefrontal cortex. *Behavioral Neuroscience*, *115*, 196–206.
Reppert, S. M., & Weaver, D. R. (1995). Melatonin madness. *Cell*, *83*, 1059–1062.
Rock, D., Greenberg, D., & Hallmayer, J. (2006). Season-of-birth as a risk factor for the seasonality of suicidal behaviour. *European Archives of Psychiatry and Clinical Neuroscience*, *256*, 98–105.
Roussos, P., Giakoumaki, S. G., & Bitsios, P. (2009). Cognitive and emotional processing in high novelty seeking associated with the L-DRD4 genotype. *Neuropsychologia*, *47*, 1654–1659.
Salib, E., & Cortina-Borja, M. (2006). Effect of month of birth on the risk of suicide. *British Journal of Psychiatry*, *188*, 416–422.
Savitz, J. B., & Ramesar, R. S. (2004). Genetic variants implicated in personality: A review of the more promising candidates. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics*, *131*, 20–32.
Schlaepfer, T. E., Cohen, M. X., Frick, C., Kosel, M., Brodesser, D., Axmacher, N., et al. (2008). Deep brain stimulation to reward circuitry alleviates anhedonia in refractory major depression. *Neuropsychopharmacology*, *33*, 368–377.
Seeger, G., Schloss, P., Schmidt, M. H., Ruter-Jungfleisch, A., & Henn, F. A. (2004). Gene-environment interaction in hyperkinetic conduct disorder (HD+CD) as indicated by season of birth variations in dopamine receptor (DRD4) gene polymorphism. *Neuroscience Letters*, *366*, 282–286.
Serretti, A., & Mandelli, L. (2008). The genetics of bipolar disorder: Genome 'hot regions' genes, new potential candidates and future directions. *Molecular Psychiatry*, *13*, 742–771.
Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., et al. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal of Clinical Psychiatry*, *59*, 22–33.
Shin, Y. C., Lim, S. W., Choi, S. W., Kim, S. W., & Grant, J. E. (2009). Comparison of temperament and character between early- and late-onset Korean male pathological gamblers. *Journal of Gambling Studies*, *25*, 447–453.
Stallings, M. C., Hewitt, J. K., Cloninger, C. R., Heath, A. C., & Eaves, L. J. (1996). Genetic and environmental structure of the Tridimensional Personality Questionnaire: Three or four temperament dimensions? *Journal of Personality and Social Psychology*, *70*, 127–140.
Swanson, J. M., Moyzis, R. K., McGough, J. J., McCracken, J. T., Riddle, M. A., Kollins, S. H., et al. (2007). Effects of source of DNA on genotyping success rates and allele percentages in the Preschoolers with Attention-Deficit/Hyperactivity Disorder Treatment Study (PATS). *Journal of Child and Adolescent Psychopharmacology*, *17*, 635–646.
Tarazi, F. I., Campbell, A., Yeghiayan, S. K., & Baldessarini, R. J. (1998). Localization of dopamine receptor subtypes in corpus striatum and nucleus accumbens septi of rat brain: Comparison of D1-D2-, and D4-like receptors. *Neuroscience*, *83*, 169–176.
Tochigi, M., Okazaki, Y., Kato, N., & Sasaki, T. (2004). What causes seasonality of birth in schizophrenia? *Neuroscience Research*, *48*, 1–11.
Torrey, E. F., Miller, J., Rawlings, R., & Yolken, R. H. (2000). Seasonal birth patterns of neurological disorders. *Neuroepidemiology*, *19*, 177–185.

Torrey, E. F., Rawlings, R. R., Ennis, J. M., Merrill, D. D., & Flores, D. S. (1996). Birth seasonality in bipolar disorder, schizophrenia, schizoaffective disorder and stillbirths. *Schizophrenia Research*, *21*, 141–149.

Webb, A. R., Kline, L., & Holick, M. F. (1988). Influence of season and latitude on the cutaneous synthesis of vitamin D3: Exposure to winter sunlight in Boston and Edmonton will not promote vitamin D3 synthesis in human skin. *Journal of Clinical Endocrinology and Metabolism*, *67*, 373–378.

Zisapel, N. (2001). Melatonin-dopamine interactions: From basic neurochemistry to a clinical setting. *Cellular and Molecular Neurobiology*, *21*, 605–616.