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

Panos Roussos, Stella G. Giakoumaki, Panos Bitsios*

Department of Psychiatry and Behavioral Sciences, Faculty of Medicine, University of Crete, Heraklion, Crete, Greece

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;

* Corresponding author at: Department of Psychiatry and Behavioral Sciences, Faculty of Medicine, PO Box 2208, University of Crete, Heraklion 71003, Crete, Greece. Tel.: +30 2810 394610; fax: +30 2810 394610.
E-mail address: pbitsios@med.uoc.gr (P. Bitsios).

0028-3932/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
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 $\pm$ SD, 26.0 $\pm$ 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