Reward sensitivity, affective neuroscience personality, symptoms of attention-deficit/hyperactivity disorder, and TPH2-703G/T (rs4570625) genotype

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Abstract

Objective: Reward sensitivity is an increasingly used construct in psychiatry, yet its possible inner structure and relationship with other affective variables are not well known. Methods: A reward sensitivity measurement scale was constructed on the basis of large item pool collected from birth cohort representative samples (the Estonian Children Personality Behaviour and Health Study; original n = 1238). Affective Neuroscience Personality Scale (ANPS) and the Adult Attention deficit hyperactivity disorder (ADHD) Self-Report Scale (ASRS) were administered in young adulthood. A variant (rs4570625) of the gene encoding tryptophan hydroxylase 2 (*TPH2*) that is responsible for the synthesis of central serotonin was genotyped. Results: Reward sensitivity consisted of two orthogonal components, operationally defined as Openness to Rewards and Insatiability by Reward, that respectively characterize the striving towards multiple rewards and the strong pursuit and fixation to a particular reward. While SEEKING and PLAY (and to lower extent CARE) of the ANPS co-varied with Openness to Rewards, FEAR, SADNESS, and ANGER were related to Insatiability by Reward. The total score of ASRS was moderately correlated with Insatiability by Reward, while the association with Openness to Rewards was negligible. However, ASRS Inattention had some negative relationship with the Social Experience facet of Openness to Rewards. The T/T homozygotes for the *TPH2* promoter polymorphism had lower Insatiability by Reward but not Openness to Rewards. Conclusions: Behaviours sensitive to rewards are separable to the components of variability and fixation, and these components are differentially related to affective aspects of personality, attention, and hyperactivity as well as to *TPH2* genotype.

Significant outcomes

• Reward sensitivity can be parsed into striving towards multiple rewards and fixation to a specific reward.

• Openness to Rewards and Insatiability by Reward sensitivity have distinct relationship with personality traits and ADHD symptoms.

• The *TPH2* promoter polymorphism was associated specifically with Insatiability by Reward.

Limitations

•The reward sensitivity instrument was developed post hoc, applied in a Fennic language and requires further development and characterization together with related instruments.

• While the sample was reasonably large, and birth cohort representative, the association of *TPH2* genotype and reward sensitivity remains to be independently replicated.

Introduction

Reinforcement sensitivity theory (RST) has been stated to occupy a unique space in literature as a strong basic construct of temperament (Corr, 2009; Gray and McNaughton, 2000; Walker et al., 2017). In describing the principal brain mechanisms behind animal and human behaviour, the Gray's RST (Gray, 1994) is arguably the most important theoretical approach to explain individual differences, via the reward and punishment sensitivities (e.g. Collins et al., 2017). The behavioural predictions of RST have been examined across a broad range of areas, including psychopathy (e.g. Broerman et al., 2014; De Pascalis et al., 2019), criminal behaviour (e.g. Arnett and Newman, 2000; Leue et al., 2008), forgiveness (e.g. Johnson et al., 2010), substance abuse (e.g. Derefinko et al., 2016; Papinczak et al., 2018), and there is considerable empirical evidence supporting the main tenets of RST (e.g. Bijttebier et al., 2009; Gaher et al., 2015; Meis et al., 2017). Three functionally independent motivational subsystems comprise RST: the behavioural approach system (BAS), the fight/flight/freeze system (FFFS), and the behavioural inhibition system (BIS) (Gray and McNaughton, 2000; Corr, 2009; Collins et al., 2017).

In Gray's theory, a psychobiological trait, called sensitivity to reward or reward sensitivity, reflects the functional outcomes of the activity in the BAS (Gray, 1994). Growing evidence

suggests that in particular reward sensitivity is associated with important behavioural choices that have major implications to health, such as excessive consumption of palatable foods and use of addictive substances (Emery and Simons, 2017; Joyner et al., 2019; Tatnell et al., 2019); it has also been found to predict recurrence of manic episodes in bipolar disorder (Kwan et al., 2020). In contrast, low reward sensitivity can predict symptoms of depression (Hausman et al., 2018). Generally, reward sensitivity as the component of temperament and personality encompasses individual differences in the tendency to detect, pursue, and derive pleasure from positive stimuli (Gray and McNaughton, 2000; Corr, 2009). The BAS is primarily organised around pathways using the neurotransmitter dopamine and can be defined as the tendency to engage in motivated approach behaviour in the presence of rewarding stimuli (Gray and McNaughton, 2000; DeYoung, 2013).

Typically reward sensitivity has been measured by the Carver & White BIS/BAS Scales (Carver and White, 1994) and, more recently, also by The Jackson 5 (J5; Jackson, 2009), Reinforcement Sensitivity Theory Personality Questionnaire (RST-PQ; Corr and Cooper, 2016), or the Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ; Torrubia et al., 2001). In recent years, careful analysis of the existing questionnaires has suggested that some significant theoretical and operational limitations exist (Corr and Cooper, 2016). It has been argued that the process of scale construction has not strongly adhered to the theoretical postulates of the RST, and as a result, the construct validity of the available questionnaires may be suboptimal. Either have the instruments defined reward sensitivity as a homogenous construct, while the case can be made that it is multidimensional (e.g. Corr, 2016), or introduced components that should not be taken as synonymous to reward sensitivity, such as impulsivity or goal directedness.

Rewards constitute a major incentive in the balance between approach and avoidance, and the sensitivity to rewards should have implications to other fundamental mechanisms guiding behaviour such as basic emotions (e.g. Collins et al., 2017; Lahvis, 2017; Montag et al., 2017). Nevertheless, no investigation has examined the relationship of reward sensitivity to the traits as measured by the Affective Neuroscience Personality Scale (ANPS; Davis et al., 2003; Davis and Panksepp, 2011) which has been constructed bottom up to study traits predicted by the basic

neuroscience research in animals (Panksepp, 1998; Montag and Panksepp, 2017). Nearly all seven proposed basic emotive systems characterized by the ANPS include brain regions that have been suggested to contribute to reward sensitivity (Panksepp, 2016). Reward sensitivity has also been strongly related to the brain areas highlighted in studies on Attention deficit hyperactivity disorder (ADHD) (e.g. Avila et al., 2008; Holroyd et al., 2008; Hahn et al., 2014; Adrián-Ventura et al., 2019; Luo et al., 2019). ADHD patients are reported to have higher scores of affective temperaments and difficulties with regulation of behaviour directed towards rewards (e.g. Torrente et al., 2017), and reward sensitivity could be considered an endophenotype of ADHD.

While much of reward sensitivity research has paid attention to the role of dopamine neurons, the function of serotonergic neurotransmission is also crucial (Fletcher et al., 1995; Bari et al., 2010). Transient activation of dorsal raphe elicits strong reinforcement signals, but 5-HT neurons of dorsal raphe enhance reward waiting (Luo et al., 2015). These neurons also change their tonic firing rates across trials of reward and punishment, suggestive of signaling on multiple timescales (Cohen et al., 2015). Of the genetic variants shaping the individual differences in the serotonergic system, the serotonin transporter promoter polymorphism has been associated with reward responses in environmentally sensitive manner (Richards et al., 2016), and the composite of risk alleles of three serotonin-related genes was associated with BAS scores (Pearson et al., 2014). Levels of serotonin in the central nervous system (CNS) depend on the activity of tryptophan hydroxylase 2, the rate-limiting enzyme of the synthesis of serotonin. The −703 G/T polymorphism of the *TPH2* gene (rs4570625) has been associated with amygdalar responsiveness (Brown et al., 2005;Canli et al., 2005), risk of affective disorder (Gao et al., 2012), and with behavioural inhibition (Latsko et al., 2016). This genotype is associated with functional connectivity (Tao et al., 2018) and white matter integrity (Ping et al., 2019) in the brain. A recent systematic review and meta-analysis concluded that the *TPH2* rs4570625 polymorphism is significantly associated with psychiatric disorders such as unipolar depression, bipolar disorder, schizophrenia, and suicide (Ottenhof et al., 2018). The risk allele has been the major, G-allele, and the well-powered studies and meta-analysis have pointed at a much larger effect if the risk allele carriers are compared to the T/T-homozygotes. The experimental studies have, however,

usually compared G/G homozygotes to T-allele carriers, owing to the low frequency of the minor T allele.

It thus appears that the minor T-allele, especially in homozygotes, is protective against a variety of mental health disorders, but the mediating mechanisms are not known. In our studies on representative birth cohort samples, the G/G homozygotes and G/T heterozygotes have appeared similar in many respects, but a rather large distinction of T/T homozygotes has been apparent with regard to lower neuroticism, higher extraversion, and higher conscientiousness (Lehto et al., 2015) as well as low aggressiveness, depressiveness, and trait anxiety (Laas et al., 2017). The strikingly low aggressiveness in the male *TPH2* rs4570625 T/T homozygotes, both during the years at school and later in adult life, however, remained unexplained by anxiety. Owing to the role of serotonin in the control of aggressive urges (Miczek et al., 1989; Harro and Oreland, 2016) and the relationship between pursuits of aggression as reward (Golden et al., 2017), it is, however, plausible that the relationship between *TPH2* genetic variation and aggression could involve reward sensitivity.

The first aim of the present study was to identify common items for operational measurement of reward sensitivity and to explore for any emerging factor structure. The second purpose was to analyse the associations of the obtained reward sensitivity construct with the ANPS, presence of symptoms of ADHD, and with the *TPH2* genotype.

Material and methods

Sample

This study was carried out on the Estonian sample of the European Youth Heart Study (1998/1999), which was subsequently incorporated into the longitudinal Estonian Children Personality Behaviour and Health Study (ECPBHS). The European Youth Heart Study sample of the ECPBHS consists of two birth cohorts. The rationale and procedure of sample formation, and further data collection waves have been described elsewhere in detail (Harro et al., 2001; Tomson-Johanson et al., 2020). ECPBHS is highly representative of two birth cohorts of a local population, as 79% of subjects of the randomised regional sample participated in the original

data collection. All the subjects are of European descent. Data collection has been conducted at ages 9 (only the younger cohort), 15, 18, 25, and 33 (only the older cohort). Data used in the present analyses were collected at age 25 or, if not available for age 25, then from the study wave at age 33. The original size of the total sample is n = 1238, but all data necessary for the analyses presented in this paper were n = 811 to 824. This study was approved by the Ethics Review Committee on Human Research of the University of Tartu, and written informed consent was obtained from all the participants and in case of minors also from their parents.

Reward Openness and Insatiability Scale

The Reward Openness and Insatiability Scale (ROIS) that is used in this manuscript to measure reward sensitivity was constructed *post hoc* making use of previously collected information on personality. Three experienced behavioural scientists independently extracted items thought to reflect reward sensitivity from the Estonian versions of International Personality Item Pool NEO (IPIP) (Goldberg, 1999; Mõttus et al., 2006), Barratt Impulsiveness Scale (BIS-11; Patton et al., 1995; Akkermann et al., 2010), the brief version of the ANPS (Davis et al., 2003; Harro et al., 2019), Spielberger State-Trait Anxiety Inventory (STAI; Spielberger et al., 1983; Akkermann et al., 2010), and Adaptive and Maladaptive Impulsivity Scale (AMIS) (Paaver et al., 2006; Tomson-Johanson et al., 2020). The extracted items were discussed, and an initial pool of items was formed with consensus. This item pool consisted of 69 items: 11 items from BIS-11, 13 items from ANPS, 9 items from AMIS, 2 items from STAI, and 34 items from IPIP. The z-value transformation for responses of the items was performed before the statistical analysis.

In order to explore preliminary factor structure of the eventual reward sensitivity instrument, principal component analysis (PCA) with Direct Oblimin rotation (delta = 0) was carried out on all 69 items. The Kaiser–Meyer–Olkin (KMO) measure of sampling adequacy value was 0.84 which indicates that the sample was adequate for factor analysis. Bartlett's test of sphericity was significant, $\chi^2(2346) = 7332.14$, $p < 0.0001$, indicating that factor analysis was appropriate for this data. To determine the number of factors to extract, both the scree plot and eigenvalues were considered. The scree plot indicated that the data best fit a two-factor or four-factor solution. The eigenvalues of the first two components were 7.551 (accounted for 10.94% of total variance)

and 7.083 (accounted for 10.27% of total variance), respectively. The next two components had eigenvalues 2.758 (accounted for 4.00% of total variance) and 2.532 (accounted for 3.67% of total variance), respectively. The communalities of items were from 0.035 to 0.539.

Affective Neuroscience Personality Scale

We used the adaptation (Harro et al., 2019) of the short version of the ANPS (Davis et al., 2003) that is a self-report instrument constructed bottom up to correspond to the activity in neural circuits underlying basic emotive systems as defined in animal research (Panksepp, 1998; Davis and Panksepp, 2011). It comprises scales termed ANGER, FEAR, SADNESS, SEEKING, CARE, and PLAY, each measured with six items, each on a 5-point scale. Data on ANPS were available for 423 subjects in the ECPBHS younger cohort and 502 subjects in the older cohort.

Measures of ADHD symptoms

Subjects filled in the Estonian version of the World Health Organization Adult ADHD Self-Report Scale (ASRS) symptom checklist (Kessler et al., 2005; Kiive and Harro, 2013; Kiive et al., 2014), an instrument composed of 18 questions based on Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria of ADHD. The ASRS consists of nine items that represent symptoms related to inattention and nine items assessing symptoms of hyperactivity/impulsivity. Each of the items is scored on a five-point Likert rating scale with 0 = “never,” 1 = “rarely,” 2 = “sometimes,” 3 = “often,” and 4 = “very often” based on the participant’s experiences over the last 6 months. Six of the 18 questions most predictive of symptoms consistent with ADHD (Kessler et al., 2005) are the basis for the ASRS Screen (M= 1.37, SD= 0.59, Cronbach α = 0.68). The total score is calculated by summing the values of all items (M= 1.30, SD = 0.50, Cronbach α = 0.86). The higher the score is the more symptoms are pronounced. In addition to the sum score, the two subscales Inattention (M= 1.42, SD = 0.55, Cronbach α = 0.80) and Hyperactivity/Impulsivity (M= 1.18, SD = 0.59, Cronbach α = 0.80) are calculated.

TPH2 rs4570625 genotyping

Genomic DNA was extracted from whole blood samples using Qiagen QIAamp® DNA Blood Midi Kit. Genotyping for *TPH2* G-703 T (rs4570625) was performed as previously described (Lehto et al., 2015) with the Applied Biosystems ViiA™ 7 Real- Time PCR System using the TaqMan® Pre-Designed SNP Genotyping Assay with Solis BioDyne 5 × HOT FIREPol® Probe qPCR Mix Plus (ROX). All DNA samples of the ECPBHS (n = 1234) were successfully genotyped. In total, the sample included 749 G/G homozygotes (60.7%), 432 G/T heterozygotes (35.0%), and 53 T/T homozygotes (4.3%). Minor allele frequency was 0.22. The genotype frequencies were in Hardy–Weinberg equilibrium (chi-squared 0.887; expected frequencies 61.2, 34.1, and 4.7%, respectively).

Statistical analysis

Statistical analysis was carried out using SPSS v. 18 software. Correlations between test scores were assessed by Pearson correlation, and assessment of factor structure of the new reward sensitivity scale was carried out by PCA with oblique rotation. In order to analyse the association of scales of ROIS and the modules of ANPS or ADHD, multiple linear regression analysis was the carried out. Hierarchical cluster analysis (cluster method: between groups linkage, measure: Pearson correlation) was used for analysis of structure of correlation pattern between modules of ANPS and subscales of ROIS. Hierarchical cluster analysis is typically applied with an eye to determining how n entities – objects, scales, sentences, subjects, etc. – can be grouped into m < n clusters that exhibit high within-group similarity and low similarity to other groups (e.g. King, 2015) and better reveal the general pattern of associations between the psychological constructs. While the relationship of ROIS and ANPS was examined, the ANPS-derived items were omitted from ROIS data. Owing to dissimilar groups sizes, ROIS test scores in *TPH2* genotype groups were assessed by both nonparametric Kruskal-Wallis test and one-way analysis of variance (ANOVA); since the results were similar the latter with *post hoc* comparisons by Tamhane's T2 tests is described in Results. Before statistical analysis for all the scales, the mean item score was computed (i.e. sum of the items is divided by number of items in scale). In the statistical analysis, the conventional 5% level was used to assess the significance.

Results

Structure of the ROIS

Out of the initial item pool, 28 items were selected on the basis of factor loadings, communalities, and internal homogeneity and included in a new factor analysis (PCA, Direct Oblimin rotation, delta = 0). The KMO measure of sampling adequacy value was 0.86 which indicated that the dateset was appropriate for factor analysis. Bartlett's test of sphericity was significant, $\chi^2(378) = 7095.7$, $p < 0.0001$, also indicating that factor analysis was appropriate for these data. The scree plot revealed a clear factor structure with the four factors accounting for 46.4% of the total variance. The communalities of items were from 0.200 to 0.620. The four factors explained 18.2%, 15.5%, 6.5%, and 6.2% of the variance, respectively, and factor loadings were, respectively, between 0.504 and 0.775, 0.514 and 0.720, 0.360 and 0.805, and 0.503 and 0.695.

The component correlation matrix demonstrated two factors (Factor 1 and Factor 4) in a positive correlation r = 0.40, as well as the two other factors (Factor 2 and Factor 3; r = 0.31). Such a pattern of correlations indicates the hierarchical structure of the test, so there are two second-order factors and four first-order factors. Figure 1 provides illustration of all 28 items located in two dimensional factor space. Content of included items translated into English, their factor loadings, and the sources where analogous items have been used are available in Supplementary Table 1.

Close inspection of items of Factor 1 reveals this factor as related to impulsive buying and excessive spending (sample Cronbach α = 0.85), so it was named *Excessive spending* subscale. The items of Factor 4 are related to low self-control and troubles in resisting to temptations (sample Cronbach α = 0.77). This subscale was named *Giving in to cravings*. These two subscales together characterise the excessive fixation to a particular reward, the higher-order factor thus representing *Insatiability by Reward* (sample Cronbach α = 0.86). Factor 2 has been labelled *Excitement and Novelty* subscale owing to its reflection of seeking of new experiences and excitement (sample Cronbach α = 0 0.79). The items of Factor 3 are largely associated with sociability and social exchange (sample Cronbach α = 0.75), so named *Social experiences* subscale. These two subscales characterise the striving towards multiplicity of rewards, so the higher-order

factor has been labelled *Openness to Rewards* (sample Cronbach α = 0.82). Correlation between scores of Openness to Rewards and Insatiability by Reward was statistically insignificant r = −0.008 (p = 0.82, N = 818). Thus, these two reward sensitivity factors are orthogonal, as reflected in item loadings in Figure 1.

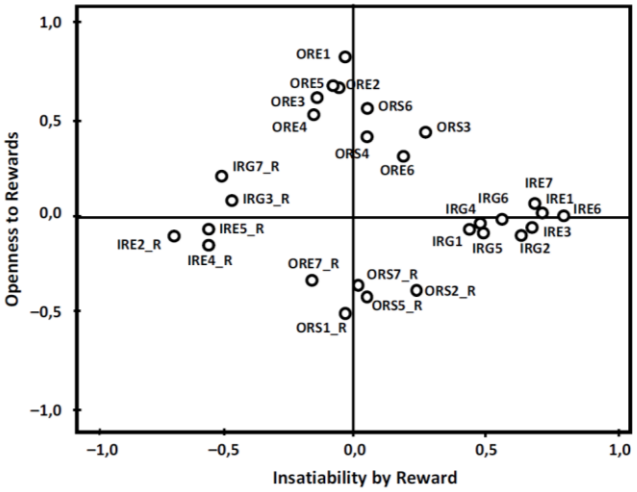

Figure 1. Items of the Reward Openness and Insatiability Scale loading on the higher-order factors Insatiablity by Reward and Openness to Rewards. Principal component analysis with oblique rotation (Direct Oblimin).

Relationship between subscales of the ROIS and factors of the ANPS

Cluster analysis (between-groups linkage method, Peason correlation measure) of the scales of ROIS and personality factors of ANPS reveals two clearly separate groupings (Figure 2). This pattern of associations is also observed in zero-order correlations (Table 1). Openness to Rewards was strongly associated with SEEKING and PLAY, and rather weakly with CARE; weak negative correlations were found with FEAR and SADNESS; and no relationship to ANGER. Insatiability by Reward was, instead, in moderate positive correlation with SADNESS, FEAR, and ANGER, had no relationship with SEEKING or CARE, and very weak but negative correlation with PLAY.

Tabel 1. Pearson correlations between the subscales of the Reward Openness and Insatiability Scale (ROIS) and Affective Neuroscience Personality Scale (ANPS). Mean item scores ± standard deviations are presented in brackets (n = 815)

	ROIS					
ANPS	OR_Excitement and Novelty (3.66 ± 0.66)	OR_Social experience (3.33 ± 0.85)	IR_Excessive spending (2.46 ± 0.82)	IR_Giving in to cravings (2.64 ± 0.69)	Openness to Rewards (3.53 ± 0.61)	Insatiability by Reward (2.55 ± 0.65)
ANGER (2.76 ± 0.76)	0.05	0.07*	0.22**	0.37**	0.07	0.34**
SADNESS (2.76 ± 0.78)	−0.09*	−0.22**	0.31**	0.40**	−0.18**	0.41**
FEAR (2.70 ± 0.73)	−0.17**	−0.19**	0.23**	0.40**	−0.22**	0.36**
CARE (3.62 ± 0.65)	0.05	0.23**	0.01	−0.04	0.16**	−0.02
PLAY (3.73 ± 0.68)	0.42**	0.46**	−0.05	−0.09*	0.53**	−0.08*
SEEKING (3.83 ± 0.60)	0.57**	0.39**	−0.04	−0.01	0.59**	−0.03

OR – Openness to Rewards, IR – Insatiability by Reward. Means ± standard deviations are presented in brackets. ROIS scores exclude the items from ANPS in this analysis. * $p < 0.05$; ** $p < 0.001$

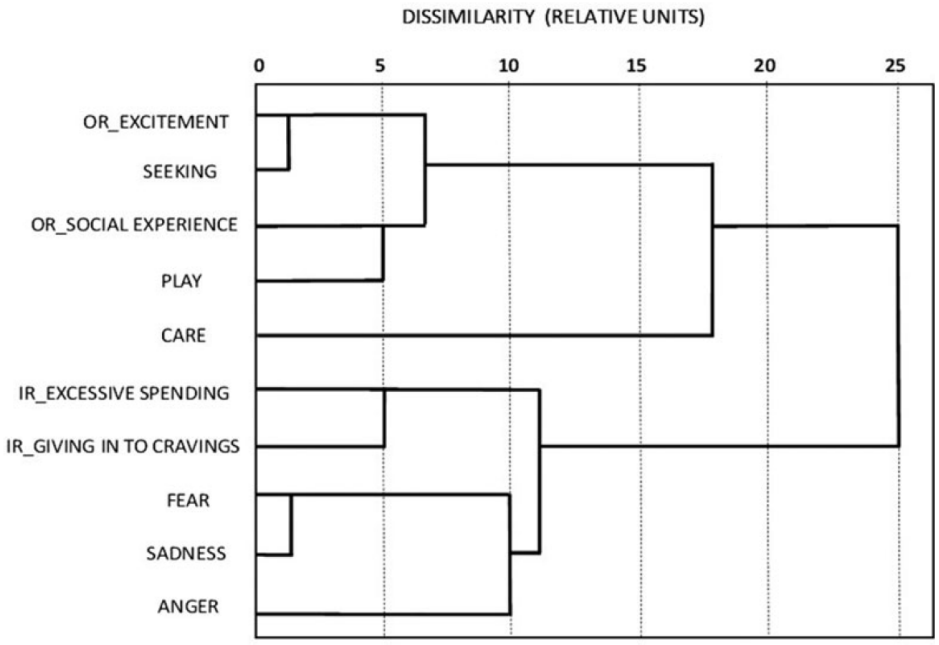

Figure 2. Dendrogram of cluster analysis of the subscales of Reward Openness and Insatiability Scale (ROIS) and dimensions of the Affective Neuroscience Personality Scale (ANPS). Hierarchical cluster analysis with between-groups linkage method and Peason correlation measure. Note: ROIS items from ANPS excluded from this analysis.

Relationship of ADHD symptoms with the ROIS and ANPS

Zero-order pair-wise correlations between scales and subscales of ROIS and ADHD measures show a clear pattern of Insatiability by Reward positively correlated with the ADHD symptoms as measured with the ASRS scales (Table 2), whereas Openness to Rewards correlated very weakly with either inattention or hyperactivity, these weak correlations also being in opposite to each other direction. Multiple regression was performed to clarify the impact of aspects of reward sensitivity and the personality factors of ANPS on ADHD symptoms. The two components of Insatiability by Reward were the major and universal predictors of ADHD symptoms, but the Excitement and Novelty aspect of Openness to Rewards not at all (Table 3). Social experience contributed to Inattention but not to Hyperactivity/Impulsivity. As to the Affective Neuroscience Personality Model, ANGER was related to ADHD Hyperactivity/Impulsivity, but not to Inattention. SADNESS and FEAR had some positive association with either component of ASRS, whereas which association was stronger, did not coincide. CARE had some association with Inattention which was negative. SEEKING was in strong positive association with both aspects of ADHD symptoms, while PLAY had relationship with neither.

Table 2. Pearson correlations between the Reward Openness and Insatiability Scale (ROIS) and Adult ADHD Self-Report Scale (ASRS)

	OR_Excitement and Novelty	OR_Social experience	IR_Excessive spending	IR_Giving in to cravings	Openness to Rewards	Insatiability by Reward	ASRS Screen test	ASRS Inattention	ASRS Hyperactivity/ Impulsivity
OR_Social experience	0.45**								
IR_Excessive spending	0.03	0.01							
IR_Giving in to cravings	−0.01	−0.05	0.48**						
Openness to Rewards	0.84**	0.86**	0.02	−0.04					
Insatiability by Reward	0.01	−0.03	0.89**	0.83**	−0.01				
ASRS Screen test	0.07*	−0.09**	0.34**	0.39**	−0.20	0.42**			
ASRS Inattention	0.02	−0.20**	0.31**	0.39**	−0.11**	0.40**	0.84**		
ASRS Hyperactivity/ Impulsivity	0.11**	−0.05	0.29**	0.42**	0.09**	0.40**	0.69**	0.56**	
ASRS Total score	0.07*	−0.08*	0.34**	0.46**	−0.01	0.46**	0.86**	0.87**	0.89**

OR - Openness to Rewards, IR – Insatiability by Reward scale ($n = 811$).
* $p < 0.05$; ** $p < 0.01$.

THP2 -703 G/T genotype and ROIS

There was no statistically significant difference in Openness to Rewards between the TPH2 genotype groups [$F(2, 821) = 0.96$; p = 0.384, $F(2, 821) = 0.41$; p = 0.667, and $F(2, 821) = 1.01$; p = 0.364 for the total score, Excitement and Novelty subscale, and Social experiences subscale, respectively; Table 4]. However, significant differences were found in Insatiability by Reward [$F(2, 814) = 6.08$; p = 0.002] as well as the Excessive spending [$F(2, 814) = 6.06$; p = 0.002] and Giving in to cravings [$F(2, 814) = 3.18$; p = 0.042] subscale. While the scores of G/G and G/T genotypes were similar, the T/T homozygotes had much lower scores.

Discussion

In this study, we have found evidence to suggest that reward sensitivity is comprising of two rather independent components that, respectively, characterise striving to and preference of multiple rewards versus strong fixation on a particular reward. This has not been described previously, possibly owing to the limitations of the existing questionnaires that may have somewhat deviated from the theoretical postulates of the RST or attempted to establish reward sensitivity as a homogenous construct (Corr and Cooper, 2016; Corr, 2016). Being in possession of the large item pool collected from a large, birth cohort representative sample to whom any recognised reward sensitivity instrument had not been administered, we have made an

Table 3. Multiple regression models for Adult ADHD Self-Report Scale (ASRS) subscores (n = 811)

	B	St. error	Beta	*t*	Sig	*F*	df	*p*	R	Adj R^2
ASRS Screen test						27.09	10 810	<0.0001	0.50	0.24
OR_ Excitement and Novelty	0.07	0.04	0.07	1.90	0.32					
OR_Social experience	−0.09	0.03	−0.13	−3.38	0.001					
IR_Excessive spending	0.12	0.03	0.17	4.77	<0.0001					
IR_Giving in to cravings	0.17	0.03	0.20	5.17	<0.0001					
ANGER	0.08	0.03	0.10	2.64	0.009					
SADNESS	0.10	0.03	0.13	3.03	0.002					
FEAR	0.05	0.04	0.06	1.40	0.16					
CARE	−0.05	0.03	−0.06	−1.73	0.09					
PLAY	−0.01	0.03	−0.01	−0.17	0.87					
SEEKING	0.13	0.04	0.13	3.14	0.002					
Inattention						31.00	10 810	<0.0001	0.53	0.27
OR_ Excitement and Novelty	0.06	0.03	0.07	1.89	0.09					
OR_Social experience	−0.13	0.02	−0.20	−5.48	<0.0001					
IR_Excessive spending	0.09	0.02	0.14	3.90	<0.0001					
IR_Giving in to cravings	0.17	0.03	0.22	5.76	<0.0001					
ANGER	0.02	0.03	0.02	0.58	0.56					
SADNESS	0.07	0.03	0.10	2.41	0.02					
FEAR	0.11	0.03	0.14	3.41	0.001					
CARE	−0.06	0.03	−0.08	−2.53	0.02					
PLAY	−0.04	0.03	−0.05	−1.27	0.21					
SEEKING	0.14	0.04	0.15	3.81	<0.0001					
Hyperactivity/Impulsivity						34.01	10 810	<0.0001	0.55	0.29
OR_ Excitement and Novelty	−0.00	0.03	−0.00	−0.07	0.94					
OR_Social experience	0.02	0.03	0.03	0.90	0.37					
IR_Excessive spending	0.06	0.03	0.09	2.47	0.01					
IR_Giving in to cravings	0.20	0.03	0.23	6.31	<0.0001					
ANGER	0.14	0.03	0.18	4.88	<0.0001					
SADNESS	0.10	0.03	0.13	3.33	0.001					
FEAR	0.06	0.03	0.08	1.85	0.06					
CARE	−0.03	0.03	−0.03	−1.10	0.27					
PLAY	−0.02	0.03	−0.02	−0.50	0.62					
SEEKING	0.21	0.04	0.21	5.47	<0.0001					
ASRS Total score						41.08	10 810	<0.0001	0.58	0.33
OR_ Excitement and Novelty	0.03	0.03	0.04	1.03	0.30					
OR_Social experience	−0.06	0.02	−0.09	−2.58	0.01					
IR_Excessive spending	0.08	0.02	0.12	3.71	<0.0001					
IR_Giving in to cravings	0.19	0.03	0.25	7.10	<0.0001					
ANGER	0.08	0.02	0.11	3.29	0.001					
SADNESS	0.09	0.03	0.13	3.39	0.001					
FEAR	0.09	0.03	0.12	3.06	0.002					
CARE	−0.05	0.03	−0.06	−2.00	0.04					
PLAY	−0.03	0.03	−0.04	−1.02	0.31					
SEEKING	0.18	0.03	0.21	5.48	<0.0001					

exploratory attempt to examine the internal structure of reward sensitivity. ECPBHS offers the advantage of a database comprising a variety of behavioural items, thus we compiled post hoc an instrument for the measurement of reward sensitivity. This approach has yielded an instrument with two orthogonal dimensions that make intuitive sense, but will require further formal development and rigorous studies to ascertain its applicability.

Table 4. TPH2 effects on reward sensitivity (ROIS subscales) group mean item scores and standard errors and multiple comparisons p-value (Tamhane's)

ROIS subscale	TPH2 G/G genotype	TPH2 G/T genotype	TPH2 T/T genotype
OR_Excitement and Novelty	3.70 ± 0.03, $n = 501$	3.70 ± 0.04, $n = 286$	3.80 ± 0.11, $n = 37$
OR_Social experience	3.58 ± 0.03, $n = 501$	3.58 ± 0.04, $n = 286$	3.74 ± 0.09, $n = 37$
IR_Excessive spending	2.47 ± 0.04, $n = 497$	2.50 ± 0.05, $n = 283$	2.00 ± 0.09, $n = 37$**
IR_Giving in to cravings	2.66 ± 0.03, $n = 497$	2.64 ± 0.04, $n = 283$	2.36 ± 0.10, $n = 37$*
Openness to Rewards	3.64 ± 0.03, $n = 501$	3.64 ± 0.03, $n = 286$	3.77 ± 0.09, $n = 37$
Insatiability by Reward	2.56 ± 0.03, $n = 497$	2.57 ± 0.04, $n = 283$	2.18 ± 0.07, $n = 37$**

OR – Openness to Rewards, IR – Insatiability by Reward.
* $p < 0.05$; ** $p < 0.0001$ significant difference of the *TPH2* T/T homozygotes from G/G homozygotes as well as G/T heterozygotes.

We selected as the next goal to reveal the relationship of reward sensitivity, as measured with the ROIS, with personality in the affective neuroscience model (Panksepp, 2016). Empirical studies addressing the position of reward sensitivity in the framework of the Five Factor Model of personality mostly have shown that reward sensitivity is positively associated with Extraversion and negatively with Neuroticism (e.g. Keiser and Ross, 2011; Segarra et al., 2014; Smillie and Wacker , 2014; Corr and Cooper, 2016; Smillie et al., 2019). The ANPS has, in contrast to lexical approaches to the structure of personality, been constructed bottom-up to measure personality as revealed in expression on primary emotion systems, defined by neurobiological studies across mammalian species (Panksepp, 1998). ANPS facets distinctly correlate with measures of white matter integrity in polydrug abusers (Unterrainer et al., 2017), a subject group with likely deviations in reward sensitivity. Recently, problematic use of internet and smartphone addiction were associated with high expression of FEAR and SADNESS, and to a lesser extent ANGER, and to low levels of CARE, PLAY, and SEEKING (Montag et al., 2016). Interestingly, the two reward sensitivity component ROIS clearly differentiated these personality facets so that Insatiability by Reward was associated with ANGER, FEAR, and SADNESS, while Openness to Rewards was, instead, related to SEEKING, PLAY, and CARE. (In relevant analyses, the ANPS

derived items were omitted from ROIS data.) Hierarchical cluster analysis revealed that both facets of Insatiability by Reward were related to the three neuroticism-related ANPS traits with high similarity. The two facets of Openness to Rewards had, however, specific relationship with ANPS traits, so that Excitement and Novelty were more close related to SEEKING than to Social Experience, and the latter was more closely related to PLAY. Of note is the complete absence of association between SEEKING and Insatiability by Reward. This was unexpected because the bottom-up construct of SEEKING was made bearing in mind what is known of dopaminergic control of reward-related behaviour (Panksepp, 1998; Montag and Panksepp, 2017). Direct evidence for a relationship of SEEKING with dopaminergic system and reward-related behavior in humans is, however, not available, therefore any neurobiological interpretation of this dissociation at present remains speculative. It is nevertheless conceivable that while the mesotelencephalic dopaminergic neurotransmission is vital for search of multiple rewards, it does not contribute to the insatiability aspect of reward sensitivity. It was recently demonstrated that reward-related firing of the ventral tegmental (VTA) dopamine neurons and dopamine release in the nucleus accumbens can be dissociated so that in conditions of orientation towards rewards there is a coupling while the immediate motivated behaviour is associated with dopamine release but not VTA activity (Mohebi et al., 2019). The former must hence be regulated locally, possibly via inhibition of the tonic action of serotonin on the 5-HT_{2C} receptors (Dremencov et al., 2005).

Higher scores of SEEKING and SADNESS predicted both components of ADHD symptomatology, higher Inattention, and Hyperactivity/Impulsivity. A higher score of ANGER was associated with higher Hyperactivity/Impulsivity, while FEAR contributed to Inattention. Also, the score of Inattention was negatively associated with CARE dimension. Similarly, a recent study of Wernicke et al. (2019) has found a higher negative emotionality, namely, ANGER, FEAR, and SADNESS, significantly associated with more inattentive, hyperactive/impulsive tendencies of young adults (Wernicke et al., 2019).

Higher scores of the Insatiability by Reward, SEEKING, ANGER SADNESS, and FEAR predicted more severe symptoms of ADHD, while the scores of Social experience and CARE were negatively

associated with ADHD symptoms. ADHD individuals are well known by their increased preference for small immediate rewards rather than large delayed ones (Marx et al., 2018) and preference of risky decisions (Luman et al., 2008). Excessive spending and giving in to cravings are also associated with poor impulse control. On the other hand, in our study, the score of Social experience subscale was negatively associated with ADHD symptoms, which supports the notion that sensation/experience seeking and impulsivity are dissociable constructs and based on partially distinct neurobiological substrates.

The *TPH2*-703 G/T polymorphism also distinguished Openness to Rewards and Insatiability by Reward in terms of being associated only with the latter. While the functional significance of this polymorphism at the cellular level requires further investigation, the T-allele may relate to hyperfunction of tryptophan hydroxylase (Lin et al., 2007; Chen et al., 2008), and if this were the case, serotonin levels should be particularly high in the T/T homozygotes. This would be well compatible with low aggressiveness, anxiety, and depressiveness. We could observe hardly any effect of the single T-allele, and this is compatible with recent studies on psychiatric patients (see Introduction for references) and with our previous findings on personality, aggressiveness, and anxiety in the ECPBHS sample (Lehto et al., 2015; Laas et al., 2017). Somewhat speculatively, the minor effect of a single T-allele may be caused by the efficient compensatory mechanisms in the synthesis of 5-HT as demonstrated in animal experiments (Kriegebaum et al., 2010).

An obvious limitation of this study lies in the current infeasibility of validation by other reward sensitivity instruments because of the database approach. On the other hand, the latter has the advantage of diverse, population-representative sample tested in uniform, laboratory conditions. Further studies should establish a novel instrument corresponding to the inner structure of reward sensitivity as revealed in the present investigation and compare the ROIS with other instruments and behavioural tests to validate the concept of the separable components of reward sensitivity. Owing to the often poor replicability of findings with candidate gene variants, the association of the *TPH2* gene with reward sensitivity requires testing in other populations.

Conclusively, striving towards multiple rewards and strong fixation on a particular reward were distinguished with a novel instrument and demonstrated to have distinct association with

affective neuroscience personality and ADHD-like traits, as well as with the genotype of tryptophan hydroxylase 2, the rate-limiting enzyme for serotonin synthesis in the brain.

Supplementary material

To view supplementary material for this article, please visit https://doi.org/10.1017/neu.2020.18

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Author contributions

The authors JH, EK, and AP contributed to the design of the study and data collection, literature searches, statistical analysis, and writing of the manuscript. All authors have approved the final manuscript.

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Conflict of Interest

None.

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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