The role of reward sensitivity in obesity and its association with Transcription Factor AP-2B: a longitudinal birth cohort study

Urmeli Katus[1], Inga Villa[1], Inge Ringmets[1], Aleksander Pulver[2], Toomas Veidebaum[3], Jaanus Harro[4]

[1]Department of Family Medicine and Public Health, University of Tartu, Tartu, Estonia

[2]School of Natural Sciences and Health, Tallinn University, Tallinn, Estonia

[3]Department of Chronic Diseases, National Institute for Health Development, Tallinn, Estonia

[4]Division of Neuropsychopharmacology, Department of Psychology, University of Tartu, Tartu, Estonia

ABSTRACT

Objective: One factor potentially contributing to obesity is reward sensitivity. We investigated the association between reward sensitivity and measures of obesity from 9 to 33 years of age, paying attention to the inner structure of reward sensitivity.

Methods: The sample included both birth cohorts (originally n = 1176) of the Estonian Children Personality Behaviour and Health Study. The association between reward sensitivity and measures of obesity was assessed using mixed-effects regression models. Associations at ages 9 (younger cohort only), 15, 18, 25 and 33 (older cohort) years were analyzed by one-way ANOVA. The indirect effect of the gene encoding transcription factor 2 beta (*TFAP2B*) on obesity through reward sensitivity was tested using mediation analysis.

Results: According to linear mixed effects regression models, an increase in scores of Insatiability by Reward and both of its components, Excessive Spending and Giving in to Cravings, significantly increased body weight, body mass index, sum of five skinfolds, waist circumference, hip circumference and waist-to-height ratio from 15 to 25 years of age. Findings were similar at age 9 and 33 years. In contrast, no association between obesity and

Openness to Rewards or its facets was observed. The *TFAP2B* genotype was also associated with fixation to rewards in females, but not with striving towards reward multiplicity.

Conclusion: Our results suggest that reward sensitivity is associated with obesity by its reward fixation component. The heterogeneity of the reward sensitivity construct should be taken into account in studies on body composition.

1. INTRODUCTION

CNS has a considerable role in the development of obesity [1]. Psychosocial stress has been associated with obesity in children [2], and obesity and mood disorders frequently co-occur. A variety of factors related to cognitive control, regulation of motivation and reward contribute to the development of obesity [1]. Individual variation in the functioning of the reward system has most influentially been conceptualized in Gray´s Reinforcement Sensitivity Theory/Behavioural Approach System, believed to generate the response to attractive stimuli that represents sensitivity to reward [3–5]. Sensitivity to reward is a psychobiological trait to seek rewarding substances or enjoyment with high reward potential [6]. Reward sensitivity has been associated with overeating [7,8], preference for foods high in fat and sugar [9,10], and use of addictive substances [11–13].

Nevertheless, contradictory reports exist about the role of reward sensitivity in obesity. Jonker et al. (2019) found no difference in reward responsivity and drive or punishment sensitivity between obese and healthy weight adolescents [14]. Moreover, attentional biases to cues that signal reward or punishment were not related to BMI [15]. In contrast, a study among 346 Dutch children (aged 6–13 years) found that children with obesity had higher scores of reward responsiveness, compared to children with overweight, normal weight and underweight [16]. Impulsivity and fun seeking also differed between children with obesity, compared to children with normal- and underweight. Another study investigating food addiction, over-eating, and reward sensitivity in women (n=374), demonstrated that reward

sensitivity was associated with greater symptoms of food addiction, which were mediated by binge-eating, emotional eating and food availability [6]. Merchán-Clavellino et al. observed a significant correlation between reward sensitivity and alcohol consumption among 384 Spanish university students [17].

Several neurotransmitter systems, most overwhelmingly dopamine and serotonin (5-hydroxytryptamine, 5-HT) regulate the rewarding effects of food [7]. Both palatable foods and substance use activate the dopaminergic pathways in the brain, indicating a higher response to reward [8], therefore it has been suggested that individuals with obesity compared to people with normal weight might differ in reward sensitivity. In addition, low 5-HT levels are a known inclination for the development of depression, anxiety disorders and addiction [18].

We recently reported an association between TFAP2B and measures of obesity, where 5-repeat homozygotes had higher BMI, compared to heterozygotes [19]. The transcription factor 2 beta gene (TFAP2B) has been associated with reward-related personality traits [20], bingeeating disorder [21], bulimia nervosa [22] and severe alcoholism in females [23], making it a highly interesting candidate gene as regards to reward sensitivity. Several genes encoding proteins of critical importance for the dopaminergic and serotonergic systems display multiple binding sites for the TFAP2B protein in their regulatory regions [24]. TFAP2B has an impact on both serotonin and dopamine systems: We have previously shown a strong correlation between TFAP2B levels in the raphe, where the serotonergic perikarya are located, and 5-HT turnover in the frontal cortex [24]; TFAP2B genotype has been associated with striatal dopamine D2-receptor availability as measured by positron emission tomography as well as with the CSF levels of homovanillic acid, a major metabolite of dopamine [25].

Thus, evidence for the association between reward sensitivity and obesity is inconclusive. The inner structure of reward sensitivity has not been sufficiently understood [26,27] and the association of components of reward sensitivity with body weight remains unexplored. We have recently been able to differentiate reward sensitivity into Openness to Rewards, the strive towards multiplicity of rewards, and Insatiability by Reward, a fixation to a particular reward [28]. These two aspects of reward sensitivity diverge in their relationship with basic personality dimensions and symptoms of attention deficit hyperactivity disorder (ADHD), a condition that is often co-morbid with obesity [29]. The selective association of Insatiability

by Reward with the ADHD symptoms led us to hypothesize that this component of reward sensitivity might be more strongly associated with obesity, and the close association of TFAP2B with body composition and central monoaminergic activity led to a hypothesis that the genotype effect could be mediated by reward sensitivity. In this analysis we investigated the relationship between reward sensitivity inner structure and measures of obesity from the age of 9–33 years in a longitudinal birth cohort study. The association between TFAP2B intron 2 variable number tandem repeat (VNTR) and reward sensitivity was examined cross-sectionally.

2. MATERIAL AND METHODS

2.1. Study sample

This study was carried out on the Estonian sample of the European Youth Heart Study (1998/1999) which was later incorporated into the Estonian Children Personality Behaviour and Health Study (ECPBHS). The study procedure and the formation of the original sample have been described in detail elsewhere [30]. The original sample consisted of 583 subjects aged 9 years and 593 subjects aged 15 years. Follow-up studies for the younger birth cohort took place in age 15 years (n=483), 18 years (n=454) and 25 years (n=441) and for the older birth cohort in age 18 years (n=417 + additional 62), 25 years (n=541) and 33 years (n=504).

Our previous studies have revealed no evidence of body composition regulation being related to birth cohort [19,31]. To increase statistical power, data of both birth cohorts of the ECPBHS were merged at ages 15, 18 and 25 years for the longitudinal analysis. Pregnant individuals were excluded from the analysis.

Written informed consent was obtained from the subjects and, in case of minors, also from their parents. The study was approved by the Ethics Review Committee on Human Research of the University of Tartu and conducted in accordance with the Declaration of Helsinki.

2.2. Reward sensitivity

Reward sensitivity was assessed using the Reward Openness and Insatiability Scale (ROIS), which specifies the inner structure of reward sensitivity [28]. The construction and description

of ROIS has been described in detail elsewhere [28]. In brief, ROIS comprises of 28 items, divided equally between two higher-order factors – *Openness to Rewards,* a strive toward multiplicity of rewards and *Insatiability by Reward*, characterized by an excessive fixation to a particular reward. *Openness to Rewards* (Cronbach α = 0.82) includes *Excitement and Novelty* (Cronbach α = 0.79)*,* with items reflecting the search for new experiences and excitement and *Social Experiences* (Cronbach α = 0.75)*,* with items largely associated with sociability and social exchange. *Insatiability by Reward* (Cronbach α = 0.86) comprises of *Excessive Spending* (Cronbach α = 0.85), with items related to impulsive buying and excessive spending and *Giving in to Cravings* (Cronbach α = 0.77)*,* with items related to low self-control and trouble in resisting to temptations. Personality information for analysis by ROIS was collected at age 25 or 33. The mean item score was used in statistical analysis.

2.3.   Anthropometric measurements and glucose metabolism

Height and body weight were measured using standardized procedures. Waist circumference was measured between the lower rib margin and the iliac crest, at the end of gentle expiration and hip circumference was measured at the widest part of the gluteal region. A Harpenden caliper (Baty, West Sussex, England) was used to measure skinfold thickness. All anthropometrical measurements were taken twice and a mean value was used.

2.4.   Genotyping of *TFAP2B* intron 2 VNTR

Genotyping of *TFAP2B* intron 2 VNTR (a tetranucleotide repeat, 4–5 times) polymorphism has been described in detail previously [32]. Genotype frequencies were as follows: 4/4 = 89 (8.0 %), 4/5 = 407 (36.5 %), 5/5 = 619 (55.5 %). Distribution of genotype frequencies at age 15 years did not differ between male (4/4=34, 6.9 %; 4/5=188, 38.0 %; 5/5=273, 55.1 %) and female (4/4=51, 8.7 %; 4/5=210, 35.8 %; 5/5=326, 55.5 %) subjects (χ^2 test, p=0.474). Genotype frequencies were in Hardy-Weinberg equilibrium (χ^2 test, p=0.261).

2.5.   Statistical analysis

Statistical analysis was performed using Stata software, version 14 (StataCorp LP, College Station, Texas, USA). Significance level was set at 0.05.

Independent group t-test was used to test differences in reward sensitivity by sex. Reward sensitivity score by *TFAP2B* intron 2 VNTR genotype and sex and the association between reward sensitivity and body mass index (BMI) category was analyzed by one-way ANOVA. The p values obtained from the pairwise comparisons were corrected by the Sidak method using the following equation $p^* = 1–(1–p)^3$ where p^* is compared with significance level 0.05.

Longitudinal association between reward sensitivity and measures of obesity were assessed using the linear mixed-effects regression models with random intercept and random slope, adjusted to daily energy intake and physical activity. Measures of obesity at baseline (age 15 years) and at follow-up points (18 years and 25 years) were defined as the dependent variables. Reward sensitivity score was defined as the independent variable. Time was treated as a continuous variable.

The likelihood-ratio (LR) test was used to assess the goodness of fit of the statistical models. Interaction with time was not included in the final models, because it was not significant and the LR test did not show superiority of the more complicated model. Unstructured or exchangeable covariance structure and restricted maximum likelihood method was used.

Mediation analysis was used to test our hypothesis that *TFAP2B* predicts measures of obesity through reward sensitivity. The significance of the indirect effect was formally tested using the bootstrapping method described by Preacher and Hayes (2008) [33]. To this, the dataset was randomly resampled 1000 times.

3. RESULTS

3.1. Association between *TFAP2B* intron 2 VNTR and reward sensitivity

Insatiability by Reward scores were available for 335 males and 483 females and Openness to Rewards scores for 340 males and 485 females. No significant (p > 0.05) difference between male and female subjects in Insatiability by Reward or its subscales nor Openness to Rewards and its Excitement and Novelty subscale was observed. Female subjects had significantly higher Social Experiences subscale score (difference –0.15, 95 % CI –0.24; –0.05, p=0.002).

Association between *TFAP2B* intron 2 VNTR and Insatiability by Reward was observed only in female subjects, where 4-repeat homozygotes had significantly lower Insatiability by Reward score compared to heterozygotes (F(2, 414) = 3.07, p = 0.048). In particular, lower (F(2, 414) = 3.36, p = 0.037) Giving in to Cravings subscale score was found in 4-repeat homozygotes, compared to heterozygotes and 5-repeat homozygotes (Figure 1). No association between *TFAP2B* genotype and Openness to Rewards or its facets was observed.
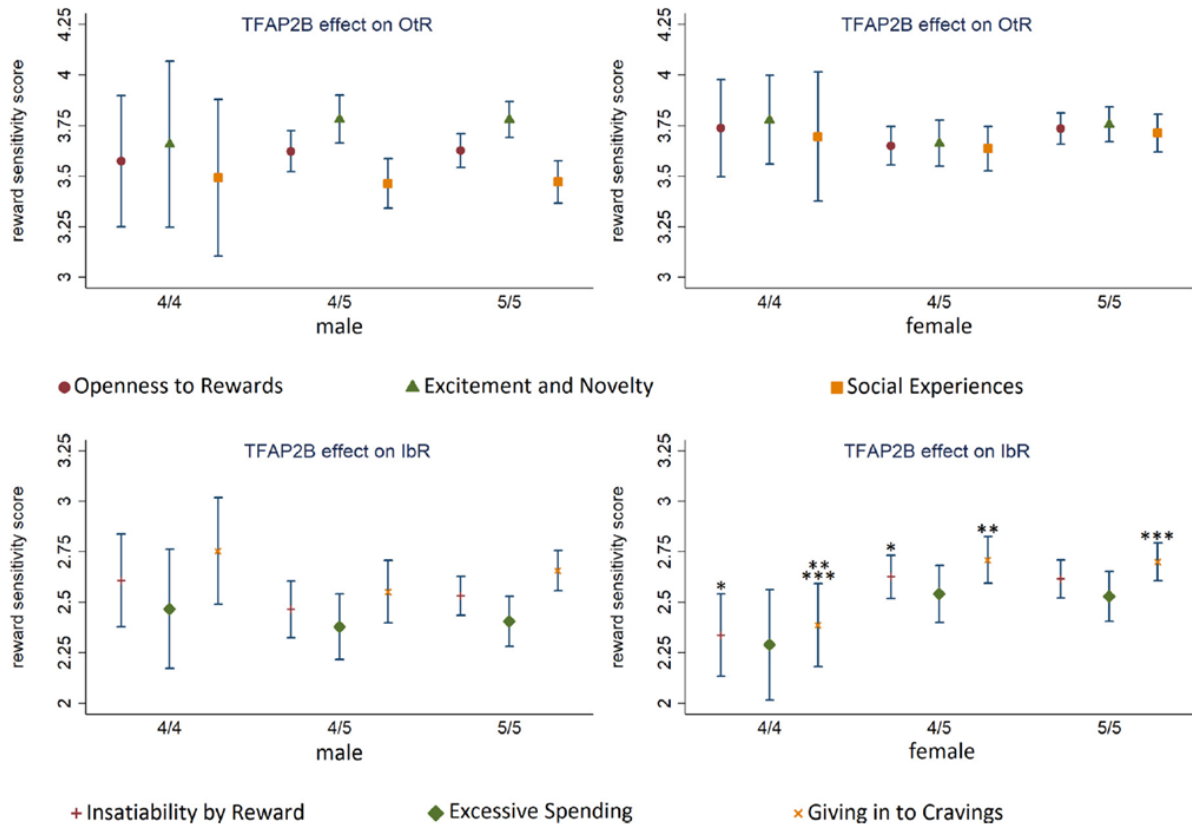

Figure 1. Association between *TFAP2B* intron 2 VNTR genotype and Openness to Rewards (OtR), Insatiability by Reward (IbR) and their subscales by sex.
* significant difference (p < 0.05) in the mean values of IbR score between *TFAP2B* intron 2 VNTR 4/4 and 4/5 genotype
** significant difference (p < 0.05) in the mean values of Giving in to Cravings score between *TFAP2B* intron 2 VNTR 4/4 and 4/5 genotypes
*** significant difference (p < 0.05) in the mean values of Giving in to Cravings score between *TFAP2B* intron 2 VNTR 4/4 and 5/5 genotypes

3.2. Reward sensitivity and measures of obesity

Linear mixed effects regression models adjusted for physical activity and daily energy intake showed a significant (p < 0.005) relationship between Insatiability by Reward and body weight, BMI, sum of five skinfolds, waist circumference, hip circumference and WHtR (Table 1). The

rate of change in body weight was 1.26 kg (95% CI 1.18; 1.34), BMI 0.31 kg/m^2 (95% CI 0.29; 0.34), sum of five skinfolds 1.92 mm (95% CI 1.68; 2.16), waist circumference 1.06 cm (95% CI 0.99; 1.12), hip circumference 0.85 cm (95% CI 0.79; 0.90) and WHtR 0.0051 units (95% CI 0.0047 to 0.0054) per year (Table 1).

A one-way ANOVA test at ages 9, 15, 18, 25 and 33 years revealed several differences in reward sensitivity between weight categories (Table 2). At age 9 years, a significant difference between weight categories, in Giving in to Cravings score, was observed ($F_{(2,362)}$ = 4.55, p = 0.011). After correcting by the Sidak method a trend, in Giving in to Cravings score, between normal weight and overweight subjects (by 0.29 units; 95% CI –0.01, 0.59; p = 0.057) was revealed. Similarly, overweight subjects had ($F_{(2,732)}$ = 4.23, p = 0.015) higher Giving in to Cravings score, compared to normal weight subjects, at age 15 years. At age 18 years, overweight subjects had ($F_{(2,655)}$ = 3.93, p = 0.020) greater Excitement and Novelty score and obese subjects had higher ($F_{(2,648)}$ = 4.09, p = 0.017) Insatiability by Reward, especially Excessive Spending ($F_{(2,648)}$ = 3.38, p = 0.035) score, compared to normal weight individuals. Both overweight and obese subjects had greater ($F_{(2,743)}$ = 8.08, p < 0.001) Insatiability by Reward scores, compared to normal weight subjects at age 25 years. At that age, obese subjects compared to normal weight subjects had also higher ($F_{(2,743)}$ = 6.35, p = 0.002) Excessive Spending and overweight subjects compared to normal weigh subjects higher ($F_{(2,743)}$ = 7.07, p = 0.001) Giving in to Cravings scores, compared to normal weight individuals. At age 33 years, overweight and obese subjects, compared to normal weight individuals had higher ($F_{(2,418)}$ = 6.34, p = 0.002) Insatiability by reward, especially Giving in to Cravings ($F_{(2,418)}$ = 7.77, p = 0.001) score, respectively (Table 2).

3.3. Reward sensitivity as a mediator

Our data met the assumptions for mediation analysis by Baron and Kenny (1986) [34] for TFAP2B genotype 4/4 (n = 33) vs. 5/5 (n = 228) and WHR at age 15 years through Giving in to Cravings subscale score in female subjects: TFAP2B was significantly associated with Giving in to Cravings score (α = 0.321, [95% CI 0.067 to 0.574], p = 0.013), Giving in to Cravings score was associated with WHR at age 15 years (β = 0.008, [95% CI 0.001 to 0.015], p = 0.019); *TFAP2B* was associated with WHR at age 15 years (γ = –0.020, [95% CI –0.034 to –0.006], p = 0.006). A trend in a natural indirect effect (NIE) was observed (p = 0.052) (Figure 2). No other associations were identified.

Table 1. Estimated main effects (mean and 95% CI) of the ECPBHS sample in anthropometric measurements from 15 to 25 years of age by reward sensitivity according to the linear mixed effects regression model adjusted for physical activity[1] and daily energy intake[2].

	Coefficient[3]	95% CI	p value		Coefficient[3]	95% CI	p value
Body weight (kg)				**Body weight (kg)**			
Openness to Rewards	0.36	−0.94; 1.66	0.588	Insatiability by Reward	2.27	1.16; 3.38	**< 0.001**
Excitement and Novelty	0.85	−0.29; 1.99	0.145	Excessive Spending	1.36	0.48; 2.24	**0.002**
Social Experiences	−0.25	−1.33; 0.83	0.648	Giving in to Cravings	2.13	1.09; 3.18	**< 0.001**
BMI (kg/m²)				**BMI (kg/m²)**			
Openness to Rewards	0.13	−0.23; 0.50	0.471	Insatiability by Reward	0.75	0.44; 1.06	**< 0.001**
Excitement and Novelty	0.16	−0.16; 0.48	0.321	Excessive Spending	0.47	0.22; 0.71	**< 0.001**
Social Experiences	0.04	−0.26; 0.34	0.784	Giving in to Cravings	0.68	0.39; 0.98	**< 0.001**
Sum of 5 skinfolds (mm)				**Sum of 5 skinfolds (mm)**			
Openness to Rewards	1.80	−1.45; 5.06	0.278	Insatiability by Reward	7.56	4.79; 10.33	**< 0.001**
Excitement and Novelty	−0.09	−2.94; 2.77	0.953	Excessive Spending	5.09	2.88; 7.30	**< 0.001**
Social Experiences	2.53	−0.15; 5.21	0.064	Giving in to Cravings	6.28	3.65; 8.91	**< 0.001**
Waist circumference (cm)				**Waist circumference (cm)**			
Openness to Rewards	0.34	−0.51; 1.19	0.437	Insatiability by Reward	1.38	0.66; 2.11	**< 0.001**
Excitement and Novelty	0.62	−0.12; 1.37	0.101	Excessive Spending	0.94	0.36; 1.51	**0.001**
Social Experiences	−0.08	−0.79; 0.62	0.816	Giving in to Cravings	1.14	0.45; 1.83	**0.001**
Hip circumference (cm)				**Hip circumference (cm)**			
Openness to Rewards	0.24	−0.56; 1.05	0.553	Insatiability by Reward	1.60	0.92; 2.29	**< 0.001**
Excitement and Novelty	0.24	−0.47; 0.94	0.508	Excessive Spending	0.98	0.43; 1.52	**< 0.001**
Social Experiences	0.13	−0.54; 0.79	0.704	Giving in to Cravings	1.48	0.83; 2.13	**< 0.001**
WHR (units)				**WHR (units)**			
Openness to Rewards	0.0006	−0.0056; 0.0067	0.854	Insatiability by Reward	0.0020	−0.0033; 0.0073	0.465
Excitement and Novelty	0.0040	−0.0013; 0.0094	0.138	Excessive Spending	0.0016	−0.0026; 0.0058	0.447
Social Experiences	−0.0028	−0.0078; 0.0023	0.285	Giving in to Cravings	0.0013	−0.0038; 0.0063	0.624
WHtR (units)				**WHtR (units)**			
Openness to Rewards	0.0020	−0.0026; 0.0065	0.390	Insatiability by Reward	0.0079	0.0040; 0.0118	**< 0.001**
Excitement and Novelty	0.0023	−0.0017; 0.0062	0.268	Excessive Spending	0.0056	0.0025; 0.0086	**< 0.001**
Social Experiences	0.0008	−0.0030	0.691	Giving in to Cravings	0.0063	0.0026; 0.0100	**0.001**

[1] Physical activity was assessed using self- and parent-reported questionnaires. Individual physical activity scores were calculated and standardized physical activity scores were used.

[2] During the day(s) before the study day, the subjects were asked to complete a 24h (year 1998), 48h (years 2001, 2004, 2007) or 72h (years 2008, 2014) diet record at home. On the study day, a face-to-face interview, to specify portion sizes, was conducted. Where data on two or three days was available the mean consumption was calculated.

[3] Coefficient can be interpreted as the mean change in anthropometric measurements at each time point if reward sensitivity score increases by one unit, adjusted for physical activity and daily energy intake

Table 2. Reward sensitivity (mean and SD) of the younger cohort at age 9, both cohorts from 15–25 years and older cohort at 33 years of the ECPBHS sample by body weight category.

	Openness to Rewards	Excitement and Novelty	Social Experiences	Insatiability by Reward	Excessive Spending	Giving in to Cravings
Age 9 years						
Individuals with normal weight[1a]	3.78 ± 0.52 (322)	3.87 ± 0.59 (322)	3.69 ± 0.66 (322)	2.57 ± 0.68 (322)	2.49 ± 0.86 (322)	2.64 ± 0.72 (322)
Individuals with overweight[1b]	3.65 ± 0.56 (36)	3.72 ± 0.68 (36)	3.58 ± 0.69 (36)	2.83 ± 0.69 (36)	2.72 ± 0.92 (36)	2.93 ± 0.64 (36)
Individuals with obesity[1c]	3.79 ± 0.48 (7)	3.86 ± 0.53 (7)	3.71 ± 0.57 (7)	2.88 ± 0.44 (7)	2.57 ± 0.76 (7)	3.18 ± 0.80 (7)$
Age 15 years						
Individuals with normal weight[1d]	3.65 ± 0.58 (661)	3.71 ± 0.65 (661)	3.58 ± 0.70 (661)	2.54 ± 0.66 (657)	2.45 ± 0.83 (657)	2.63 ± 0.69 (567)*
Individuals with overweight[1e]	3.65 ± 0.54 (69)	3.70 ± 0.66 (69)	3.59 ± 0.65 (69)	2.72 ± 0.64 (68)	2.55 ± 0.83 (68)	2.88 ± 0.71 (68)*
Individuals with obesity[1f]	3.84 ± 0.59 (11)	3.87 ± 0.53 (11)	3.82 ± 0.75 (11)	2.72 ± 0.80 (10)	2.78 ± 0.93 (10)	2.67 ± 0.83 (10)
Age 18 years						
Individuals with normal weight[2g]	3.64 ± 0.57 (566)	3.70 ± 0.65 (566)*	3.58 ± 0.68 (566)	2.51 ± 0.66 (561)#	2.41 ± 0.82 (561)#	2.60 ± 0.70 (561)
Individuals with overweight[2h]	3.81 ± 0.54 (74)	3.92 ± 0.55 (74)*	3.69 ± 0.72 (74)	2.62 ± 0.65 (72)	2.48 ± 0.86 (72)	2.76 ± 0.69 (72)
Individuals with obesity[2i]	3.60 ± 0.68 (18)	3.68 ± 0.67 (18)	3.52 ± 0.82 (18)	2.91 ± 0.50 (18)#	2.91 ± 0.67 (18)#	2.91 ± 0.62 (18)
Age 25 years						
Individuals with normal weight[2g]	3.68 ± 0.58 (540)	3.75 ± 0.65 (540)	3.61 ± 0.70 (540)	2.49 ± 0.66 (537)*#	2.39 ± 0.83 (537)#	2.59 ± 0.70 (537)*
Individuals with overweight[2h]	3.60 ± 0.55 (142)	3.64 ± 0.63 (142)	3.55 ± 0.66 (142)	2.69 ± 0.61 (141)*	2.57 ± 0.81 (141)	2.81 ± 0.62 (141)*
Individuals with obesity[2i]	3.69 ± 0.50 (70)	3.77 ± 0.55 (70)	3.61 ± 0.67 (70)	2.74 ± 0.65 (68)#	2.71 ± 0.82 (68)#	2.78 ± 0.67 (68)
Age 33 years						
Individuals with normal weight [2g]	3.54 ± 0.62 (251)	3.59 ± 0.70 (251)	3.49 ± 0.72 (251)	2.42 ± 0.66 (249)*#	2.34 ± 0.85 (249)	2.50 ± 0.67 (249)*#
Individuals with overweight[2h]	3.52 ± 0.53 (128)	3.56 ± 0.60 (128)	3.48 ± 0.69 (128)	2.62 ± 0.54 (127)*	2.52 ± 0.66 (127)	2.73 ± 0.63 (127)*
Individuals with obesity[2i]	3.67 ± 0.54 (48)	3.71 ± 0.61 (48)	3.64 ± 0.66 (48)	2.68 ± 0.58 (45)#	2.53 ± 0.65 (45)	2.83 ± 0.64 (45)#

[1] definition by Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ*. 2000; 320(7244):1240-3.

[2] definition by World Health Organization. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Health Organ Tech Rep Ser 2000;894:1–253.

[a] Individuals with normal weight (BMI < 19.10 kg/m^2 in males and < 19.07 kg/m^2 in females); [b] individuals with overweight (BMI ≥ 19.10 kg/m^2 and < 22.77 kg/m^2 in males and ≥ 19.07 kg/m^2 and < 22.81 kg/m^2 in females); [c] individuals with obesity (BMI ≥ 22.77 kg/m^2 in males and ≥ 22.81 kg/m^2 in females)

[d] Individuals with normal weight (BMI < 23.29 kg/m^2 in males and < 23.94 kg/m^2 in females); [e] individuals with overweight (BMI ≥ 23.29 kg/m^2 and < 28.30 kg/m^2 in males and ≥ 23.94 kg/m^2 and < 29.11 kg/m^2 in females); [f] individuals with obesity (BMI ≥ 28.30 kg/m^2 in males and ≥ 29.11 kg/m^2 in females)

[g] Individuals with normal weight (BMI < 25.00 kg/m^2); [h] individuals with overweight (BMI ≥ 25.00 and < 30.00 kg/m^2); [i] individuals with obesity (BMI ≥ 30.00 kg/m^2)

* P < 0.05 significant difference in the mean values of reward sensitivity between individuals with normal weight and individuals with overweight corrected by the Sidak method

# P < 0.05 significant difference in the mean values of reward sensitivity between individuals with normal weight and individuals with obesity corrected by the Sidak method

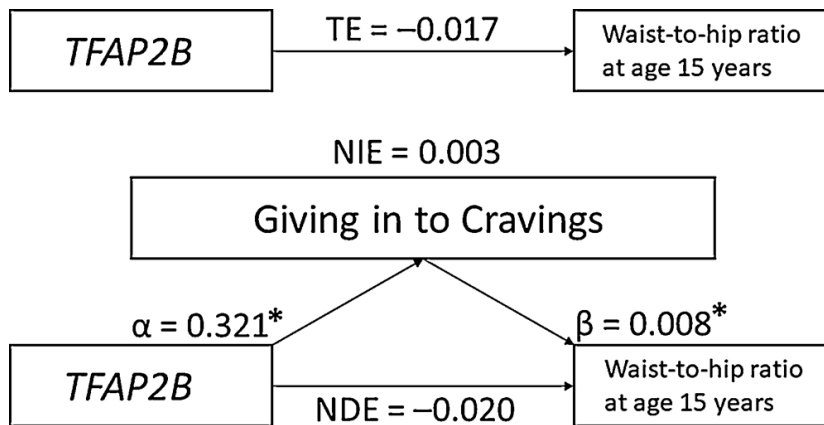$ P > 0.05 significant differences were not found between weight groups after correcting by the Sidak method

Figure 2. Mediation model with parameter estimates for *TFAP2B* (*p < 0.05). Observed variables are shown in boxes. The pathways are indicated with letters: pathway α represents the direct effect of the *TFAP2B* on the mediator Giving in to Cravings; pathway β represents the direct effect of the mediator Giving in to Cravings on waist-to-hip ratio at age 15 years; TE represents the total effect of *TFAP2B* on waist-to-hip ratio at age 15 years; natural direct effect (NDE) represents the effect of *TFAP2B* on waist-to-hip ratio at age 15 years unmediated by the mediator Giving in to Cravings; natural indirect effect (NIE) is the effect of change in the mediator Giving in to Cravings on waist-to-hip ratio at age 15 years if *TFAP2B* genotype is 4/4.

4. Discussion

Inconsistent findings on the role of reward sensitivity in obesity, from no relationship between reward sensitivity and BMI [14,15,35] to a positive [10] or a U-shaped relationship [36,37], have been described. Two systematic reviews have reported that reward sensitivity is increased in people with obesity, and appears to be more pronounced in individuals with binge eating disorder [38,39]. Franken and Muris (2005) demonstrated that reward sensitivity was significantly correlated with BMI in women, which remained significant after adjusting for food cravings [40]. Jonker et al. (2019) found no difference between reward responsiveness, reward drive, attention for cues signaling and reward punishment sensitivity in adolescents with obesity or with normal weight [14]. The effect of the unique inner structure of reward sensitivity on measures of obesity, which may explain for the controversial results, has previously remained unexplored.

The ROIS scale [28], was used to assess the relationship between reward sensitivity and measures of obesity from 9 to 33 years of age. We observed that higher Insatiability by Reward and its subscale scores, which consist of items reflecting trouble resisting temptations and cravings, overindulging, excessive spending and impulsivity, were associated with higher measures of overall and abdominal obesity from 15 to 25 years of age. Moreover, a trend in Giving in to Cravings score, between normal weight and overweight subjects at age 9 years,

and a dose-response relationship at age 33 years in Insatiability by Reward, especially in Giving in to Cravings score, where reward sensitivity score increased together with BMI category, was observed. However, no longitudinal association between obesity and scores of Openness to Rewards, including items such as openness to new things and experiences, adventures and social situations, were detected. Our results suggest that it is necessary to consider different types of reward sensitivity in exploring the causes and mechanisms behind obesity.

We demonstrated that Insatiability by Reward and more specifically the Giving in to Cravings subscale scores were significantly lower in female *TFAP2B* 4/4 homozygotes compared to heterozygotes and 5/5 homozygotes. Differences between the sexes in personality traits, estimated by Karolinska Scales of Personality, have been described previously [20]. Because of its impact on both serotonin and dopamine systems, and our previous results demonstrating *TFAP2B* 5/5 homozygotes having higher measures of obesity, we hypothesized that *TFAP2B* and measures of obesity were indirectly associated through reward sensitivity. Mediation analysis however did not render such associations beyond the indirect relationship between *TFAP2B* and waist-to-hip ratio at age 15 years in female subjects through Giving in to Cravings, which was not statistically significant (p = 0.052). The small sample in our analysis, and thus limited statistical power, means the possibility of type II error is considerable. Therefore, we cannot be certain whether the associations are truly zero.

There are several limitations to our study. The ECPBHS is a longitudinal birth cohort study with a population representative sample of individuals of European descent. Therefore, the results cannot be extrapolated to other ethnicities. Secondly, the ROIS instrument [28], used for the assessment of reward sensitivity, was developed *post hoc*, applied in a Finnic language, and requires further development and characterization together with related instruments; nevertheless, it provides a unique inner structure for reward sensitivity that is consistent with the predictions of the affective neuroscience approach to personality [41-43]: Openness to Rewards and Insatiability by Reward are clearly dissociated in this model, the former being positively associated with SEEKING and PLAY (and less with CARE), and the latter with FEAR, SADNESS and ANGER [28].

Our results suggest differences between the inner structure of reward sensitivity and measures of obesity. Understanding the inner structure of reward sensitivity and its relation

with obesity is of great importance in developing behavioural interventions. Studies with larger sample size are needed to assess the possible indirect effect of *TFAP2B* on measures of obesity through reward sensitivity. Reward sensitivity cannot directly cause obesity, therefore further studies should clarify the relationship between the inner structure of reward sensitivity and eating behaviours, including disordered eating, and explore associations with physical activity.

ACKNOWLEDGEMENTS

COMPETING INTERESTS

The authors declare no competing financial interests.

Colors need not be used for any figures in print.

REFERENCES

[1] R.B. Mansur, E. Brietzke, R.S. McIntyre, Is there a "metabolic-mood syndrome"? A review of the relationship between obesity and mood disorders, Neurosci. Biobehav. Rev. 52 (2015) 89–104.
[2] M.K. Campbell, Biological, environmental, and social influences on childhood obesity, Pediatr. Res. 79 (2016) 205–211.
[3] J.A. Gray, Three fundamental emotion systems, in: P. Ekman, J.R. Davidson (Eds.), In The Nature of Emotion: Fundamental Questions, Oxford University Press, 1994.
[4] J. Gray, N. McNaughton, The Neuropsychology of Anxiety, Oxford University Press, 2000.
[5] L.D. Smillie, A.D. Pickering, C.J. Jackson, The new reinforcement sensitivity theory: implications for personality measurement, Pers. Soc. Psychol. Rev. 10 (2006) 320–335.
[6] N.J. Loxton, R.J. Tipman, Reward sensitivity and food addiction in women, Appetite 115 (2017) 28–35.
[7] N.D. Volkow, G.J. Wang, R.D. Baler, Reward, dopamine and the control of food intake: implications for obesity, Trends. Cogn. Sci. 15 (2011) 37–46.

[8] C. Davis, Compulsive overeating as an addictive behavior: overlap between food addiction and binge eating disorder, Curr. Obes. Rep. 2 (2013) 171–178.

[9] C. Davis, K. Patte, R. Levitan, et al., From motivation to behaviour: a model of reward sensitivity, overeating, and food preferences in the risk profile for obesity, Appetite 48 (2007) 12–19.

[10] A. De Decker, I. Sioen, S. Verbeken, et al., Associations of reward sensitivity with food consumption, activity pattern, and BMI in children, Appetite 100 (2016) 189–196.

[11] D.G. Tatnell, N.J. Loxton, K.L. Modecki, et al., Testing a model of reward sensitivity, implicit and explicit drinker identity and hazardous drinking, Psychol. Health 34 (2019) 1407–1420.

[12] N.C. Jonker, B.D. Ostafin, K.A. Glashouwer, et al., Reward and punishment sensitivity and alcohol use: the moderating role of executive control, Addict. Behav. 39 (2014) 945–948.

[13] N.N. Emery, J.S. Simons, A reinforcement sensitivity model of affective and behavioral dysregulation in marijuana use and associated problems, Exp. Clin. Psychopharmacol. 25 (2017) 281–294.

[14] N.C. Jonker, E. van Malderen, K.A. Glashouwer, et al., No differential reward responsivity and drive, punishment sensitivity or attention for cues signaling reward or punishment in adolescents with obesity, Front. Psychol. 10 (2019) 2363.

[15] N.C. Jonker, K.A. Glashouwer, B.D. Ostafin, et al., Attentional Bias for reward and punishment in overweight and obesity: the TRAILS study, PLoS One 11 (2016) e0157573.

[16] L. van den Berg, K. Pieterse, J.A. Malik, et al., Association between impulsivity, reward responsiveness and body mass index in children, Int. J. Obes. 35 (2011) 1301–1307.

[17] A. Merchán-Clavellino, M.P. Salguero-Alcañiz, R. Guil, et al., Impulsivity, emotional ntelligence, and alcohol consumption in young people: a mediation analysis, Foods 9 (2020) 71.

[18] A.G. Fischer, M. Ullsperger, An update on the role of serotonin and its interplay with dopamine for reward, Front. Hum. Neurosci. 11 (2017) 484.

[19] U. Joost, I. Villa, E. Comasco, et al., Association between Transcription Factor AP-2B genotype, obesity, insulin resistance and dietary intake in a longitudinal birth cohort study, Int. J. Obes. 43 (2019) 2095–2106.

[20] M. Damberg, H. Garpenstrand, J. Alfredsson, et al., A polymorphic region in the human transcription factor AP-2beta gene is associated with specific personality traits, Mol. Psychiatry 5 (2000) 220–224.

[21] M. Damberg, H. Garpenstrand, J. Hallman, et al., Genetic mechanisms of behavior - don't forget about the transcription factors, Mol. Psychiatry 6 (2001) 503–510.

[22] C. Gamero-Villarroel, L.M. González, R. Rodríguez-López, et al., Influence of TFAP2B and KCTD15 genetic variability on personality dimensions in anorexia and bulimia nervosa, Brain Behav. 7 (2017) e00784.

[23] N. Nordquist, C. Göktürk, E. Comasco, et al., Transcription factor AP2 beta involved in severe female alcoholism, Brain Res. 1305 (2009) S20–26.

[24] M. Damberg, M. Eller, M. Tõnissaar, et al., Levels of transcription factors AP-2alpha and AP-2beta in the brainstem are correlated to monoamine turnover in the rat forebrain, Neurosci. Lett. 313 (2001) 102–104.

[25] M. Damberg, C. Berggård, L. Farde, et al., Transcription factor AP-2beta genotype, striatal dopamine D2 receptor density and cerebrospinal fluid monoamine metabolite concentrations in humans, J. Neural Transm. 111 (2004) 537–545.

[26] P. Corr, The Reinforcement Sensitivity Theory of Personality: Introduction, Cambridge University Press, 2008.

[27] P. Corr, D. Krupic, Motivating Personality: Approach, Avoidance, and Their Conflict, Elsevier Academic Press, 2017.

[28] A. Pulver, E. Kiive, J. Harro, Reward sensitivity, affective neuroscience personality, symptoms of attention deficit/hyperactivity disorder, and TPH2-703G/T (rs4570625) genotype, Acta. Neuropsychiat. (2020), https://doi.org/10.1017/neu.2020.18 [in press].

[29] Q. Chen, C.A. Hartman, J. Haavik, et al., Common psychiatric and metabolic comorbidity of adult attention-deficit/hyperactivity disorder: a population-based cross-sectional study, PLoS One 13 (2018) e0204516.

[30] M. Harro, D. Eensoo, E. Kiive, et al., Platelet monoamine oxidase in healthy 9- and 15-years old children: the effect of gender, smoking and puberty, Prog. Neuropsychopharmacol. Biol. Psychiatry 25 (2001) 1497–1511.

[31] E. Mäestu, J. Harro, T. Veidebaum, et al., Changes in cardiorespiratory fitness through adolescence predict metabolic syndrome in young adults, Nutr. Metab. Cardiovasc. Dis. 30 (2020) 701–708.

[32] N. Nordquist, C. Göktürk, E. Comasco, et al., The transcription factor TFAP2B is associated with insulin resistance and adiposity in healthy adolescents, Obesity 17 (2009) 1762–1767.

[33] K.J. Preacher, A.F. Hayes, Asymptotic and resampling strategies for assessing and comparing indirect effects in multiple mediator models, Behav. Res. Methods 40 (2008) 879–891.

[34] R.M. Baron, D.A. Kenny, The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations, J. Pers. Soc. Psychol. 51 (1986) 1173–1182.

[35] A. Matton, L. Goossens, C. Braet, et al., Punishment and reward sensitivity: are naturally occurring clusters in these traits related to eating and weight problems in adolescents? Eur. Eat. Disord. Rev. 21 (2013) 184–194.

[36] S. Verbeken, C. Braet, J. Lammertyn, et al., How is reward sensitivity related to bodyweight in children? Appetite 58 (2012) 478–483.

[37] A. Dietrich, M. Federbusch, C. Grellmann, et al., Body weight status, eating behavior, sensitivity to reward/punishment, and gender: relationships and interdependencies, Front. Psychol. 5 (2014) 1073.

[38] K. Schag, J. Schönleber, M. Teufel, et al., Food-related impulsivity in obesity and binge eating disorder - a systematic review, Obes. Rev. 14 (2013) 477–495.

[39] K.E. Giel, M. Teufel, F. Junne, et al., Food-related impulsivity in obesity and binge eating disorder - a systematic update of the evidence, Nutrients 9 (2017) 1170.

[40] I.H.A. Franken, P. Muris, Individual differences in reward sensitivity are related to food craving and relative body weight in healthy women, Appetite 45 (2005) 198–201.

[41] J. Panksepp, Affective Neuroscience: The Foundations of Human and Animal Emotions, Oxford University Press, 1998.

[42] C. Montag, J. Panksepp, Primary emotional systems and personality: an evolutionary perspective, Front. Psychol. 8 (2017) 464.

[43] K.L. Davis, C. Montag, Selected principles of Pankseppian affective neuroscience, Front. Neurosci. 12 (2018) 1025.