Published in final edited form as:

Acta Neuropsychiatr. 2020 August ; 32(4): 218–225. doi:10.1017/neu.2020.14.

Association Between GLP-1 Receptor Gene Polymorphisms with Reward Learning, Anhedonia, and Depression Diagnosis

Hale Yapici Eser^{1,2}, Vivek Appadurai^{3,4}, Candan Yasemin Eren², Dilek Yazici¹, Chia-Yen Chen^{5,6}, Dost Ongur^{6,7}, Diego A. Pizzagalli^{6,8}, Thomas Werge^{3,4,9}, Mei-Hua Hall^{6,7,10}

¹Koç University, School of Medicine, Istanbul, Turkey

²Koç University, Research Center for Translational Medicine, Istanbul, Turkey

³The Lundbeck Foundation Initiative for Integrative Psychiatric Research, iPSYCH, Aarhus, Denmark.

⁴Institute of Biological Psychiatry, Mental Health Center St. Hans, Mental Health Services Copenhagen, Roskilde, Denmark.

⁵Psychiatric and Neurodevelopmental Genetics Unit and Analytic and Translational Genetics Unit, Massachusetts General Hospital, Boston, MA, USA

⁶Department of Psychiatry, Harvard Medical School, Boston, MA, USA

⁷Schizophrenia and Bipolar Disorder Research Program, McLean Hospital, Belmont, MA, USA

⁸Center for Depression, Anxiety and Stress Research, McLean Hospital, Belmont, MA, USA.

⁹Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark.

¹⁰Psychosis Neurobiology Laboratory, McLean Hospital, Harvard Medical School, Belmont, MA, USA.

Abstract

CORRESPONDING AUTHOR: Hale Yapici Eser, M.D., Ph.D., Address: Koc University Hospital, Davutpasa Caddesi No:4, Topkapi, Istanbul, Turkey, Phone number: +90 850 250 8 250, Fax number: +90 850 250 8 250, hyapici@ku.edu.tr.

Authors Contributions

All authors contributed substantially to either conception and design of, or acquisition of data or analysis and interpretation of data. Data from McLean hospital has been provided by MHH and imputed for missing genetic data by CYC. Statistical analysis for McLean data has been conducted by HYE and statistical analysis of PGC-MDD data has been conducted by VA. HYE wrote the draft and all authors contributed substantially to drafting the article or revising it critically for important intellectual content and all authors approved the final version to be published.

Statement of interest

Over the past three years, DAP has received consulting fees from Blackthorn Therapeutics, Boehringer Ingelheim, Compass, Takeda and an honorarium from Alkermes for activities unrelated to the current research. Dr. Pizzagalli has a financial interest in BlackThorn Therapeutics, which has licensed the copyright to the Probabilistic Reward Task through Harvard University. Dr. Pizzagalli's interests were reviewed and are managed by McLean Hospital and Partners HealthCare in accordance with their conflict of interest policies. DO served on a scientific advisory board for Neurocrine Inc on 12/2016.

Ethical Standards

This study was approved by McLean Hospital Institutional Review Board. All subjects provided a written informed consent and procedures were in accordance with the Declaration of Helsinki. 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.

Background: Glucagon-like peptide-1 receptors (GLP-1R) are widely expressed in the brain. Evidence suggests that they may play a role in reward responses and neuroprotection. However, the association of GLP-1R with anhedonia and depression diagnosis has not been studied. Here, we examined the association of GLP-1R polymorphisms with objective and subjective measures of anhedonia, as well as depression diagnosis.

Methods: Objective (response bias assessed by the Probabilistic Reward Task (PRT)) and subjective (Snaith-Hamilton Pleasure Scale (SHAPS)) measures of anhedonia, clinical variables and DNA samples were collected from 100 controls and 164 patients at McLean Hospital. An independent sample genotyped as part of the Psychiatric Genomics Consortium (PGC) was used to study the effect of putative GLP-1R polymorphisms linked to response bias in PRT on depression diagnosis.

Results: The C allele in rs1042044 was significantly associated with increased PRT response bias, when controlling for age, sex, case-control status and PRT discriminability. AA genotype of rs1042044 showed higher anhedonia phenotype based on SHAPS scores. However, analysis of PGC MDD data showed no association between rs1042044 and depression diagnosis.

Conclusion: Findings suggest a possible association of rs1042044 with anhedonia, but no association with depression diagnosis.

Keywords

GLP-1; polymorphism; anhedonia; reward; depression

1. Introduction

Mood disorders are one of the most costly and debilitating psychiatric conditions worldwide, and are associated with impairments, as disrupted reward processing. Patients with mood disorders show deficits in reward learning and they present with anhedonia (Sharma et al., 2015; Lewandowski et al., 2016). Reduced reward sensitivity is also considered a core feature of depression (Nusslock and Alloy, 2017). Disrupted reward learning correlates with mood fluctuations (Peterson et al., 2011) and predicts persistence of depressive symptoms (Vrieze et al., 2013). However, altered reward processing is not unique to mood disorders as major depressive disorder (MDD), since it has emerged also in schizophrenia spectrum disorders (SZ), substance use disorders and other behavioural addictions (Luijten et al., 2017).

Dopaminergic signaling and frontostriatal circuits have been hypothesized to play an essential role in the reward system. However, reward processing includes pleasure, motivation, satiety, salience and even trust, that are modulated by various neuromodulators (Dichter et al., 2012). Also, reward prediction, evaluation and learning contribute to reward processing and they are suggested to have different neuroanatomical correlates, that may be specifically targeted by specific neuromodulators (Delgado et al., 2005). Therefore, it is essential to understand the other neuromodulators that take part in reward processing which may ultimately yield better treatment targets and neuropathological markers (Gold et al., 2018). As one of these neuromodulators, glucagon-like peptide-1 (GLP-1) is likely to play a role in modulating reward circuitry. Current evidence links GLP-1 with food-related reward

(Skibicka, 2013), social reward (Clark-Elford et al., 2014), stress (Rinaman and Rothe, 2002) and despair-like behaviors (Sharma et al., 2015; Anderberg et al., 2016).

GLP-1 is an incretin hormone secreted by intestinal cells in response to food consumption. Its main role has been explored for peripheral blood glucose level regulation and control of type 2 diabetes mellitus (T2DM) (Aroda, 2018). On the other hand, GLP-1 can also be produced centrally by neurons of the nucleus tractus solitarius and microglia (Kappe et al., 2012) by cleavage of preproglucagon and act through GLP-1 receptors (GLP-1R) in the brain (GLP-1R).

Critically, GLP-1 receptors (GLP-1R) are widely expressed in reward-related regions, such as the hypothalamus, amygdala, nucleus accumbens, paraventricular nucleus, ventral tegmental area, locus coeruleus and brain stem (Heppner et al., 2015), and have been found to modulate food-related activation in the insula and putamen (Farr et al., 2016). All GLP-1R are stimulatory G protein coupled and when activated, they cause increases in cAMP and intracellular calcium, they activate protein kinase A, and induce gene transcription (Drucker, 2006). These receptors are expressed in both dendrites and synapses of neurons, in addition to glial cells (Chowen et al., 1999). Evidence from animal and molecular studies suggests that they may have a role in reward processing and neuroprotection. Overexpression/upregulation of GLP-1R or modulating GLP-1R functions by using pharmaceutical agents that can pass the blood-brain barrier, promotes learning of spatial tasks, memory formation, synaptic plasticity, neurite outgrowth and neurogenesis (Erbil et al., 2019).

Animal studies also support a role of GLP-1 with reward responses and depression. Activation of GLP-1R reduces cocaine-mediated behaviors and modulates substance use through regulating dopamine release (Hernandez et al., 2019) and corticosterone levels through corticotropin releasing hormone (CRH) function in the hypothalamus-pituitary-adrenal (HPA) axis (Zheng et al., 2019). More specifically, GLP-1 receptor knock down rats showed prolonged corticosterone levels after stress induction (Zheng et al., 2019) and administration of exendin-4, which is a GLP-1 receptor agonist, increased plasma levels of ACTH (Malendowicz et al, 2003) and corticosterone in plasma of rats (Malendowicz et al, 2003; Krass et al, 2012) and mice (Krass et al, 2015), suggesting a role of GLP-1 on regulating hypothalamus-pituitary-adrenal (HPA) axis. GLP-1 neurons synapse on CRH neurons of paraventricular nucleus (Sarkar et al., 2003) and restraint stress in mice changes GLP-1 function (Williams et al., 2018). Prenatal stress reduces GLP-1R levels in hippocampus and hypothalamus (Detka et al., 2019). GLP-1 levels alter glutamatergic transmission and excitotoxicity (Koshal et al., 2018), and increased GLP-1R levels improve neurogenesis and decrease cell loss in hippocampal area (Erbil et al., 2019). Decreased hippocampal neurogenesis, neuronal atrophy and synaptic loss in the hippocampus represent key neurobiological findings of stress-related disorders and anhedonia (Duman and Aghajanian, 2012). Chronic central administration (Anderberg et al., 2016) or injection (Sharma et al., 2015) of GLP-1 agonists decrease despair-like behavior and have an antidepressant-like effect measured by mobility in forced swim test in rats, although two studies found no change in anxiety (assessed using light-dark box) and mobility (assessed using forced swim test) after acute (Krass et al, 2012) or two weeks (Krass et al, 2015)

treatments of GLP-1 agonist administration in mice. GLP-1 changes serotonin turnover in the amygdala (Anderberg et al., 2016) and affects basal serotonin levels (Brunetti et al., 2008). GLP-1 also acts on oxytocin and NPY neurons, which regulate social rewards and resilience to stress (Clark-Elford et al., 2014).

These preclinical findings highlight the effects of GLP-1 on reward circuitry, depressive behaviors and stress, suggesting that GLP-1 is a promising candidate for modulating reward learning in humans. However, as evidence from animal studies on the effect of GLP-1 on neuroprotection and reward responses is accumulating, there is limited human research testing its relationship with depressive episode and reward learning. In humans, GLP-1R polymorphisms may modulate basal GLP-1 levels (de Luis et al., 2015), and importantly, a recent post-mortem study found that, compared to healthy controls, patients with MDD diagnosis had decreased GLP-1R expression in the dorsolateral prefrontal cortex and hippocampus, even when adjusting for age, sex, treatments, substance use and body mass index (Mansur et al., 2019).

Aims of the Study

Building on this knowledge, in the current study, we first aimed to assess the association of GLP-1R polymorphisms with reward learning in a case-control sample, using a well-established laboratory-based task, the Probabilistic Reward Task (PRT). Reward learning includes processes that shape the experience-dependent learning that guides future behaviours, and is used to assess how participants modulate their behavior as a function of rewards (Pizzagalli et al., 2005). Total response bias measured by PRT is used to capture reward learning. We predicted that GLP-1R polymorphisms modulated response bias in PRT, regardless of a psychiatric diagnosis. Secondly, we tested the effect of GLP-1R polymorphisms on a subjective measure of anhedonia (Rizvi et al., 2016) using the Snaith-Hamilton Pleasure Scale (SHAPS) (Snaith et al., 1995; Rizvi et al., 2016). SHAPS probes the capacity to experience pleasure over the past few days. In the association analyses, we adjusted for clinical measures that could be the potential moderators of response bias, such as the The General Distress related to Anxiety (GDA) and Anxious Arousal (AA) subscales of the Mood and Anxiety Symptom Questionnaire (MASQ), The Montgomery Asberg Depression Rating Scale (MADRS), Positive and Negative Symptom Scale (PANSS) and the Young Mania Rating Scale (YMRS). Lastly, we tested the effect of putative GLP-1R polymorphisms linked to response bias with lifetime depression diagnosis by examining the association of GLP-1R polymorphisms with depression diagnosis using summary statistics from the GWAS of Major Depressive Disorder from the Psychiatric Genomics Consortium (Wray et al., 2018).

2. Materials & Methods

2.1. Association of GLP-1 polymorphisms with Reward Learning and Anhedonia

In order to assess the effect of GLP-1R polymorphisms on reward learning, we first analysed each GLP-1R polymorphism's impact on reward learning using data from a case-control cohort from McLean Hospital (Lewandowski et al., 2016; Hall et al., 2015). For a stringent test, analyses were corrected for possible moderator variables that could affect reward

learning. As reward learning dysfunction is found across diagnostic boundaries, including MDD, bipolar disorder (BPD) and SZ (Pizzagalli et al., 2008; Whitton et al., 2015) diagnoses, our study cohort included patients with mood disorders, psychotic disorders and healthy controls.

2.1.1 Participants—Data from 264 participants (100 healthy controls and 164 patients; 126 females (47.7%), 138 males (52.3 %)) were available for analyses. All subjects were assessed using the The Structured Clinical Interview for DSM-IV (SCID-IV) (Allen, 1998). Patients were recruited through the Schizophrenia and Bipolar Disorder program at McLean Hospital. Of the 164 patients who had a history of lifetime psychotic episode, 70 were diagnosed with a schizophrenia spectrum disorder, 92 with bipolar disorder and two with a major depressive disorder. Patients were included if they had no substance abuse (excluding nicotine) in the preceding 6 months or dependence in the preceding 12 months and no history of seizures or ECT treatment in the preceding 12 months. The control sample was recruited through local advertisements. Additional inclusion criteria for controls were: no current or past history of psychotic disorder, bipolar disorder, or SZ, no affective disorder in the preceding 12 months, no substance abuse in the preceding 12 months or previous chronic dependence, and no first-degree relative with a history of psychosis or bipolar disorder. All subjects self-reported European ancestry, which was confirmed based on principal component analyses of genotype data. All participants were between 18 and 69 years old (range: 18–69, mean±SD: 38.8±13.8) with no known neurological disorder, no prior head injury with loss of consciousness, normal hearing confirmed by audiometry, and normal intellectual ability based on the North American Adult Reading Test (NAART) or years of education (high school level or higher). As dysfunction of reward learning is found transdiagnostically (Pizzagalli et al., 2008; Whitton et al., 2015), analyses used case-control status as a moderator variable, instead of splitting into diagnostic groups. This study was approved by McLean Hospital Institutional Review Board. All subjects provided a written informed consent and procedures were in accordance with the Declaration of Helsinki.

2.1.2. Evaluation of Reward Learning—The Probabilistic Reward Task (PRT) was used to derive an objective measure of reward learning, and has been described in details (Pizzagalli et al., 2005; Pizzagalli et al., 2008). The task includes three blocks with 100 trials each. In each trial, participants are shown a face with a long (13 mm) or short (11.5 mm) mouth, and instructed to decide whether the mouth was long or short, as quickly and accurately as possible. They are further instructed that correct responses would be followed by a monetary reward (“Correct. You won 20 cents”) but that not every correct answer would be followed by a monetary reward. Unbeknownst to participants, one stimulus is rewarded three times more frequently than the other, which induces a response bias, that is, a preference for the stimulus paired with more reward in the past. Using signal-detection theory, performance can be decomposed into response bias and discriminability. Response bias measures subject’s preference for the response paired with the more frequent reward and discriminability measures how well the participant can differentiate between two very close visual stimuli. Here, we used total response bias scores as the major outcome variable to detect reward learning.

2.1.3. Self-Report Measurement of Anhedonia and Other Psychiatric

Symptom Scales—All participants were also evaluated with clinical scales to control for other variables that could moderate reward responses and anhedonia, and to document the clinical status of the patients. The Snaith-Hamilton Pleasure Scale (SHAPS) was used to assess subjective anhedonia (Snaith et al., 1995). While scoring, the answer of each item of SHAPS scale was converted to binary categories (0 and 1), so that the total score ranged between 0 to 14 and higher scores indicated higher anhedonia. Participants with scores higher or equal to 3 in SHAPS score were recategorized as the anhedonic group (Snaith et al., 1995; Franken et al., 2007).

The General Distress related to Anxiety (GDA) and Anxious Arousal (AA) subscales of the Mood and Anxiety Symptom Questionnaire (MASQ) were used to assess anxiety symptoms. The Montgomery Asberg Depression Rating Scale (MADRS) was used to assess depression severity. PANSS Positive and PANSS Negative scales were used to evaluate symptoms related to psychosis and the Young Mania Rating Scale (YMRS) was used to evaluate (hypo)manic symptoms.

2.1.4. Selection of GLP-1R Polymorphisms and Genotyping Procedure—The sample reported in this study was part of a larger genome-wide association study previously published (Hall et al., 2015). GLP-1 gene lies in the 6p21.2. Results from previous genetic studies on the role of GLP-1R polymorphisms revealed associations with peripheral effects such as weight loss after obesity surgery (de Luis et al., 2014a), insulin resistance and obesity complications (Sathananthan et al., 2010; de Luis et al., 2014b), as well as central effects as antipsychotic response (Ramsey and Brennan, 2014) and stress and cortisol responses (Sheikh et al., 2010b; Sheikh et al., 2010a). We reviewed the current literature for GLP-1R SNPs and found 9 SNPs in the GLP-1R gene, which are not in linkage disequilibrium, for an association analysis and 7 could be genotyped in our sample: rs10305420, rs10305421, rs1042044, rs6923761, rs587654, rs761386, rs10305492. Of the 7 SNPs examined here, rs10305420 and rs1042044 were genotyped and remaining were imputed by author CHC, since the polymorphism was not included in the CHIP. Genotype imputation was performed using a 2-step prephasing and imputation procedure implemented in SHAPEIT (O'Connell et al., 2016) and IMPUTE2 (Howie et al., 2011) on a total of 1,293 psychosis patients and 381 healthy controls collected at McLean Hospital that included the samples described above (Hall et al., 2015). We divided the genome into 3 Mb partitions and performed pre-imputation quality control and imputation with the default parameters of the software. The pre-imputation quality control filters include discordant sex information, missing genotype rate per individual, heterozygosity rate, call rate per SNP, deviation from Hardy-Weinberg equilibrium. We used phased haplotypes from the full 1,000 Genomes Project data set (Altshuler et al., 2015) as the imputation reference panel.

2.1.5. Statistics—Genotypes of GLP-1R polymorphisms were compared for the mean response bias scores in the PRT and anhedonia scores measured by SHAPS scale, using Mann Whitney U test for dominant models. The anhedonic group defined based on SHAPS score was then compared to non-anhedonic group for the distribution of the significant dominant genotype, using chi-square test. Next, to control for possible moderator variables

that could have an effect on response bias, a multivariate linear regression model was used. In the first model, age, sex, discriminability in the PRT task and case-control status were included, in addition to the SNP genotype (in dominant model) found to be significantly associated with response bias. Recent literature points that episodic memory and other cognitive features, in addition to negative symptoms may affect reward learning (Wimmer et al., 2014; Lewandowski et al., 2016a). In the second model, instead of case-control status, clinical variables that may affect response bias such as GDA and AA subscales of MASQ, YMRS, PANSS total and MADRS were also included in the model, to control possible associations for moderator variables as cognitive and negative symptoms (Wimmer et al., 2014; Lewandowski et al., 2016a).

P values were not corrected for multiple comparison after the first level analysis (Mann Whitney U test), however the significance of associated SNPs was further tested for their association with response bias in the second level analysis of regression models. In addition, the association signals found were tested using an independent cohort of patients with depression diagnosis and controls from PGC MDD dataset, as described below.

2.2. Association of the putative GLP-1R polymorphisms linked to response bias with Depression Diagnosis

We attempted to replicate the diagnostic analyses and test the association of significant SNPs linked to response bias, with MDD in a genome-wide meta-analysis of 75,607 cases and 231,747 controls assembled from seven different cohorts as part of the Psychiatric Genomics Consortium (Wray et al., 2018). The design, and quality control performed as part of the PGC have been extensively described elsewhere (Wray et al., 2018). Briefly, individual genotype data for each of the participating cohorts were processed using the PGC ricopili pipeline to ensure standardized quality control, phasing and imputation protocols across all datasets. Initially, SNPs were excluded for excessive missingness (>0.05), differential missingness between cases and controls, deviations from expected autosomal heterozygosity, violations of Hardy Weinberg equilibrium ($p < 10^{-6}$ in controls and $p < 10^{-10}$ in cases). Samples with excessive missingness (>0.02) and outliers in ancestry were excluded. Pre-phasing and genotype imputation were performed using SHAPEIT/IMPUTE2 with a chunk size of 3mb and default parameters with the 1000 genomes phase 3 release as reference haplotypes. Post impute quality control included selecting SNPs with high INFO (>0.8) scores and low missingness ($<1\%$). This yielded a sample size of 75,607 MDD cases and 231,747 controls and 9.6 million high quality markers to be used for meta-analysis. The diagnostic criteria used in each of the individual cohorts was carefully analyzed by the PGC consortium and phenotype compatibility between cohorts was ensured by computing genetic correlations using common variants between each pair of individual cohorts and genetic risk prediction analyses.

3. Results

3.1.1. Association of GLP-1 polymorphisms with Reward Learning and Anhedonia

The A allele in rs10305492 was significantly associated with decreased response bias in the PRT and the C allele in rs1042044 was significantly associated with increased response bias

in a dominant model. Other SNPs in GLP-1R were not associated with response bias or SHAPS scores ($p > 0.05$) (Table 1).

C dominant model (CC and AC genotypes) in rs1042044 showed significantly lower anhedonia phenotype, compared to AA genotype (Chi-square test, $\chi^2: 5.2$, $p = 0.02$), based on the SHAPS scores. AG genotype in rs10305492 was not significantly different in the distribution of anhedonia phenotype, when compared to GG genotype in rs10305492 (Chi-square test, $\chi^2: 0.69$, $p = 0.4$).

3.1.2. GLP-1R Polymorphisms and Moderator Variables of Response Bias

A multivariate linear regression was carried out to investigate whether age, gender, case-control status, discriminability, having A allele in rs10305492 and C allele in rs1042044 significantly predicted response bias. The results of the regression indicated that the model explained 7.8 % of the variance and that the model was a significant predictor of response bias scores ($F(6, 233) = 3.28$, $p = 0.004$). While A allele in rs10305492 ($B = -0.1$, $p = 0.004$) and C allele in rs1042044 significantly predicted response bias scores ($B = 0.47$, $p = 0.018$), age, sex, discriminability in PRT and case-control status did not (Table 2). In a second model where we added clinical variables, such as GDA, AA subscale of MASQ, YMRS, PANSS total and MADRS scores as covariates, instead of the case-control status, the results of the regression indicated that the model explained 9.4 % of the variance and was a significant predictor of response bias ($F(10, 222) = 2.3$, $p = 0.014$). While discriminability ($B = -0.1$, $p = 0.04$), A allele in rs10305492 ($B = -0.15$, $p = 0.007$) and C allele in rs1042044 ($B = 0.044$, $p = 0.03$) significantly predicted response bias scores, none of the clinical scales, age and sex were a significant predictor of response bias (Table 3). When only A allele in rs10305492 and C allele in rs1042044, defined as dominant alleles, were included in the model to predict response bias, the model explained 5.2 % of the variance ($F(2, 258) = 7.04$, $p = 0.001$).

3.2. Association of the Putative GLP-1R Polymorphisms Linked To Response Bias With Depression Diagnosis

Analysis of PGC MDD data as described in 2.2 showed no statistical association between the loci rs1042044 or rs10305492 and depressive disorder. The effect sizes and p-values from the association tests are shown in Table 4.

4. Discussion

To our knowledge, this study is the first study to assess the impact of GLP-1R polymorphisms on response bias in a reward learning task, anhedonia and depression phenotypes in humans. The A allele in rs10305492 was significantly associated with decreased response bias in a dominant model (Table 1). However, as observed in many populations, A allele has a lower frequency (around 1–2 %) compared to G allele (Database of Single Nucleotide Polymorphisms (dbSNP). Bethesda (MD): National Center for Biotechnology Information, National Library of Medicine. Available from: <http://www.ncbi.nlm.nih.gov/SNP/>). Here, we did not exclude this SNP in our analyses because it has been identified to be significantly associated with fasting glucose (FG) in several large scale genetic studies (Wessel et al., 2015) and is implicated to play an important role in

modulating glucose levels, diabetes and cardiovascular risk (Scott et al., 2016). The neurobiology of diabetes might be related with certain psychiatric disorders and GLP-1R polymorphisms might also affect insulin physiology both in the brain and in the periphery. Therefore, rs10305492 could be one of the major shared pathways between peripheral and central effects of GLP-1. However, in our sample, only 3 individuals carried the A allele, consistent with the expected frequency. As such, it is possible for our results about rs10305492 to be false positive and the association of rs10305492 with reward learning needs to be validated in larger populations. Accordingly, this finding will not be further discussed or interpreted.

Our findings suggest that among GLP-1R SNPs, rs1042044 showed an association with reward learning and anhedonia in a cross-diagnostic sample of individuals with schizophrenia and mood disorders (mainly, bipolar spectrum disorders), after controlling for possible confounding effects (Tables 1,2, and 3). However, this effect was small and it was not associated with depression diagnosis in the PGC sample. Also, our analysis for the first step (Table 1) was not corrected for multiple comparisons, but the association was still significant in the regression models.

GLP-1 related SNPs were not reported among the SNPs that reached a genome-wide significance for the association with anhedonia, but significant SNPs on different locations of chromosome 6 were identified in previous published genome-wide association studies (GWAS) for anhedonia (Ren et al., 2018; Ward et al., 2019). Different measurement methods for anhedonia and clinical features of the cohorts may account for the negative findings. The measure of anhedonia employed in Ward et al was based on a single question from a depression screening instrument within the preceding two weeks. The measure of anhedonia employed in Ren et al was based on a composite “baseline interest-activity” score, derived from anhedonia related items in the Montgomery-Asberg Depression Scale, Hamilton Depression Scale, and Beck Depression Inventory. Moreover, our study cohort included patients with psychotic disorders whereas the study cohort in Ward et al. was drawn from healthy individuals with high socioeconomic status and education level and the study cohort in Ren et al. was drawn from individuals with unipolar depression diagnosis. Independent replication of association between anhedonia and reward-based phenotypes are warranted in future studies to validate our results.

A allele in rs1042044 has been previously related to altered antipsychotic responses (Ramsey and Brennan, 2014) and homozygous C allele was related to higher morning cortisol levels (Sheikh et al., 2010a), which highlights a possible modulatory role of GLP-1 on HPA axis regulation and dopaminergic pathways. We hypothesize that C allele in rs1042044 might be modulating GLP-1R expression, function or distribution in the brain. While this genotype might modulate neurobiological responses to rewards and stress, it did not appear to increase vulnerability for depression per se.

Notably, activation of GLP-1R in human brain changes glucose utilization in food-related reward areas, including the insula, striatum, orbitofrontal cortex, amygdala (Daniele et al., 2015) and globus pallidus (Suchankova et al., 2015), and this expression was related to altered responses to food or monetary rewards. However, comparisons with prior studies are

limited, since they mainly focused on food reward, instead of anhedonia. GLP-1R might modulate hypothalamic responses related to satiety and food intake (Schlogl et al., 2013). It may affect substance use development (Erreger et al., 2012) without altering mood, as evidenced by a study linking GLP-1R 168Ser allele in s6923761 with higher alcohol consumption in humans (Suchankova et al., 2015).

Growing evidence indicates that depression is a heterogeneous diagnosis with multifactorial aetiology. Multiple independent genetic variants take part in its development (Howard et al., 2019; Mistry et al., 2018; Wray et al., 2018), in addition to multiple environmental factors, affecting various regions in the brain (Howard et al., 2019) and multiple cellular and molecular pathways (Pitsillou et al., 2019). It is possible that rs1042044 is linked to reward processing phenotype specifically, consistent with preclinical findings about GLP-1 on reward circuitry. This effect in turn may modulate the propensity of development of anhedonia (described below). In rodents, GLP-1R are expressed in the mesolimbic reward pathway (Skibicka, 2013) and evidence from preclinical studies shows that activation of GLP-1 may decrease despair-like behavior in the long term (Anderberg et al., 2016a). However, most of the studies on animals focused on addictive behaviors and found that administration of GLP-1 agonists decreases cocaine and amphetamine seeking behavior, consumption doses, and substance-induced behaviors (Tuesta et al., 2017; Graham et al., 2013). The pathways that GLP-1 uses in nucleus accumbens and ventral tegmental area could be mainly linked with food, substance and monetary-related reward, instead of other vegetative and mood related symptoms of depression.

This study has several limitations, including relative small sample size, uncorrected p values for the first step of statistical analysis and limited statistical power for the reward learning analysis. Diagnoses assessed are both multifactorial and polygenic and we probed putative relationship of a group of SNPs at GLP-1R without controlling for the polygenic risk score for other genes. Still, a reliable effect of GLP-1R polymorphisms on reward learning and anhedonia emerged.

In conclusion, our findings suggest a possible association of rs1042044 with reward learning and anhedonia. However, we could not find an association with depression diagnosis. Further studies with larger sample size are needed to replicate our findings and to evaluate the role of GLP-1R polymorphisms in the course and severity of reward related disorders.

Acknowledgements

We gratefully thank Dr. Hande Kandemir, for her help in search of literature for the list of GLP-1 SNPs and Dr. Mehmet Gonen for his help about statistical analysis.

Financial support

DAP was partially supported by National Institute of Mental Health (NIMH) Grant No. R37 MH068376. DO was supported by grant no. K24MH104449. MHH was supported by NIMH grant 5R01MH109687. The funder has no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication. iPSYCH is funded by the Lundbeck Foundation (grant nos. R102-A9118 and R155-2014-1724).

REFERENCES

- Allen JG (1998) User's guide, administration booklet, and scoresheet for the Structured Clinical Interview for DSM-IV Axis I Disorders, clinician version. *Bulletin of the Menninger Clinic* 62, 126–126.
- Altshuler DM, Durbin RM, Abecasis GR, Bentley DR, Chakravarti A, Clark AG, et al. (2015) A global reference for human genetic variation. *Nature* 526, 68–+. [PubMed: 26432245]
- Anderberg RH, Richard JE, Hansson C, Nissbrandt H, Bergquist F & Skibicka CP (2016) GLP-1 is both anxiogenic and antidepressant; divergent effects of acute and chronic GLP-1 on emotionality. *Psychoneuroendocrinology* 65, 54–66. [PubMed: 26724568]
- Anderberg RH, Richard JE, Hansson C, Nissbrandt H, Bergquist F & Skibicka KP (2016) GLP-1 is both anxiogenic and antidepressant; divergent effects of acute and chronic GLP-1 on emotionality. *Psychoneuroendocrinology* 65, 54–66. [PubMed: 26724568]
- Aroda VR (2018) A review of GLP-1 receptor agonists: Evolution and advancement, through the lens of randomised controlled trials. *Diabetes, Obesity and Metabolism* 20 Suppl 1, 22–33.
- Brunetti L, Orlando G, Recinella L, Leone S, Ferrante C, Chiavaroli A, et al. (2008) Glucagon-like peptide 1 (7–36) amide (GLP-1) and exendin-4 stimulate serotonin release in rat hypothalamus. *Peptides* 29, 1377–81. [PubMed: 18502539]
- Chowen JA, de Fonseca FR, Alvarez E, Navarro M, Garcia-Segura LM & Blazquez E (1999) Increased glucagon-like peptide-1 receptor expression in glia after mechanical lesion of the rat brain. *Neuropeptides* 33, 212–5. [PubMed: 10657494]
- Clark-Elford R, Nathan PJ, Auyeung B, Voon V, Sule A, Muller U, et al. (2014) The effects of oxytocin on social reward learning in humans. *International Journal of Neuropsychopharmacology* 17, 199–209. [PubMed: 24160414]
- Daniele G, Iozzo P, Molina-Carrion M, Lancaster J, Ciociaro D, Cersosimo E, et al. (2015) Exenatide Regulates Cerebral Glucose Metabolism in Brain Areas Associated With Glucose Homeostasis and Reward System. *Diabetes* 64, 3406–12. [PubMed: 26116695]
- de Luis DA, Aller R, Izaola O & Bachiller R (2015) Role of rs6923761 gene variant in glucagon-like peptide 1 receptor in basal GLP-1 levels, cardiovascular risk factor and serum adipokine levels in naive type 2 diabetic patients. *Journal of endocrinological investigation* 38, 143–7. [PubMed: 25200998]
- de Luis DA, Pacheco D, Aller R & Izaola O (2014a) Role of the rs6923761 gene variant in glucagon-like peptide 1 receptor gene on cardiovascular risk factors and weight loss after biliopancreatic diversion surgery. *Annals of Nutrition and Metabolism* 65, 259–63. [PubMed: 25376673]
- de Luis DA, Pacheco D, Aller R, Izaola O & Bachiller R (2014b) Roles of rs 6923761 gene variant in glucagon-like peptide 1 receptor on weight, cardiovascular risk factor and serum adipokine levels in morbid obese patients. *Nutricion Hospitalaria* 29, 889–93. [PubMed: 24679032]
- Delgado MR, Miller MM, Inati S & Phelps EA (2005) An fMRI study of reward-related probability learning. *Neuroimage* 24, 862–73. [PubMed: 15652321]
- Detka J, Slusarczyk J, Kurek A, Kucharczyk M, Adamus T, Konieczny P, et al. (2019) Hypothalamic insulin and glucagon-like peptide-1 levels in an animal model of depression and their effect on corticotropin-releasing hormone promoter gene activity in a hypothalamic cell line. *Pharmacological Reports* 71, 338–346. [PubMed: 30831439]
- Dichter GS, Damiano CA & Allen JA (2012) Reward circuitry dysfunction in psychiatric and neurodevelopmental disorders and genetic syndromes: animal models and clinical findings. *Journal of Neurodevelopmental Disorders* 4, 19. [PubMed: 22958744]
- Drucker DJ (2006) The biology of incretin hormones. *Cell Metabolism* 3, 153–65. [PubMed: 16517403]
- Duman RS & Aghajanian GK (2012) Synaptic Dysfunction in Depression: Potential Therapeutic Targets. *Science* 338, 68–72. [PubMed: 23042884]
- Erbil D, Eren CY, Demirel C, Kucuker MU, Solaroglu I & Eser HY (2019) GLP-1's role in neuroprotection: a systematic review. *Brain Injury* 1–85.

- Erreger K, Davis AR, Poe AM, Greig NH, Stanwood GD & Galli A (2012) Exendin-4 decreases amphetamine-induced locomotor activity. *Physiology & behavior* 106, 574–8. [PubMed: 22465309]
- Farr OM, Sofopoulos M, Tsoukas MA, Dincer F, Thakkar B, Sahin-Efe A, et al. (2016) GLP-1 receptors exist in the parietal cortex, hypothalamus and medulla of human brains and the GLP-1 analogue liraglutide alters brain activity related to highly desirable food cues in individuals with diabetes: a crossover, randomised, placebo-controlled trial. *Diabetologia* 59, 954–65. [PubMed: 26831302]
- Franken IHA, Rassin E & Muris P (2007) The assessment of anhedonia in clinical and non-clinical populations: Further validation of the Snaith-Hamilton Pleasure Scale (SHAPS). *Journal of Affective Disorders* 99, 83–89. [PubMed: 16996138]
- Gold MS, Blum K, Febo M, Baron D, Modestino EJ, Elman I, et al. (2018) Molecular role of dopamine in anhedonia linked to reward deficiency syndrome (RDS) and anti-reward systems. *Front Biosci (Schol Ed)* 10, 309–325. [PubMed: 29293435]
- Graham DL, Erreger K, Galli A & Stanwood GD (2013) GLP-1 analog attenuates cocaine reward. *Molecular Psychiatry* 18, 961–2. [PubMed: 23089631]
- Hall MH, Chen CY, Cohen BM, Spencer KM, Levy DL, Ongur D, et al. (2015) Genomewide Association Analyses of Electrophysiological Endophenotypes for Schizophrenia and Psychotic Bipolar Disorders: A Preliminary Report. *American Journal of Medical Genetics Part B-Neuropsychiatric Genetics* 168, 151–161.
- Heppner KM, Kirigiti M, Secher A, Paulsen SJ, Buckingham R, Pyke C, et al. (2015) Expression and distribution of glucagon-like peptide-1 receptor mRNA, protein and binding in the male nonhuman primate (*Macaca mulatta*) brain. *Endocrinology* 156, 255–67. [PubMed: 25380238]
- Hernandez NS, O'Donovan B, Ortinski PI & Schmidt HD (2019) Activation of glucagon-like peptide-1 receptors in the nucleus accumbens attenuates cocaine seeking in rats. *Addiction Biology* 24, 170–181. [PubMed: 29226617]
- Howard DM, Adams MJ, Clarke TK, Hafferty JD, Gibson J, Shirali M, et al. (2019) Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions. *Nature Neuroscience* 22, 343–352. [PubMed: 30718901]
- Howie B, Marchini J & Stephens M (2011) Genotype Imputation with Thousands of Genomes. *G3-Genes Genomes Genetics* 1, 457–469.
- Kappe C, Tracy LM, Patrone C, Iverfeldt K & Sjöholm A (2012) GLP-1 secretion by microglial cells and decreased CNS expression in obesity. *Journal of Neuroinflammation* 9, 276. [PubMed: 23259618]
- Krass M, Rünkorg K, Vasar E, & Volke V. (2012). Acute administration of GLP-1 receptor agonists induces hypolocomotion but not anxiety in mice. *Acta neuropsychiatrica* 24(5), 296–300. [PubMed: 25286994]
- Krass M, Volke A, Rünkorg K, Wegener G, Lund S, Abildgaard A et al. (2015). GLP-1 receptor agonists have a sustained stimulatory effect on corticosterone release after chronic treatment. *Acta neuropsychiatrica* 27(1), 25–32. [PubMed: 25469828]
- Koshal P, Jamwal S & Kumar P (2018) Glucagon-like Peptide-1 (GLP-1) and neurotransmitters signaling in epilepsy: An insight review. *Neuropharmacology* 136, 271–279. [PubMed: 29129776]
- Lewandowski KE, Whitton AE, Pizzagalli DA, Norris LA, Ongur D & Hall MH (2016) Reward Learning, Neurocognition, Social Cognition, and Symptomatology in Psychosis. *Frontiers in Psychiatry* 7.
- Luijten M, Schellekens AF, Kuhn S, Machielse MW & Sescousse G (2017) Disruption of Reward Processing in Addiction : An Image-Based Meta-analysis of Functional Magnetic Resonance Imaging Studies. *JAMA Psychiatry* 74, 387–398. [PubMed: 28146248]
- Malendowicz LK, Nussdorfer GG, Nowak KW, Ziolkowska A, Tortorella C, & Trejter M. (2003). Exendin-4, a GLP-1 receptor agonist, stimulates pituitary-adrenocortical axis in the rat: investigations into the mechanism (s) underlying Ex4 effect. *International journal of molecular medicine* 12(2), 237–241. [PubMed: 12851724]
- Mansur RB, Fries GR, Trevizol AP, Subramaniapillai M, Lovshin J, Lin KG, et al. (2019) The effect of body mass index on glucagon-like peptide receptor gene expression in the post mortem brain from

- individuals with mood and psychotic disorders. *European Neuropsychopharmacology* 29, 137–146. [PubMed: 30409537]
- Mistry S, Harrison JR, Smith DJ, Escott-Price V & Zammit S (2018) The use of polygenic risk scores to identify phenotypes associated with genetic risk of bipolar disorder and depression: A systematic review. *Journal of Affective Disorders* 234, 148–155. [PubMed: 29529547]
- Nusslock R & Alloy LB (2017) Reward processing and mood-related symptoms: An RDoC and translational neuroscience perspective. *Journal of Affective Disorders* 216, 3–16. [PubMed: 28237133]
- O’Connell J, Sharp K, Shrine N, Wain L, Hall I, Tobin M, et al. (2016) Haplotype estimation for biobank-scale data sets. *Nature Genetics* 48, 817–+. [PubMed: 27270105]
- Peterson DA, Lotz DT, Halgren E, Sejnowski TJ & Poizner H (2011) Choice modulates the neural dynamics of prediction error processing during rewarded learning. *Neuroimage* 54, 1385–94. [PubMed: 20884356]
- Pitsillou E, Bresnehan SM, Kagarakis EA, Wijoyo SJ, Liang J, Hung A, et al. (2019) The cellular and molecular basis of major depressive disorder: towards a unified model for understanding clinical depression. *Molecular biology reports*, 1–18.
- Pizzagalli DA, Jahn AL, & O’Shea JP (2005) Toward an objective characterization of an anhedonic phenotype: a signal-detection approach. *Biological psychiatry* 57(4), 319–327. [PubMed: 15705346]
- Pizzagalli DA, Iosifescu D, Hallett LA, Ratner KG & Fava M (2008) Reduced hedonic capacity in major depressive disorder: Evidence from a probabilistic reward task. *Journal of Psychiatric Research* 43, 76–87. [PubMed: 18433774]
- Ramsey TL & Brennan MD (2014) Glucagon-like peptide 1 receptor (GLP1R) haplotypes correlate with altered response to multiple antipsychotics in the CATIE trial. *Schizophrenia Research* 160, 73–9. [PubMed: 25449714]
- Ren H, Fabbri C, Uher R, Rietschel M, Mors O, Henigsberg N et al. (2018) Genes associated with anhedonia: a new analysis in a large clinical trial (GENDEP). *Translational psychiatry* 8(1), 1–11. [PubMed: 29317594]
- Rinaman L & Rothe EE (2002) GLP-1 receptor signaling contributes to anorexigenic effect of centrally administered oxytocin in rats. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology* 283, R99–106.
- Rizvi SJ, Pizzagalli DA, Sproule BA & Kennedy SH (2016) Assessing anhedonia in depression: Potentials and pitfalls. *Neuroscience and Biobehavioral Reviews* 65, 21–35. [PubMed: 26959336]
- Sarkar S, Fekete C, Legradi G & Lechan RM (2003) Glucagon like peptide-1 (7–36) amide (GLP-1) nerve terminals densely innervate corticotropin-releasing hormone neurons in the hypothalamic paraventricular nucleus. *Brain Research* 985, 163–8. [PubMed: 12967720]
- Sathananthan A, Man CD, Micheletto F, Zinsmeister AR, Camilleri M, Giesler PD, et al. (2010) Common genetic variation in GLP1R and insulin secretion in response to exogenous GLP-1 in nondiabetic subjects: a pilot study. *Diabetes Care* 33, 2074–6. [PubMed: 20805279]
- Schlogl H, Kabisch S, Horstmann A, Lohmann G, Muller K, Lepsien J, et al. (2013) Exenatide-Induced Reduction in Energy Intake Is Associated With Increase in Hypothalamic Connectivity. *Diabetes Care* 36, 1933–1940. [PubMed: 23462665]
- Scott RA, Freitag DF, Li L, Chu AY, Surendran P, Young R, et al. (2016) A genomic approach to therapeutic target validation identifies a glucose-lowering GLP1R variant protective for coronary heart disease. *Science Translational Medicine* 8, 341ra76.
- Sharma AN, Ligade SS, Sharma JN, Shukla P, Elased KM & Lucot JB (2015) GLP-1 receptor agonist liraglutide reverses long-term atypical antipsychotic treatment associated behavioral depression and metabolic abnormalities in rats. *Metabolic brain disease* 30, 519–27. [PubMed: 25023888]
- Sheikh HI, Dougherty LR, Hayden EP, Klein DN & Singh SM (2010) Glucagon-like peptide-1 receptor gene polymorphism (Leu260Phe) is associated with morning cortisol in preschoolers. *Progress in Neuro-Psychopharmacology Biological Psychiatry* 34, 980–983. [PubMed: 20483198]
- Skibicka KP (2013) The central GLP-1: implications for food and drug reward. *Frontiers Neuroscience* 7, 181.

- Snaith RP, Hamilton M, Morley S, Humayan A, Hargreaves D & Trigwell P (1995) A Scale for the Assessment of Hedonic Tone - the Snaith-Hamilton Pleasure Scale. *British Journal of Psychiatry* 167, 99–103. [PubMed: 7551619]
- Suchankova P, Yan J, Schwandt ML, Stangl BL, Caparelli EC, Momenan R, et al. (2015) The glucagon-like peptide-1 receptor as a potential treatment target in alcohol use disorder: evidence from human genetic association studies and a mouse model of alcohol dependence. *Translational Psychiatry* 5.
- Tuesta LM, Chen Z, Duncan A, Fowler CD, Ishikawa M, Lee BR, et al. (2017) GLP-1 acts on habenular avoidance circuits to control nicotine intake. *Nature Neuroscience* 20, 708–716. [PubMed: 28368384]
- Vrieze E, Pizzagalli DA, Demyttenaere K, Hompes T, Sienaert P, de Boer P, et al. (2013) Reduced reward learning predicts outcome in major depressive disorder. *Biological Psychiatry* 73, 639–45. [PubMed: 23228328]
- Ward J, Lyall LM, Bethlehem RA, Ferguson A, Strawbridge RJ, Lyall DM et al. (2019). Novel genome-wide associations for anhedonia, genetic correlation with psychiatric disorders, and polygenic association with brain structure. *Translational psychiatry* 9(1), 1–9. [PubMed: 30664621]
- Wessel J, Chu AY, Willems SM, Wang S, Yaghootkar H, Brody JA, et al. (2015) Low-frequency and rare exome chip variants associate with fasting glucose and type 2 diabetes susceptibility. *Nature Communications* 6, 5897.
- Whitton AE, Treadway MT & Pizzagalli DA (2015) Reward processing dysfunction in major depression, bipolar disorder and schizophrenia. *Current Opinion in Psychiatry* 28, 7–12. [PubMed: 25415499]
- Williams DL, Lilly NA, Edwards IJ, Yao P, Richards JE & Trapp S (2018) GLP-1 action in the mouse bed nucleus of the stria terminalis. *Neuropharmacology* 131, 83–95. [PubMed: 29221794]
- Wimmer GE, Braun EK, Daw ND & Shohamy D (2014) Episodic Memory Encoding Interferes with Reward Learning and Decreases Striatal Prediction Errors. *Journal of Neuroscience* 34, 14901–14912. [PubMed: 25378157]
- Wray NR, Ripke S, Mattheisen M, Trzaskowski M, Byrne EM, Abdellaoui A, et al. (2018) Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. *Nature Genetics* 50, 668–681. [PubMed: 29700475]
- Zheng HY, Reiner DJ, Hayes MR & Rinaman L (2019) Chronic Suppression of Glucagon-Like Peptide-1 Receptor (GLP1R) mRNA Translation in the Rat Bed Nucleus of the Stria Terminalis Reduces Anxiety-Like Behavior and Stress-Induced Hypophagia, But Prolongs Stress-Induced Elevation of Plasma Corticosterone. *Journal of Neuroscience* 39, 2649–2663. [PubMed: 30683681]

Significant Outcomes

- rs1042044 is significantly associated with reward learning and anhedonia.
- No association between putative GLP-1R polymorphisms and depression diagnosis has been found.
- Further studies are needed to evaluate the role of GLP-1R polymorphisms in the course and severity of reward related disorders.

Limitations

- This study has a relatively small sample size for the reward learning analysis.
- Depression is a multifactorial diagnosis and we could not consider other environmental variables in the analysis for depression.

Table 1.

Mean Response Bias in PRT and SHAPS scores for each GLP-1R SNP's genotype

SNP	Genotype	n	RESPONSE BIAS		n	SHAPS	
			Mean Response Bias Score	Std. Dev.		Mean SHAPS Score	Std. Dev.
rs1030542	CC	12	0.137	0.128	12	0.750	1.765
	CT	63	0.103	0.166	62	1.113	1.775
	TT	76	0.099	0.179	75	1.347	2.496
	<i>p1 (T dominant)</i>			0.536			0.249
	<i>p2 (C dominant)</i>			0.731			0.653
	CC	99	0.103	0.185	98	1.204	2.168
	CT	116	0.106	0.190	115	1.244	2.199
	TT	37	0.101	0.168	37	1.270	2.169
rs10305421							
	<i>p1 (T dominant)</i>			0.877			0.591
	<i>p2 (C dominant)</i>			0.895			0.851
rs10305492	AG	3	-0.177	0.169	3	2.000	3.464
	GG	258	0.107	0.180	256	1.242	2.156
	<i>p1 (G dominant)</i>			0.014			0.979
	<i>p2 (A dominant)</i>						
	AA	25	0.020	0.211	25	1.800	2.415
	AC	122	0.118	0.170	121	1.240	2.401
	CC	117	0.107	0.183	116	1.172	1.880
rs1042044							
	<i>p1 (A dominant)</i>			0.897			0.978
	<i>p2 (C dominant)</i>			0.033			0.197
	AA	50	0.118	0.188	49	1.245	1.843
	AC	137	0.116	0.165	137	1.153	2.169
	CC	77	0.074	0.202	76	1.474	2.419
rs6923761							
	<i>p1 (C dominant)</i>			0.487			0.487
	<i>p2 (A dominant)</i>			0.128			0.327
	AG	4	0.085	0.144	4	0.750	0.957
	GG	257	0.106	0.181	255	1.286	2.208
rs5875654							
	<i>p1 (G dominant)</i>			0.852			1.000
	<i>p2 (A dominant)</i>						
	CC	244	0.107	0.175	242	1.310	2.257
rs761386	TC	19	0.071	0.255	19	0.737	0.806
	<i>p1 (T dominant)</i>			0.258			0.913

RESPONSE BIAS					SHAPS		
SNP	Genotype	n	Mean Response Bias Score	Std. Dev.	n	Mean SHAPS Score	Std. Dev.
<i>p2 (C dominant)</i>							

Table 2.

Association of A allele in rs10305492 or C allele in rs1042044 with response bias in PRT when controlling for case-control status, discriminability in PRT, age and sex

Variables	Coefficient (B)	SE	95 % CI	p
Constant	0.195	0.098	0.002–0.388	0.048
Case-control status	–0.021	0.027	–0.073–0.032	0.437
Discriminability score in PRT	–0.089	0.047	–0.181–0.003	0.057
A allele in rs10305492	–0.154	0.053	–0.25–0.049	0.004
C allele in rs1042044	0.047	0.020	0.008–0.086	0.018
Age	0.001	0.001	–0.001–0.003	0.402
Sex	–0.015	0.024	–0.062–0.033	0.543

Table 3.

Association of A allele in rs10305492 and C allele in rs1042044 with response bias in PRT when controlling for discriminability in PRT, GDA subscale of MASQ, AA subscale of MASQ, YMRS, MADRS and PANSS total scores, age and sex

Variables	Coefficient (B)	SE	95 % CI	p
Constant	0.252	0.107	0.042–0.462	0.02
Discriminability score in PRT	–0.100	0.048	–0.194–0.005	0.04
A allele in rs10305492	–0.149	0.055	–0.257–0.042	0.007
C allele in rs1042044	0.044	0.020	0.004–0.083	0.03
PANSS Total score	–0.001	0.001	–0.002–0.001	0.36
MADRS score	0.003	0.002	–0.001–0.006	0.15
GDA subscore of MASQ	–0.001	0.003	–0.007–0.005	0.73
AA subscore of MASQ	–0.001	0.002	–0.005–0.003	0.60
	–0.002	0.002	–0.005–0.002	0.37
YMRS score				
Age	0.001	0.001	–0.001–0.003	0.43
Sex	–0.018	0.025	–0.068–0.031	0.46

Table 4.

Association of GLP-1R polymorphisms linked to response bias with depression in PGC depression GWAS, 2018 excluding 23andMe

SNP	A1	A2	OR	SE	P
rs1042044	A	C	0.99	0.0079	0.3
rs10305492	A	G	0.99	0.0349	0.8