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Exploring Association of Opioid Receptor Genes Polymorphism with Positive and Negative Moods using Positive and Negative Affective States Scale (PANAS)

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Abstract

Using a sample of 2,986 subjects we studied that gene polymorphisms for the *OPRM1* (rs1799971, rs17174794), *OPRK1* (rs16918875, rs963549) and *OPRD1* (rs569356, rs1042114) receptor genes have differential associations with the Positive (PA) and Negative (NA) dimensions of the affect schedule (PANAS) scale (categorized as positive and negative moods). The study finds that *OPRM1* gene polymorphisms have both negative and positive associations with the NA and PA dimension of PANAS, respectively. The *OPRK1* gene polymorphisms have positive associations with the NA but not with the PA dimension of PANAS. The *OPRD1* gene polymorphisms have negative associations with the NA but not with the PA dimension of PANAS. In addition, both NA and PA dimensions of PANAS are associated with acute and chronic depression and anxiety. This genetic approach provides evidence that the three opioid receptors gene polymorphisms have divergent associations with phenotypes related to moods.

Keywords: *OPRM1*; *OPRK1*; *OPRD1*; PANAS; Opioid receptor; Moods; Depression; Anxiety

Introduction

Positive well-being is an important aspect of life that most people desire to attain. One aspect of a person's well-being is their experience of positive moods as opposed to negative moods [1]. One way to measure people's moods is the Positive (PA) and Negative (NA) Affect Schedule (PANAS), a self-reported scale developed by Watson et al. [2] widely used in the field of psychology for both clinical and non-clinical populations. The PA and NA dimensions also have been identified as pleasantness versus unpleasantness [2] and they are "linked to psychobiological and psychodynamic constructs of sensitivity to signals of reward and punishment" [2]. PA and NA are conceived as two dimensions [3] that in general are negatively correlated in healthy individuals, and also associate with psychiatric disorders such as depression and anxiety [4].

Depending on the instructions set, a person's score on the PANAS scale is conceived as a dispositional trait affect ("In general, how often do you feel.…") or as a momentary affect ("Recently, how often have you felt....") [3]. In this study, we build on a data base that contains people's genetic makeup and phenotypes (https://www.lifelines.nl) [5]. From this database studied associations with constitutive genetic make-up and the self-reported PANAS scores which reflect mood of the respondents. Examples of the PA dimension of the scale include feeling alert, excited or proud while examples of the NA dimension include feeling scared, jittery or hostile. Accordingly, we studied whether genetic variability is associated with scores on the PA and NA dimension of the PANAS scale. We focused on candidate genes from the endogenous opioid system, a peptidergic neuro-modulatory system that has a well-established role in mediating people's feelings of pleasure or distress [6]. To our knowledge no other study has looked at the relationship between PANAS scale and opioid genes.

When people experience unpleasant feelings such as social exclusion and pain, or pleasant feelings such as when engaging in play [7] and being close to attachment figures [8], they endogenously produce opioid peptides: endorphins, dynorphins and encephalin [9]. These peptides produce their biological effects by recruiting three G-protein coupled Opioid Receptors (OPR) named *OPRM1, OPRK1* and *OPRD1* also known as Mu Opioid Receptors (MOR), Kappa Opioid Receptors (KOR) and Delta Opioid Receptors (DOR) [10-12]. G-proteins then affect a complex cascade of intracellular process that in turn lead to the modulation of the activity and connectivity between brain nuclei, thereby ultimately contributing to the emergence of pleasant or unpleasant effects [13,14]. Here, we focused on gene polymorphism of *OPRM1* (MOR), *OPRK1* (KOR) and *OPRD1* (DOR), respectively, and chose to analyze a collection of candidate Single Nucleotide Polymorphisms (SNPs) that have been previously shown to associate with disorders characterized by a dysfunction of reward processes [15]. We studied: a) Whether the candidate SNPs of the three OPR genes affect peoples' score on both PA (positive mood) and NA (negative mood) dimensions of the PANAS scale and b) Whether their score on both PA (positive mood) and NA (negative mood) dimensions of PANAS affects their score on both acute and chronic depression as well as anxiety. As a cross-check we study whether there is a direct association between the candidate SNPs of the three OPR gene polymorphisms and the dimensions of acute and chronic depression and anxiety [16].

Key in our reasoning is that OPRs are densely expressed among the peripheral and central nervous systems, including in monoaminergic neuronal systems, which all originate in the brain stem. They include the dopaminergic system beginning in the ventral tegmental areas, the serotonin system beginning in the raphe nuclei, and the noradrenaline

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system beginning in the locus coeruleus. All these systems send dense axonal projections to different regions of the brain, such as the prefrontal cortex, hippocampus, amygdala and bed nucleus of stria terminalis, that are regarded as part of the limbic system or the emotional brain. Across these regions, the sustained neuronal activity of opioid receptors modulates the functioning of monoamine systems, in coordination with other brain substrates such as oxytocinergic signaling [17] or the activity of the hypothalamic-pituitary-adrenal axis. This affects the human response to reward, emotions and moods as well as the motivation to seek pleasure in consuming food or social contact. It has also been implicated in the emergence of mood disorders such as anxiety and depression, as summarized in several recent exhaustive reviews [13,16,18,19].

When people experience both pleasure and social pain, they produce opioid peptides that bind to the *OPRM1* and produce feelings of pleasure or euphoria, and in the case of physical or social pain that reduce pain and discomfort [20]. In addition, *OPRM1* activation motivates people to seek proximity with attachment figures, which reduces social pain in both adults and young children [17,20]. Similar findings were made in human genetics where the *OPRM1* gene, specifically the SNP called A118G polymorphism, is associated with the degree to which people experience social hedonic capacity [21] and the degree of pain reduction [18,22]. In general, we expect that certain candidate SNPs from the *OPRM1* gene will be associated with PA and NA dimensions of PANAS. The *OPRK1* is also widely distributed in the brain, including in the hypothalamus, nucleus accumbens and hippocampus [23] where it affects dopamine and serotonin systems and has been clearly implicated in the regulation of the stress response and in stress-related disorders such as anxiety and depression [24,25]. Again, we expected that certain candidate SNPs from the *OPRK1* gene would associate with the NA and PA of PANAS. Activation of the *OPRD1* has been associated with anxiolytic- and antidepressive-like effects in rodent models [10,26], and we postulated that certain candidate SNPs from the *OPRD1* gene may show some association with the NA and PA scales.

Finally, researchers have been investigating whether the PA and NA dimensions of PANAS are correlated with feelings of acute and chronic depression as well as anxiety [27]. Here we explored this relationship because finding a correlation between the PANAS scale and self-reports of acute and chronic depression and anxiety would add to the ecological significance of our findings on OPR genes and PA and NA dimensions of PANAS.

Methods and Materials

Data source

Data were collected from the Lifelines Cohort Study biobank in Groningen, the Netherlands [5]. This large-scale study collects data and biological samples and makes them available for research on healthy aging, based on a standard application procedure (the present study is coded under Proposal no. OV16_0366 (https://www.lifelines.nl/). This study considered data from the adult cohort with the permission of the ERIM ethics commission of Erasmus University

Demographics

The population consisted of 893 (43.4%) females and 1164 (53.6%) males. All respondent were Caucasians and their ages ranged between 18 and 65 years (mean=44.61, SD=8.26)

Genotype selection

We adopted from Lifelines [5] the following description on how the genetic analysis was performed. 2986 participants were selected from Genome-Wide Genotype (GWAS) data based on the Illumina CytoSNP-12v2 array, all independent and Caucasian-ancestry samples have also been imputed using the Genome of the Netherlands (GoNL) release 5 [28] and the 1000 Genomes phase1 v3 (1000 genomes project consortium, 2010) reference panels. Quality controls of the data is based on SNP filtering on MAF above 0.001, HWE (p>1e-6), call rate of 0.95 using Plink [29], and PCA to check for population outliers for genome-wide association analysis. 6 candidate SNPs *OPRM1* (rs17174794, rs1799971), *OPRK1* (rs16918875, rs963549), and *OPRD1* (rs569356, rs1042114) in the lifelines genotype database were chosen as candidate genes based on literature. The reference allele was coded '0' and effect allele was coded as '1' [27,30].

Phenotype selection

PANAS was chosen as the phenotype of interest from the Lifelines phenotype database [2,5]. The PANAS scale covers a series of items, posing questions like "how often did you feel nervous in the past four weeks", that cover both acute and chronic time periods (Table 1).

Based on the median factor scores, for PA=3.67 and NA=2.00, we created four configurations for PA and NA combinations, thus placing the subjects in these groups of PA and NA each. It was done for the ease in study of correlations with OPR gene polymorphisms.

High PA: Individuals who scored higher than the median on both PA (score>3.67) and were coded at "1"on PA scale of PANAS.

Low PA: Individuals who scored lower than the median on PA (score<3.67) and were coded at "0"on PA scale of PANAS.

High NA: Individuals who scored higher than the median NA (score<2.0) and were coded at "1"on NA scale of PANAS.

Low NA: Individuals who scored lower than median score on NA (score<2.0) were coded at "0"on PA scale of PANAS.

To make study more concrete, self-reported depression (acute and chronic) and anxiety were also selected as phenotypes to be studied with PANAS and OPR candidate SNPs. Depression (acute and chronic) and anxiety were chosen from mental health segment of Lifelines phenotype database [5,31]. The statements asked for acute depression was "did you feel depressed in past 2 months" and for chronic depression "did you feel depressed in past 2 years". For anxiety the statement asked was "did you feel anxious in past 6 months." Responses were obtained as "Yes" or "No", coded as "1" and "0" respectively for all the participants.

Statistical analysis

Data were analyzed using SPSS (version 20) at Lifelines online desktop. The level of significance was set at p<0.05 at 95% confidence interval.

Phi-correlation (Φ) coefficient: Since all the variables were dichotomous and had binary coding, thus Phi-correlation (Φ) coefficient was performed to study the strength of associations. Correlations were studied between PA and NA of PANAS and OPRs' candidate SNPs (*OPRM1, OPRK1,* and *OPRD1*). Correlations were also calculated for depression and anxiety with OPRs and PA and NA of PANAS [5,16,19,32].

Results

Developing PA and NA dimensions of PANAS scale

SPSS factor analysis and Bartlett's test of sphericity (significant

				Reference allele as '0'	Effect allele as '1'		
OPR	**SNP**	**Position**	**Mean (SD)**	**p^2**	**pq**	**q^2**	**Gene Consequence**
OPRM1	rs17174794	chr6:154089975 (GRCh38.p7)	0.22 (0.41)	CC=2334	CG=601	GG=51	*OPRM1:*Upstream
OPRM1	rs1799971	chr6:154039662 (GRCh38.p7)	0.21 (0.41)	AA=2352	AG=587	GG=47	*OPRM1:*Exon Variant
OPRK1	rs16918875	chr8:53229594 (GRCh38.p7)	0.18 (0.39)	GG=2444	AG=410	AA=132	*OPRM1:*Exon Variant
OPRK1	rs963549	chr8:53229264 (GRCh38.p7)	0.22 (0.41)	CC=2342	CT=558	TT=86	*OPRK1:*UTR 3
OPRD1	rs1042114	chr1:28812463 (GRCh38.p7)	0.99 (0.11)	TT=2297	GT=650	GG=39	*OPRD1:*Exon Variant
OPRD1	rs569356	chr1:28810174 (GRCh38.p7)	0.23 (0.42)	AA=2299	AG=6488	GG=39	*OPRD1:*2KB Upstream Variant
Note: All SNP were checked for minor allele frequency (MAF) ≥ 0.1% and deviation from the Hardy Weinberg equilibrium (p<10−6).							

Table 1: Sample characteristics (N=2986).

level of p<0.05) were used to confirm that the PANAS scale sample has patterned relationships at Kaiser-Meyer-Olkin value of 0.86. After running factor analysis, two major factors were extracted from 20 items (Table 2) for factor loading in the pattern matrix). Using the factor loadings, the items were grouped into respective factors. For PA the items were respectively: inspired, enthusiastic, alert, attentive, interested, strong, determined, active, proud and satisfied (α=0.86) and for NA the respective items were: nervous, jittery, scared, afraid, upset, guilty, ashamed, distressed, irritable and hostile (α=0.78). The PA and NA dimensions of PANAS correlate negatively with each other at a correlation score of -0.18 (p=0.01) [31].

Phi-coefficient (Φ) correlation: To check strength of association:

a) Phi-coefficient (Φ) correlation for PA and NA of PANAS and OPRs followed by Binary logistic regression.

b) We studied that candidate SNPs were found significantly correlated with NA of PANAS at 0.01 level of significance while few candidate SNPs were found significantly correlated with PA of PANAS at 0.05 level of significance. *OPRM1* candidate SNPs, rs1799971 (Φ=-0.08; p = 0.01) and rs17174794 (Φ=-0.07; p=0.01) were negatively correlated with NA of PANAS while candidate SNPs, rs540825 (Φ=0.04; p=0.05) and rs62638690 (Φ=0.04; p=0.05) were positively correlated with PA of PANAS. *OPRK1* candidate SNPs, rs16918875 (Φ=0.08; p=0.01) and rs963549 (Φ=0.08; p=0.01) were positively correlated with NA. Finally, *OPRD1* candidate SNPs, rs1042114 (Φ=-0.08; p=0.01) and rs569356 (Φ=-0.07; p=0.01) were negatively correlated with NA (Table 3).

Phi-coefficient (Φ) correlation for PA and NA of PANAS with depression and anxiety: Next we studied Phi-coefficient (Φ) correlation between PA and NA of PANAS with self-reported acute and chronic depression and anxiety. We found PA of PANAS was negatively correlated with depression and anxiety. PA of PANAS has a correlation of Φ=-0.05 (p=0.01) with acute depression and a correlation of Φ=-0.03 (p=0.05) with chronic depression and a correlation of Φ=-0.04 (p=0.05) anxiety. Next, we found NA of PANAS was positively correlated with depression and anxiety. NA of PANAS has a correlation of Φ=0.03 (p=0.01) with acute depression and a correlation of Φ=0.02 (p=0.01) with chronic depression and a correlation of Φ=0.02 (p=0.01) anxiety (Table 4).

Phi-coefficient (Φ) correlation for OPRs' candidate SNPs with depression and anxiety: Finally, strengthening our findings, we identified correlations of OPRs' candidate SNPs (*OPRM1, OPRK1,* and *OPRD1*) with acute and chronic depression and anxiety. None of the OPMR1 candidate SNPs correlate with both acute and chronic depression as well as with anxiety. However, SNPs of *OPRK1* namely, rs16918875 (Φ acute depression=0.09, Φ chronic depression=0.09, Φ anxiety=0.03; p=0.01) and rs963549 (Φ acute depression=0.04, Φ chronic depression=0.03, Φ anxiety=0.03; p=0.05) correlate with both acute and chronic depression as well as with anxiety. Finally, none of the candidate SNPs of the *OPRD1* gene correlated with acute and chronic depression and anxiety (Table 5).

PANAS Factors			
NA		**PA**	
Nervous	0.745	Inspired	0.654
Jittery	0.734	Enthusiastic	0.622
Scared	0.729	Alert	0.604
Afraid	0.712	Attentive	0.603
Upset	0.647	Interested	0.580
Guilty	0.494	Strong	0.576
Ashamed	0.490	Determined	0.566
Distressed	0.484	Active	0.549
Irritable	0.454	Proud	0.414
Hostile	0.432	Satisfied	0.403
Nervous	0.745	Inspired	0.654

Table 2: Factor loadings in the pattern matrix for PANAS scale loaded as NA and PA factors.

Gene	Candidate SNPs	Phi-coefficient (Φ) correlation with PA	Phi-coefficient (Φ) correlation with NA
OPRM1	rs17174794	0.03	-0.07**
OPRM1	rs1799971	0.03	-0.08**
OPRK1	rs963549	-0.01	0.08**
OPRK1	rs16918875	-0.01	0.08**
OPRD1	rs569356	-0.01	-0.07**
OPRD1	rs1042114	-0.01	-0.08**
Note: *p<0.05; **p<0.01.			

Table 3: Phi-coefficient (Φ) correlation between PANAS dimension (PA &NA) and candidate SNPs.

	PA (Positive mood)	NA (Negative mood)	Depression (Chronic)	Depression (Acute)	Anxiety
PA (Positive mood)	1	-0.18**	-0.03*	-0.05**	-0.04*
NA (Negative mood)		1.00	0.16**	0.27**	0.17**
Depression (Chronic)			1.00	0.45**	0.12**
Depression (Acute)				1.00	0.12**
Anxiety					1
Note: *p<0.05; **p<0.0.					

Table 4: Phi-coefficient (Φ) correlation between PANAS dimension (PA-Positive mood & NA-negative mood), depression (acute and chronic) and anxiety.

Discussion

In this paper, we sought to study how candidate SNPs of three OPR

Gene	SNP	Acute depression	Chronic depression	Anxiety
OPRM1	rs17174794	0.00	-0.01	0.00
OPRM1	rs1799971	-0.01	-0.02	-0.01
OPRK1	rs16918875	0.09**	0.09**	0.03**
OPRK1	rs963549	0.04*	0.03*	0.03*
OPRD1	rs1042114	0.05	0.01	0.02
OPRD1	rs569356	0.01	-0.01	0.01
Note: *p<0.05; **p<0.01.				

Table 5: Phi-coefficient (Φ) correlation between depression (acute and chronic) and anxiety and candidate SNPs.

genes, *OPRM1, OPRK1* and *OPRD1* are associated with the PA and NA dimensions of the PANAS scale which is considered here as chronic positive and negative mood. Note that this study focused on all three main OPR genes and this endeavor of looking comprehensively at all three OPRs is to our knowledge relatively rare. Our main findings are visually presented in Figure 1. The findings are reasonably robust, as indicated by the substantially high correlation scores, given that we studied the relationships between SNPs of three candidate genes with a self-reported indication of mood. Subsequently, in order to enhance the ecological validity of the findings, we also studied the relationship between the PA and NA dimensions of PANAS with acute and chronic depression and anxiety and there we found significant correlations. Finally, we also tested the relationships between the candidate SNPs of all three genes on the acute and chronic depression and anxiety and found unique correlations which differed from those of the OPR-PANAS study. Hereunder we explain our findings related to the association between the three OPR genes and the PA and NA dimensions of PANAS as well as its relationship with chronic and acute depression and anxiety (Figure 1).

First, our study shows a significant negative association between two *OPRM1* SNPs (rs1799971 and rs17174794) and NA and the positive association between two *OPRM1* SNPs (rs540825, rs62638690) and PA. The rs1799971 is an exon variant on chromosome 6 and is also known as the A118G SNP while the rs17174794 is an upstream variant on chromosome 6 [21]. These findings indicate that the polymorphisms of *OPRM1* and its effect on *OPRM1* functioning is related to both positive and negative moods [16,20]. Here rs1799971 compared to rs17174794 had a higher association with NA which resonates with (or replicates) the work by Mague and Blendy [13] who show that this SNP is associated with both sensitivity to and reduction of pain. This reduction, occurring in pain-related incidents such as social exclusion, activates *OPRM1* that comes with dopamine release and release of 5-HT thus affecting the emotional brain functioning. *OPRM1* activation also motivates people to seek proximity with attachment figures when stressed in order to reduce social pain. Our finding replicates earlier studies; e.g., the G allele carriers, compared to AA homozygotes of the candidate SNPs of *OPRM1* (rs1799971), show an overall reduction of baseline μ-opioid receptor availability in regions implicated in pain and affective regulation [18]. G carriers also reported higher NEO-neuroticism scores; a personality trait previously associated with increased pain and lower placebo responses, which negatively correlated with baseline μ-opioid receptor availability in the aINS and subgenual anterior cingulate cortex [18]. *OPRM1* helps to overcome acute (short-term) psychosocial stress and negative mood in humans by reducing anxiety and stress levels [33]. Note that we do not know of any earlier studies involving NA or pain management and rs17174794.

Second, the two *OPRK1* SNPs (rs16918875 and rs963549) were positively associated with NA and not with the PA dimensions. Here rs16918875 and rs963549 are an exon variant and an upstream variant at chromosome 8, respectively. Candidate SNP rs16918875 and rs963549 at the *OPRK1* is known to be associated with pain sensitivity and negative mood [34]. We might infer that *OPRK1* is involved in increasing negative mood and depressive behavior due to the fact that *OPRK1* is associated with dynorphin production which inhibits dopamine release in the striatum (NAc and caudate putamen) and induces a negative mood in humans and animals [34]. *OPRK1* has an antagonist effect on acute (short-term) psychosocial stress and negative mood in humans by increasing anxiety and stress levels [33] and this negative mood e.g., attenuates nicotine- and opioid-withdrawal symptomatology. Note we also found these same candidate SNPs (rs16918875 and rs963549) associated with acute depression. In addition, *OPRK1* functioning is also related to chronic stress, a complex experience that carries both aversive and motivating properties. *OPRK1* agonists elevate brain reward thresholds [35], and produce depressive-like effects including increased immobility in the forced swim test in rats [36]. Again, note that this study also found these two candidate SNPs (rs16918875 and rs963549) to be associated with chronic depression. In humans, selective *OPRK1* agonists produce negative mood states including dysphoria, anxiety, and abnormal behavior along with psychotomimesis at higher doses [37]. Note that in this study the rs16918875 and the rs963549 were also related to anxiety. There is now considerable evidence that *OPRK1* antagonists block the effects of *OPRK1* agonist and have antidepressant- and anxiolytic-like effects on their own [38]. Just as noteworthy, only the candidate SNPs from the OPRK1 gene, and not those of the *OPRM1* and *OPRD1* genes correlate with acute and chronic depression and anxiety, thus showing that this finding could well be considered a substantiation of the role of *OPRK1* in the emergence of these psychological phenotypes.

Finally, the two *OPRD1* candidate SNPs (rs1042114 and rs569356) were negatively correlated with NA. Here the rs1042114 and rs569356 are an exon variant and an upstream variant on chromosome 1, respectively. Some polymorphism of this candidate SNP rs1042114 has already been found to be associated with negative mood and pain (thermal pain) [39]. Thus, it can be concluded that *OPRD1* emerges as a potent mood enhancer; *OPRD1* activation is known to make a person fight stress (chronic stress) and thus helps reduce stress and anxiety. In addition, activation of the enkephalin-*OPRD1* system and regulation of DA release in NAc have mood-enhancing effects. *OPRD1* receptor activation also has antidepressive effects; hence, candidate SNPs from the exon of the *OPRD1* gene were negatively associated with the NA of PANAS. *OPRD1* polymorphism is a genetic candidate also known for mediating corticolimbic-based risk of chronic pain [26].

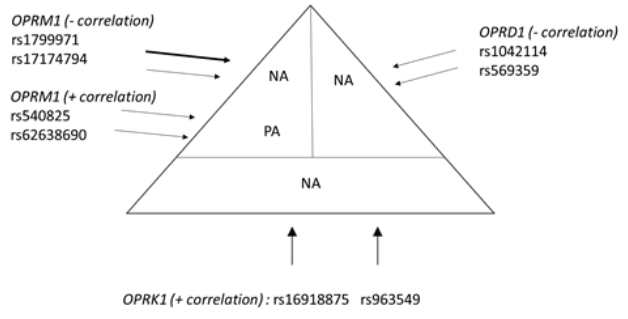

Figure 1: Overall view of how candidate SNPs of OPR genes affect PA and NA of PANAS.

While the PA and NA scores of PANAS were calculated using self-reported mood variables we sought to enhance the ecological validity of the study by studying the correlation of the PA and NA of PANAS with acute and chronic depression and anxiety scores [40]. The literature considers the PANAS scale an instrument that helps distinguish between depression and anxiety [2]. Watson et al. [31] find that while both anxiety and depression scores are positively correlated with the NA dimension of PANAS and PA, only depression negatively correlates with the scores of the PA dimension of PANAS and NA. Hence this study also shows ecological validity as the PANAS scale relates to other psychological phenotypes related to mood disorder [41-47].

Conclusion

Taking a bird's eye view of our findings, we conjecture the following OPR gene dynamic on the candidate phenotypes studied in this paper: when people temporarily experience negative mood states *OPRM1* activation starts, which reduces the negative mood hence the negative relationship of *OPRM1* gene polymorphism with NA. *OPRM1* activation also enhances positive moods, hence the positive relationships the *OPRM1* gene polymorphism have with PA. Next, *OPRK1* activity is affected by dynorphin production which enhances negative moods, making people sensitive to drug addiction and relapse. In addition, when people experience discomfort, *OPRK1* activity is activated, which enhances the chronic negative mood. The OPKR1 gene polymorphisms were indeed positively related to NA dimensions of PANAS. Finally, when people experience discomfort, they produce enkephalin which affects the *OPRD1* activation that prepares people to fight stressful situations or be resilient to stress. Indeed, we found a negative relationship between OPDR1 and the NA dimension of PANAS. Most important is that the NA dimensions of the PANAS scale correlated positively with both acute and chronic depression and anxiety. Concretely, the PA dimension of PANAS correlated negatively while the NA dimension correlated positively with both acute and chronic depression and anxiety. We also found in our cross-check study that only *OPRK1* candidate SNPs correlate to acute and chronic depression and anxiety. This further strengthens our finding that *OPRK1* induces depression and anxiety. *OPRM1* and *OPRD1* did not correlate with acute and chronic depression and anxiety, since both have mood-enhancing effects.

Limitations of the Study

The study had few limitations, for example, while the Lifelines database is large and extensive, the data set also has limitations. First, not all our candidate SNPs were represented in the sample and thus we were limited to those SNPs found inss the Lifelines database.

The Lifelines database has many incomplete IDs, which is why we focused only on the set of data that shared both PANAS scales and all the SNPs. This placed a limit on the size of the data set.

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Disclosure

The authors declare no conflict of interest.

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