



# Genetic polymorphisms related to behavioral approach and behavioral inhibition scales



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## ARTICLE INFO

### Article history:

Received 5 June 2015

Received in revised form 7 September 2015

Accepted 11 September 2015

Available online 25 September 2015

### Keywords:

Behavioral approach

Behavioral inhibition

Genetic polymorphism

BDNF

OPRM1

## ABSTRACT

Genetic polymorphisms relevant to behavioral approach and behavioral inhibition are examined, using a polygenic approach while also considering the role of early adversity. Undergraduates ( $N = 343$ ) completed the well-validated Behavioral Inhibition System/Behavioral Activation System (BIS/BAS) scales and provided blood for genotyping. The BDNF met allele was related to higher BIS scores. OPRM1 status interacted with a measure of early adversity to predict the BAS Reward Responsiveness subscale. Results provide additional support for the validity of the BIS/BAS scales, and suggest combined genetic and environmental influences on the development of these traits.

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## 1. Introduction

The behavioral approach system (BAS) and the behavioral inhibition system (BIS) have been conceptualized as broad-band motivational systems that guide behavioral and cognitive responses to cues of reward and threat, respectively (Gray, 1990). There are stable individual differences in the sensitivity of these systems (Brown, 2007), and neural correlates of these systems have also been identified (Gray & McNaughton, 2000; Knutson & Greer, 2008).

Extreme levels of BIS and BAS sensitivity have both been hypothesized to relate to diverse psychopathologies. For example, high BIS sensitivity relates to anxiety disorders, whereas low BAS sensitivity, perhaps in combination with high BIS sensitivity, relates to depressive disorders (Carver, Johnson, & Joormann, 2008; Gray, 1987; Nelson et al., 2013). Indeed, given the strong ties to multiple psychopathologies, BAS and BIS have been identified as two of the five core dimensions that form the centerpiece of new funding initiatives at NIMH (termed research domain operating criteria, or RDoC; Cuthbert & Insel, 2013).

### 1.1. Genes related to BAS and BIS sensitivity

Considerable research in both animals and humans suggests that the sensitivity of these systems is heritable (Bogdan & Pizzagalli, 2009).

Several studies have examined specific genetic polymorphisms and BAS sensitivity. Most have focused on genes related to dopamine function, including those related to D2, D3, and D4 receptors, and the dopamine transporter (DAT). In studies of neural responses to reward, researchers have documented effects for ANKK1, related to synthesis of dopamine (Felsted, Ren, Chouinard-Decorte, & Small, 2010), the 141C Ins/Del polymorphism related to the D2 receptor (Forbes et al., 2009), DRD4 (Camara et al., 2010), and DAT1 (SLC6A3; Dreher, Kohn, Kolachana, Weinberger, & Berman, 2009). Carriers of the 9-repeat allele of the DAT1 polymorphism have also been found to take more risks in pursuit of reward during a decision-making task (Zhong et al., 2009) and to show more striatal response to reward cues (Zhong, Chark, Ebstein, & Chew, 2012).

Genes have also been considered that are indirectly relevant to dopamine function, such as the Catechol-O-methyltransferase (COMT) and brain-derived neurotrophic factor (BDNF) genes. The COMT gene guides the production of the enzyme COMT, which is involved in catalysis of dopamine and other catecholamines (Chen et al., 2004). Among other neurobiological effects, the BDNF gene has effects on the mesolimbic dopamine pathway (Berton et al., 2006; Guillin et al., 2001). Some evidence has linked both COMT and BDNF genes to responses to reward. As examples, the met allele of the Val<sup>158</sup>Met COMT polymorphism has been found to relate to greater neural and psychophysiological response to reward anticipation (Dreher et al., 2009; Marco-Pallares et al., 2009).

Recent research also suggests involvement of the opioid receptor mu subunit gene (OPRM1) in neural responses to reward (Ray et al., 2014). Mu-opioid receptors are located in the nucleus accumbens and appear

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related to wanting and liking of naturally occurring rewards as well as drugs of abuse (Cui et al., 2014; Kawahara et al., 2013).

Polymorphisms have also been considered as correlates of BIS sensitivity. Few genes have received as much attention as the serotonin transporter gene, which has been linked to amygdala activation in response to threat cues (Munafò, Brown, & Hariri, 2007). Others, however, have suggested that this gene relates not so much to threat sensitivity (Sen, Burmeister, & Ghosh, 2005) as to more general constraint over emotional responses (Carver et al., 2008). This suggests the importance of considering serotonergic polymorphisms in regard to both BIS and BAS levels.

Other polymorphisms have also shown promise regarding BIS sensitivity. The Val variant of COMT has been related to greater engagement of the prefrontal cortex in response to emotionally-relevant stimuli (Mier, Kirsch, & Meyer-Lindenberg, 2010) and to elevated psychophysiological responses to threat cues (Montag et al., 2008a). The BDNF MET66 + variant has also been related to amygdala activation to threat cues (Montag, Reuter, Newport, Elger, & Weber, 2008) and higher harm avoidance (Montag et al., 2010). The COMT and BDNF genes thus would also appear relevant to both BIS and BAS sensitivities.

### 1.2. Genes related to Carver and White BIS/BAS scale scores

The Carver and White (1994) BIS/BAS self-report scales are widely used and well-validated. Several large scale studies have found these scales to have robust links with multiple psychopathologies (Brown, 2007; Johnson, Turner, & Iwata, 2003), and longitudinal research supports these links as well (Alloy et al., 2008; Naragon-Gainey, Gallagher, & Brown, 2013). Twin studies support a genetic contribution, with heritability estimates of .28 to .35 in BIS/BAS scale scores (Takahashi et al., 2007).

Despite the evidence for heritability, findings relating genetic polymorphisms to these scales have been mixed. In studies using the BAS scales, carriers of at least one A1 allele of ANKK1 have been found to have higher BAS Reward responsiveness scores (Davis et al., 2008; Lee et al., 2007) and lower BAS Drive scores (Felsted et al., 2010). DRD3 was related to BAS Drive in one sample, but not in a second sample (Henderson et al., 2000). Other null findings have been reported regarding other dopaminergic genes: BAS self-report scales were not found to relate to the DAT1 (Jorm et al., 2000), DRD2 markers of the –141 Ins/Del gene (Davis et al., 2008), the C957T mutation related to the D2 receptor (Davis et al., 2008), or COMT (Henderson et al., 2000).

Recent work suggests that composite scores, which aggregate the number of risk alleles across candidate polymorphisms, may be more powerful than single polymorphisms for predicting behavioral outcomes (Nikolova, Ferrell, Manuck, & Hariri, 2011). In one study, a composite score composed of several serotonergic polymorphisms was correlated with BAS scores among persons who had been exposed to early adversity (Pearson, McGeary, & Beevers, 2014).

In contrast to the mixed findings with BAS scales, research findings regarding genetic polymorphisms with the BIS scale have yielded null results. That is, BIS scores have not been found to relate to COMT (Henderson et al., 2000), DAT1 (SLC6A3) (Jorm et al., 2000), or the serotonin transporter (Jorm et al., 1998), and initial findings regarding DRD3 were not replicated in a second sample (Henderson et al., 2000). In sum, despite promising evidence for genetic polymorphisms related to behavioral and neural indices of BIS and BAS, there has been less progress in identifying genetic polymorphisms related to the self-report BIS/BAS scales.

Several limitations of existing work may help explain the mixed and null results. First, some studies have used samples of less than 100 persons, greatly reducing power (Davis et al., 2008). Second, many of the above studies have failed to consider that effects of polymorphisms on behavior often differ by gender and ethnicity. For example, effects of COMT on BIS may be stronger for men than for women (Chen et al., 2011), and a COMT effect might be missed if it existed for only one

gender. Third, some genes that would seem relevant conceptually, such as OPRM1 (described above) or tryptophan hydroxylase genes (which guide the synthesis of serotonin) have not been tested in relation to the BIS/BAS scales. Fourth, early life adversity shapes tendencies toward threat and reward sensitivity (Burghy et al., 2012; Henderson et al., 2000) and yet has not been considered as a potentiating factor in evaluating genetic contributions to threat and reward sensitivity.

Last, it is worth noting that more promising results have been obtained when serotonergic composite scores were used in place of specific polymorphisms in the prediction of BAS scores (Pearson et al., 2014). Composite scores have not been considered in understanding the role of the dopaminergic genes implicated in BAS function, nor have composite scores been used to assess effects of genes on BIS.

The analyses reported here addressed these concerns while assessing the contribution of genetic polymorphisms to BIS and BAS self-report scores. Drawing on the above literature, we hypothesized that BAS would be related to a dopamine polymorphism composite score, and that both BIS and BAS would be related to a serotonergic polymorphism composite score, COMT, and BDNF. We further hypothesized that OPRM1 would be related specifically to the BAS Reward Responsiveness subscale. We hypothesized that early family adversity would amplify the effects of genetic polymorphisms on the BIS/BAS scales, and we included gender and ethnicity in analyses as control variables.

## 2. Method

The 343 undergraduates (221 female; age  $M = 18.79$ ,  $SD = 1.93$ ). The sample was approximately half non-Hispanic Whites (178), a quarter Hispanic (77), with fewer African American (19), Caribbean (14), Asian (26), "Other" (16), and non-reporting (18).

Study procedures were approved by the university ethics board before data collection began. After completing informed consent, participants completed the BIS/BAS scales in group sessions. A departmental website provided opportunities for students to participate in further sessions 1–3 weeks later, in which blood was drawn for genotyping and other measures were completed in group sessions.

### 2.1. BIS/BAS scales

The BIS/BAS (Carver & White, 1994) is a widely used questionnaire with good psychometric properties that measures sensitivity to reward (BAS) and punishment (BIS). For the BIS scale, items reflect responses to potentially punishing events (e.g., "Criticism or scolding hurts me quite a bit"). BAS sensitivity is reflected in 3 empirically derived scales: Reward Responsiveness (e.g., "When I get something I want, I feel excited and energized"), Drive (e.g., "When I want something, I usually go all-out to get it"), and Fun Seeking (e.g., "I crave excitement and new sensations"). Individuals responded to items on a scale ranging from 1 ("I agree a lot") to 5 ("I disagree a lot"). Item responses were averaged (with reversals as necessary), BIS  $M = 3.79$ ,  $SD = .66$ , BAS Reward  $M = 4.36$ ,  $SD = .46$ , BAS Drive  $M = 3.57$ ,  $SD = .73$ , BAS Fun-seeking  $M = 3.81$ ,  $SD = .72$ . Reliability was moderate to high in this sample, with alpha coefficients of .78 (BIS), .68 (Reward Responsiveness), .72 (Drive), and .71 (Fun Seeking).

### 2.2. Childhood adversity

Childhood adversity was measured using the self-report Risky Families scale (Taylor, Lerner, Sage, Lehman, & Seeman, 2004). Thirteen items assess early family environment characteristics such as the extent to which the respondent had felt loved and cared for (reversed); was insulted, verbally or physically abused; or observed violence between family members. Item responses ranging from 1 (not at all) to 5 (very often or very much) were averaged ( $M = 1.82$ ,  $SD = .57$ ). The

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