Genetics of Behavioral Inhibition and Approach Systems:
A Review of the Literature
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Abstract
Individual differences in sensitivities of the Behavioral Inhibition System (BIS) and Behavioral Approach System (BAS) have been posited to underlie stable differences in individuals' unique patterns of responding to cues of punishment and reward in their environment. Conceived from the outset as neurological systems, the BIS and BAS have repeatedly been linked to brain structure and function through magnetic resonance imaging and electroencephalogram studies. These significant links to biology suggest an underlying genetic basis for BIS and BAS. Research concerning BIS/BAS in twin pairs as well as BIS/BAS associations with COMT, DRD2, DRD3, DRD4, and 5-HTTLPR genes is reviewed in hopes of elucidating genetic factors underlying personality and psychopathology.

Key words: behavioral inhibition system, behavioral approach system, BIS, BAS, behavioral activation, Gray, reinforcement sensitivity theory, DRD2, DRD3, DRD4, COMT, 5-HTTLPR, dopamine, serotonin, impulsivity, personality, genes, heritability.

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In 1970, Dr. Jeffrey Gray proposed a psychophysiological theory of anxiety and impulsivity as resulting from punishment and reward mechanisms (Gray, 1970). This theory has since been extended into a model of personality referred to as the Reinforcement Sensitivity Theory (RST; Gray, 1970). RST involves three neurological systems thought to underlie emotional behavior: the Behavioral Inhibition System (BIS), the Behavioral Approach System (BAS), and the Fight or Flight System (FFS; Gray, 1987). Individual differences in sensitivities of BIS and BAS have been posited to underlie stable differences in individuals' unique patterns of responding to cues of punishment and reward in their environment.

BIS is thought to underlie trait anxiety. It activates in response to novelty, threat, punishment, and frustrative non-reward (i.e., the omission of anticipated reward). BIS is thus thought to regulate aversive motivation by inhibiting ongoing behavior that may lead to negative or painful outcomes and increase arousal and attention to environmental stimuli (Carver & White, 1994; Takahashi et al., 2007). BIS is also related to negative affect, including fear, anxiety, frustration, and sadness, as these feelings may be experienced as part of the response to aversive stimuli (Carver & White, 1994). BIS has been shown to correlate highly with risk-avoidance (Lorian & Grisham, 2010), neuroticism, and the processing of unpleasant information (Gomez, Gomez, & Cooper, 2002).

Individuals with higher BIS sensitivity might be more attentive to the presence of uncertainty and sources of potential punishments in the environment. In response to such stimuli, they may be more likely to inhibit behavior, waiting until there is more information and certainty in outcomes before taking action. When a punishment is received, they may experience more negative affect. On the other hand, individuals with lower BIS sensitivity might be less attentive to sources of punishment in the environment and, as a result, may exhibit more risk-taking behavior due to the lack of attention to negative outcomes. Individuals who score low on BIS are less likely to experience negative affect in response to negative outcomes.

BAS, on the other hand, relates to impulsivity, or a proclivity to engage in goal-directed behavior (Carver & White, 1994). BAS activation is thought to regulate responses to reward and non-punishment by motivating goal-directed activity and increasing arousal. BAS is further related to the experience of positive affect, including feelings of hope, elation, and happiness, especially in response to rewards (Carver & White, 1994). BAS has been linked to positive affect, extraversion, and the processing of pleasant information (Gomez et al., 2002).

Individuals with higher BAS sensitivity are thought to be more attentive to sources of reward in the environment and, in response to cues of reward, feel excitement and motivation to pursue the reward, activating behavior to take the steps necessary to obtain it. When a reward is obtained, individuals with high BAS may experience more positive feelings. Individuals with lower BAS sensitivity may be less perceptive of sources of reward in the environment. They might experience less drive and motivation to take steps toward obtaining rewards and may be less likely to feel positive affect when rewards are received.

To assess varying levels of BIS and BAS sensitivity, Carver and White (1994) developed a standardized self-report questionnaire: the BIS/BAS Scales. While traits such as introversion, extraversion, impulsivity, fearfulness, and constraint that are measured through assessments such as Eynsenck's Personality Inventory, the Toddler Temperament Scale, and Cloninger's Temperament and Character Inventory are related to BIS and BAS, the BIS/BAS Scales specifically measure BIS and BAS (Eynsenck & Eynsenck, 1968; Rickman & Davidson, 1994;

Fullard, McDevitt, & Caret, 1984; Matheny, 1989; Cloninger, Svrakic, & Przybeck, 1993; Reuter & Hennig, 2005). Items on the BIS/BAS Scales ask how people would respond to certain events on a 4-point Likert scale with anchors of "extremely true of me" to "not at all true of me" (Carver & White, 1994). Items pertaining to the BIS refer to potentially punishing stimuli. BAS includes three subscales: Drive (concerning the persistent pursuit of desired goals), Fun Seeking (focusing on the desire for new rewards and willingness to approach a potentially rewarding event on the spur of the moment), and Reward Responsiveness (concerning positive responses to the occurrence or anticipation of rewards).

　　　　Well-balanced BIS and BAS result in adaptive behavior, with decisions and actions appropriately guided by the cues of the environment. Yet extreme sensitivity or insensitivity of either BIS or BAS is maladaptive and linked to psychopathology (Bijttebier, Beck, Claes, & Vandereycken, 2009; Johnson, Turner, & Iwata, 2003). High BIS is associated with anxiety and depression (Campbell-Sills, Liverant, & Brown, 2004; McFarland, Shankman, Tenke, Bruder, & Klein, 2006; Vervoort et al., 2010), while strong BAS is linked to mania (Urošević, Abramson, Harmon-Jones, & Alloy, 2008; Meyer, Johnson, & Winters, 2001), hyperactive-impulsive symptoms of ADHD (Hundt, Kimbrel, Mitchell, Nelson-Gray, 2008), and substance abuse (Hundt, Kimbrel, Mitchell, Nelson-Gray, 2008; Franken, Muris, Georgieva, 2006; Krmpotich et al., 2013). Inversely, extremely low BAS is associated with anhedonia (Franken, Rassin, & Muris, 2007), the loss of interest or pleasure in usual activities sometimes exhibited in depression, and low BIS is linked to psychopathy (Newman, MacCoon, Vaughn, & Sadeh, 2005). Investigating BIS and BAS thus helps elucidate mechanisms of psychopathology. Furthermore, while the study of psychopathology through syndromes has its benefits, more discrete constructs, such as BIS and BAS, may be better suited to investigations of the biological substrates of maladaptive behavior.

Neurological Correlates

　　　　From the outset, BIS and BAS were conceived as neurological systems. Gray's Reinforcement Sensitivity Theory posited that dopaminergic pathways in the limbic circuits make up the BAS, whereas the BIS is comprised of a set of circuits involving the hippocampus, subiculum, septum, and related structures (Gray, 1987). While BAS is more closely associated with dopamine, it has been theorized that BIS is associated with noradrenergic and serotonergic neurotransmitter systems in the brain (Gray & McNaughton, 2000). Modern technologies such as magnetic resonance imaging (MRI) and electroencephalography (EEG) provide opportunities to study the structure and function of the brain in relation to BIS and BAS. Because BIS and BAS are stable personality traits, there should be some relation between brain structure, as well as brain resting-state activity, and BIS and BAS. In addition, because BIS and BAS are sensitive to cues of reward and punishment, there should also be associations between trait measurements of BIS and BAS and brain activation in the context of behavioral tasks.

Structure

　　　　Several structural MRI studies have shown associations between BIS and BAS and regional brain volumes. Cherbuin et al. (2008) analyzed hippocampal and amygdalar volumes in relation to BIS and BAS. They found no association between the amygdala and either BIS or BAS; however, they did find a positive association between BIS and hippocampal volume as well as a weak positive association between BAS Reward Responsivity and hippocampal volume. Barrós-Loscertales et al. (2006a) found an association between sensitivity to

punishment, a component of BIS measured by the Sensitivity to Rewards and Punishments Questionnaire (SPSRQ; Torrubia, Ávila, Moltó, & Caseras, 2001), and larger hippocampal and amygdalar gray matter volumes. Whereas Barrós-Loscertales et al. (2006b) demonstrated an association between sensitivity to reward (a measure of BAS; Torrubia et al., 2001), and reduced gray matter volume in the bilateral caudate and putamen, left globus pallidus, and right superior frontal cortex. Fuentes, Barrós-Loscertales, Bustamante, Rosell, Costumero, and Ávila (2012) found higher BIS to be associated with reduced right medial orbitofrontal cortex (OFC) and bilateral precuneus volumes. In a longitudinal study, Urošević, Collins, Muetzel, Lim, and Luciana (2012) found that increases in sensitivity to reward across adolescent development were predicted by individual differences in nucleus accumbens (Nacc) and medial OFC baseline volumes. Larger Nacc volume at baseline predicted a more drastic increase in BAS Reward Responsiveness, and larger medial OFC volume at baseline predicted a more drastic increase in global BAS (Urošević et al., 2012). Additional research is needed to replicate these findings across genders and age groups. However, BIS appears to be associated with increased hippocampal and potentially increased amygdalar volumes, as well as decreased volumes of the right medial OFC and bilateral precuneus, while BAS appears to be associated with reduced volumes in the bilateral caudate, putamen, left globus pallidus, and right superior frontal cortex, but increased volumes in the hippocampus, Nacc, and medial OFC.

Function

While gross regional volumetric measurements provide a general depiction of the underlying structure of certain neural systems, these measurements are not directly related to brain function. Thus, studies of neural activity in the brain provide an important perspective in the study of neurological substrates of BIS and BAS. Functional MRI studies analyze the blood-oxygen-level dependent signal (BOLD) as a measure of brain activity, assuming there is increased blood flow to active brain regions (Logothetis, 2003; Ogawa, Menon, Kim, & Ugurbil, 1998). EEG, on the other hand, measures electrical activity on the scalp, which results from the collection of firings from pyramidal neurons with axons perpendicular to the scalp (Kirschstein & Köhling, 2009). Both of these measures can be collected in relation to events in behavioral tasks as well as during resting-state, when the participant is usually instructed not to think about anything in particular, in order to get at the brain's "default" state.

Several event-related fMRI studies have linked BIS and BAS to brain activation. Hahn et al. (2009) found that higher reward sensitivity was associated with increased activation in the ventral striatum and OFC during reward anticipation. Simon et al. (2010) found a positive correlation between BAS and activity in the medial OFC during the receipt and omission of reward, and a negative correlation between BIS and activation in the ventral striatum during the receipt of reward, supporting the idea that individuals with high BIS sensitivity might show a blunted response to rewards. Beaver et al. (2006) found that BAS was positively correlated with activation in the ventral striatum, amygdala, midbrain, OFC, and ventral pallidum in response to pictures of appetizing foods, which would be rewarding stimuli. Beaver, Lawrence, Passmonti, and Calder (2008) found that increased BAS-Drive (Carver & White, 1994) was associated with increased amygdala activation but decreased ventral anterior cingulate cortex (ACC) and ventral striatum activation in response to facial expressions of aggression relative to sad and neutral expressions. They found that BIS, on the other hand, was associated with increased activation in the dorsal ACC. Additionally, Gray and Braver (2002) found an association between higher BAS and lower working-memory related activation in the caudal ACC and that individuals with higher BAS had better working-memory performance. In an event-related EEG paradigm, Amodio, Master, Yee, and Taylor (2008) found a positive association between BIS and the N200 event-related potential (ERP) on No-Go trials of a Go/No-Go task. The N200 ERP has been linked to the ACC, thus linking BIS with increased ACC activity (van Veen & Carter, 2002).

Resting-state EEG studies have reliably demonstrated a relationship between BAS and left-biased frontal activity (Sutton & Davidson, 1997; Amodio et al., 2008; Coan & Allen, 2003; Harmon-Jones & Allen, 1997; Harmon-Jones & Allen, 1998). Somewhat less reliably, BIS has also been associated with right-biased asymmetrical activity (Sutton & Davidson, 1997). Interestingly, the well-established association between left-biased asymmetrical activity in EEG and BAS has so far failed to be replicated in resting-state fMRI. However, Berkman and Lieberman (2010) did find a positive relationship between BAS and greater left-biased activity in the dorsolateral prefrontal cortex (DLPFC) during approach actions in event-related fMRI. Krmpotich et al. (2013) also found a positive association between BAS and BOLD signal fluctuation in the left DLPFC at rest, but this activity in the left DLPFC was not analyzed in relation to activity in the right hemisphere. Recent PET studies have supported the theory that asymmetrical dopamine signaling from the striatum underlies the asymmetrical frontal activity associated with BIS and BAS (Tomer et al., 2014; Tomer, Goldstein, Wang, Wong, & Volkow, 2008).

BIS and BAS are associated with neural systems involving prefrontal, limbic, and striatal regions, which are heavily influenced by dopaminergic and serotonergic activity. These strong links to biology suggest an underlying genetic basis for BIS and BAS.

Heritability

Studies of monozygotic (MZ) and dizygotic (DZ) twins provide evidence for the heritability of traits. MZ twins share 100% of their genes, while DZ twins share only 50% of their genetic material—the same percentage as any pair of siblings. Thus, if the correlation of a trait in MZ twins is higher than the correlation in DZ twins, it can be deduced that the trait is heritable. The correlation between MZ twin pairs is assumed to be a result of both additive genetic and shared environmental influences. The additive genetic effect is the sum of the average effects of the individual alleles, and shared environmental effects are the environmental influences that make twin siblings similar. In DZ twin pairs, the within-pair correlation is assumed to be due to the sum of *half* the additive genetic effects and shared environmental influences. Through model-fitting analyses, the extent that a disorder is heritable can be estimated.

Matheny (1989) studied 33 MZ and 32 DZ twin pairs at 12, 18, 24, and 30 months of age. The infants participated in multiple vignette activities designed to assess their behavior in various situations with and without their co-twin and their mother. Videotapes of the vignettes were later coded for the infants' emotional tone for each 2-minute period. Infants also completed the Bayley Scales of Infant Development, including a rating scale of fearfulness of the infant's behavior during Bayley testing (Bayley, 1969). Additionally, mothers of the infants completed the Toddler Temperament Scale, which includes items pertaining to approach and withdrawal in regards to specific activities and events at home. Emotional tone, fearfulness, and (lack of) approach were interpreted as measures of behavioral inhibition. Matheny (1989) found that MZ pair correlations were significantly higher than DZ pair correlations for emotional tone and fearfulness at ages 18, 24, and 30 months, and for approach at ages 12, 18, and 30 months. This consistent pattern of differences supports the hypothesis that there is a strong genetic influence on these aspects of BIS across infant development from 12 to 30 months. Matheny (1989) also found MZ twin pairs shared a more similar pattern of change over time than DZ twin pairs. Age-to-age changes in behavior were more closely synchronized within MZ pairs, providing evidence for a genetic influence on change in behavior over time. While the measurements employed by Matheny (1989) are associated with certain aspects of BIS and BAS, studies of adults may be better equipped to measure BIS and BAS more specifically.

Takahashi et al. (2007) administered a Japanese version of Carver and White's (1994) BIS/BAS Scales to a sample of 117 adult twin pairs at two separate time points, a little more than

2 years apart. MZ twin-pair correlations for BIS and BAS were higher than correlations for DZ twin-pairs, indicating a moderate genetic influence for BIS and BAS that accounted for approximately one-third of the variance. Because different genes may be influential at different time points (Plomin, 1986), the study employed a longitudinal design to assess changes in genetic influence on BIS and BAS over time. Takahashi et al. (2007) found that genetic influence did not vary across time points and that change in observed temperament was solely due to non-shared environmental influences, thus supporting the hypothesis that BIS and BAS are more genetically stable than other personality traits.

　　　Twin studies support the heritability of BIS and BAS. However, twin studies are not well disposed to illustrate the specific biological mechanisms underlying heritable traits. Candidate gene studies provide more detailed information about the specific biological mechanisms that may underlie the heritability and biological foundations of BIS and BAS.

Genes related to BIS and BAS

COMT.
COMT Val158Met is a coding variant encoding the catechol-O-methyltransferase enzyme, which metabolizes dopamine and other catecholamines by inactivating them in the synaptic cleft (Gogos et al., 1998). COMT contains a common functional single nucleotide polymorphism (SNP) in codon 158, resulting from a G-to-A base-pair substitution in the coding sequence of the gene (Lachman et al., 1996). This substitution results in the gene coding for the production of methionine instead of valine, altering the form of the catechol-O-methyltransferase enzyme. The methionine form of the enzyme is less thermostable than the valine form, and thus has 3 to 4 times lower activity at physiologically relevant temperatures. Met/Met genotypes have low catechol-O-methyltransferase enzyme activity, while Val/Val genotypes have high catechol-O-methyltransferase enzyme activity, and Val/Met genotypes have intermediate levels of the enzyme activity.

　　　Since the catechol-O-methyltransferase enzyme catabolizes dopamine, the COMT gene is of interest in relation to BIS/BAS. Reuter and Hennig (2005) studied extraversion and the COMT Val158Met polymorphism in 363 healthy Caucasian university students of German ancestry. Extraversion was assessed by the NEO-Five Factor Inventory (NEO-FFI; Costa & McCrae, 1992), which has five scales: Extraversion, Openness to Experience, Conscientiousness, Agreeableness, and Neuroticism. Cloninger's Temperament and Character Inventory (TCI; Cloninger et al., 1993) provided additional assessment of traits related to BIS/BAS and includes measures of novelty seeking, harm avoidance, reward dependence (which includes aspects of both Reward Responsivity and Drive), and persistence. The TCI also includes subdimensions of Novelty Seeking, such as Exploratory Excitability and Impulsiveness. Reuter and Hennig (2005) found that the COMT Val158Met polymorphism had a significant main effect on both Extraversion and Exploratory Excitability, with Val homozygous genotypes scoring significantly higher on Extraversion and Exploratory Excitability scales than heterozygous individuals, or individuals homozygous for Met. These findings support the idea that there is a genetic basis for BAS as the system relates to extraversion and aspects of novelty seeking, however, better support comes from gene studies utilizing the BIS/BAS-specific scales designed by Carver and White (1994).

DRD2.

Reuter, Schmitz, Corr, and Hennig (2007) sought to clarify a number of biological relations to BIS and BAS. In addition to COMT, the researchers also assessed DRD2 genotype and prolactin levels (in a subset of males) and employed the BIS/BAS Scales. Since dopamine inhibits the secretion of prolactin from the pituitary, prolactin concentration is interpreted as being inversely related to the concentration of dopamine (see Ben-Jonathan & Hnasko, 2001). The DRD2 TaqIA polymorphism is correlated with the density of dopamine D2 receptors in the brain (Ritchie & Noble, 2003). Ritchie and Noble (1996) demonstrated that individuals with the A1 allele for DRD2 have a 30-40% reduction in dopamine D2 receptor density compared to individuals homozygous for the A2 allele. The A1A1 genotype occurs in only about 3% of healthy Caucasians (Noble, 2000). Thus, carriers of A1, including heterozygous individuals (A1A2) and individuals homozygous for A1, are often classified as A1+, in contrast to individuals homozygous for the A2 allele, who are classified as A1-. In analyzing interactions with COMT genotypes, carriers of Val (i.e., the combination of heterozygous individuals and those homozygous for Val), will be referred to as Val+, and contrasted to individuals homozygous for Met (Val-).

Reuter et al. (2007) found a significant interaction of COMT and DRD2 on BAS, though a main effect was not noted for either gene. In their sample of 295 German Caucasians, individuals with higher BAS scores were associated with A1+/Val+ and A1-/Val- carriers, whereas low BAS was associated with A1+/Val-, and A1-/Val+ carriers. Additionally, individuals with A1-/Val- and A1+/Val+ genotypes (which predicted higher BAS) had significantly lower baseline prolactin concentrations than individuals with A1-/Val+ and A1+/Val- genotypes (predicting lower BAS scores). Thus, it appears the combination of alleles associated with low receptor density (A1+) and alleles associated with high catechol-O-methyltransferase enzyme activity (Val+), as well as the combination of alleles associated with high receptor density (A1-) but low catechol-O-methyltransferase enzyme activity (Val-) have higher dopamine concentrations and higher BAS scores than individuals with the contrasted genotypes (A1+/Val- and A1-/Val+). This supports the hypothesis that dopamine activity is associated with BAS (Gray, 1994; Depue, Luciana, Arbisi, Collins, & Leon, 1994).

Montag et al. (2008) tested for associations between the DRD2 TaqIA and the COMT Val158Met polymorphisms, the BIS/BAS Scales, and a psychological measure of emotion processing: the acoustic Affective Startle Reflex Modulation (ASRM) paradigm. The ASRM is a psychophsyiological paradigm measuring startle reflex that involves a set of involuntary responses to sudden, intense stimuli and is measured in humans by the amplitude of the eye-blink reflex. It has been shown that the amplitude of the startle reflex is modified by the presentation of affective stimuli of differing emotional valence. Compared to neutral scenes, startle amplitude is potentiated by aversive scenes but attenuated by appetitive scenes (Grillon & Baas, 2003; Bradley, Codispoti, Cuthbert, & Lang, 2001). Additionally, differences in potentiated startle have been shown in individuals scoring low on trait measures of sensation seeking and those scoring high on measures of behavioral inhibition (Lissek & Powers, 2003; Hawk & Kowmas, 2003). Montag et al. (2008) studied 96 healthy females of German origin who were chosen from a larger genetic databank according to their genotype/allele pattern (COMT: Val/Val, Val/Met, and Met/Met; DRD2: A1- and A1+) to form six groups of 16 participants each. Participants watched pictures alternating in valence on a computer screen, with 35 ms startle probes of 106 dB white noise randomly presented during picture presentation. Montag et al. (2008) demonstrated a significant influence of the COMT genotype on the startle reflex in response to the unpleasant picture condition, in which Met/Met genotypes had increased startle compared to either type of

Val allele carrying participants. BIS was also negatively correlated with ASRM in the unpleasant picture condition and in the pleasant picture condition. At a trend level, participants with high BIS more often had the Met/Met genotype than either of the Val+ genotypes. Montag et al. (2008) found no significant associations between DRD2 and BIS or BAS.

DRD3.

The dopamine D3 receptor has been shown to exert an inhibitory effect on locomotion in rodents (Svensson, Carlsson, & Waters, 1994). Mice with DRD3 knocked out demonstrate increased locomotion in novel environments (Xu et al., 1997). This exploratory behavior in novel environments can be likened to novelty seeking and BAS in humans, highlighting DRD3 as a candidate gene in the study of BAS. A point mutation in DRD3 sometimes results in the substitution of a Serine by a Glycine (Lannfelt et al., 1992). While the in-vivo functional significance of Ser versus Gly alleles is unclear, the receptor products of the two alleles show differential binding affinity for dopamine (Lundstrom & Turpin, 1996).

Henderson et al. (2000) studied associations of BIS, BAS, and COMT and DRD3. Analyses were split into two stages in order to allow replication and to avoid the time and expense of genotyping the entire sample should there be no significant findings in the first set of analyses. In approximately one-third of the sample included in the first analyses (N=862), a significant association between BIS and DRD3 was found. Individuals with at least one Ser allele had higher BIS than individuals homozygous for the Gly allele. A relationship between BIS and DRD3 was not replicated in the second sample (N=1,465). In addition, no association between COMT and either BIS or BAS was demonstrated. The initial positive findings of Henderson et al. (2000) are intriguing, and future research is warranted to determine if group differences between the first and second samples may have played a role in the disparate results. For example, the frequency of other genetic variants may have differed between the samples. Additional candidate genes should be investigated for interactions with DRD3 or contrasting main effects that could obscure the effect of DRD3.

DRD4.

The DRD4 gene is associated with the function of the dopamine D4 receptor in the brain. Associations between novelty seeking and the long form (seven-repeat allele) of the DRD4 polymorphism have been reported (Benjamin, Patterson, Greenberg, Murphy, & Hamer, 1996; Ebstein et al. 1996). Thus DRD4 is of interest in relation to BIS and BAS. Keltikangas-Järvinen et al. (2003) studied the relation between aspects of novelty seeking and DRD4 in 150 individuals who scored in the top 10% or bottom 10% on the Novelty Seeking scale of the TCI. While the researchers did not find any association between the different DRD4 alleles and novelty seeking overall, they did find significant associations between different DRD4 alleles and subscales of Novelty Seeking -- in particular, the Exploratory Excitability and Impulsiveness scales. Keltikangas-Järvinen et al. (2003) found scores on Exploratory Excitability and Impulsiveness were related to two of the shorter alleles (two- and five-repeats), which conflicts with earlier findings of novelty seeking being associated with seven-repeat DRD4 allele (Benjamin, Patterson, Greenberg, Murphy, & Hamer, 1996; Ebstein et al. 1996). Future research may help explain these disparities by using multiple measures of novelty seeking in multiple populations. Novelty seeking is related to BAS but does not encompass the full range of behaviors associated with the system. There is a paucity of research studying associations between DRD4 and BIS and BAS as measured by the BIS/BAS Scales, which warrants future research.

5-HTTLPR.

The majority of research into genes related to BIS and BAS have focused on candidate genes related to the dopamine system, but studies of genes related to serotonin are also important in this context, especially in relation to BIS. Whisman, Richardson, and Smolen (2011) studied the relation of BIS and BAS to the serotonin transporter gene (5-HTTLPR) using three-variant genotyping in a sample of 211 undergraduates. Short variants of 5-HTTLPR include 14 copies of a 20-23 base pair repeat unit and are less transcriptionally efficient compared to the long variant, which has 16 copies (Lesch et al., 1996). Recent research suggests that a SNP within the long version is associated with different functional activity (Hu et al., 2005). Most frequently, this SNP (rs25531) is A; however, when it is G, functional activity is more comparable to the short allele. Thus, participants with the long allele that contained the G rs25531 SNP were grouped with those who had the short allele for three-variant analyses and compared to those with the long allele that contained A at rs25531. Higher BIS was associated with one or two copies of the alleles linked with low expression of serotonin transporters (i.e., short and long-G alleles), which are theoretically coupled with increased serotonin neurotransmission.

Conclusions

Dopamine and serotonin affect behavior through complex systems in the brain. Neurotransmission of dopamine and serotonin is affected by reuptake, enzyme activity in the synaptic cleft, and the activity of other neurotransmitters. In addition, different types of receptors have distinct functions, and the density of various receptor types varies throughout different brain regions (e.g., D3 receptors are more concentrated in the ventral striatum; Piggott et al., 1999). Neurotransmission will have different effects on behavior depending on the area of the brain implicated. The complexity of neurotransmission underlines the importance of studying multiple genes in relation to behavior, as interactions between the biological features that are coded for by different candidate genes can result in very different phenotypes than could be understood by studying single genes in isolation. As demonstrated by Reuter et al., (2007)'s finding of an interaction between COMT and DRD2, a gene variant may have different associations with behavior depending on which variant of another gene is present.

Genetics are not the only factor underlying biology, and experiences throughout life can significantly impact the structure of the brain. Following the diathesis-stress model, the environment will differentially impact an individual's biology depending upon his or her genetic makeup, which can make him or her predisposed to certain effects. Furthermore, the relationship is not 1:1; that is, an individual with genetic makeup A, when exposed to environmental stressor B, will not always have the outcome C, which can make the detection of interactions more elusive.

Complex traits can be expected to result from complex interactions of environmental factors with a number of genes and their biological consequences. In order to understand the mechanisms of human behavior, we first need valid and reliable measures of discrete aspects of behavior that are representative of the underlying biological mechanisms. BIS and BAS are refined constructs that are advantaged over symptom clusters of psychopathology in their precision. In addition to good psychological measurements, interactions between multiple genes and environmental factors need to be investigated.

Gray's Reinforcement Sensitivity Theory has remained a prominent model of personality, although it has evolved through the years (Gray 1970, 1982, 1987, 1994; Gray & McNaughton, 2000). The theory is well supported by behavioral research, and its integration of biological mechanisms as the source of personality provides a wide range of interesting research inquiries. RST is relevant to a number of disciplines, including psychology, psychiatry, pharmacology, genetics, and neuroscience. By combining methods from these areas of research, the correlates

between the BIS and BAS, genetics, neurochemistry, brain structure, personality, and psychopathology may be elucidated. This is a valuable pursuit, as RST has shown promise as a model of personality and psychopathology. By disentangling the many interactions between these psychological and biological phenomena, the etiology of psychopathology may be illuminated, and treatments based on underlying biology and individual genetic makeups may be advanced.

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