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Review

Neurogenetics of depression: A focus on reward processing and stress sensitivity

Ryan Bogdan [a,b,*], Yuliya S. Nikolova [b], Diego A. Pizzagalli [c]

[a] BRAIN Laboratory, Department of Psychology, Washington University in St. Louis, Box 1125, One Brookings Drive, St. Louis, MO 63130, USA
[b] Laboratory of NeuroGenetics, Department of Psychology and Neuroscience, Duke University, Box 90086, 417 Chapel Drive, Durham, NC, 27708, USA
[c] Center for Depression, Anxiety and Stress Research & McLean Imaging Center, McLean Hospital, Harvard Medical School, 115 Mill St., Belmont, MA 02478, USA

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ABSTRACT

Major depressive disorder (MDD) is etiologically complex and has a heterogeneous presentation. This heterogeneity hinders the ability of molecular genetic research to reliably detect the small effects conferred by common genetic variation. As a result, significant research efforts have been directed at investigating more homogenous intermediate phenotypes believed to be more proximal to gene function and lie between genes and/or environmental effects and disease processes. In the current review we survey and integrate research on two promising intermediate phenotypes linked to depression: reward processing and stress sensitivity. A synthesis of this burgeoning literature indicates that a molecular genetic approach focused on intermediate phenotypes holds significant promise to fundamentally improve our understanding of the pathophysiology and etiology of depression, which will be required for improved diagnostic definitions and the development of novel and more efficacious treatment and prevention strategies. We conclude by highlighting challenges facing intermediate phenotype research and future development that will be required to propel this pivotal research into new directions.

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* Corresponding author at: BRAIN Laboratory, Department of Psychology, Washington University in St. Louis, Box 1125, One Brookings Drive, St. Louis, MO 63130, USA. Tel.: +1 617 407 5645.
E-mail address: bogdan.ryan@gmail.com (R. Bogdan).
Available online on ScienceDirect (www.sciencedirect.com).

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Table 1
Definitions of common genetics terminology.

Epigenetic effects	Changes in gene expression caused by factors (*e.g.*, methylation affecting gene transcription) other than variation in DNA sequence
Epistatic effects	Gene interactions that can affect phenotypes
Single nucleotide polymorphism (SNP)	A small genetic variation in the DNA sequence. The four nucleotide adenine (A), cytosine (C), thymine (T), and guanine (G) represent the building block of the genetic code. A SNP occurs when a single nucleotide (*e.g.*, C) replaces another nucleotide in a given location (*e.g.*, G). For example, AGTTA is replaced by ACTTA
Variable number of tandem repeats (VNTR)	A VNTR is a short nucleotide sequence that is organized into clusters of tandem repeats (*e.g.*, ATGCC, ATGCC, ATGCC).

Introduction

Major depressive disorder (MDD) is a common, recurrent, and etiologically complex mental illness. Family, twin, and adoption studies have shown that this disabling disorder is moderately heritable, with approximately 37% of the variance explained by additive genetic effects (Sullivan et al., 2000). Building upon this evidence, candidate gene and genome-wide association studies (GWAS) have begun to link common DNA sequence variation (polymorphisms; Table 1) to MDD (Caspi et al., 2003; Levinson, 2006; Lohoff, 2010; Sullivan et al., 2009). The potential of such molecular genetic research is undeniable. In addition to furthering our understanding of the genetic basis of depression, molecular genetic research has the potential to inform our etiologic conceptualization of the disorder and identify novel treatment targets. When polymorphisms are of known functionality (i.e., when they have been associated with differences in gene and/or protein expression), they can serve as proxies for individual differences in neurochemistry, which can, in turn, inform our understanding of the molecular processes underlying depression (Hariri, 2009). Additionally, GWAS allow for the identification of novel candidate loci within biological pathways whose role in MDD may have never been suspected (Cichon et al., 2009), while treatment research can uncover genetic variants predicting therapeutic outcomes, bringing psychiatry one step closer to personalized treatment (Fox et al., 2011; Smeraldi et al., 1998). Finally, research on epigenetic factors (Table 1) can inform the mechanisms by which experience, including exposure to stress, shapes biology to influence depression risk (Zhang and Meaney, 2010).

With such promise also come substantial challenges (Bogdan et al., in press; Hasler and Northoff, 2011). One of the largest challenges is that individual common polymorphisms will have, at most, only a small effect on complex polygenetic diseases and related processes, making relationships difficult to uncover and replicate, particularly within small samples characteristic of most non-consortia efforts. This weak penetrance is further compounded by the complexity and heterogeneity of psychiatric diagnoses, including MDD (Hasler and Northoff, 2011; Hasler et al., 2004; Hyman, 2007; Meyer-Lindenberg and Weinberger, 2006).

Specifically, current classification systems for psychopathology (e.g., DSM-IV-TR, American Psychiatric Association, 2000; ICD-10, World Health Organization., 2004) adopt an atheoretical approach with respect to the etiology and pathophysiology of mental illness, and instead rely on symptom clusters and clinical course as diagnostic criteria (Cannon and Keller, 2006; Kendler and Gardner, 1998). While this descriptive nosological system has dramatically improved diagnostic reliability, it also yields heterogeneous disease categories with unknown validity. MDD, as defined by the DSM-IV-TR, requires endorsement of 5 out of 9 symptoms (one of which must be depressed mood or anhedonia), yielding more than 100 unique symptom combinations that presumably reflect distinct pathophysiologies. Moreover, these symptoms are themselves complex and heterogeneous(e.g., anhedonia– classically defined as loss of pleasure or reactivity to pleasurable stimuli – might stem from dysfunction in incentive motivation, consummatory behavior, and/or reward learning; Berridge et al., 2009; Pizzagalli et al., 2008; Treadway and Zald, 2011), disorder-unspecific(e.g., negative affect cuts across anxiety and depressive disorders; Watson et al., 1995), and may even have opposing pathophysiologies (e.g., insomnia vs. hypersomnia). This heterogeneity undoubtedly hinders the search for susceptibility genes because distinct presentations of MDD are likely associated with unique polygenetic clusters and environmental experiences.

To address disorder heterogeneity, many have advocated for the use of intermediate phenotypes (e.g., particular behavioral manifestations or brain function) believed to lie between genes and/or environmental experiences and disease processes (Cannon and Keller, 2006; Hasler et al., 2004; Hasler and Northoff, 2011; Insel and Cuthbert, 2009; Kendler and Neale, 2010; Meyer-Lindenberg and Weinberger, 2006;but see also Flint and Munafo, 2007).[1] These intermediate phenotypes are a more accessible target for genetic research because they are presumably not only more specific, quantifiable, and reliable than diagnostic phenotypes, but also more proximal to gene function. Because categorical diagnoses collapse across multiple distinct presentations that may not be characterized by shared pathophysiologies, they will inevitably involve many neural circuits and an exponentially larger number of proteins and genes. As a result, it is unlikely that small effects conferred by single genetic variants affecting the expression/function of a single protein will be detected.

In contrast, by relying upon continuous and quantifiable measures of specific, neurobiologically more homogeneous behavior and brain function, an intermediate phenotypic approach promises to capture biology more directly, thus enhancing penetrance and reducing the number of genes involved in phenotypic expression(Goldman and Ducci, 2007; but see also Flint and Munafo, 2007). Within this context, the National Institute of Mental Health has recently launched the Research Domain Criteria (RDoC) project in an attempt to (1) integrate neuroscience and genetic research into future diagnostic systems, (2) advance our etiologic understanding, and (3) propel treatment development. Specifically, the RDoC project aims to stimulate research conducted on intermediate phenotypes across multiple levels of analyses (from genes to neural circuits to behaviors) and traditionally defined diagnostic borders (Insel et al., 2010; Sanislow et al., 2010). In the spirit of an RDoC conceptualization, this review summarizes and integrates research linking genetic variation to individual differences in *reward processing*, which is considered one of the most promising intermediate phenotypes of depression (Hasler and Northoff, 2011; Hasler et al., 2004). Moreover, we explore how genetically conferred differences in a second promising intermediate phenotype, *stress sensitivity* (Hasler and Northoff, 2011; Hasler et al., 2004), may further impact reward processing in the context of stress.

Reward processing

Anhedonia is a cardinal symptom of depression associated with elevated severity and poor treatment response (American Psychiatric

[1] We chose to use the term "intermediate phenotype" as opposed to "endophenotype" because various criteria including specificity, state-independence, heritability, familial association, cosegregation, biological and clinical plausibility have been proposed as criteria on which to evaluate endophenotypes (Gottesman and Gould, 2003; Hasler et al., 2004). However, in light of evidence of shared pathophysiology across disorders (as well as potential problems in our diagnostic classification), intermediate phenotypes should not be constrained to a particular disorder as currently defined (i.e., exhibit specificity). Moreover, in light of documented GxE and epigenetic regulation, intermediate phenotypes may appear to be state-dependent (e.g., require stress to be unmasked). In an effort to avoid these evaluative criteria we chose to use the term intermediate phenotype instead and emphasize validity criteria from Robins and Guze (1970).

Association, 2000; Hasler et al., 2004; Kasch et al., 2002). Although anhedonia is present in up to 50% of individuals with MDD(Fawcett et al., 1983; Oei et al., 1990; Pelizza and Ferrari, 2009), it transcends diagnostic boundaries and plays prominent roles in other disorders, including schizophrenia and substance abuse (Diekhof et al., 2008; Dowd and Barch, 2010). In the context of a rich theoretical background postulating that a genetic predisposition to hedonic deficits may leave individuals vulnerable to the development of depression(Klein, 1987; Loas, 1996; Meehl, 1975; Myerson, 1922; Willner, 1993)and evidence that reward-related behavior is heritable (Bogdan and Pizzagalli, 2009; Loas, 1996), research has begun to investigate how genetic background and environmental experience contribute to the vast array of individual differences in reward-related behavior and brain function with important implications for our understanding of depression.

Processing and integration of rewards relies on an interconnected dopamine-rich neural network, including the midbrain, amygdala, striatum, anterior cingulate cortex, orbitofrontal cortex, and medial prefrontal cortex (Berridge et al., 2009; Haber and Knutson, 2009; Knutson et al., 2000; O'Doherty et al., 2003). Several studies have linked MDD and elevated depressive symptoms to structural abnormalities (Blood et al., 2010; Pizzagalli et al., 2009) and reduced reward-related activation in this network (Diekhof et al., 2008; Epstein et al., 2006; Forbes et al., 2006; Heller et al., 2009; Keedwell et al., 2005a,b), particularly the medial prefrontal cortex (PFC) and striatum (Knutson et al., 2008; Kumar et al., 2008; Pizzagalli et al., 2009; Stoy et al., 2011). Moreover, hypoactivation in these regions, as well as reduced striatal volume, has been linked to anhedonia, suggesting that dysfunction in this network may be associated with the clinical expression of reward processing deficits (Epstein et al., 2006; Keedwell et al., 2005b; Pizzagalli et al., 2009; Stoy et al., 2011). Thus, uncovering factors, including genetic ones, that contribute to variability in reward-related neural activation, is an important step for understanding the etiology of anhedonia, and, potentially, depression (Bijttebier et al., 2011).

Genetics of reward processing

Dopamine

Dopamine (DA) plays a critical role in reward processing. A variety of primary and secondary rewards, including food, sex, and drugs can elicit DA release (Egerton et al., 2009; Knutson and Gibbs, 2007; Salimpoor et al., 2011). Initially, DA was thought to code for the hedonic value of reward (Wise, 1978), but more recent research suggests that it is instead involved in coding complex information about appetitive stimuli and facilitating the learning of stimulus-outcome and action-outcome contingencies (Wise, 2008). Schultz (2007), in particular, has shown that DA neurons originating in the ventral tegmental area fire in phasic bursts in response to unexpected rewards or predictors indicating that reward delivery is imminent. Thus, DA appears to be primarily involved in reward learning and anticipation of reward, as opposed to hedonic responding.

Following synthesis and release DA may: 1) bind to postsynaptic DA receptors; 2) bind to presynaptic DA autoreceptors; 3) be taken back into presynaptic neurons by the DA transporter (primarily in limbic regions); or 4) be degraded by enzymes (primarily in PFC regions). Functional polymorphisms within genes involved in regulating each of these steps are likely to lead to individual differences in DA function, and more subtle differences in reward-related behavior and neural activation that may contribute to depression. In the current review, we focus on the most studied genes within this system: the DA receptor type 2 (*DRD2*), DA receptor type 4 (*DRD4*), dopamine transporter (*SLC6A3*), and catechol-o-methyltransferase (*COMT*) genes.

Dopamine Receptor D2 (DA D2, DRD2) and D4 (DA D4, DRD4)

DRD2 is most expressed in the striatum where DA binding inhibits pre- and postsynaptic neurons. Several polymorphisms within *DRD2* affect its expression and reward-related reactivity. For instance, the deletion variant of an insertion/deletion polymorphism (rs1799732; -141 Ins/Del) has been associated with enhanced *in vivo* receptor availability suggesting that the deletion confers increased DA D2 binding sites (Jonsson et al., 1999; but see also Ritchie and Noble, 2003 who reported no differenes in binding across genotype groups and Arinami et al., 1997 who described reduced expression in individuals carrying the deletion variant). The deletion allele has also been associated with enhanced striatal response to reward (Forbes et al., 2009). Similarly, the C allele (i.e., A2) of the *DRD2* Taq1A [actually located downstream from *DRD2* in the ankyrin repeat and kinase-domain containing 1 (*ANKK1*) gene]single nucleotide polymorphism (SNP; Table 1), rs1800497, has been associated with relatively increased DA D2 receptor availability (Jonsson et al., 1999; Noble, 2003; Pohjalainen et al., 1998) and increased striatal reactivity to reward (Stice et al., 2008). Collectively, these studies suggest that genetically driven reductions in striatal DA signaling may lead to blunted reward-related neural responsiveness and anhedonic behavior, providing a background against which depression may develop.

Notably, conflicting data exist regarding the molecular function of the *DRD2* insertion/deletion polymorphism, with some studies reporting that the deletion is associated with *increased* DA D2 receptor density *in vivo* (e.g., Jonsson et al., 1999) but *reduced DRD2* expression *in vitro* (Arinami et al., 1997). The reason that *in vivo* and *in vitro* examinations produced opposite patterns of receptor density is unclear and may be related to system-level adaptations that occur *in vivo*. Consistent with Arinami et al. (1997), neurogenetics research has interpreted the increased striatal response to reward in deletion carriers as reflective of reduced inhibitory *DRD2* signaling (Forbes et al., 2009; Nikolova et al., 2011). Moreover, another polymorphic variant, i.e., the A2 (C) allele of the *DRD2* Taq1A, associated with relatively increased DA D2 receptor density *in vivo* (Jonsson et al., 1999; Noble, 2003; Pohjalainen et al., 1998), has been linked to elevated striatal response to reward (Cohen et al., 2005), which is inconsistent with speculations that reduced *DRD2* signaling results in greater BOLD response in the ventral striatum due to less inhibitory stimulation. The conflicting functional characterizations of the insertion/deletion *DRD2* polymorphism, as well as opposite interpretations of the effect of *DRD2* on striatal circuit function across polymorphisms (e.g., ins/del vs. Taq1A), make it difficult to discern the molecular mechanisms by which *DRD2* variants may affect reward processing. The *DRD2* story only becomes more complicated by evidence of concentration-dependent actions (Williams and Millar, 1990; Trantham-Davidson et al., 2004), synergistic effects between DA D1 and DA D2 receptor binding (Gerfen et al., 1995), and the formation of D1/D2 receptor complexes (Pei et al., 2012) that further moderate the function of the receptors

Unlike DA D2, DA D4 is located primarily in cortical regions. A variable number of tandem repeats (VNTR; Table 1) polymorphism within exon 3 of *DRD4* results in alleles ranging in length from 2 to 11. The 7-repeat allele has been linked to reduced DA D4 sensitivity and postsynaptic inhibition (Asghari et al., 1995), elevated ventral striatal reactivity to reward (Forbes et al., 2009), and potentiated approach-related behavior (Garcia et al., 2010; Roussos et al., 2010). These divergent associations between limbic (*DRD2*) and cortical (*DRD4*) DA function are consistent with a bidirectional relationship between cortical and limbic DA. Specifically, elevated cortical DA has been associated with reduced limbic DA phasic burst firing critical for reward learning (Bilder et al., 2004; Deutch, 1992; Grace, 1993; Taber et al., 1995). Accordingly, the additive effects of genetically conferred reductions in striatal DA signaling but potentiation in cortical DA signaling may leave individuals particularly vulnerable to reward processing, and in particular reward learning, dysfunction.

Dopamine Transporter (DAT, SLC6A3)

After release into the synapse, excessive DA can be returned to the presynaptic neuron by DAT; as a result, DAT regulates the magnitude and duration of DA available to bind toreceptors. DAT is predominantly expressed in the striatum, making it the primary constraint on striatal DA receptor binding. A VNTR with in the 3' untranslated region is the most studied DAT polymorphism. Several *in vitro* (Brookes et al., 2007) and *in vivo* (Cheon et al., 2005; Heinz et al., 2000) studies have linked the 9-repeat allele to reduced DAT availability relative to the 10-repeat (but see Martinez et al., 2001; Mill et al., 2005). Thus, the 9-repeat allele likely results in less efficient DA reuptake and increased synaptic DA available to bind to limbic receptors. Consistent with this evidence, 9-repeat allele carriers, who presumably have elevated limbic synaptic DA levels, show increased ventral striatal reactivity to anticipation (Aarts et al., 2010; Dreher et al., 2009; Yacubian et al., 2007) and receipt (Forbes et al., 2009) of rewards. Thus, these studies complement the *DRD2* research reviewed above, providing an independent mechanism (enhanced DAT expression) that may also produce reduced reward-related striatal responses.

Catechol-O-methyltransferase (COMT)

The COMT enzyme degrades DA and other catecholamines. Unlike DAT, which is expressed predominantly in the striatum, *COMT* is primarily expressed in the PFC. A SNP within *COMT* results in a Valine (Val) to Methionine (Met) amino acid substitution in the final protein product (Val158Met, rs4680). The 158Met allele is associated with a 3–4 fold reduction in COMT activity (Lotta et al., 1995) and presumably higher DA in the PFC (Chen et al., 2004). Consistent with inhibitory effects of cortical DA on striatal DA transmission, the Val158 allele (associated with reduced cortical DA) has been linked to increased DA synthesis in limbic regions (Akil et al., 2003; Meyer-Lindenberg et al., 2005), flexible reward-related decision making (Krugel et al., 2009), and increased striatal reactivity to unexpectedly high monetary gains (Camara et al., 2010).

In apparent contrast, the 158Met allele (associated with increased cortical DA) has been linked to increased striatal activation during reward anticipation in two studies (Dreher et al., 2009; Yacubian et al., 2007). Recently documented epistatic (Table 1) (Buckholtz et al., 2007) and epigenetic(Ursini et al., 2011) effects, may explain these contradictory results. In addition, these findings raise the possibility that the 158Met allele may be associated with heightened neural reactivity to reward in predictable environments (less dependent on striatal DA bursts inhibited by elevated cortical DA), while the Val158 allele may be associated with more efficient reward learning in the context of changing environmental contingencies (Belsky et al., 2009; Bilder et al., 2004).

Biologically informed multilocus DA profile

The majority of genetic studies of reward processing have examined single polymorphisms independently, with few exceptions examining epistatic effects (Bertolino et al., 2009; Buckholtz et al., 2007; Dreher et al., 2009; Yacubian et al., 2007). However, reward processing, like other complex phenomena, is shaped by a multitude of genetic factors within and across neurotransmitter systems, which may explain the relatively small effects observed in studies of single variants. For example, one could imagine how the effects of a polymorphism conferring increased *DRD2* expression could be masked by a variant linked to increased DAT expression because synaptic DA may be cleared more quickly from the synapse by DAT, preventing the possibility of binding at the additional DA D2 receptors.

In an effort to better capture genetically-driven variation across neural systems, additive genetic scores within multiple pathways of a particular system (often referred to as *biologically informed multilocus profiles*) may be created. Such biologically informed multilocus profiles are similar to genetic risk scores currently used to cumulatively represent genetic associations with disorder (e.g., Purcell et al., 2009). However, there is a key distinction in that biologically informed multilocus profiles are determined based upon known associations with biological function and as such, unlike genetic risk profiles, can inform our mechanistic etiologic understanding.

In support of this approach, a recent study showed that a genetic profile for DA signaling based on five of the polymorphic loci reviewed above (*COMT* Val158Met, DAT1 40-bp VNTR, *DRD4* 48-bp VNTR, *DRD2* -141 C Ins/Del, and *DRD2* Taq1A) explained nearly 11% of variability in reward-related ventral striatal reactivity, while none of the loci taken individually contributed significantly (Nikolova et al., 2011; Fig. 1). Similar multilocus genetic profile approaches could be harnessed to increase power by better capturing genetically driven individual differences within interlinked neural circuits increasing the biological complexity and plausibility of tested models (Bogdan et al., in press).

With the introduction of biologically informed multilocus profiles, several new challenges arise. First, a limited number of polymorphisms have been functionally characterized, limiting the number of systems that can be presently probed (e.g., 5-HT, DA, HPA axis); those that have been characterized may have limited and conflicting data on their function (e.g., see the discussion of *DRD2* receptors above) making their interpretation and assignment difficult. As our functional understanding of individual polymorphisms increases, it may be possible to weight specific polymorphisms differentially according to their effects as opposed to the simple additive approach currently used. Second, such profiles introduce the possibility for a multitude of combinations, making it difficult to determine which polymorphisms to include. When selecting polymorphisms, it will

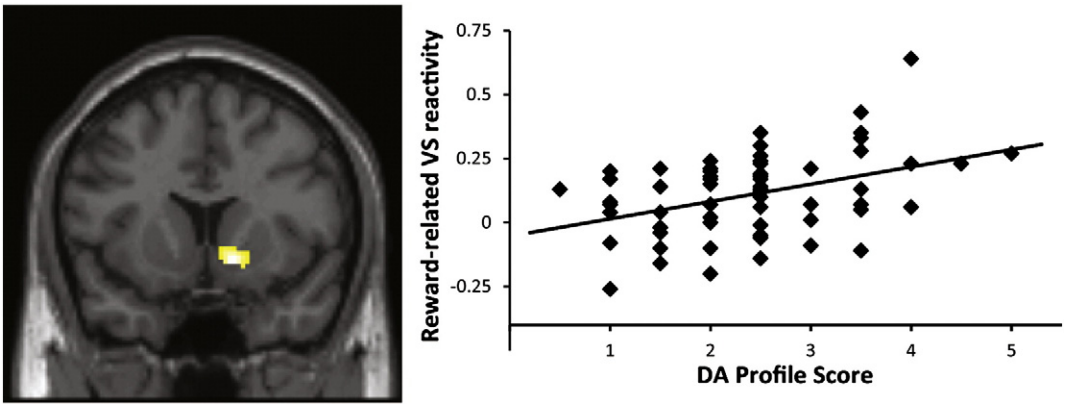

Fig. 1. A biologically-informed multilocus dopamine profile across five polymorphic loci accounts for 10.9% of the variance in right ventral striatal reactivity (shown on the left) to reward within a card guessing paradigm. Summation used to capture increased DA signaling: *DRD2*rs1799732 (deletion = 1, insertion = 0), rs1800497 (C/C = 1, C/T = 0.5, T/T = 0); *DRD4* exon 3 VNTR (7-R = 1, all others = 0); *SLC6A3* 3' UTR VNTR (9-R = 1, 10/10 = 0); *COMT* rs4680 (Met/Met = 1, Val/Met = 0.5, Val/Val = 0). Adapted from Nikolova et al. (2011).

be important to consider linkage disequilibrium across polymorphisms within created profiles to ensure that profiles do not disproportionately weight effects. Along similar lines, it is important to consider the distribution of the profile within samples; for example if rare variants are included, cells with extremely limited numbers of subjects will be created which may produce statistical instability. If these challenges can be overcome, biologicallyinformed multilocus profiles promise to substantially advance our knowledge of individual differences associated with resilience and vulnerability to psychopathology. Moreover, the interaction between profiles could be particularly useful for examining interactions across (e.g., 5-HT x DA) or within (e.g., DA production x DA degradation/reuptake) neural systems to test specified hypotheses.

Beyond DA

In addition to DA, emerging research has emphasized the importance of other neural systems in reward processing. For instance, non-human animal data have linked endocannabinoid function to anticipatory reward processing or "wanting," as well as consummatory reward processing or "liking" (Berridge et al., 2009). In line with this preclinical evidence, neuroimaging studies have recently highlighted the effects of genetic variation within fatty acid amide hydrolase (*FAAH*), a membrane bound enzyme that degrades endocannabinoids, on reward-related neural activation. Specifically, the A allele of a common functional SNP in *FAAH* (rs324420) has been associated with reduced FAAH expression, and presumably increased endocannabinoid signaling (Chiang et al., 2004). Fitting this molecular mechanism, A allele carriers have heightened striatal reactivity to reward (Hariri et al., 2009) and marijuana cues in regular marijuana users (Filbey et al., 2010). Highlighting the impact of multiple genes within a system, Filbey et al. (2010) further demonstrated that a SNP (rs2023239) in the cannabinoid type 1 receptor (*CNR1*) independently and additively (with rs324420) moderated reward-related reactivity to marijuana cues. Other SNPs within *CNR1* have been shown to moderate striatal responses and approach behavior (Agrawal et al., in press; Chakrabarti and Baron-Cohen, 2011; Chakrabarti et al., 2006), emphasizing the potential importance of this system for reward processing.

In addition to these findings, genetic variation in other systems – including the mu-opiod receptor (*OPRM1*; Lee et al., 2011), TREK1 (*KCNK2*; Dillon et al., 2010), nitric oxide synthase (*NOS1*; Hoogman et al., 2011), inhibitory γ-amino butyric acid α2 receptor subunit (*GABRA2*; Villafuerte et al., 2011), and *Bcl-2* (Salvadore et al., 2009)– have been associated with individual differences in reward-related brain structure, neural activation, and/or behavior. As more knowledge about the functional role of common polymorphisms emerges it will be critical to probe biologically-informed multilocus profiles to represent function within distinct neurotransmitter systems (e.g., DA, opiod, endocannabinoid), allowing for examination of synergistic effects.

Links to Depression

As reviewed above, a host of polymorphisms within DA and other systems have been associated with individual differences in reward-related neural activation and behavior, which have, in turn, been linked to clinical depression and depressive symptoms in healthy individuals (Knutson et al., 2008; Pizzagalli et al., 2005, 2008, 2009). However, while a few studies report associations between these variants and depression (Liou et al., 2009; López-León et al., 2007), the vast majority of studies do not (Koks et al., 2006; Opmeer et al., 2010) [for review see (Noble, 2003)]. While the lack of cross-association between polymorphisms linked to depression and those linked to reward-related brain function and behavior (in predominantly healthy or clinically unassessed populations) may be disappointing, it is not entirely surprising. In light of evidence suggesting that anhedonia may reach clinical significance in half of patients with MDD (Fawcett et al., 1983; Oei et al., 1990; Pelizza and Ferrari, 2009), a large portion of patients included in studies of depressed individuals will likely not feature reward processing deficits, thereby suppressing the detection of genetic effects increasing vulnerability to MDD via anhedonia-related mechanisms. Such heterogeneity highlights the potential utility of using continuous and specific measures in clinical and healthy populations to better represent distinct disorder components associated with given pathophysiological processes.

Similarly, possible MDD susceptibility genes emerging from GWAS studies not yet been linked to reward processing dysfunction. To the best of our knowledge, the only exception is the piccolo gene (*PCLO*; Bochdanovits et al., 2009; Hek et al., 2010; Sullivan et al., 2009). Piccolo is a presynaptic scaffolding protein believed to play an important role in neurotransmitter release. Non-human animal research has documented the importance of piccolo to DA function; in addition to being widely expressed in the nucleus accumbens, experimental reductions in piccolo result in heightened reward-related behavior as well as elevated accumbal dopamine (Cen et al., 2008). However, specificity of *PCLO* is unlikely as it affects general monoamine neurotransmission and has been shown to influence other constructs (e.g., spatial learning, hippocampal long-term potentiation; Ibi et al., 2010). Interestingly, the *PCLO* genotype associated with depression in GWAS has been linked to individual differences in hypothalamic-pituitary-adrenal (HPA) axis function (Kuehner et al., 2011; Schuhmacher et al., 2011), the body's central regulator of stress responsiveness. In light of links between stress and anhedonia discussed below, *PCLO* polymorphisms may be particularly relevant for reward processing deficits in the context of stress.

Conclusions

Consistent with a long-standing theoretical tradition positing that reward processing dysfunction plays a causal role in the development of depression (e.g., Klein, 1987; Loas, 1996; Meehl, 1975), emerging research suggests that intact hedonic capacity and robust neural reward-related circuitry protect against depressive symptoms (Aschbacher et al., 2012; Bijttebier et al., 2011; Nikolova et al., in press). Given these robust links, it is important to understand the factors, including genetic ones that are associated with individual differences in reward-related neural function.

Accumulating research suggests that genetic differences conferring relatively increased subcortical DA or reduced cortical DA signaling (via either receptor availability or synaptic clearance) are associated with enhanced reward-related neural activation and behavior. These findings complement theoretical work suggesting an inverse relationship between cortical and limbic DA (e.g., Bilder et al., 2004). However, much like in MDD, the heterogeneity of reward processing warrants attention. It is now clear that reward processing is not a monolithic phenomenon, but can be parsed into distinct neurochemical, neuroanatomical, and psychological components, including incentive motivation, reward consumption, and reward learning (Berridge et al., 2009). For the most part, molecular genetics research has largely ignored these phenotypic nuances. However, given emerging links between genetic variation within neurochemical systems (e.g., endocannabinoids) linked to specific neurochemical subcomponents of reward processing, it will be important for future neurogenetics research to not only examine polymorphisms within these candidate neural systems, but to also deconstruct their effects on specific reward processing components.

One important concern currently confronting intermediate phenotype research on reward processing is that, for the most part, genetic variants associated with individual differences in reward processing in healthy individuals have not been linked to depression. It will be important to ascertain whether these polymorphisms may be associated with clinically significant anhedonic presentations in

patients with depression using refined and construct-specific measurements. Most critically, as our knowledge of genetically-driven variation in reward processing expands, it may be possible to use this knowledge to select and guide more personalized treatments. For example, delineating reward processing dysfunction might suggest *a priori* selection of psychological (e.g., Dichter et al., 2009) or pharmacological (e.g., Nestler and Carlezon, 2006; Ossewaarde et al., 2011) interventions directly targeting such abnormalities or used in a preventative context.

Stress sensitivity

Both retrospective and prospective research has linked stress to depression (Brown and Harris, 1978; Hammen, 2005; Kendler et al., 1999; Muscatell et al., 2009; van Praag et al., 2004). Major stressful life events precede depression in more than 80% of cases (particularly first depressive episodes) and a general linear relationship between the severity and frequency of negative life events and the probability of a depressive episode has been reported (Mazure, 1998). Interestingly, emerging evidence suggests that stress sensitivity may be related to reward processing dysfunction. A large body of animal literature (Anisman and Matheson, 2005; Willner, 2005) and emerging human research (Berenbaum and Connelly, 1993; Bijttebier et al., 2011; Bogdan and Pizzagalli, 2006; Bogdan et al., 2011; Dillon et al., 2009; Pizzagalli et al., 2007) suggests that stress-induced anhedonia is a promising mechanism underlying the association between stress and depression. Moreover, research suggests that this effect may be particularly relevant for women (Lighthall et al., 2011), consistent with speculation that stress sensitivity phenotypes may be gender specific (Hasler et al., 2004). Complementing this research and providing clues to potential biological mechanisms, studies have linked HPA axis activity to individual differences in DA with non-human animal research suggesting that stress-related HPA axis activation can directly alter DA function (Duval et al., 2006; Pascucci et al., 2007; Piazza et al., 1996). In light of these findings, it is important to understand individual difference variables that may confer vulnerability/resiliency to stress-related deficits in reward processing.

The HPA axis is a key regulator of stress reactivity (de Kloet et al., 2005; Ulrich-Lai and Herman, 2009). Briefly, multiple regulatory pathways converge within the hypothalamus to stimulate corticotropin releasing hormone (CRH) in response to stress perception. CRH binding in the anterior pituitary gland triggers the release of adrenocorticotropic hormone (ACTH), which stimulates cortisol secretion after binding to receptors within the adrenal gland. Cortisol binding then inhibits CRH and ACTH release forming a negative feedback loop wherein the body returns to homeostasis after the stressor. Nearly 50 years of research has demonstrated that depression, among other psychopathologies, is characterized by HPA axis dysfunction (Gibbons and Mc, 1962; Lopez-Duran et al., 2009; Yehuda, 2002). Moreover, in support of the relationship between stress and anhedonia, HPA axis dysfunction is particularly prevalent in individuals with melancholic depression, a severe subtype characterized by anhedonia (Gold and Chrousos, 1999; Gold et al., 2002; Pintor et al., 2007; Stetler and Miller, 2011). Consistent with these associations, emerging research has linked variation in HPA axis activity and stress response with functional and structural differences in striatal and other limbic regions central to reward processing (Jahn et al., 2010; McEwen and Gianaros, 2010; Pruessner et al., 2010; Urry et al., 2006).

Genetics of stress sensitivity

Hypothalamic-Pituitary-Adrenal (HPA) axis

There is substantial individual variability in HPA axis function that is relatively stable over time (Fox et al., 2006; Kudielka et al., 2009; Marquez et al., 2005), suggesting that genetically-conferred variation in HPA axis function may contribute to stable differences in stress responsiveness and hence vulnerability/resilience to the depressogenic effects of stress. Because evidence suggests that HPA axis pathophysiology is largely related to CRH (Binder and Nemeroff, 2009; Hauger et al., 2006), we focus on this critical hormone and neurotransmitter in the next section.

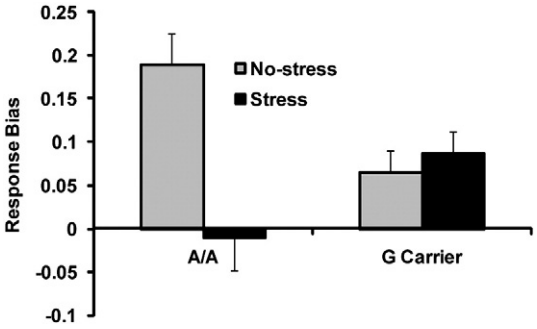

Fig. 2. A homozygosity at rs12938031 within *CRHR1* is associated with deficits in reward learning (as represented by response bias) under stress. Stress was manipulated experimentally (threat-of-shock) in a within-subject design. Adapted from Bogdan et al. (2011).

CRH

The CRH system plays a pivotal role in the physiological, behavioral, and cognitive responses to stress. In rodents, CRH administration and overexpression can result in depression-like behavior, while CRH antagonists have antidepressant properties (Hauger et al., 2006; Zieba et al., 2008). Consistent with this evidence, elevated CRH is seen in various forms of stress-related psychopathology, including depression with anhedonic features (Gold and Chrousos, 1999; Pintor et al., 2007). Moreover, emerging research suggests that CRH influences DA and reward-related behavior. Interestingly, this research suggests that CRH increases tonic striatal DA levels and phasic responses to already conditioned stimuli, but may prevent phasic DA bursts from meaningfully associating novel rewards with environmental contingencies (Beckstead et al., 2009; Pecina et al., 2006). This mechanism may explain why stress has been associated with increased habitual responding but blunted novel reward learning (Bogdan and Pizzagalli, 2006; Bogdan et al., 2011; Pecina et al., 2006; Schwabe and Wolf, 2011). In light of evidence most strongly linking CRH pathophysiology to the corticotropin releasing hormone type 1 receptor (CRH R1) (Hauger et al., 2006), we focus on genetic variation within the CRH R1 gene (*CRHR1*).

The A allele of a SNP within the promoter of *CRHR1* (rs12938031; A/G) has been associated with enhanced *CRHR1* mRNA expression as well as diminished HPA axis response to CRH infusion – a pattern also seen in patients with depression (Thode et al., 2009). We have recently extended these findings by reporting that A homozygotes are more susceptible to stress-related behavioral and neural reward learning deficits using an experimentally manipulated within-subject design (Bogdan et al., 2011; Fig. 2). Collectively, these studies suggest that genetically driven variation within the HPA axis may confer differences in HPA axis function, as well as vulnerability/resilience to the depressogenic effects of stress, possibly via reward processing disruptions. Further emphasizing the importance of *CRHR1* to stress system function and depression, several other reports have linked *CRHR1* SNPs to differential HPA axis activation and depression in the context of childhood maltreatment (Blomeyer et al., 2008; Bradley et al., 2008; Polanczyk et al., 2009; Tyrka et al., 2009). Finally, several polymorphisms at different nodes within the HPA axis – including the mineralocorticoid receptor (*MR*; Bogdan et al.,

2010; Kuningas et al., 2007), glucocorticoid receptor (*NR3C1;* Derijk et al., 2008) and FK506 binding protein (*FKBP*5; Zimmermann et al., 2011) – have been associated with individual differences in HPA axis function, differences in reward processing and/or depression.

Beyond the HPA axis

A discussion of genetics, stress sensitivity, and depression would be incomplete without inclusion of serotonin transporter research. A repeat polymorphism in the promoter region of the serotonin transporter (5-HTT) gene (*SLC6A4*) known as the serotonin-transporter-linked polymorphic region (5-HTTLPR) results in common short and long alleles (Heils et al., 1996; Lesch et al., 1996; Murphy et al., 2008). The short allele is associated with reduced 5-HTT mRNA and protein expression, as well as reduced binding (Lesch et al., 1996). A wealth of research suggests that short 5-HTTLPR allele carriers are more vulnerable to environmental circumstances (Caspi et al., 2010). In brief, short allele carriers are characterized by heightened neuroticism (Lesch et al., 1996), elevated threat-related amygdala reactivity (Hariri et al., 2002; Munafo et al., 2008), elevated cortisol upon awakening (Chen et al., 2009), and elevated rates of depression following stressful experiences (Caspi et al., 2003, 2010; Karg et al., 2011; Kendler et al., 2005; but see Risch et al., 2009). These findings have been replicated in humans and corroborated by preclinical data across species (Caspi et al., 2010; Karg et al., 2011). Collectively, these results have led to the conclusion that the short allele moderates effects of environmental variables (Caspi et al., 2010).

Importantly, the mechanisms underlying the association between 5-HTTLPR and depression in the context of stress remain unknown. Three studies suggest that one potential mechanism, among others, may be stress-related reward processing dysfunctions. In a first study conducted in monkeys, the short allele was associated with risk-aversion under stressful conditions, but risk-seeking in long homozygotes – a pattern interpreted as suggesting enhanced sensitivity to social punishment and reward, respectively (Watson et al., 2009). A second study found that, relative to individuals homozygous for the long allele, human youth with the short allele report lower or higher positive affect in the context of negative or positive parenting, respectively – a finding replicated across three independent cohorts (Hankin et al., 2011). Third, our group described that elevated stress perception regarding an upcoming school exam was associated with reduced reward learning in short allele carriers but enhanced reward learning in long homozygotes (Nikolova et al., 2012).

Links to depression

HPA axis dysregulation and stress exposure are among the variables most reliably linked to depression, each occurring in up to 80% of MDD patients (Mazure, 1998). As such, several stress-system variants have been linked to depression and other stress-related psychopathologies (Binder, 2009; Caspi et al., 2010; Derijk et al., 2008). Critically, however, these relationships are generally only uncovered when considering the role of the environment. For stress-related disorders such as MDD, genome-wide association studies may be particularly well served to include environmental measures of stress experience. Evidence highlighting the potential of this approach exists in other research fields: for example, the inclusion of environmental factors into GWAS has uncovered novel insights into asthma (Ege et al., 2011). While to our knowledge neuropsychiatriatric GWAS have yet to include environmental effects, this approach promises to be fruitful given: (1) consistent links between stress and psychopathology, (2) candidate gene studies documenting gene x environment interactions (e.g., Caspi et al., 2003), and (3) emerging work documenting that epigenetic effects can be moderated by genotype (Ursini et al., 2011).

Similar to research on reward-related function, the only gene associated with MDD through GWAS known to play a role in the HPA axis is the piccolo gene (*PCLO*). Specifically, healthy controls with the A allele at rs2522833, which has been linked to depression through GWAS, show blunted cortisol awakening response, elevated diurnal cortisol levels, and reduced changes in HPA axis function following antidepressant treatment (Kuehner et al., 2011; Schuhmacher et al., 2011). Because *PCLO* affects DA function and the variant linked to MDD has been associated with individual differences in HPA axis function, it is a particularly appealing candidate for investigations probing relations between stress and reward function.

Conclusions

Converging evidence from mouse to man suggests that the depressogenic effects of stress may result, at least partially, from stress-induced anhedonia. Moreover, research has linked HPA axis variability to reward-related brain function (Duval et al., 2006; Pascucci et al., 2007; Piazza et al., 1996). As such, it is important to understand how individual differences may leave individuals more or less vulnerable to stress-related reward system dysfunction. Moreover, because cortisol binding to corticosteroid receptors can access the nucleus and bind to glucocorticoid response elements within genes (thereby affecting the transcription of hundreds of other genes), individual differences in HPA axis function are likely to have widespread and pleiotropic effects.

Polymorphisms within the HPA axis are associated with differential physiological and psychological responses to stress providing putative proxies of HPA axis system activity and elicited activation that may partially explain vulnerability and resiliency to stress. Of note, HPA axis-related polymorphisms that have been associated with increased and prolonged HPA axis activity have been also associated with depression, but generally only in the context of stress exposure. Building upon this work, emergent research raises the possibility that such increased vulnerability to depression may be partially related to a propensity for stress-induced reward processing dysfunction. Importantly, however, research needs to deconstruct which aspects of HPA axis activation are associated with stress-related depression and reward processing dysfunction. Equally important will be to elucidate which aspects of reward processing might be particularly perturbed by stress. Interestingly, research suggests that increased HPA axis activation is associated with blunted novel reward learning (e.g., Bogdan and Pizzagalli, 2006; Bogdan et al., 2011), but a reliance on past impulsive rewarding behaviors (e.g., comfort food consumption, drug use; Brady et al., 2009; George et al., 2010; Ulrich-Lai et al., 2010), which has clear consequences for our understanding of impulse control disorders and substance abuse. As such, the role of stress in the development of anhedonia may be more specific to behaviors that are novel for individuals and may be more specifically associated with novel reward-related learning.

Discussion

Euphoric expectations about the potential of genetic research to rapidly improve our etiological understanding and treatment of mental illness have been largely replaced by sober realizations that individual common polymorphisms will have small, if any, effects on complex polygenetic diseases, making it exceptionally difficult to reliably link them to psychopathology. Critically, the ability to discern these small effects is largely dependent on the phenotypic variables measured and their proximity to the functional consequences of genetic variation. The closer one measures the direct functional consequences of genetic variation, the larger the effect will be (Flint and Munafo, 2007; Goldman and Ducci, 2007); however, the closer one studies the direct functional consequences of polymorphisms (e.g., mRNA expression), the more removed one becomes from

clinical relevance. The aim of this review was to survey and integrate molecular genetics research on reward processing and stress sensitivity, two promising depressive intermediate phenotypes, that are not only clinically relevant to MDD and other disorders (Diekhof et al., 2008), but also presumably more closely linked to the functional consequences of genetic variation than DSM-defined MDD.

Importantly, intermediate phenotype and traditional disorder-based genetics research can mutually inform our understanding of psychopathology. The widespread availability and limited cost of psychiatric symptomatology measures facilitates the establishment of large datasets that may be useful for detecting small genetic effects. Indeed, GWAS have begun to link genes never before suspected to MDD, although these associations have not been well replicated (Bosker et al., 2011; Lewis et al., 2010; Lohoff, 2010; Muglia et al., 2010; Rucker et al., in press; Shi et al., 2011; Shyn et al., 2011; Sullivan et al., 2009). While GWAS of psychiatric diagnoses inform who may be at risk for a particular disorder, they cannot pinpoint the mechanisms by which identified polymorphisms confer risk or resilience. As such, intermediate phenotype neurogenetics research can powerfully complement traditional disorder-based GWAS by evaluating the biological and behavioral mechanisms that may drive associations with psychopathology. As an illustration, we emphasized in the current review how emerging knowledge about the role of *PCLO*, a gene recently linked to MDD through GWAS, may be used to guide intermediate phenotypic research aimed at uncovering its mechanistic role in MDD.

Challenges and future directions

Various challenges confront intermediate phenotype neurogenetics research (Bogdan et al., in press). For example, our ability to research a construct is dependent on how precisely we can measure it (Kendler and Neale, 2010). As such it will be pivotal for future research to establish reliability for intermediate phenotypes. Of the intermediate phenotypes we discussed, HPA axis function has good reliability (Fox et al., 2006; Kudielka et al., 2009; Marquez et al., 2005). We are only aware of two studies investigating the reliability of reward-related reactivity, with one suggesting good reliability (Schacht et al., 2011) and another reporting relatively poor reliability (Fliessbach et al., 2010). In addition to establishing reliability, a major priority will be to establish the validity of intermediate phenotypes. In 1970, Robins and Guze proposed that psychiatric diagnoses are valid when they: 1) have high inter-rater reliability, 2) predict future behavior, 3) predict course, outcome, and treatment response, 4) predict family history, and 5) differentiate between diagnoses.[1] Currently, research on intermediate phenotypes has largely ignored these classic validity criteria. Although the field is far from diagnostic classifications of mental illnesses rooted in pathophysiology and etiology, we expect that a close evaluation of promising intermediate phenotypes with respect to these criteria will be pivotal for fulfilling this challenging – yet critical – goal. Ultimately, only an improved understanding of the pathophysiology and etiology of mental illnesses will allow the field to address many unmet needs, including the development of novel and more efficacious intervention and prevention strategies.

Related to establishing validity and reliability of intermediate phenotypes used in neurogenetics research, there is presently widespread variability in paradigms used to measure the same or similar constructs, as well as analysis techniques. For example, studies assessing "reward processing" may use paradigms that can differentiate anticipatory vs. consummatory phases (e.g., Knutson et al., 2000; Dillon et al., 2008), while others may aggregate across these effects (e.g., Hariri et al., 2006). Convergence across studies using different paradigms assessing the same construct will lead to greater confidence in reported findings; however, when a lack of replication is observed it may not necessarily represent an original false positive finding but may reflect experimental or population differences.

Another challenge confronting intermediate phenotype neurogenetics research is obtaining adequate sample sizes to investigate the small effects of common polymorphisms, conduct GWASs, and examine rare variants. Neurogenetics data collection is often time- and resource-intensive (e.g., fMRI); however, collaborations and consortia are beginning to accrue the sample sizes needed to conduct GWAS that include neuroscientific data and consider rare variants.

In this context, although neurogenetics research has primarily focused on common polymorphisms, emerging psychiatric sequencing research has documented large associations between rare variants and depression (Haenisch et al., 2009), as well and other complex polygenic disorders (Rodriguez-Murillo et al., 2012). As such, it is important for neurogenetics research to not only functionally characterize such variants (e.g., associations with gene transcription), but also examine how these rare variants affect intermediate phenotypes. Given how infrequently these variants occur, this represents a major challenge, whereby samples will likely need to be selected based upon the presence of rare variants, potentially through consortia of large imaging genetic studies, or selected recruitment from sequencing studies.

The potential of GWAS on intermediate phenotypes is just beginning to be realized through the combination of datasets and large-scale independent studies. Confronted with the pervasive clinical, etiological, and pathophysiological heterogeneity of psychiatric disorders, neurogenetics research targeting intermediate phenotypes promises to provide a novel window towards a better understanding of psychopathology. Critically, and consistent with the assumption that homogenous intermediate phenotypes are more proximally related to gene function than psychiatric syndromes, unlike the vast majority of GWAS on psychiatric diagnoses, including depression (Lohoff, 2010), many neurogenetics GWAS have identified SNPs reaching genome-wide significance (i.e., 10×10^{-8}), with positive replication in some cases (Bakken et al., 2011; Bis et al., 2012; Hodgkinson et al., 2010; Potkin et al., 2009a,b; Shen et al., 2010; Stein et al., 2012).

Lastly, it will be imperative for neurogenetics research to translate findings to the clinic (Bogdan et al., in press). First, neurogenetics research must document that genetically-associated differences in neural structure, function, and connectivity meaningfully predict differences in psychopathology. An ideal strategy to pursue this would be to conduct longitudinal prospective studies with multiple timepoints. Additionally, in light of the current largely trial-and-error treatment approach and the significant percentage of patients failing to respond to antidepressant treatments (e.g., Trivedi et al., 2006), it would be particularly valuable for neurogenetics research to inform treatment strategies. In addition to determining for whom a specific treatment may work best, neurogenetics research may contribute to the development of novel treatments alongside non-human animal research. An example of such potential comes from recent research on TREK1 (*KCNK2*), a background potassium channel. Mice that have TREK1 knockout display resiliency to depression (Heurteaux et al., 2006) and in humans, genetic variation within TREK1 has been linked to differences in reward-related neural function (Dillon et al., 2010) and treatment response to antidepressant medication (Perlis et al., 2008). More recently, researchers (Mazella et al., 2010) have developed a treatment that inhibits TREK1 and has been associated with a positive antidepressant response, increased serotonergic signaling, and hippocampal neurogenesis in rodents. However, the true clinical potential of this novel treatment has yet to be tested in humans. Ultimately, important benchmarks to evaluate the success of neurogenetics research focused on intermediate phenotypes will be directly tied to its ability to inform pathophysiological understandings of psychiatric disorders, identify at-risk individuals, and guide treatment decisions.

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