Published in final edited form as:

J Pers. 2008 December ; 76(6): 1447–1484. doi:10.1111/j.1467-6494.2008.00528.x.

A Neurogenetic Approach to Impulsivity

Eliza Congdon¹ and Turhan Canli^{1,2}

¹Department of Psychology, Stony Brook University

²Graduate Program in Genetics, Stony Brook University

Abstract

Impulsivity is a complex and multidimensional trait that is of interest to both personality psychologists and to clinicians. For investigators seeking the biological basis of personality traits, the use of neuroimaging techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) revolutionized personality psychology in less than a decade. Now, another revolution is under way, and it originates from molecular biology. Specifically, new findings in molecular genetics, the detailed mapping and the study of the function of genes, have shown that individual differences in personality traits can be related to individual differences within specific genes. In this article, we will review the current state of the field with respect to the neural and genetic basis of trait impulsivity.

The purpose of this article is to highlight new directions in an individual differences approach to personality by reviewing recent work on the neural and molecular genetic correlates of impulsivity. We will follow a reductionistic path, starting out at the behavioral level of personality psychology, then moving to the brain-systems level of biopsychology, down to the molecular level of genetics. We begin with a review of impulsivity within personality psychology, which we believe makes a case for the need to refine the definition and measurement of the construct. We will review separately the evidence supporting a neural and genetic basis of impulsivity, with a particular focus on one component of impulsivity—behavioral inhibition—and then review recent attempts to combine methodologies to elucidate the neurogenetic basis of impulsivity and other complex traits and behaviors. We will end with suggestions for future research, particularly with respect to the neurogenetics of impulsivity, and a discussion of the implications of this research for personality psychologists.

A comprehensive review of the literature on impulsivity is beyond the scope of this (or any) review article due to the variety of constructs used, the resulting variety of task paradigms, and the wide range of clinical, pharmacological, and genetics studies utilizing these constructs and paradigms. For example, there is substantial evidence suggesting a role for serotonin in some aspects of impulsive behavior (Carver & Miller, 2006; Evenden, 1999; Manuck et al., 2003). There is also elegant work conducted on cognitive processes related to impulsivity, such as delay discounting (Hariri, Brown, Williamson, Flory, de Wit, & Manuck, 2006). Due to space constraints, we will not review this work here. Instead, we will narrow the focus to one specific impulsivity construct, *behavioral inhibition*. We chose this construct because it represents a core aspect of impulsivity—the ability to inhibit a motor response. Furthermore, the neural circuitry mediating this behavior is well characterized. Finally, there is evidence suggesting a role for dopaminergic genetic regulation of this behavior. Thus, behavioral inhibition serves as a case study in how one can integrate neural

and genetic data in the study of impulsivity, using what is known as the endophenotype approach. We hope that interested readers will draw inspiration from this particular example to apply it to other forms of impulsive behavior and other genes in their own future work.

Personality Psychology: The Behavioral Level of Analysis

Impulsivity Among Other Traits: Its Placement in Eysenck's and Later Personality Models

In the context of this special issue, we cannot begin our article on new directions in personality research without reference to the seminal contributions of Hans Eysenck. Eysenck's biosocial model of behavior (Eysenck, 1967) continues to be an influential model in personality research. This is particularly true as advances in noninvasive neuroimaging and in molecular genetics open new avenues of inquiry, which will benefit from the guidance of integrative theories and models of personality. Eysenck's model has done much to catalyze research on the biological basis of personality, and his changing views on the placement of impulsivity within his model led the way to more sophisticated multidimensional views in biological studies of this trait.

Eysenck originally proposed two orthogonal dimensions of Extraversion and Neuroticism as major factors of normal personality (Eysenck, 1957). Extraversion and Neuroticism were conceptualized as superfactors, or traits, within a hierarchical model of personality; that is, each broad dimension was conceptualized as being composed of a set of lower-order, more specific traits, which in turn were composed of habits and behaviors. Eysenck's biologically based model of personality proposed that personality differences were related to cortical arousal and to autonomic arousal (Eysenck, 1990). These traits represented one dimension ranging from Extraversion to Introversion and a second, orthogonal, dimension ranging from Neuroticism to Emotional stability. Within the original model, impulsivity and sociability were considered lower-order components of Extraversion.

This model was revised, however, to include a third dimension representing Psychoticism (H. J. Eysenck & S. B. Eysenck, 1977). Within the revised model, the construct of impulsivity was reevaluated to be included in Psychoticism. The placement of impulsivity within this framework, however, remained complex because subscales of impulsivity differentially correlate with Extraversion, Psychoticism, and Neuroticism (S. B. Eysenck & H. J. Eysenck, 1977).

The placement of impulsivity within H. J. Eysenck's model of personality is just one example of how theorists have wrestled with the proper placement of this complex trait. In some alternative models, impulsivity is not considered a major factor but instead a component, or a combination, of factors (Evdenden, 1999). For example, in Costa and McCrae's five-factor model, impulsivity reflects mostly low Conscientiousness (Costa & McCrae, 1992); in Cloninger's three-factor model, impulsivity reflects a combination of low Harm Avoidance and high Novelty Seeking (Cloninger, Svrakic, & Przybeck, 1993); and in Tellegen's model, impulsivity is represented as a lower-order factor of Constraint, labeled as control versus impulsiveness (Tellegen, 1982). Thus, in the history of personality research, there has been a lack of consensus about where to place impulsivity among other fundamental traits. A critical consequence of this diversity of views is that there is no consensus on how to conceptualize the structure of impulsivity itself, or how to best measure it.

The Structure of Impulsivity

There is accumulating evidence that impulsivity is a multidimensional factor. Recent reviews suggest that the impulsivity construct is composed of at least two major dimensions: One dimension reflects disinhibition (or impulsive action), while a second dimension

reflects impulsive decision making (or impulsive choice; Avila, Cuenca, Felix, Parcet, & Miranda, 2004; Franken & Muris, 2006; Reynolds, Ortengren, Richards, & de Wit, 2006; Winstanley, Eagle, & Robbins, 2006).

Analytical approaches have revealed more complex structural models of impulsivity. One example comes from a principal components analysis of impulsivity-related traits (assessed with the Tridimensional Personality Questionnaire (TPQ)/Temperament and Character Inventory (TCI), the Zuckerman Sensation Seeking scale (SS-V), the Barratt Impulsiveness scale (BIS-11), the NEO Personality Inventory (NEO-PI-R), and the Buss Durkee Hostility Inventory (BDHI)/Buss Perry Aggression Questionnaire (BPAQ) in a community sample and a separate sample of borderline personality disorder (BPD) patients, which provides support for a three-factor model, including Nonplanning, Disinhibition, and Thrill-Seeking factors (Flory et al., 2006). These factors were moderately correlated with each other and showed an adequate fit to both the community and BPD samples.

In perhaps the most comprehensive analysis of measures of impulsivity, Whiteside and Lynam (2001) conducted a factor analysis on a number of scales in an attempt to identify and separate distinct personality facets that were previously grouped together under impulsivity. Their analysis provided evidence for four factors of impulsivity, including urgency (the tendency to experience and act on strong impulses, frequently under conditions of negative affect), lack of premeditation (the inability to think and reflect on consequences before engaging in an act), lack of perseverance (the inability to remain focused on a task that may be boring or difficult), and sensation seeking (the tendency to enjoy and pursue activity that are exciting and/or new; Whiteside & Lynam, 2001). From their analyses, they constructed the UPPS Impulsive Behavior Scale (UPPS), which they propose assesses four “discrete psychological processes that lead individuals to engage in behavior without a proper appreciation of the potential negative consequences” (Whiteside & Lynam, 2003, p. 211).

Corresponding to the variety of views on the placement of impulsivity among other traits and its internal structure, theorists have developed a multitude of instruments. For example, within the Psychoticism dimension of the Eysenck Personality Questionnaire (EPQ) alone, impulsivity is a combination of four basic traits: narrow impulsivity, nonplanning, liveliness, and risk taking (S. B. Eysenck & H. J. Eysenck, 1977). Analyses of the EPQ and Zuckerman's Sensation Seeking Scale (Form V) revealed two distinct components of impulsivity, which were subsequently operationalized in the Impulsiveness-Venturesomeness-Empathy Scale (IVE) (S. B. Eysenck & H. J. Eysenck, 1978). Specifically, the IVE (later revised into the I7, S. B. Eysenck, Pearson, Easting, & Allsopp, 1985) assesses the distinct components of impulsiveness, the tendency to act without thinking (which is more closely related to EPQ P), and venturesomeness, the tendency to take risks and seek thrill and adventure (which is more closely related to EPQ E), in addition to empathy, which reflects a sensitivity to the feelings and reactions of others and a susceptibility to social cues (S. B. Eysenck & H. J. Eysenck, 1977; S. B. Eysenck & Zuckerman, 1978). According to S. B. Eysenck, impulsivity and venturesomeness may represent unconscious and conscious forms of risk taking, respectively (Eysenck et al., 1985).

An alternative conceptualization of impulsivity is represented by the Barratt Impulsiveness Scale-Version 11 (BIS-11), which is currently one of the most widely used measures of impulsivity. The BIS-11 conceptualizes impulsivity to contain three main components: a nonplanning component, in which the individual does not plan or think carefully; a motor component, which is characterized by a tendency to act without thinking or an inability to withhold responses; and a cognitive component, which is characterized by a difficulty

paying attention (Patton, Stanford, & Barratt, 1995). Other instruments focus on a distinction between functional and dysfunctional impulsivity (Dickman Impulsiveness Scale; Dickman, 1990) or the degree of efficiency of information processing in the face of rewarding stimuli (Lifetime History of Impulsive Behaviors Interview; Schmidt, Fallon, & Coccaro, 2004).

A Link to Dysfunctional Behaviors and Psychopathology

Results of these analyses revealing independent dimensions of impulsivity also support a relationship between particular factors of impulsivity and problem behaviors. In particular, there is support for the strong and unique association between a disinhibition component (lack of premeditation) and variables representing problem behaviors, such as tobacco use, alcohol abuse/dependence, history of suicide attempts, and aggression (Flory et al., 2006). In another case, this factor predicted crime and delinquency, aggression, substance use, number of sexual partners, age of sexual debut, symptoms of depression, and ADHD measures (specifically hyperactivity and impulsivity symptoms; Miller, Stephen, & Tudway, 2004). Results such as these suggest that a core factor of impulsivity construct, the inability to inhibit actions without considering potential consequences, may be driving the association with psychopathology.

In fact, one major catalyst for increased research on impulsivity has been the recognition that impulsivity is of extreme significance for psychopathology. A meta-analysis provides support for a significant relationship between impulsivity (more broadly defined as impulsivity/disinhibition) and antisocial behavior and demonstrates that this relationship between antisocial behavior and impulsivity/disinhibition was greater than those with the dimensions of extraversion/sociability and neuroticism/emotionality (Cale, 2006). Indeed, impulsivity in its extreme form is associated with a wide range of mental disorders, such as antisocial and borderline personality disorder (Bagge et al., 2004; Conrod, Pihl, Stewart, & Dongier, 2000; Fossati et al., 2004; Links, Heslegrave, & van Reekum, 1999; Newman et al., 1997), disorders related to abuse and addiction (Sher, Bartholow, & Wood, 2000), mood disorders (Swann, Pazzaglia, Nicholls, Dougherty, & Moeller, 2003), suicide (Dougherty, Mathias, Marsh, Moeller, & Swann, 2004; Esposito & Spirito, 2003; Swann, Dougherty, Pazzaglia, Pham, & Moeller, 2004; Yen et al., 2004), impulse control disorders (ICDs), and attention-deficit/hyperactivity disorder (ADHD; Avila et al., 2004; Barkley, 1997; Beauchaine, Katkin, Strassberg, & Snarr, 2001; Lijffijt, Kenemans, Verbaten, & van Engeland, 2005; R. J. Schachar, Tannock, & Logan, 1993). These disorders affect a large percentage of the general population: Even when limiting the analysis to ICDs and ADHD alone, they add up to a 12-month prevalence rate of 8.9% and a lifetime prevalence of 24.8% in the general population (Kessler, Berglund, et al., 2005; Kessler, Chiu, Demler, Merikangas, & Walters, 2005).

Towards Underlying Mechanisms

The prevalence of impulsivity-related psychopathology is but one factor motivating efforts to attain a deeper understanding of the biological basis of this trait. Yet the fact that patients are classified based on a taxonomy that is not biologically based poses a serious challenge to efforts to investigate the biological basis of impulsivity. Indeed, because patients are categorized based on diagnoses that represent a heterogeneous constellation of symptoms, impulsivity is rarely studied in isolation of these other symptoms. Therefore, any study of impulsivity-related behaviors in patients is usually confounded with a disease-specific symptomatology.

The multiple dimensions of impulsivity have also been an area of research in cognitive psychology and cognitive neuroscience, which have characterized impulsivity in terms of

inhibitory control processes. In fact, the multidimensionality of impulsivity reviewed above maps well onto a taxonomy of inhibitory processes that is based on personality, behavioral, and neuroanatomical data (Nigg, 2000). This taxonomy organizes inhibitory control into a framework in which interference control, cognitive inhibition, behavioral inhibition, and oculomotor inhibition are executive inhibition processes (and can be thought of as top-down processes), while response to punishment cues and response to novelty are separate motivational inhibition processes (and can be thought of as bottom-up processes).

The importance of using such a framework extends the recognition that impulsivity is multidimensional and provides a more specific and testable approach to impulsive behavior that is amenable to investigations into the neural and genetic correlates of impulsivity. We apply the definition of impulsivity as a predisposition to respond to internal or external stimuli without regard to the potentially negative consequences to the individual or to others (Moeller, Barratt, Dougherty, Schmitz, & Swann, 2001). In the remainder of this article, we have chosen to focus on behavioral inhibition, or the ability to suppress a prepotent response as opposed to the suppression of mental events (Nigg, 2000). There are other components of inhibitory control which may represent phenotypes suitable for genetic and neuroimaging research, such as delay of gratification and resistance to interference (Avila et al., 2004). For the present article, however, we argue that at the core of the impulsivity construct is an inability to inhibit an action, since all behaviors in which impulsivity manifests are essentially characterized by a lack of planning or a lack of consideration of potential consequences or outcomes of an action, and therefore focus our efforts to identify the neurogenetic correlates of this facet of impulsivity.

In support of the notion that behavioral inhibition is at the core of the impulsivity construct are studies showing that behavioral inhibition is impaired in impulsive samples (Schachar & Logan, 1990; Schachar et al., 2005) and that behavioral inhibition is correlated with measures of self-reported impulsivity (Logan, Schachar, & Tannock, 1997, but see Enticott, Ogloff, & Bradshaw, 2006). In addition, behavioral inhibition is measured by well-characterized tasks (Nigg, 2000), and, as we will review in the next section, has known neural correlates. Reliably assessed, and considered the most direct expression of inhibitory control, behavioral inhibition is therefore ideal for an intermediate phenotype, or endophenotype, approach to impulsivity.

Neuroimaging: The Brain Systems Level of Analysis

Unlike the diversity of approaches in the psychological literature, the neuroimaging literature related to impulsivity has used a fairly narrow set of task paradigms, mostly contrasting the inhibition and execution of a motor response. The two most commonly used tasks, the Go/NoGo and stop-signal tasks, both share the characteristic that successful performance requires the inhibition of a prepotent response. Briefly, the Go/NoGo task requires a participant to respond to one set of frequent stimuli (for example, every letter but “X”) but to inhibit responding to a separate set of infrequent stimuli (in this example, “X”). A limitation of the Go/NoGo task is that Go stimuli are presented more frequently than NoGo stimuli, which confounds processes of behavioral inhibition with attentional processes that detect infrequent stimuli. The stop-signal task also requires the participant to inhibit a prepotent response, but in this paradigm, the response to be inhibited has already been initiated. That is, a stop signal appears *after* the onset of a go signal on a subset of trials, requiring the participant to interrupt a response to the go signal that has already been triggered and thereby making greater demands on inhibitory control.

Using these tasks, investigations into the neural correlates of behavioral inhibition have been conducted on a range of samples, including healthy adults (Aron & Poldrack, 2006; Braver,

Barch, Gray, Molfese, & Snyder, 2001; Garavan, Ross, & Stein, 1999; Konishi et al., 1999; Konishi, Nakajima, Uchida, Sekihara, & Miyashita, 1998; Liddle, Kiehl, & Smith, 2001; Rubia, 2001; Rubia, Smith, Brammer, & Taylor, 2003), children or adolescents (Casey, Trainor et al., 1997; Durston et al., 2006; Eagle et al., 2006; Rubia et al., 2000; Tamm, Menon, & Reiss, 2002), and samples characterized by impaired inhibitory control (Altshuler et al., 2005; Durston, 2003; Kaufman, Ross, Stein, & Garavan, 2003; Moeller et al., 2005; Schulz et al., 2004; Soloff et al., 2003; Soloff, Meltzer, Greer, Constantine, & Kelly, 2000; Tamm, Menon, Ringel, & Reiss, 2004; Vollm et al., 2004). While the use of divergent measures, tasks, samples, and even data-analysis techniques limits consensus across these range of studies, the bulk of such data suggest that a right frontostriatal pathway underlies behavioral inhibition and that individual differences in impulsivity relate to differences in the pattern of neural activity seen during behavioral inhibition.

Functional Activation Relevant to Impulsivity

fMRI studies in healthy adults using behavioral inhibition-related task paradigms such as the Go/NoGo and stop-signal tasks have consistently implicated a right-lateralized neural circuit (for a review, see Congdon & Canli, 2005, for a meta-analysis see Buchsbaum, Greer, Chang, & Berman, 2005). These imaging studies are further supported by data from lesion (Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003; Rieger, Gauggel, & Burmeister, 2003) and transcranial magnetic stimulation (Chambers et al., 2006) studies. Within this circuit, the two critical regions are the right inferior frontal cortex (IFC) and the subthalamic nucleus (STN). The IFC plays a central role in controlling behavioral inhibition (as opposed to motor planning or response selection). The STN, on the other hand, plays a central role in the stopping of a motor response, and its position within this frontostriatal circuit is particularly well-suited for braking ongoing motor commands that are in the later stages of being processed by the brain (Aron & Poldrack, 2005; Gerfen, 2000; Mink, 1996; Nambu, Tokuno, & Takada, 2002). Functional connectivity analysis finds that activation in these two structures is positively correlated (Aron & Poldrack, 2006), consistent with the view that both areas may be required for successful inhibition.

Of particular interest to personality psychologists are studies that have begun to investigate how individual differences within this frontostriatal circuit are related to individual differences in self-reported trait impulsivity. These studies illustrate two significant complications for the study of impulsivity using brain imaging. The first complication is *divergence across measurement instruments*: different self-report instruments of impulsivity, even when administered to the same individuals doing the same task, can implicate different brain regions. The second complication is *divergence across task paradigms*: one and the same self-report instrument can implicate different brain regions across different (but conceptually similar) tasks.

To illustrate the first complication, divergence across measurement instruments, take the example of one study that correlated activation within the frontostriatal circuit of behavioral inhibition during a Go/NoGo task with measures of H. J. Eysenck's impulsiveness scale and with the BIS-11 (Horn, Dolan, Elliott, Deakin, & Woodruff, 2003). This study revealed that related but different self-report measures of impulsivity can produce divergent results when associated with activation during behavioral inhibition. Impulsivity captured with H. J. Eysenck's impulsiveness scale correlated positively with activation in the right IFG (BA 44/45), right inferior parietal lobule and insula during inhibition. On the other hand, impulsivity captured with the BIS-11 correlated positively with activation in the left superior temporal gyrus and medial frontal gyrus during inhibition.

To illustrate the second complication, divergence across task paradigms, consider the divergent data obtained when different sets of investigators used the BIS-11 in different

impulsivity-related tasks. In the Go/NoGo task, BIS-11 correlated positively with activation in the superior temporal and medial frontal gyri (Horn et al., 2003), and (the motor subscale) correlated negatively with activation in the right dorsolateral prefrontal cortex (RDLPFC; Asahi, Okamoto, Okada, Yamawaki, & Yokota, 2004). In the Immediate and Delayed Memory Task (IMT/DMT), which assesses both impulsivity and aspects of working memory, BIS-11 correlated positively with bilateral activation in the dorsolateral prefrontal cortex (DLPFC; Valdes et al., 2006). Brown and colleagues (Brown, Manuck, Flory, & Hariri, 2006) correlated BIS-11 scores in the same subjects while they were scanned using two different tasks. Using an emotional face-matching paradigm, they reported positive correlations in the ventral amygdala and parahippocampal gyrus and negative correlations in the dorsal amygdala and ventral prefrontal cortex. Using a Go/NoGo paradigm, they reported a positive correlation in the caudate nucleus and anterior cingulate cortex. Of course, it should not come as a surprise that different task paradigms will activate different neural circuits, which may or may not be associated with self-reported impulsivity. But it highlights the importance of matching impulsivity constructs and subfacets with appropriate task paradigms when attempting to map self-reported impulsivity onto neural circuits. Across studies, the interaction between self-report measures and impulsivity-related task paradigms further complicates the interpretation of available data.

Structural Features Relevant to Impulsivity

The individual differences approach can also be extended to structural brain features. In particular, studies have quantified white matter microstructure and myelination and gray matter volume and density in relation to individual differences in impulsivity. Results of studies looking at white matter microstructure suggest that elevated impulsivity is associated with poor axonal and/or myelin fiber integrity and that individual differences in white matter microstructure appear to predict behavioral inhibition in healthy adults (de Win et al., 2006; Hoptman et al., 2004; Liston et al., 2006; Moeller et al., 2005). Similarly, results of studies looking at gray matter volume and density suggest that elevated impulsivity is associated with reduced gray matter density and that individual differences in gray matter volume appear to correlate with behavioral inhibition (at least in healthy boys; Antonucci et al., 2006; Carmona et al., 2005; Casey, Castellanos et al., 1997; Casey, Trainor, et al., 1997; Hazlett et al., 2005).

Genetics: The Molecular Level of Analysis

Heritability of Impulsivity

Moving along the reductionistic path, we now turn to consider the role of genes in impulsivity. There is considerable evidence that impulsive behavior has a strong heritable component, justifying the search for specific candidate genes that contribute to this trait. Familial transmission of impulsivity has been demonstrated both outside of DSM categories of mental disorders (defined as commission errors on a task designed to measure impulsive responding; Dougherty et al., 2003) and within DSM categories (defined as impulsive personality disorder traits assessed with interviews; Silverman et al., 1991). Data from twin studies specifically support a genetic component of impulsivity. A twin study using the Control scale of Tellegen's MPQ reports that approximately 45% of the variance in this trait, reflecting impulsivity in this model, was accounted for by genetic factors (Hur & Bouchard, 1997). Remarkably similar estimates were reported in a twin study using the Karolinska Scales of Personality to assess the trait of impulsivity, which reported a heritability estimate of 0.45 (Pedersen, Plomin, McClearn, & Friberg, 1988), and a twin study that assessed impulsivity using the BIS-11 self-report measure, which reported a heritability estimate of 0.44 (Seroczynski, Bergeman, & Coccaro, 1999). Converging evidence, therefore, suggests

that around 45% of the variance in self-reported impulsivity is accounted for by nonadditive genetic factors.

From Twin Studies to Molecular Genetics

In addition to the twin studies familiar to most personality psychologists, recent technical advances in the field of molecular genetics have made it possible to map the entire human genome's nucleotide sequence. This form of molecular genetics goes “beyond heritability” (Plomin & Colledge, 2001) because it has the potential to explain mechanisms of genetic function, rather than merely cataloguing heritability estimates.

The genetic contributions to impulsivity may be mediated through many channels, including genetic mediation of neurotransmitter systems such as serotonin and dopamine (Evenden, 1999; Robbins, 2005). Indeed, the role of serotonin in impulsivity is well recognized, and interested readers are referred to these reviews (Carver & Miller, 2006; Evenden, 1999; Manuck et al., 2003). In this article, however, we will focus only on dopamine because the neural substrate mediating behavioral inhibition (reviewed above) is known to be under dopaminergic modulatory control. Furthermore, psychostimulant drugs that target the dopaminergic system are effective in treating symptoms of ADHD (Volkow, Wang, Fowler, & Ding, 2005). Additional evidence for a role of dopamine in impulsivity comes from pharmacological studies in humans (de Wit et al., 2002; Friedel, 2004) and from pharmacological, metabolite, lesion, and knockout studies in animals (Cardinal, Pennicott, Sugathapala, Robbins, & Everitt, 2001; Dellu-Hagedorn, 2006; Dulawa, Grandy, Low, Paulus, & Geyer, 1999; Puumala, 1998; Rubinstein et al., 1997; Winstanley, Theobald, Cardinal, & Robbins, 2004; Winstanley, Theobald, Dalley, Cardinal, & Robbins, 2006).

Within the dopaminergic system, there are certain gene polymorphisms that may influence impulsivity. Three gene polymorphisms, in particular, have received considerable interest; these include polymorphisms of the genes coding for the D4 dopamine receptor (*DRD4*), the dopamine transporter (*DAT*), and the catechol-O-methyltransferase enzyme (*COMT*). A brief description of each component of the dopaminergic system will be followed by a review of evidence relating the gene variant to impulsivity or impulsive-related measures. It is worth noting at the outset that the significance of these gene variations is that they appear to confer individual differences in impulse-related behaviors and are differentially distributed across the frontostriatal network underlying behavioral inhibition.

Dopamine D4 Receptor (*DRD4*)

One of the receptors that dopamine (DA) can bind to is the D4 receptor, which is expressed in the cerebral cortex, amygdala, hypothalamus, hippocampus, pituitary, and basal ganglia (Asghari et al., 1995). Although reports of D4 gene expression have not been entirely consistent, D4 receptor gene expression in the human brain is most abundant in the prefrontal cortex and low in the striatum (Meador-Woodruff et al., 1996; Mulcrone & Kerwin, 1997). Evidence for the critical role of the D4 receptor in mediating behavior comes from mice missing the *DRD4* gene who show a significantly reduced response to novel stimuli, compared to genetically intact mice (Dulawa et al., 1999).

The gene coding the D4 receptor contains a VNTR polymorphism that comes in a number of variants, ranging from two to ten repeats, with the 2-, 4-, and 7-repeat variants being most common (Asghari et al., 1995). The 7-repeat variant of the dopamine D4 receptor gene is associated with less efficient function than the 2- or 4-repeat alleles, and the 10-repeat allele is more efficient than the 2-repeat allele (Asghari et al., 1995; Jovanovic, Guan, & Van Tol, 1999). The 7-repeat allele may result in a reduced, or suboptimal, response to dopamine (Swanson et al., 2000). As dopamine is critical for behavioral inhibition, and the D4 receptor

is expressed in regions known to underlie behavioral inhibition, subsensitive dopaminergic receptor stimulation may result in impaired functioning of the system and, in turn, impaired inhibitory control.

Two initial reports of an association between presence of the 7-repeat allele of the *DRD4* and the personality trait of novelty seeking (Benjamin et al., 1996b; Ebstein et al., 1996) were not supported by subsequent replication studies, perhaps due to methodological differences, such as small samples, choice of study populations, and selection of trait questionnaires. A meta-analysis of such studies did not find support for an association between novelty seeking and the *DRD4* polymorphism when samples were dichotomized according to the presence versus absence of the 7-al-lele, although there was evidence for a small association when samples were dichotomized according to the presence of long-versus short-repeat alleles (Schinka, Letsch, & Crawford, 2002). In line with this, another review reported a positive association between novelty seeking or related personality traits and the presence of either the 7-repeat allele or the grouping of long-repeat alleles (Savitz & Ramesar, 2004). Furthermore, in support of this association is a report of an association between the *DRD4* polymorphism and novelty seeking in vervet monkeys (Bailey, Breidenthal, Jorgensen, McCracken, & Fairbanks, 2007).

The *DRD4* polymorphism is also associated with a diagnosis of ADHD; a meta-analysis supports a small but significant association between the 7-repeat allele of the *DRD4* and ADHD (Faraone, Doyle, Mick, & Biederman, 2001). A subsequent meta-analysis conducted on all association studies of European and Asian populations up to October 2005 also provided strong evidence that the 7-repeat allele of the *DRD4*, along with the 5-repeat allele, confers increased risk for ADHD, while the 4-repeat allele provides a protective effect (Li, Sham, Owen, & He, 2006). Despite the small effect sizes reported in such association studies, we suggest that novelty seeking in healthy individuals, and ADHD in patients, share impulsivity as a common dimension. As such, it is likely that genetic variation within the *DRD4* polymorphism taps into this common dimension of impulsivity.

Dopamine Transporter (DAT)

The DAT is a protein that plays a critical role in dopamine neurotransmission because it is responsible for removing dopamine from the extracellular space (Bannon, Michelhaugh, Wang, & Sacchetti, 2001). DAT is expressed and acts primarily throughout the midbrain, but there is a noted lack of DAT in the frontal cortex (Lewis et al., 2001; Sesack, Hawrylak, Matus, Guido, & Levey, 1998). The *DAT* contains a VNTR polymorphism, resulting in variants that range from 3- to 13-repeats, with 9- and 10-repeats occurring most commonly (Bannon et al., 2001). While some studies suggest that the 10-repeat variant is associated with increased expression of the DAT (VanNess, Owens, & Kilts, 2005), and individuals with the 10/10 genotype have been characterized as having excessive amounts of the transporter (Fuke et al., 2001; Heinz et al., 2000; Mill, Asherson, Browes, D'Souza, & Craig, 2002; Swanson et al., 2000), there are also studies to suggest increased expression is associated with the 9-repeat variant (Jacobsen et al., 2000; Michelhaugh, Fiskerstrand, Lovejoy, Bannon, & Quinn, 2001) or that carriers of the 9-repeat variants have increased DAT protein availability (van Dyck et al., 2005). However, there are also studies to suggest no functional significance of the VNTR (Martinez et al., 2001; Mill, Asherson, Craig, & D'Souza, 2005).

Excessive amounts of the DAT could lead to an overly efficient reuptake of dopamine, reducing extracellular dopamine below optimal levels. Brain regions such as the striatum play a critical role in some forms of impulsivity, such as behavioral inhibition (Aron & Poldrack, 2006; Brown et al., 2006), and also rely on an optimal range of dopamine. Therefore, based on evidence suggesting an increase in expression of the DAT in individuals

with the 10-repeat variant, the 10-repeat variant (especially the 10/10 genotype) may be associated with impaired inhibitory control.

There have been a number of association studies with the *DAT*, with particular focus on ADHD or ADHD-related variables. Results suggest that the association between the 10-allele of the *DAT* and a diagnosis of ADHD is tenuous, showing only a small but significant main effect of *DAT* on ADHD (Faraone et al., 2005). However, the 10-allele (or 10/10 genotype) has been associated with more specific phenotypes, including symptom, as well as cortical inhibitory activity, response after medication treatment in ADHD children (Bellgrove, Hawi, Kirley, Fitzgerald, et al., 2005; Gilbert et al., 2006; Kirley et al., 2003), greater neuropsychological impairment (Bellgrove, Hawi, Kirley, Fitzgerald, et al., 2005; Bellgrove, Hawi, Kirley, Gill, & Robertson, 2005), impulsive responding on a continuous performance task (Loo et al., 2003), and severity of hyperactivity/impulsivity symptoms (Waldman et al., 1998). Other data suggest that the effect of *DAT* on ADHD may be moderated through interaction with other variables, such as subject demographics (Cornish et al., 2005) or other gene polymorphisms, including *DRD4*. For example, increased hyperactive-impulsive scores were reported in ADHD children with at least one 7-allele of the *DRD4* and both 10-alleles for the *DAT* (Roman et al., 2001) and an increased rate of having at least one 7-allele of the *DRD4* and both 10-alleles for the *DAT* was reported in a separate sample of ADHD children (Carrasco et al., 2006).

As with studies of the *DRD4* polymorphism, our conclusions about genetic variation in the *DAT* polymorphism and its effects on impulsivity are tenuous because studies to date have not directly assessed trait impulsivity or measured behavioral inhibition outside of clinical samples. Yet insofar as ADHD includes impulsivity as a major dimension, we suggest that genetic variation of the *DAT* polymorphism taps into this common dimension.

Catechol-O-Methyltransferase (COMT)

The COMT enzyme is also central to dopaminergic functioning, has a known functional polymorphism, and has been studied in relation to individual differences in cognition and emotion. COMT degrades dopamine, (as well as its chemical relatives, the catecholamines epinephrine and norepinephrine) and is widely distributed throughout the brain (Hong, Shu-Leong, Tao, & Lap-Ping, 1998). The role of COMT in regulating dopamine in the frontal cortex is particularly important, because the frontal cortex lacks the *DAT* (Chen et al., 2004), leaving dopaminergic disposal to COMT. The COMT gene contains a particular SNP, which results in the substitution of the amino acid methionine (met) for valine (val). Studies support a functional effect of the SNP, with the met enzyme having one third to one half of the activity of the val enzyme (Lotta et al., 1995). As the function of the COMT enzyme is to break down dopamine, the met variant (associated with low enzymatic activity) results in *high* levels of extrasynaptic dopamine, whereas the val variant (associated with high enzymatic activity) results in *low* levels of extrasynaptic dopamine (Chen et al., 2004; Lotta et al., 1995; Mannisto & Kaakkola, 1999).

As a result of its crucial role in prefrontal regions and the significant differences in function between variants, the *COMT* polymorphism is hypothesized to affect cognitive functioning directly, based on the differential effects of the met and val variants on levels of dopamine in prefrontal and subcortical regions (Bilder, Volavka, Lachman, & Grace, 2004). Briefly, the val variant is thought to facilitate transitions between states or enhance flexibility, though this may disrupt inhibitory control and predispose to impulsivity. On the other hand, the met variant is thought to reduce cortical noise and enhance stability, thereby facilitating inhibitory control.

The *COMT* polymorphism has been associated with self-reported levels of suicidal and aggressive behavior (Jones et al., 2001; Rujescu, Giegling, Gietl, Hartmann, & Moller, 2003; Strous et al., 2003), with novelty seeking (in interaction with other polymorphisms; Benjamin et al., 2000), and with ADHD (Eisenberg et al., 1999). However, the *COMT* polymorphism has been most consistently associated with performance differences in tasks of executive functioning (Bruder et al., 2005; Diamond, Briand, Fossella, & Gehlbach, 2004; Egan et al., 2001; Fossella et al., 2002; Malhotra et al., 2002; Nolan, Bilder, Lachman, & Volavka, 2004; Rosa et al., 2004). An analysis of *COMT* association studies, especially those directly addressing the effects of these variants on dopaminergic tone, reveals that inhibition and conflict may be central to the effects of *COMT* (Nolan et al., 2004). Processes including the maintenance, reordering, and manipulation of information in prefrontal neural networks, as well as behavioral inhibition and the switching of task sets, are proposed to be most sensitive to the effects of *COMT* genotype (Bruder et al., 2005). Although there are no studies to date which have assessed the role of *COMT* using direct measures of impulsivity or behavioral inhibition, the central role that *COMT* has in the prefrontal cortex (supported by findings of differential activation as a function of *COMT* genotype), and the evidence implicating specific frontal areas in behavioral inhibition, motivates future investigations into the possible role of *COMT* in behavioral inhibition.

The Endophenotype Approach: Integrating Across Levels of Analysis

Despite the advances on the neural and genetic correlates of impulsivity we discussed above, further progress is currently limited by two obstacles. The first obstacle is the continued use of an approach based on diagnostic categories. This is particularly the case in association studies, in which psychiatric groups are compared to controls. The problem is that the underlying mechanisms related to impulsivity per se are confounded with disease-specific variables, which prevents the identification of phenotypes closer to the influence of genetic variants (Gottesman & Gould, 2003). In addition, DSM criteria have been criticized for creating heterogeneous categories in that one diagnostic category may contain multiple subtypes, each of which may represent a different etiology.

The second obstacle is an overreliance on self-report measures. Most studies have not measured impulsivity per se, but have relied on self-reported traits such as novelty seeking (Munafo et al., in press). As we reviewed above, there is a range of conceptualizations and impulsivity measures, and the use of inappropriate or divergent measures across studies makes it difficult to identify a useful phenotype. In addition, self-report inventories may be an insensitive measure that carries only a small effect size for genetic influences (Gottesman & Gould, 2003; Hariri & Weinberger, 2003).

To overcome these obstacles, some have advocated an alternative approach (Baud, 2005; Castellanos & Tannock, 2002; Congdon & Canli, 2005; de Geus, Wright, Martin, & Boomsma, 2001; Gottesman & Gould, 2003; Hasler, Drevets, Manji, & Charney, 2004; MacQueen, Hajek, & Alda, 2005; New & Siever, 2003), which replaces complex phenotypes (e.g., diagnostic categories combining heterogeneous symptoms) with simpler intermediate or “endo”-phenotypes (e.g., isolated cognitive processes or localized brain measures) that are presumed to be more closely linked to the biological processes regulated by genes of interest. Indeed, we have chosen to focus on the neurogenetic basis of behavioral inhibition in this article in order to illustrate the advantage of this approach in integrating molecular genetic and neuroimaging methods to better understand of the role of biology in determining personality.

Neuroimaging of Polymorphic Function and Impulsivity

As discussed above, neuroimaging studies of behavioral inhibition have reported activation within a frontostriatal network, particularly the right IFC, during inhibition. Furthermore, several studies have linked individual differences in impulsivity to both functional and structural variation within this network. We propose that dopaminergic gene polymorphisms have a functional role in modulating this network, affecting either its structure (e.g., by altering dopaminergic neurotransmission during development) or function (e.g., altering neural response during behavioral inhibition). In other words, dopaminergic gene variation may alter structural or functional aspects of this frontostriatal circuit to generate individual differences in behavioral inhibition. Indirect support for this hypothesis comes from studies that have integrated neuroimaging and molecular genetic approaches.

With regard to genetic influences on brain structure, differences in brain volume as measured with anatomical MRI scans have been reported between the *DAT* and the *DRD4*, such that ADHD boys with the *DAT* 10/10 genotype had smaller caudate volumes than those without the 10/10 genotype, and the unaffected siblings of ADHD boys with the *DRD4* 4/4 genotype had smaller prefrontal gray matter volumes than those without the 4/4 genotype (primarily a 7- or 2-repeat allele; Durston et al., 2005).

With regard to genetic influences on brain functional activation, a SPECT study revealed higher perfusion (an indicator of metabolism) in the right middle temporal gyrus in ADHD children who had the 10/10 *DAT* genotype and at least one *DRD4* 7-allele, as compared to all other groups (Szobot et al., 2005). *DAT* binding sites are located in the temporal cortex and, although the relationship between the higher perfusion in the medial temporal cortex and behaviors related to ADHD is less clear, the results highlight the increased sensitivity of an approach which addresses the possible effect of genetic variation on the actual response of brain regions. Furthermore, studies testing for differences in neural activity as a function of *DAT* have reported evidence for different patterns of neural responding between *DAT* genotype groups (Bertolino et al., 2006; Schott et al., 2006), though the exact pattern differs across tasks used.

Another polymorphic candidate that may play a role in impulsivity, specifically behavioral inhibition, is the *COMT* genotype. Although there is currently no empirical evidence linking *COMT* directly to impulsivity (although there is indirect evidence, reviewed above), we hypothesize a significant role for *COMT* in behavioral inhibition. We base this hypothesis on the fact that *COMT* is the predominant enzyme in the catabolism of dopamine in the prefrontal cortex (Bilder et al., 2004) and that several imaging studies have shown that *COMT* genotype differentially affects activation in prefrontal regions (Mattay et al., 2003; Smolka et al., 2005), some of which also play a role in behavioral inhibition. For example, an association between the met allele and less reactive (more efficient) neural response has been reported during an executive function task in the dorsolateral prefrontal cortex (Egan et al., 2001) and during an attentional control task in the dorsal cingulate cortex (Blasi et al., 2005). *COMT* genotype has also been associated with differential regional Cerebral Blood Flow (rCBF) and presynaptic dopaminergic function during a working memory (N-back) task in prefrontal cortex (Meyer-Lindenberg et al., 2005).

Thus, in this article we have highlighted several candidate polymorphisms that affect brain structure and/or function in brain regions that are implicated in behavioral inhibition. Because so few studies have integrated molecular genetics and neuroimaging, and none of them have focused on behavioral inhibition or impulsivity, there is a paucity of empirical data to test our hypotheses. Ongoing work in our laboratory and elsewhere will, we hope, rectify this shortcoming.

Challenges and Future Directions

We see three kinds of challenges that will have to be overcome to advance our understanding of the biological basis and structure of impulsivity. These fall in the domains of clinical, conceptual, and empirical challenges.

Clinical Challenges

We have criticized the taxonomic, categorical approach to study impulsivity in patients. While it is possible, perhaps likely, that there may be disease-specific genetic contributions to impulsivity, we have focused on impulsivity as a trait that is present in healthy individuals and cuts across diagnostic categories in patients. If correct, then future studies need to be designed with multiple patient categories that are quite different on the surface, but all share impulsivity as a symptom in their respective patient cohorts. This poses a challenge in terms of patient recruitment, experimenter expertise, collaborations between clinicians who specialize on different patient populations, credit sharing on grants and publications, and so on. Overcoming these challenges should be a high priority because impulsivity cuts across so many disorders. The endophenotype approach could lead to the identification of diagnostic markers, be used to create more homogenous categories (or subtypes) within diagnoses, aid in the identification of at-risk individuals, and lead to a better understanding of the etiology of a disorder.

Conceptual Challenges

The multiple dimensions of impulsivity proposed by various theorists are not all rooted in biology (although some are). The conceptual challenge is to better integrate theoretical and empirical approaches to understanding the structure of impulsivity. On the one hand, clear theoretical models of the structure of impulsivity can inspire empiricists to develop experimental tests of these models. Although there is a neuroimaging literature on behavioral inhibition, many other dimensions of impulsivity remain unexplored. On the other hand, biological data could help constrain models of impulsivity. Clearly, models that propose dimensions of impulsivity that map poorly onto neural circuits should be replaced by models that map better.

The motivation for overcoming these obstacles is, therefore, the prospect of more precise, biologically rooted conceptual models of impulsivity. Evidence is already accumulating to support the biological basis of behavioral inhibition and this, along with studies into other components of impulsivity (such as delay discounting; Eisenberg et al., 2007; Hariri, Brown, Williamson, Flory, de Wit, & Manuck, 2006), offers the possibility of future neural and genetic indices better defining the construct of impulsivity, which may put to rest many of the discrepancies and disagreements across the literature.

Empirical Challenges

Following the first reports of polymorphic associations with complex traits such as neuroticism (Lesch et al., 1996) or novelty seeking (Benjamin et al., 1996a), a large number of replication studies have been conducted, with mixed results. A number of variables may have contributed to nonreplications, such as small sample sizes, heterogeneous subject populations, differing methods of personality assessment, or selection of extreme scorers (Reif & Lesch, 2003). On the other hand, critics argue that poor replications reflect an inherent problem of relating gene variations of small effect size (e.g., the Lesch et al., 1996, study reported that the serotonin transporter gene polymorphism contributed 3–4% of the total variance in personality scores) to complex traits (Ioannidis, 2006). Similar concerns may apply to work on impulsivity.

One way to overcome this obstacle, of course, has been the endophenotype approach, particularly with respect to neuroimaging. Indeed, Hamer (2002) noted that the effect size in neuroimaging studies of gene function appears to be tenfold higher than for studies employing self-report personality measured. For example, with respect to the serotonin transporter gene polymorphism, it is striking that neuroimaging studies have had a remarkable track record of consistent findings, even though the interpretation of the data continues to be a matter of debate (Canli & Lesch, 2007). Nonetheless, future imaging studies of polymorphic function are likely to require large samples, as more complex functions such as gene-gene (Herrmann et al., 2007) or gene-environment (Canli et al., 2006) interactions will be studied.

Future Directions

The above challenges notwithstanding, we anticipate a number of exciting developments, particularly with respect to molecular mechanisms. One of these will be the increased use of whole-genome scans to discover novel gene polymorphisms associated with impulsivity in healthy and in patient populations. Gene chips with 500,000 SNPs exist already, and chips with twice that many SNPs will soon be available, that can be used to compare the frequency of particular SNPs with complex traits such as impulsivity. Of course, investigating such a large number of SNPs for association with a complex trait requires large samples, but research protocols have been developed that make possible the rigorous analysis of whole-genome scans with manageable sample sizes (Papassotiropoulos et al., 2006).

Yet the integration of very large datasets, such as whole genome scans with functional or high-resolution structural MRI data, will require further innovations in biostatistical approaches to data analysis. Already, efforts are underway to integrate complex genomic and neural data sets (Wessel, Zapala, & Schork, 2007; Zapala & Schork, 2006), which will be further aided by the development of computational genomic and neuroscience models to constrain hypothesis testing. The combination of large-scale genome-wide scanning techniques and novel computational and biostatistical analysis tools will eventually make it possible to assess the combined effects of hundreds of gene polymorphisms across the entire genome on impulsivity. While not feasible today, existing research approaches point towards a development of this kind of genomic psychology in the future (Canli, 2007).

Another future direction will be the study of epigenetic mechanisms. We anticipate that, as discoveries about the neurogenetic basis of impulsivity accrue, the role of the environment, and of gene-environment interactions, will become a rich area of future research. Already, work out of Meaney's laboratory (Weaver et al., 2004) is beginning to reveal the underlying mechanisms by which life experience modulates gene expression.

We hope that this article served as a useful orientation for personality psychologists interested in the biology of impulsivity. Although we narrowed our focus on one aspect of impulsivity to illustrate the opportunity to integrate across levels of analysis, we hope that readers can see how this approach can be applied to any other aspect of impulsive behavior. The charge for the next generation of personality psychologists is to become more familiar with neuroscience and molecular biology, to build collaborations across disciplines, and to develop comprehensive theoretical models that can integrate genetic, neural, and behavioral data. Hans Eysenck was a leader in his era in accomplishing such a daunting task. The current and next generation of investigators can draw inspiration from his example, as they begin to develop comprehensive biobehavioral models to explain and understand human individual differences.

Acknowledgments

The work from our laboratory discussed in this article was supported by the National Science Foundation (BCS-0224221).

References

- Altshuler LL, Bookheimer SY, Townsend J, Proenza MA, Eisenberger N, Sabb F, et al. Blunted activation in orbitofrontal cortex during mania: A functional magnetic resonance imaging study. *Biological Psychiatry* 2005;58(10):763–769. [PubMed: 16310510]
- Antonucci AS, Gansler DA, Tan S, Bhadelia R, Patz S, Fulwiler C. Orbitofrontal correlates of aggression and impulsivity in psychiatric patients. *Psychiatry Research* 2006;147(2–3):213–220. [PubMed: 16952446]
- Aron AR, Fletcher PC, Bullmore ET, Sahakian BJ, Robbins TW. Stop-signal inhibition disrupted by damage to right inferior frontal gyrus in humans. *Nature Neuroscience* 2003;6(2):115–116.
- Aron AR, Poldrack RA. The cognitive neuroscience of response inhibition: relevance for genetic research in attention-deficit/hyperactivity disorder. *Biological Psychiatry* 2005;57(11):1285–1292. [PubMed: 15950000]
- Aron AR, Poldrack RA. Cortical and subcortical contributions to Stop signal response inhibition: Role of the subthalamic nucleus. *Journal of Neuroscience* 2006;26(9):2424–2433. [PubMed: 16510720]
- Asahi S, Okamoto Y, Okada G, Yamawaki S, Yokota N. Negative correlation between right prefrontal activity during response inhibition and impulsiveness: a fMRI study. *European Archives of Psychiatry and Clinical Neuroscience* 2004;254(4):245–251. [PubMed: 15309395]
- Asghari V, Sanyal S, Buchwaldt S, Paterson A, Jovanovic V, Van Tol HH. Modulation of intracellular cyclic AMP levels by different human dopamine D4 receptor variants. *Journal of Neurochemistry* 1995;65(3):1157–1165. [PubMed: 7643093]
- Avila C, Cuenca I, Felix V, Parcet MA, Miranda A. Measuring impulsivity in school-aged boys and examining its relationship with ADHD and ODD ratings. *Journal of Abnormal Child Psychology* 2004;32(3):295–304. [PubMed: 15228178]
- Bage C, Nickell A, Stepp S, Durrett C, Jackson K, Trull TJ. Borderline personality disorder features predict negative outcomes 2 years later. *Journal of Abnormal Psychology* 2004;113(2):279–288. [PubMed: 15122948]
- Bailey JN, Breidenthal SE, Jorgensen MJ, McCracken JT, Fairbanks LA. The association of DRD4 and novelty seeking is found in a nonhuman primate model. *Psychiatric Genetics* 2007;17(1):23–27. [PubMed: 17167341]
- Bannon MJ, Michelhaugh SK, Wang J, Sacchetti P. The human dopamine transporter gene: gene organization, transcriptional regulation, and potential involvement in neuropsychiatric disorders. *European Neuropsychopharmacology* 2001;11(6):449–455. [PubMed: 11704422]
- Barkley RA. Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. *Psychological Bulletin* 1997;121(1):65–94. [PubMed: 9000892]
- Baud P. Personality traits as intermediary phenotypes in suicidal behavior: Genetic issues. *American Journal of Medical Genetics C Seminars in Medical Genetics* 2005;133(1):34–42.
- Beauchaine TP, Katkin ES, Strassberg Z, Snarr J. Disinhibitory psychopathology in male adolescents: discriminating conduct disorder from attention-deficit/hyperactivity disorder through concurrent assessment of multiple autonomic states. *Journal of Abnormal Psychology* 2001;110(4):610–624. [PubMed: 11727950]
- Bellgrove MA, Hawi Z, Kirley A, Fitzgerald M, Gill M, Robertson IH. Association between dopamine transporter (DAT1) genotype, left-sided inattention, and an enhanced response to methylphenidate in attention-deficit hyperactivity disorder. *Neuropsychopharmacology* 2005;30(12):2290–2297. [PubMed: 16123773]
- Bellgrove MA, Hawi Z, Kirley A, Gill M, Robertson IH. Dissecting the attention deficit hyperactivity disorder (ADHD) phenotype: sustained attention, response variability and spatial attentional asymmetries in relation to dopamine transporter (DAT1) genotype. *Neuropsychologia* 2005;43(13):1847–1857. [PubMed: 16168728]

- Benjamin J, Li L, Patterson C, Greenberg BD, Murphy DL, Hamer DH. Population and familial association between the D4 dopamine receptor gene and measures of Novelty Seeking. *Nature Genetics* 1996a;12(1):81–84. [PubMed: 8528258]
- Benjamin J, Li L, Patterson C, Greenberg BD, Murphy DL, Hamer DH. Population and familial association between the D4 dopamine receptor gene and measures of novelty seeking. *Nature Genetics* 1996b;12:81–84. [PubMed: 8528258]
- Benjamin J, Osher Y, Kotler M, Gritsenko I, Nemanov L, Belmaker RH, et al. Association between tridimensional personality questionnaire (TPQ) traits and three functional polymorphisms: dopamine receptor D4 (DRD4), serotonin transporter promoter region (5-HTTLPR) and catechol O-methyltransferase (COMT). *Molecular Psychiatry* 2000;5(1):96–100. [PubMed: 10673775]
- Bertolino A, Rubino V, Sambataro F, Blasi G, Latorre V, Fazio L, et al. Prefrontal-hippocampal coupling during memory processing is modulated by COMT Val158Met genotype. *Biological Psychiatry* 2006;60(11):1250–1258. [PubMed: 16950222]
- Bilder RM, Volavka J, Lachman HM, Grace AA. The catechol-O-methyltransferase polymorphism: Relations to the tonic-phasic dopamine hypothesis and neuropsychiatric phenotypes. *Neuropsychopharmacology* 2004;29(11):1943–1961. [PubMed: 15305167]
- Blasi G, Mattay VS, Bertolino A, Elvevag B, Callicott JH, Das S, et al. Effect of catechol-O-methyltransferase val158met genotype on attentional control. *Journal of Neuroscience* 2005;25(20):5038–5045. [PubMed: 15901785]
- Braver TS, Barch DM, Gray JR, Molfese DL, Snyder A. Anterior cingulate cortex and response conflict: Effects of frequency, inhibition and errors. *Cerebral Cortex* 2001;11(9):825–836. [PubMed: 11532888]
- Brown SM, Manuck SB, Flory JD, Hariri AR. Neural basis of individual differences in impulsivity: Contributions of corticolimbic circuits for behavioral arousal and control. *Emotion* 2006;6(2):239–245. [PubMed: 16768556]
- Bruder GE, Keilp JG, Xu H, Shikhman M, Schori E, Gorman JM, et al. Catechol-O-methyltransferase (COMT) genotypes and working memory: associations with differing cognitive operations. *Biological Psychiatry* 2005;58(11):901–907. [PubMed: 16043133]
- Buchsbaum BR, Greer S, Chang WL, Berman KF. Meta-analysis of neuroimaging studies of the Wisconsin card-sorting task and component processes. *Human Brain Mapping* 2005;25(1):35–45. [PubMed: 15846821]
- Cale EM. A quantitative review of the relations between the “Big 3” higher order personality dimensions and antisocial behavior. *Journal of Research in Personality* 2006;40(3):250–284.
- Canli T. Genomic Psychology: An emerging paradigm. *EMBO Reports (Special Edition on Science and Society (S1))* 2007;8:S30–34. [PubMed: 17726440]
- Canli T, Lesch KP. Long story short: The serotonin transporter in emotion regulation and social cognition. *Nature Neuroscience* 2007;10(9):1103–1109.
- Canli T, Qiu M, Omura K, Congdon E, Haas BW, Amin Z, et al. Neural correlates of epigenesis. *Proceedings of the National Academy of Sciences, USA* 2006;103(43):16033–16038.
- Cardinal RN, Pennicott DR, Sugathapala CL, Robbins TW, Everitt BJ. Impulsive choice induced in rats by lesions of the nucleus accumbens core. *Science* 2001;292(5526):2499–2501. [PubMed: 11375482]
- Carmona S, Vilarroya O, Bielsa A, Tremols V, Soliva JC, Rovira M, et al. Global and regional gray matter reductions in ADHD: A voxel-based morphometric study. *Neuroscience Letters* 2005;389(2):88–93. [PubMed: 16129560]
- Carrasco X, Rothhammer P, Moraga M, Henriquez H, Chakraborty R, Aboitiz F, et al. Genotypic interaction between DRD4 and DAT1 loci is a high risk factor for attention-deficit/hyperactivity disorder in Chilean families. *American Journal of Medical Genetics B: Neuropsychiatric Genetics* 2006;141(1):51–54.
- Carver CS, Miller CJ. Relations of serotonin function to personality: Current views and a key methodological issue. *Psychiatry Research* 2006;144(1):1–15. [PubMed: 16914207]
- Casey BJ, Castellanos FX, Giedd JN, Marsh WL, Hamburger SD, Schubert AB, et al. Implication of right frontostriatal circuitry in response inhibition and attention-deficit/hyperactivity disorder.

- Journal of the American Academy of Child and Adolescent Psychiatry 1997;36(3):374–383. [PubMed: 9055518]
- Casey BJ, Trainor RJ, Orendi JL, Schubert AB, Nystrom LE, Giedd JN, et al. A developmental functional MRI study of prefrontal activation during performance of a Go-No-Go task. *Journal of Cognitive Neuroscience* 1997;9(6):835–847.
- Castellanos FX, Tannock R. Neuroscience of attention-deficit/hyperactivity disorder: The search for endophenotypes. *Nature Reviews Neuroscience* 2002;3(8):617–628.
- Chambers CD, Bellgrove MA, Stokes MG, Henderson TR, Garavan H, Robertson IH, et al. Executive “brake failure” following deactivation of human frontal lobe. *Journal of Cognitive Neuroscience* 2006;18(3):444–455. [PubMed: 16513008]
- Chen J, Lipska BK, Halim N, Ma QD, Matsumoto M, Melhem S, et al. Functional analysis of genetic variation in catechol-O-methyltransferase (COMT): Effects on mRNA, protein, and enzyme activity in postmortem human brain. *American Journal of Human Genetics* 2004;75(5):807–821. [PubMed: 15457404]
- Cloninger CR, Svrakic D, Przybeck T. A psychobiological model of temperament and character. *Archives of General Psychiatry* 1993;50:975–990. [PubMed: 8250684]
- Congdon E, Canli T. The endophenotype of impulsivity: Reaching consilience through behavioral, genetic, and neuroimaging approaches. *Behavioral and Cognitive Neuroscience Reviews* 2005;4(4):262–281. [PubMed: 16585800]
- Conrod PJ, Pihl RO, Stewart SH, Dongier M. Validation of a system of classifying female substance abusers on the basis of personality and motivational risk factors for substance abuse. *Psychology of Addictive Behavior* 2000;14(3):243–256.
- Cornish KM, Manly T, Savage R, Swanson J, Morisano D, Butler N, et al. Association of the dopamine transporter (DAT1) 10/10-repeat genotype with ADHD symptoms and response inhibition in a general population sample. *Molecular Psychiatry* 2005;10(7):686–698. [PubMed: 15809660]
- Costa, PT.; McCrae, RR. Revised NEO personality inventory: Professional manual. Odessa, FL: Psychological Assessment Resources; 1992.
- de Geus EJ, Wright MJ, Martin NG, Boomsma DI. Genetics of brain function and cognition. *Behavior Genetics* 2001;31(6):489–495. [PubMed: 11838528]
- de Win MM, Reneman L, Jager G, Vlieger EJ, Olabbariaga SD, Lavini C, et al. A prospective cohort study on sustained effects of low-dose Ecstasy use on the brain in new Ecstasy users. *Neuropsychopharmacology* 2006;32(2):458–470. [PubMed: 17077812]
- de Wit H, Enggasser JL, Richards JB. Acute administration of d-amphetamine decreases impulsivity in healthy volunteers. *Neuropsychopharmacology* 2002;27(5):813–825. [PubMed: 12431855]
- Dellu-Hagedorn F. Relationship between impulsivity, hyperactivity and working memory: A differential analysis in the rat. *Behavior and Brain Function* 2006;2:10.
- Diamond A, Briand L, Fossella J, Gehlbach L. Genetic and neurochemical modulation of prefrontal cognitive functions in children. *American Journal of Psychiatry* 2004;161(1):125–132. [PubMed: 14702260]
- Dickman SJ. Functional and dysfunctional impulsivity: Personality and cognitive correlates. *Journal of Personality and Social Psychology* 1990;58(1):95–102. [PubMed: 2308076]
- Dougherty, Mathias, Marsh, Moeller, Swann. Suicidal behaviors and drug abuse: Impulsivity and its assessment. *Drug and Alcohol Dependence* 2004;76(Suppl. 1):S93–S105. [PubMed: 15555820]
- Dougherty DM, Bjork JM, Moeller FG, Harper RA, Marsh DM, Mathias CW, et al. Familial transmission of Continuous Performance Test behavior: Attentional and impulsive response characteristics. *Journal of General Psychology* 2003;130(1):5–21. [PubMed: 12635853]
- Dulawa SC, Grandy DK, Low MJ, Paulus MP, Geyer MA. Dopamine D4 receptor-knock-out mice exhibit reduced exploration of novel stimuli. *Journal of Neuroscience* 1999;19(21):9550–9556. [PubMed: 10531457]
- Durston S. A review of the biological bases of ADHD: What have we learned from imaging studies? *Mental Retardation & Developmental Disabilities Research Reviews* 2003;9(3):184–195. [PubMed: 12953298]

- Durston S, Davidson MC, Tottenham N, Galvan A, Spicer J, Fossella JA, et al. A shift from diffuse to focal cortical activity with development. *Developmental Science* 2006;9(1):1–8. [PubMed: 16445387]
- Durston S, Fossella JA, Casey BJ, Hulshoff Pol HE, Galvan A, Schnack HG, et al. Differential effects of DRD4 and DAT1 genotype on fronto-striatal gray matter volumes in a sample of subjects with attention deficit hyperactivity disorder, their unaffected siblings, and controls. *Molecular Psychiatry* 2005;10(7):678–685. [PubMed: 15724142]
- Eagle DMB, Durston S, Davidson MC, Tottenham N, Galvan A, Spicer J, Fossella JA, et al. A shift from diffuse to focal cortical activity with development. *Developmental Science* 2006;9(1):1–8. [PubMed: 16445387]
- Epstein RP, Novick O, Umansky R, Priel B, Osher Y, Blaine D, et al. Dopamine D4 receptor (D4DR) exon III polymorphism associated with the human personality trait of Novelty Seeking. *Nature Genetics* 1996;12:78–80. [PubMed: 8528256]
- Egan MF, Goldberg TE, Kolachana BS, Callicott JH, Mazzanti CM, Straub RE, et al. Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. *Proceedings of the National Academy of Sciences USA* 2001;98(12):6917–6922.
- Eisenberg DT, Mackillop J, Modi M, Beauchemin J, Dang D, Lisman SA, et al. Examining impulsivity as an endophenotype using a behavioral approach: a DRD2 TaqI A and DRD4 48-bp VNTR association study. *Behavior and Brain Function* 2007;3:2.
- Eisenberg J, Mei-Tal G, Steinberg A, Tartakovsky E, Zohar A, Gritsenko I, et al. Haplotype relative risk study of catechol-O-methyltransferase (COMT) and attention deficit hyperactivity disorder (ADHD): Association of the high-enzyme activity Val allele with ADHD impulsive-hyperactive phenotype. *American Journal of Medical Genetics* 1999;88(5):497–502. [PubMed: 10490706]
- Enticott PG, Ogloff JRP, Bradshaw JL. Associations between laboratory measures of executive inhibitory control and self-reported impulsivity. *Personality and Individual Differences* 2006;41(2):285–294.
- Esposito, C.; Spirito, A. Behavioral factors: Impulsive and aggressive behavior. In: Overholser, ASJ., editor. *Evaluating and treating adolescent suicide attempters: From research to practice*. San Diego, CA: Academic Press; 2003.
- Evenden JL. Varieties of impulsivity. *Psychopharmacology (Berl)* 1999;146(4):348–361. [PubMed: 10550486]
- Eysenck, HJ. *Sense and nonsense in psychology*. Penguin; 1957.
- Eysenck, HJ. *The biological basis of personality*. Springfield, IL: Charles C. Thomas; 1967.
- Eysenck, HJ. Biological dimensions of personality. In: Pervin, LA., editor. *Handbook of personality: Theory and research*. New York: Guilford Press; 1990. p. 244–276.
- Eysenck, HJ.; Eysenck, SB. *Psychoticism as a dimension of personality*. Oxford, UK: Carne & Russak; 1977.
- Eysenck SB, Eysenck HJ. The place of impulsiveness in a dimensional system of personality description. *British Journal of Social and Clinical Psychology* 1977;16(1):57–68. [PubMed: 843784]
- Eysenck SB, Eysenck HJ. Impulsiveness and venturesomeness: Their position in a dimensional system of personality description. *Psychol Rep* 1978;43(3 Pt 2):1247–1255. [PubMed: 746091]
- Eysenck SB, Pearson PR, Easting G, Allsopp JF. Age norms for impulsiveness, venturesomeness and empathy in adults. *Personality & Individual Differences* 1985;6(5):613–619.
- Eysenck SB, Zuckerman M. The relationship between sensation-seeking and Eysenck's dimensions of personality. *British Journal of Psychology* 1978;69(4):483–487.
- Faraone SV, Doyle AE, Mick E, Biederman J. Meta-analysis of the association between the 7-repeat allele of the dopamine D(4) receptor gene and attention deficit hyperactivity disorder. *American Journal of Psychiatry* 2001;158(7):1052–1057. [PubMed: 11431226]
- Faraone SV, Perlis RH, Doyle AE, Smoller JW, Goralnick JJ, Holmgren MA, Sklar P. Molecular genetics of attention-deficit/hyperactivity disorder. *Biological Psychiatry* 2005;57(11):1313–1323. [PubMed: 15950004]
- Flory JD, Harvey PD, Mitropoulou V, New AS, Silverman JM, Siever LJ, et al. Dispositional impulsivity in normal and abnormal samples. *J Psychiatry Research* 2006;40(5):438–447.

- Fossati A, Barratt ES, Carretta I, Leonardi B, Grazioli F, Maffei C. Predicting borderline and antisocial personality disorder features in nonclinical subjects using measures of impulsivity and aggressiveness. *Psychiatry Research* 2004;125(2):161–170. [PubMed: 15006439]
- Fossella J, Sommer T, Fan J, Wu Y, Swanson JM, Pfaff DW, et al. Assessing the molecular genetics of attention networks. *BMC Neuroscience* 2002;3(1):14. [PubMed: 12366871]
- Franken IHA, Muris P. Gray's impulsivity dimension: A distinction between reward sensitivity versus rash impulsiveness. *Personality and Individual Differences* 2006;40(7):1337–1347.
- Friedel RO. Dopamine dysfunction in borderline personality disorder: A hypothesis. *Neuropsychopharmacology* 2004;29(6):1029–1039. [PubMed: 15039763]
- Fuke S, Suo S, Takahashi N, Koike H, Sasagawa N, Ishiura S. The VNTR polymorphism of the human dopamine transporter (DAT1) gene affects gene expression. *Pharmacogenomics J* 2001;1(2):152–156. [PubMed: 11911442]
- Garavan H, Ross TJ, Stein EA. Right hemispheric dominance of inhibitory control: An event-related functional MRI study. *Proceedings of the National Academy of Sciences USA* 1999;96(14):8301–8306.
- Gerfen CR. Molecular effects of dopamine on striatal-projection pathways. *Trends in Neurosciences* 2000;23(Supplement 1):S64–S70. [PubMed: 11052222]
- Gilbert DL, Wang Z, Sallee FR, Ridel KR, Merhar S, Zhang J, et al. Dopamine transporter genotype influences the physiological response to medication in ADHD. *Brain* 2006;129(Pt 8):2038–2046. [PubMed: 16760197]
- Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. *American Journal of Psychiatry* 2003;160(4):636–645. [PubMed: 12668349]
- Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. *American Journal of Psychiatry* 2003;160(4):636–645. [PubMed: 12668349]
- Hamer D. Genetics Rethinking behavior genetics. *Science* 2002;298(5591):71–72. [PubMed: 12364769]
- Hariri A, Brown SM, Williamson DE, Flory JD, de Wit H, Manuck SB. Preference for immediate over delayed rewards is associated with magnitude of ventral striatal activity. *Journal of Neuroscience* 2006;26(51):13213–13217. [PubMed: 17182771]
- Hariri AR, Weinberger DR. Imaging genomics. *British Medical Bulletin* 2003;65:259–270. [PubMed: 12697630]
- Hasler G, Drevets WC, Manji HK, Charney DS. Discovering endophenotypes for major depression. *Neuropsychopharmacology* 2004;29(10):1765–1781. [PubMed: 15213704]
- Hazlett EA, New AS, Newmark R, Haznedar MM, Lo JN, Speiser LJ, et al. Reduced anterior and posterior cingulate gray matter in borderline personality disorder. *Biological Psychiatry* 2005;58(8):614–623. [PubMed: 15993861]
- Heinz A, Goldman D, Jones DW, Palmour R, Hommer D, Gorey JG, et al. Genotype influences in vivo dopamine transporter availability in human striatum. *Neuropsychopharmacology* 2000;22(2):133–139. [PubMed: 10649826]
- Herrmann MJ, Huter T, Muller F, Muhlberger A, Pauli P, Reif A, et al. Additive effects of Serotonin Transporter and Tryptophan Hydroxylase-2 Gene variation on emotional processing. *Cereb Cortex* 2007;17(5):1160–1163. [PubMed: 16801378]
- Hong J, Shu-Leong H, Tao X, Lap-Ping Y. Distribution of catechol-O-methyltransferase expression in human central nervous system. *Neuroreport* 1998;9(12):2861–2864. [PubMed: 9760135]
- Hoptman MJ, Ardekani BA, Butler PD, Nierenberg J, Javitt DC, Lim KO. DTI and impulsivity in schizophrenia: A first voxelwise correlational analysis. *Neuroreport* 2004;15(16):2467–2470. [PubMed: 15538176]
- Horn NR, Dolan M, Elliott R, Deakin JF, Woodruff PW. Response inhibition and impulsivity: An fMRI study. *Neuropsychologia* 2003;41(14):1959–1966. [PubMed: 14572528]
- Hur YM, Bouchard TJ Jr. The genetic correlation between impulsivity and sensation seeking traits. *Behavior Genetics* 1997;27(5):455–463. [PubMed: 9336082]
- Ioannidis JP. Common genetic variants for breast cancer: 32 largely refuted candidates and larger prospects. *Journal of the National Cancer Institute* 2006;98:1350–1353. [PubMed: 17018776]

- Jacobsen LK, Staley JK, Zoghbi SS, Seibyl JP, Kosten TR, Innis RB, et al. Prediction of dopamine transporter binding availability by genotype: A preliminary report. *American Journal of Psychiatry* 2000;157(10):1700–1703. [PubMed: 11007732]
- Jones G, Zammit S, Norton N, Hamshire ML, Jones SJ, Milham C, et al. Aggressive behaviour in patients with schizophrenia is associated with catechol-O-methyltransferase genotype. *British Journal of Psychiatry* 2001;179:351–355. [PubMed: 11581117]
- Jovanovic V, Guan HC, Van Tol HH. Comparative pharmacological and functional analysis of the human dopamine D4.2 and D4.10 receptor variants. *Pharmacogenetics* 1999;9(5):561–568. [PubMed: 10591536]
- Kaufman JN, Ross TJ, Stein EA, Garavan H. Cingulate hypoactivity in cocaine users during a GO-NOGO task as revealed by event-related functional magnetic resonance imaging. *J Neurosci* 2003;23(21):7839–7843. [PubMed: 12944513]
- Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry* 2005;62(6):593–602. [PubMed: 15939837]
- Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry* 2005;62(6):617–627. [PubMed: 15939839]
- Kirley A, Lowe N, Hawi Z, Mullins C, Daly G, Waldman I, et al. Association of the 480 bp DAT1 allele with methylphenidate response in a sample of Irish children with ADHD. *American Journal of Medical Genetics* 2003;121B(1):50–54. [PubMed: 12898575]
- Konishi S, Nakajima K, Uchida I, Kikyo H, Kameyama M, Miyashita Y. Common inhibitory mechanism in human inferior prefrontal cortex revealed by event-related functional MRI. *Brain* 1999;122(Pt 5):981–991. [PubMed: 10355680]
- Konishi S, Nakajima K, Uchida I, Sekihara K, Miyashita Y. No-go dominant brain activity in human inferior prefrontal cortex revealed by functional magnetic resonance imaging. *European Journal of Neuroscience* 1998;10(3):1209–1213. [PubMed: 9753190]
- Lesch KP, Bengel D, Heils A, Sabol SZ, Greenberg BD, Petri S, et al. Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science* 1996;274(5292):1527–1531. [PubMed: 8929413]
- Lewis DA, Melchitzky DS, Sesack SR, Whitehead RE, Auh S, Sampson A. Dopamine transporter immunoreactivity in monkey cerebral cortex: Regional, laminar, and ultrastructural localization. *Journal of Comparative Neurology* 2001;432(1):119–136. [PubMed: 11241381]
- Li D, Sham PC, Owen MJ, He L. Meta-analysis shows significant association between dopamine system genes and attention deficit hyperactivity disorder (ADHD). *Human Molecular Genetics* 2006;15(14):2276–2284. [PubMed: 16774975]
- Liddle PF, Kiehl KA, Smith AM. Event-related fMRI study of response inhibition. *Human Brain Mapping* 2001;12(2):100–109. [PubMed: 11169874]
- Lijffijt M, Kenemans JL, Verbaten MN, van Engeland H. A meta-analytic review of stopping performance in attention-deficit/hyperactivity disorder: Deficient inhibitory motor control? *Journal of Abnormal Psychology* 2005;114(2):216–222. [PubMed: 15869352]
- Links PS, Heslegrave R, van Reekum R. Impulsivity: Core aspect of borderline personality disorder. *Journal of Personality Disorders* 1999;13(1):1–9. [PubMed: 10228922]
- Liston C, Watts R, Tottenham N, Davidson MC, Niogi S, Ulug AM, et al. Frontostriatal microstructure modulates efficient recruitment of cognitive control. *Cerebral Cortex* 2006;16(4):553–560. [PubMed: 16033925]
- Logan GD, Schachar RJ, Tannock R. Impulsivity and inhibitory control. *Psychological Science* 1997;8:60–64.
- Loo SK, Specter E, Smolen A, Hopfer C, Teale PD, Reite ML. Functional effects of the DAT1 polymorphism on EEG measures in ADHD. *Journal of the American Academy of Child and Adolescent Psychiatry* 2003;42(8):986–993. [PubMed: 12874502]
- Lotta T, Vidgren J, Tilgmann C, Ullmanen I, Melen K, Julkunen I, et al. Kinetics of human soluble and membrane-bound catechol O-methyl-transferase: A revised mechanism and description of the thermolabile variant of the enzyme. *Biochemistry* 1995;34(13):4202–4210. [PubMed: 7703232]

- MacQueen GM, Hajek T, Alda M. The phenotypes of bipolar disorder: Relevance for genetic investigations. *Molecular Psychiatry* 2005;10(9):811–826. [PubMed: 15970930]
- Malhotra AK, Kestler LJ, Mazzanti C, Bates JA, Goldberg T, Goldman D. A functional polymorphism in the COMT gene and performance on a test of prefrontal cognition. *American Journal of Psychiatry* 2002;159:652–654. [PubMed: 11925305]
- Mannisto PT, Kaakkola S. Catechol-O-methyltransferase (COMT): biochemistry, molecular biology, pharmacology, and clinical efficacy of the new selective COMT inhibitors. *Pharmacological Reviews* 1999;51(4):593–628. [PubMed: 10581325]
- Manuck, SB.; Flory, JD.; Muldoon, MF.; Ferrell, RE.; Loewenstein, G.; Read, D., et al. A neurobiology of intertemporal choice. New York: Russell Sage Foundation; 2003.
- Martinez D, Gelernter J, Abi-Dargham A, van Dyck CH, Kegeles L, Innis RB, et al. The variable number of tandem repeats polymorphism of the dopamine transporter gene is not associated with significant change in dopamine transporter phenotype in humans. *Neuropsychopharmacology* 2001;24(5):553–560. [PubMed: 11282255]
- Mattay VS, Goldberg TE, Fera F, Hariri AR, Tessitore A, Egan MF, et al. Catechol O-methyltransferase val158-met genotype and individual variation in the brain response to amphetamine. *Proceedings of the National Academy of Sciences USA* 2003;100(10):6186–6191.
- Meador-Woodruff JH, Damask SP, Wang J, Haroutunian V, Davis KL, Watson SJ. Dopamine receptor mRNA expression in human striatum and neocortex. *Neuropsychopharmacology* 1996;15(1):17–29. [PubMed: 8797188]
- Meyer-Lindenberg A, Kohn PD, Kolachana B, Kippenhan S, McInerney-Leo A, Nussbaum R, et al. Midbrain dopamine and prefrontal function in humans: Interaction and modulation by COMT genotype. *Nature Neuroscience* 2005;8(5):594–596.
- Michelhaugh SK, Fiskerstrand C, Lovejoy E, Bannon MJ, Quinn JP. The dopamine transporter gene (SLC6A3) variable number of tandem repeats domain enhances transcription in dopamine neurons. *Journal of Neurochemistry* 2001;79(5):1033–1038. [PubMed: 11739616]
- Mill J, Asherson P, Browes C, D'Souza U, Craig I. Expression of the dopamine transporter gene is regulated by the 3' UTR VNTR: Evidence from brain and lymphocytes using quantitative RT-PCR. *American Journal of Medical Genetics* 2002;114(8):975–979. [PubMed: 12457396]
- Mill J, Asherson P, Craig I, D'Souza UM. Transient expression analysis of allelic variants of a VNTR in the dopamine transporter gene (DAT1). *BMC Genetics* 2005;6(1):3. [PubMed: 15683546]
- Miller E, Stephen J, Tudway J. Assessing the component structure of four self-report measures of impulsivity. *Personality & Individual Differences* 2004;37:349–358.
- Mink JW. The basal ganglia: Focused selection and inhibition of competing motor programs. *Progress in Neurobiology* 1996;50(4):381–425. [PubMed: 9004351]
- Moeller FG, Barratt ES, Dougherty DM, Schmitz JM, Swann AC. Psychiatric aspects of impulsivity. *American Journal of Psychiatry* 2001;158(11):1783–1793. [PubMed: 11691682]
- Moeller FG, Hasan KM, Steinberg JL, Kramer LA, Dougherty DM, Santos RM, et al. Reduced anterior corpus callosum white matter integrity is related to increased impulsivity and reduced discriminability in cocaine-dependent subjects: Diffusion tensor imaging. *Neuropsychopharmacology* 2005;30(3):610–617. [PubMed: 15637640]
- Mulcrone J, Kerwin RW. The regional pattern of D4 gene expression in human brain. *Neuroscience Letters* 1997;234(2–3):147–150. [PubMed: 9364519]
- Munafo MR, Yalcin B, Willis-Owen SA, Flint J. Association of the Dopamine D4 Receptor (DRD4) gene and approach-related personality traits: Meta-analysis and new data. *Biological Psychiatry*. in press.
- Nambu A, Tokuno H, Takada M. Functional significance of the cortico-subthalamo-pallidal “hyperdirect” pathway. *Neuroscience Research* 2002;43(2):111–117. [PubMed: 12067746]
- New AS, Siever LJ. Biochemical endophenotypes in personality disorders. *Methods in Molecular Medicine* 2003;77:199–213. [PubMed: 12298370]
- Newman JP, Wallace JF, Schmitt WA, Arnett PA. Behavioral inhibition system functioning in anxious, impulsive and psychopathic individuals. *Personality and Individual Differences* 1997;23:583–592.

- Nigg JT. On inhibition/disinhibition in developmental psychopathology: Views from cognitive and personality psychology and a working inhibition taxonomy. *Psychological Bulletin* 2000;126(2): 220–246. [PubMed: 10748641]
- Nolan KA, Bilder RM, Lachman HM, Volavka J. Catechol O-methyltransferase Val158Met polymorphism in schizophrenia: Differential effects of Val and Met alleles on cognitive stability and flexibility. *American Journal of Psychiatry* 2004;161(2):359–361. [PubMed: 14754787]
- Papassotiropoulos A, Stephan DA, Huentelman MJ, Hoerndli FJ, Craig DW, Pearson JV, et al. Common Kibra alleles are associated with human memory performance. *Science* 2006;314:475–478. [PubMed: 17053149]
- Patton JH, Stanford MS, Barratt ES. Factor structure of the Barratt impulsiveness scale. *Journal of Clinical Psychology* 1995;51(6):768–774. [PubMed: 8778124]
- Pedersen NL, Plomin R, McClearn GE, Friberg L. Neuroticism, extraversion, and related traits in adult twins reared apart and reared together. *Journal of Personality and Social Psychology* 1988;55(6): 950–957. [PubMed: 3216289]
- Plomin R, Colledge E. Genetics and psychology: Beyond heritability. *European Psychologist* 2001;6(4):229–240.
- Puumala S. Changes in activities of dopamine and serotonin systems in the frontal cortex underlie poor choice accuracy and impulsivity of rats in an attention task. *Neuroscience* 1998;83(2):489–499. [PubMed: 9460757]
- Reif A, Lesch KP. Toward a molecular architecture of personality. 1 *Behavioral Brain Research* 2003;39(1–2):1–20.
- Reynolds B, Ortengren A, Richards JB, de Wit H. Dimensions of impulsive behavior: Personality and behavioral measures. *Personality and Individual Differences* 2006;40(2):305–315.
- Rieger M, Gauggel S, Burmeister K. Inhibition of ongoing responses following frontal, nonfrontal, and basal ganglia lesions. *Neuropsychology* 2003;17(2):272–282. [PubMed: 12803433]
- Robbins TW. Chemistry of the mind: neurochemical modulation of prefrontal cortical function. *Journal of Comparative Neurology* 2005;493(1):140–146. [PubMed: 16254988]
- Roman T, Schmitz M, Polanczyk G, Eizirik M, Rohde LA, Hutz MH. Attention-deficit hyperactivity disorder: a study of association with both the dopamine transporter gene and the dopamine D4 receptor gene. *American Journal of Medical Genetics* 2001;105(5):471–478. [PubMed: 11449401]
- Rosa A, Peralta V, Cuesta MJ, Zarzuela A, Serrano F, Martinez-Larrea A, et al. New evidence of association between COMT gene and prefrontal neurocognitive function in healthy individuals from sibling pairs discordant for psychosis. *American Journal of Psychiatry* 2004;161(6):1110–1112. [PubMed: 15169701]
- Rubia EA. Mapping motor inhibition: Conjunctive brain activations across difference versions of Go/No-Go and Stop Tasks. *Neuroimage* 2001;13:250–261. [PubMed: 11162266]
- Rubia K, Overmeyer S, Taylor E, Brammer M, Williams SC, Simmons A, et al. Functional frontalisation with age: Mapping neurodevelopmental trajectories with fMRI. *Neuroscience and Biobehavioral Reviews* 2000;24(1):13–19. [PubMed: 10654655]
- Rubia K, Smith AB, Brammer MJ, Taylor E. Right inferior prefrontal cortex mediates response inhibition while mesial prefrontal cortex is responsible for error detection. *Neuroimage* 2003;20(1):351–358. [PubMed: 14527595]
- Rubinstein M, Phillips TJ, Bunzow JR, Falzone TL, Dziewczapolski G, Zhang G, et al. Mice lacking dopamine D4 receptors are supersensitive to ethanol, cocaine, and methamphetamine. *Cell* 1997;90(6):991–1001. [PubMed: 9323127]
- Rujescu D, Giegling I, Gietl A, Hartmann AM, Moller HJ. A functional single nucleotide polymorphism (V158M) in the COMT gene is associated with aggressive personality traits. *Biological Psychiatry* 2003;54(1):34–39. [PubMed: 12842306]
- Savitz JB, Ramesar RS. Genetic variants implicated in personality: A review of the more promising candidates. *American Journal of Medical Genetics* 2004;131B(1):20–32. [PubMed: 15389772]
- Schachar R, Logan G. Are hyperactive children deficient in attentional capacity? *Journal of Abnormal Child Psychology* 1990;18(5):493–513. [PubMed: 2266222]

- Schachar RJ, Crosbie J, Barr CL, Ornstein TJ, Kennedy J, Malone M, et al. Inhibition of motor responses in siblings concordant and discordant for Attention Deficit Hyperactivity Disorder. *American Journal of Psychiatry* 2005;162(6):1076–1082. [PubMed: 15930055]
- Schachar RJ, Tannock R, Logan G. Inhibitory control, impulsiveness, and attention deficit hyperactivity disorder. *Clinical Psychology Review* 1993;13(8):721–739.
- Schinka JA, Letsch EA, Crawford FC. DRD4 and novelty seeking: Results of meta-analyses. *American Journal of Medical Genetics* 2002;114(6):643–648. [PubMed: 12210280]
- Schmidt CA, Fallon AE, Coccaro EF. Assessment of behavioral and cognitive impulsivity: Development and validation of the Lifetime History of Impulsive Behaviors Interview. *Psychiatry Research* 2004;126(2):107–121. [PubMed: 15123390]
- Schott BH, Seidenbecher CI, Fenker DB, Lauer CJ, Bunzeck N, Bernstein HG, et al. The dopaminergic midbrain participates in human episodic memory formation: Evidence from genetic imaging. *Journal of Neuroscience* 2006;26(5):1407–1417. [PubMed: 16452664]
- Schulz KP, Fan J, Tang CY, Newcorn JH, Buchsbaum MS, Cheung AM, et al. Response inhibition in adolescents diagnosed with attention deficit hyperactivity disorder during childhood: An event-related fMRI study. *American Journal of Psychiatry* 2004;161(9):1650–1657. [PubMed: 15337656]
- Seroczynski AD, Bergeman CS, Coccaro EF. Etiology of the impulsivity/aggression relationship: Genes or environment? *Psychiatry Research* 1999;86(1):41–57. [PubMed: 10359481]
- Sesack SR, Hawrylak VA, Matus C, Guido MA, Levey AI. Dopamine axon varicosities in the prelimbic division of the rat prefrontal cortex exhibit sparse immunoreactivity for the dopamine transporter. *Journal of Neuroscience* 1998;18(7):2697–2708. [PubMed: 9502827]
- Sher KJ, Bartholow BD, Wood MD. Personality and substance use disorders: A prospective study. *Journal of Consulting and Clinical Psychology* 2000;68(5):818–829. [PubMed: 11068968]
- Silverman JM, Pinkham L, Horvath TB, Coccaro EF, Klar H, Schear S, et al. Affective and impulsive personality disorder traits in the relatives of patients with borderline personality disorder. *American Journal of Psychiatry* 1991;148(10):1378–1385. [PubMed: 1897620]
- Smolka MN, Schumann G, Wrase J, Grusser SM, Flor H, Mann K, et al. Catechol-O-methyltransferase val158met genotype affects processing of emotional stimuli in the amygdala and prefrontal cortex. *Journal of Neuroscience* 2005;25(4):836–842. [PubMed: 15673663]
- Soloff PH, Meltzer CC, Becker C, Greer PJ, Kelly TM, Constantine D. Impulsivity and prefrontal hypometabolism in borderline personality disorder. *Psychiatry Research* 2003;123(3):153–163. [PubMed: 12928103]
- Soloff PH, Meltzer CC, Greer PJ, Constantine D, Kelly TM. A fenfluramine-activated FDG-PET study of borderline personality disorder. *Biological Psychiatry* 2000;47(6):540–547. [PubMed: 10715360]
- Strous RD, Nolan KA, Lapidus R, Diaz L, Saito T, Lachman HM. Aggressive behavior in schizophrenia is associated with the low enzyme activity COMT polymorphism: A replication study. *American Journal of Medical Genetics B: Neuropsychiatric Genetics* 2003;120(1):29–34.
- Swann AC, Dougherty DM, Pazzaglia PJ, Pham M, Moeller FG. Impulsivity: A link between bipolar disorder and substance abuse. *Bipolar Disorders* 2004;6(3):204–212. [PubMed: 15117399]
- Swann AC, Pazzaglia P, Nicholls A, Dougherty DM, Moeller FG. Impulsivity and phase of illness in bipolar disorder. *Journal of Affective Disorders* 2003;73(1–2):105–111. [PubMed: 12507743]
- Swanson JM, Flodman P, Kennedy J, Spence MA, Moyzis R, Schuck S, et al. Dopamine genes and ADHD. *Neuroscience and Biobehavioral Reviews* 2000;24(1):21–25. [PubMed: 10654656]
- Szobot C, Roman T, Cunha R, Acton P, Hutz M, Rohde LA. Brain perfusion and dopaminergic genes in boys with attention-deficit/hyperactivity disorder. *American Journal of Medical Genetics B: Neuropsychiatric Genetics* 2005;132(1):53–58.
- Tamm L, Menon V, Reiss AL. Maturation of brain function associated with response inhibition. *Journal of the American Academy of Child & Adolescent Psychiatry* 2002;41(10):1231–1238. [PubMed: 12364845]
- Tamm L, Menon V, Ringel J, Reiss AL. Event-related fMRI evidence of frontotemporal involvement in aberrant response inhibition and task switching in attention-deficit/hyperactivity disorder.

- Journal of the American Academy of Child & Adolescent Psychiatry 2004;43(11):1430–1440. [PubMed: 15502603]
- Tellegen, A. Brief manual for the Multidimensional Personality Questionnaire. Minneapolis: University of Minnesota Press; 1982.
- Valdes IH, Steinberg JL, Narayana PA, Kramer LA, Dougherty DM, Swann AC, et al. Impulsivity and BOLD fMRI activation in MDMA users and healthy control subjects. *Psychiatry Research* 2006;147(2–3):239–242. [PubMed: 16890410]
- van Dyck CH, Malison RT, Jacobsen LK, Seibyl JP, Staley JK, Laruelle M, et al. Increased Dopamine Transporter availability associated with the 9-Repeat Allele of the SLC6A3 Gene. *Journal of Nuclear Medicine* 2005;46(5):745–751. [PubMed: 15872345]
- VanNess SH, Owens MJ, Kilts CD. The variable number of tandem repeats element in DAT1 regulates in vitro dopamine transporter density. *BMC Genetics* 2005;6:55. [PubMed: 16309561]
- Volkow ND, Wang GJ, Fowler JS, Ding YS. Imaging the effects of methylphenidate on brain dopamine: New model on its therapeutic actions for attention-deficit/hyperactivity disorder. *Biological Psychiatry* 2005;57(11):1410–1415. [PubMed: 15950015]
- Vollm B, Richardson P, Stirling J, Elliott R, Dolan M, Chaudhry I, et al. Neurobiological substrates of antisocial and borderline personality disorder: preliminary results of a functional fMRI study. *Criminal Behaviour and Mental Health* 2004;14(1):39–54. [PubMed: 14654860]
- Waldman ID, Rowe DC, Abramowitz A, Kozel ST, Mohr JH, Sherman SL, et al. Association and linkage of the dopamine transporter gene and attention-deficit hyperactivity disorder in children: Heterogeneity owing to diagnostic subtype and severity. *American Journal of Human Genetics* 1998;63(6):1767–1776. [PubMed: 9837830]
- Weaver IC, Cervoni N, Champagne FA, D'Alessio AC, Sharma S, Seckl JR, et al. Epigenetic programming by maternal behavior. *Nature Neuroscience* 2004;7(8):847–854. Epub 2004 Jun 2027.
- Wessel J, Zapala MA, Schork NJ. Accommodating pathway information in expression quantitative trait locus analysis. *Genomics* 2007;90:132–142. [PubMed: 17493783]
- Whiteside SP, Lynam DR. The Five Factor Model and impulsivity: Using a structural model of personality to understand impulsivity. *Personality and Individual Differences* 2001;30(4):669–689.
- Whiteside SP, Lynam DR. Understanding the role of impulsivity and externalizing psychopathology in alcohol abuse: Application of the UPPS Impulsive Behavior Scale. *Experimental and Clinical Psychopharmacology* 2003;11(3):210–217. [PubMed: 12940500]
- Winstanley CA, Eagle DM, Robbins TW. Behavioral models of impulsivity in relation to ADHD: Translation between clinical and preclinical studies. *Clinical Psychology Review* 2006;26(4):379–395. [PubMed: 16504359]
- Winstanley CA, Theobald DE, Cardinal RN, Robbins TW. Contrasting roles of basolateral amygdala and orbitofrontal cortex in impulsive choice. *Journal of Neuroscience* 2004;24(20):4718–4722. [PubMed: 15152031]
- Winstanley CA, Theobald DE, Dalley JW, Cardinal RN, Robbins TW. Double dissociation between serotonergic and dopaminergic modulation of medial prefrontal and orbitofrontal cortex during a test of impulsive choice. *Cerebral Cortex* 2006;16(1):106–114. [PubMed: 15829733]
- Yen S, Shea MT, Sanislow CA, Grilo CM, Skodol AE, Gunderson JG, et al. Borderline personality disorder criteria associated with prospectively observed suicidal behavior. *American Journal of Psychiatry* 2004;161(7):1296–1298. [PubMed: 15229066]
- Zapala MA, Schork NJ. Multivariate regression analysis of distance matrices for testing associations between gene expression patterns and related variables. *Proceedings of the National Academy of Sciences, USA* 2006;103:19430–19435.