Genetic Factors Modulating the Response to Stimulant Drugs in Humans

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Abstract Individuals vary in their responses to stimulant drugs, and several lines of evidence suggest that the basis for this variation is at least partially genetic in origin. Association studies have examined the effects of polymorphisms in specific genes on acute and chronic responses to stimulant drugs. Several of these genetic polymorphisms are also associated with other psychiatric dimensions and disorders. This chapter examines the evidence for genetic associations between the genes that have been most carefully examined for their influence on the response to stimulant drugs.

Keywords Stimulants · Inter-individual variation · Drug response · Candidate gene · Genetic association · Genetic polymorphism

Contents

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Curr Topics Behav Neurosci
DOI: 10.1007/7854_2011_187

1 Introduction

A growing body of evidence suggests that genetic variation underlies inter-individual variability in the response to drugs, including stimulant drugs. Stimulant drugs produce behavioral and subjective effects that include increased vigilance and attention, and feelings of energy and euphoria (Lamb and Henningfield 1994; Martin et al. 1971; Sevak et al. 2009). However, there is substantial individual variation in these responses (Brown et al. 1978; de Wit et al. 1986; Holdstock and de Wit 2001), and some of this variation has been shown to be heritable (Crabbe et al. 1983; Nurnberger et al. 1982). Genetic variation in the response to stimulants may contribute to the potential to develop drug abuse (Fergusson et al. 2003; Haertzen et al. 1983), and may also be relevant for therapeutic uses of stimulants.

In this review we will focus on five prototypic stimulant drugs that have been studied most intensively: amphetamine, methamphetamine, methylphenidate, cocaine, and bupropion. All of these drugs inhibit the reuptake of dopamine, norepinephrine, and serotonin, thereby increasing the levels of these monoamine neurotransmitters in the synaptic cleft. These drugs differ in their potency, synaptic actions, degree of reuptake blockade, pharmacokinetic properties and their specificity and actions on other neurotransmitter systems. Some of the drugs (e.g., amphetamine) also cause the reuptake transporters to work in reverse, leading to non-impulse dependent release of neurotransmitters. Additionally, some stimulants inhibit the monoamine oxidase enzymes (MAO-A and MAO-B), thus preventing the degradation of monoamines (Seiden et al. 1993). Finally, there is evidence that stimulant drugs disrupt the function of the vesicular monoamine transporter type 2 (VMAT2), which transports monoamine neurotransmitters from stores in the cytoplasm to synaptic vesicles (Uhl et al. 2000). Genetic variation in these genes as well as in their up- or down-stream neighbors make them likely candidates to contribute to inter-individual variation in the response to stimulant drugs.

We will focus on two types of genetic studies in this review, twin and association studies. Twin studies estimate the heritability of traits, whereas association studies examine specific polymorphisms in relation to a phenotype. We will not include family-based linkage studies of drug abuse or animal studies on genetic determinants of stimulant effects, both which have been carefully reviewed elsewhere (Phillips et al. 2008; Kreek et al. 2005; Uhl 2006). We will also not discuss the stimulant caffeine, because it acts by distinct neurochemical mechanisms and because we have recently reviewed the genetics of caffeine elsewhere

(Yang et al. 2010). We will discuss two types of association studies: candidate gene studies and genome-wide association studies. Candidate gene studies draw on prior pharmacological knowledge of how stimulants affect the brain to select 'candidate' genes that are likely to be the source of genetic differences. In these studies, polymorphisms within or near the candidate gene are tested to see if they are statistically associated with relevant phenotypes. Phenotypes might include measures of acute response, patterns of drug use or therapeutic response in patients, or clinical diagnoses of drug dependence or abuse. Other studies use a genome-wide association (GWAS) approach to examine many or most of the common polymorphisms in the genome; these studies do not depend on prior hypotheses about which genes might be important.

In all of the studies discussed: twin, candidate gene association, and genome-wide association, we will address two types of genetic polymorphisms: single nucleotide polymorphisms (SNPs) and variable number tandem repeats (VNTRs). SNPs are sites at which a single nucleotide differs among individuals within a population. SNPs can either occur in the coding sequence of a gene and thus alter amino acid sequence (termed non-synonymous) or, more commonly, they may be outside the coding sequence and alter gene regulation. In both cases, a SNP may alter a biological function itself (coding or gene expression), or be linked to another polymorphism that is functionally significant. VNTRs are polymorphisms in which a variable number of short repetitive sequences (tandem repeats) are present at a given locus; as with SNPs they may have direct functional consequences or may be linked to some other functionally significant polymorphism.

We will attempt to synthesize genetic studies of acute, sub-chronic, and chronic administration of stimulant drugs in this review. First, we will discuss overall heritability of stimulant drug-related phenotypes based on twin studies. Next, we will discuss candidate gene and genome-wide association studies that implicate specific genes in modulating responses. Last, we will highlight the key conclusions and identify future directions for study.

2 Twin Studies of Stimulant Drug Phenotypes

Two early twin studies provide strong evidence for the heritability of acute responses to stimulant drugs (Nurnberger et al. 1982; Crabbe et al. 1983). Twin studies estimate heritability by comparing the concordance rate between monozygotic twins, who share a familial environment and all genes, to dizygotic twins, who share the same environment but only half of their genes. Typically, biometric modeling is used to explain variability due to genetic or environmental effects. Heritability estimates can range from 0 (no variation contributed by genetic sources) to 1 (all variation contributed by genetic sources). Nurnberger et al. (1982) administered *d*-amphetamine intravenously (0.3 mg/kg) to 13 pairs of monozygotic twins and 3 pairs of dizygotic twins and measured physiological and subjective effects of the drug. Responses to the drug in monozygotic twins were

highly concordant for a subjective measure of excitation, as well as growth hormone and prolactin release, suggesting a large genetic component underlying these traits. Consistent with this, Crabbe et al. (1983) administered 10 mg *d*-amphetamine sulfate to six pairs of monozygotic twins and found less variation in physiological and subjective responses within pairs than between pairs, which suggests these traits are heritable.

More recently, twin studies have examined the heritability of lifetime stimulant use, dependence, and abuse using liability threshold model fitting (Kendler et al. 1999, 2003, 2000). In their most recent study, Kendler et al. (2005) estimated heritability for lifetime use of stimulant drugs excluding cocaine to be 0.42, and heritability for lifetime use of cocaine to be 0.70. They also found substantial familial environmental contributions to the variance (i.e., 0.20) for lifetime use of other stimulant drugs, but not for cocaine use. Specific environmental effects, which are distinguished from shared familial environmental effects, were estimated at 0.38 for other stimulant use and 0.30 for cocaine use. In addition to this study, a study of male twin war veterans yielded similar results (Tsuang et al. 1996). That study estimated the heritability of stimulant abuse (including cocaine abuse) based on *DSM-III-R* criteria (American Psychiatric Association 1987) to be 0.44, but with 0.49 of the variance contributed by specific environmental effects, and no contribution of familial environment in the best-fit model. Although this was a slightly higher estimate of heritability than by Kendler et al. (2005), both studies suggest a fairly large contribution of genetic factors to heritability of stimulant drug abuse.

3 Association Studies

Genetic determinants of response to acute, sub-chronic, and chronic administration of stimulant drugs have been examined using association studies in several different populations. We have conducted a series of association studies of the acute responses to amphetamine (e.g., Lott et al. 2005; Dlugos et al. 2010). In this double-blind, placebo-controlled study, healthy young adults (ranging from $n = 99$ to $n = 152$, depending on the analysis) received oral doses of *d*-amphetamine (10 and 20 mg) and placebo over the course of three different sessions. Measures of subjective, cardiovascular and behavioral responses were obtained at regular intervals. The subjective measures included the Profile of Mood States (POMS; McNair et al. 1971), Drug Effects Questionnaire (DEQ; Johanson and Uhlenhuth 1980) and Addiction Resource Center Inventory (ARCI; Martin et al. 1971). In children diagnosed with ADHD, methylphenidate is typically administered daily or several times a day in a therapeutic context, and the outcome measure is usually therapeutic response as measured by the Clinical Global Impression-Severity scale (CGI-S; Guy 1976) and the ADHD Rating Scale-IV (ARS; DuPaul et al. 1998). In both studies of healthy adults and studies of children diagnosed with ADHD, neuroimaging has also been used to examine variation

in brain responses to acute amphetamine and methylphenidate administration. These include techniques such as single photon emission computerized tomography (SPECT), functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) to assess the binding of specific ligands (Warwick 2004; Cabeza and Nyberg 2000).

Sub-chronic (i.e., <8 weeks) or chronic (>8 weeks) stimulant responses have been measured in patients receiving methylphenidate for ADHD or bupropion for smoking cessation. Other studies have examined the phenotypes of dependence, abuse, and consequences of abuse such as drug-induced psychosis. Although it is not possible to accurately determine the doses in studies of active drug abusers, it is safe to assume that they involve higher doses than are found in acute or therapeutic studies. In addition, drug users commonly self-administer drugs via injection, inhalation (smoking) or intranasal routes, where the acute laboratory studies and therapeutic studies most commonly involve oral administration.

Studies of responses to stimulant drugs have focused on a small number of candidate genes that have also been associated with other psychiatric phenotypes. Many of these genes are the direct targets of stimulant drugs or other known psychoactive agents. Table 1 lists these studies and they are also discussed in the following sections. Genes that have been less well studied both in relation to stimulant drugs and other psychiatric phenotypes are only briefly mentioned in the "Exploratory Studies" section and summarized in Table 2.

4 Monoamine Transporters

SLC6A3

The dopamine transporter (*SLC6A3*; *DAT1; DAT)* is a direct target of stimulant drugs and thus a logical candidate gene for studies or stimulant sensitivity. Polymorphisms in this gene have been extensively studied in relation to stimulant drug responses and susceptibility to ADHD (reviewed in Banaschewski et al. 2010). In particular, attention has focused on a 40 bp variable nucleotide tandem repeat (VNTR) located in the 3′-untranslated region (UTR) of the gene, with a range of 3–11 repeats. The two most common alleles have either 9, or more commonly, 10 repeats (Vandenbergh et al. 1992). The 10-repeat allele has been associated with both higher and lower expression of the dopamine transporter in the brain (Fuke et al. 2001; van de Giessen et al. 2009; Van Dyck et al. 2005). The evidence described below suggests that polymorphisms in *SLC6A3* play an important role in responses to stimulant drugs, although the direction of the association is inconsistent across studies.

In analyses examining associations of amphetamine response with the *SLC6A3* 3′-UTR VNTR, we found that individuals homozygous for the 9-repeat allele showed decreased responses to amphetamine at 20 mg, compared to heterozygous (9/10) and homozygous (10/10) individuals (Lott et al. 2005). Using a larger

Table 1 Candidate genes associated with responses to stimulant drugs and associated SNPs

Strong Candidate Genes Gene name	Locus symbol	Administration type	Study	Phenotype	Number	Ethnicity	Group	Dose	Associated polymorphisms	Notes
Dopamine transporter	*SLC6A3; DAT1; DAT*	Chronic	Bellgrove et al. (2005)	Methylphenidate therapeutic response	43	Irish	Children with ADHD	–	3′-UTR VNTR	10-repeat allele associated with better treatment response
		Acute	Cheon et al. (2005)	Methylphenidate therapeutic response	11	Korean	Children with ADHD	Up to 0.7 mg/kg/day	3′-UTR VNTR	10/10 associated with poor treatment response
		Chronic	Gelernter et al. (1994)	Cocaine-induced paranoia	58	Caucasian, African–American	Cocaine users	–	3′-UTR VNTR	9-repeat allele associated with increased risk
		Acute	Hamidovic et al. (2010a)	Amphetamine subjective response	152	Caucasian	Healthy volunteers	Placebo, 10 mg, 20 mg	rs460000	C/C increased Euphoria and Stimulation at 10 and 20 mg
		Acute	Kooij et al. (2008)	Methylphenidate therapeutic response	42	–	Adults with ADHD	Placebo, 0.5 mg/kg/day by week 1, 0.75 mg/kg/day by week 2, up to 1.0 mg/kg/day by week 3	3′-UTR VNTR	10/10 associated with poor response

(continued)

Table 1 (continued)

Strong Candidate Genes Gene name	Locus symbol	Administration type	Study	Phenotype	Number	Ethnicity	Group	Dose	Associated polymorphisms	Notes
		Sub-chronic	Joober et al. (2007)	Methylphenidate therapeutic response	159	–	Children with ADHD	Placebo, 0.5 mg/kg/day	3′-UTR VNTR	9/9 associated with poor treatment response
		Acute	Lott et al. (2005)	Amphetamine subjective response	101	67 Caucasian, 20 African–American, 12 Asian, 2 unknown	Healthy volunteers	Placebo, 10 mg, 20 mg	3′-UTR VNTR	9/9 associated with poor response at 20 mg
		Acute	Purper-Ouakil et al. (2008)	Methylphenidate therapeutic response	141	132 Caucasian; 8 Other	Children with ADHD	10–60 mg/day	3′-UTR VNTR	10/10 associated with poor treatment response
		Acute	Rohde et al. (2003)	Methylphenidate therapeutic response	8	–	Children with ADHD (male)	0.35–0.7 mg/kg	3′-UTR VNTR	10/10 associated with higher cerebral blood flow
		Sub-chronic	Stein et al. (2005)	Methylphenidate therapeutic response	47	–	Children with ADHD	Placebo, 18 mg, 36 mg, 54 mg	3′-UTR VNTR	9/9 associated with poor response
		Chronic	Ujike et al. (2003)	Methamphetamine-induced psychosis	124 cases 160 controls	Japanese	Methamphetamine dependence/psychosis patients	–	3′-UTR VNTR	Possession of allele with 8 = 9 or fewer repeats associated with prolonged psychosis

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Table 1 (continued)

Strong Candidate Genes Gene name	Locus symbol	Administration type	Study	Phenotype	Number	Ethnicity	Group	Dose	Associated polymorphisms	Notes
Serotonin transporter	*SLC6A4; 5-HTT*	Acute	Lott et al. (2006)	Amphetamine subjective response	101	67 Caucasian, 20 African–American, 12 Asian, 2 unknown	Healthy volunteers	Placebo, 10 mg, 20 mg	5-HTTLPR & Intron 2 VNTR haplotype	L/L and 12/12 genotype combination associated with weak subjective response
		Chronic	Ezaki et al. (2008)	Methamphetamine-induced psychosis	166 cases 197 controls	Japanese	Methamphetamine-induced psychosis patients	–	5-HTTLPR	Frequency of S allele higher in patients with prolonged psychosis
		Sub-chronic	Thakur et al. (2010)	Methylphenidate therapeutic response	157	–	Children with ADHD	Placebo, 0.5 mg/kg/day	5-HTTLPR triallelic	L_G/L_G associated with best treatment response

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Table 1 (continued)

Strong Candidate Genes Gene name	Locus symbol	Administration type	Study	Phenotype	Number	Ethnicity	Group	Dose	Associated polymorphisms	Notes
Norepinephrine transporter	*SLC6A2; NET*	Acute	Dlugos et al. (2007)	Amphetamine subjective response	99	65 Caucasian, 20 African–American, 12 Asian, 2 unknown	Healthy volunteers	Placebo, 10 mg, 20 mg	rs36017, rs47958 rs36017-rs2270935-rs47958 haplotype	rs36017 C/C, G–C–C haplotype associated with increased positive mood; rs47958 C/C associated with increased elation
		Acute	Dlugos et al. (2009a)	Amphetamine subjective response	159	Caucasian	Healthy volunteers	Placebo, 10 mg, 20 mg	rs36017, rs1861647 rs36017-rs10521329-rs3785155 haplotype	rs36017 C/C, rs1861647 A/A associated with increased elation and vigor; C–C–G haplotype associated with increased vigor

(continued)

Table 1 (continued)

Strong Candidate Genes Gene name	Locus symbol	Administration type	Study	Phenotype	Number	Ethnicity	Group	Dose	Associated polymorphisms	Notes
Dopamine D2 receptor	*DRD2*	Sub-chronic	David et al. (2007)	Bupropion therapeutic response	722	Caucasian	Smokers	Placebo, 150 mg/day first 3 days, then 300 mg/day	Taq1A (rs1800497; T/C)	A2/A2 3x more likely to abstain from smoking after treatment; no effect for A1/A1, A1/A2
		Acute	Hamidovic et al. (2009)	Impulsivity amphetamine response	93	Caucasian	Healthy volunteers	Placebo, 10 mg, 20 mg	rs12364283	rs12364283 A/G, G/G increased reaction time at 10 mg
		Chronic	Ujike et al. (2009)	Methamphetamine-induced psychosis	202 cases 243 controls	Japanese	Methamphetamine dependence patients	–	Taq1A (rs1800497; T/C) *DRD2*-141 Ins/Del	A2/A2, A1/A2 associated with prolonged methamphetamine-induced psychosis Del/Del, Ins/Del associated with rapid onset

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Table 1 (continued)

Strong Candidate Genes Gene name	Locus symbol	Administration type	Study	Phenotype	Number	Ethnicity	Group	Dose	Associated polymorphisms	Notes
Dopamine D4 receptor	*DRD4*	Acute	Lee et al. (unpublished data)	Amphetamine subjective response	100	66 Caucasian, 20 African–American, 12 Asian, 2 unknown	Healthy volunteers	Placebo, 10 mg, 20 mg	Exon III VNTR	Single 7-repeat allele associated with increased elation, friendliness, heart rate, decreased dysphoria and anxiety at 10 and 20 mg
		Chronic	Chen et al. (2004a)	Methamphetamine abuse	416 cases 435 controls	Taiwanese	Methamphetamine abusers	–	Exon III VNTR	Higher frequency of 6-repeat allele in cases
		Chronic	Hamarman et al. (2004)	Methylphenidate therapeutic response	45	–	Children with ADHD	–	Exon III VNTR	Subjects with 7-repeat allele require higher doses of methylphenidate
		Chronic	Li et al. (2004)	Methamphetamine abuse	416 cases 435 controls	Taiwanese	Methamphetamine abusers	–	Promoter VNTR + exon III VNTR haplotype	Higher frequency of 7-repeat allele in cases
μ-opioid receptor	*OPRM1*	Acute	Dlugos et al. (2010)	Amphetamine subjective response	162	Caucasian	Healthy volunteers	Placebo, 10 mg, 20 mg	rs510769, rs2281617	rs510769 G/G A/G, rs2281617 C/C associated increased euphoria and energy at 10 mg
		Chronic	Ide et al. (2004)	Methamphetaime psychosis	138 cases 213 controls	Japanese	Methamphetamine dependence/ psychosis patients	–	A118G (rs1799971)	G/G associated with psychosis within 3 years of first use
		Chronic	Ide et al. (2006)	Methamphetamine abuse/ psychosis	128 cases 232 controls	Japanese	Methamphetamine dependence/ psychosis patients	–	IVS2 + G691C (rs2075572)	G/G associated with methamphetamine abuse and psychosis

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Table 1 (continued)

Strong Candidate Genes Gene name	Locus symbol	Administration type	Study	Phenotype	Number	Ethnicity	Group	Dose	Associated polymorphisms	Notes
Adenosine A_{2A} receptor	*ADORA2A*	Acute	Hohoff et al. (2005)	Amphetamine subjective response	99	65 Caucasian, 20 African–American, 12 Asian, 2 unknown	Healthy volunteers	Placebo, 10 mg, 20 mg	1976C/T (rs5751876) 2592C/T ins (rs3032740)	rs5751876 & rs3032740 associated with increased anxiety at 10 & 20 mg
Catechol O-methyl transferase	*COMT*	Acute	Hamidovic et al. (2010b)	Cognitive response to amphetamine	161	Caucasian	Healthy volunteers	Placebo, 10 mg, 20 mg	val158met (rs4680; G/A)	Val/Val, Val/Met performance improves with amphetamine; Met/Met no change
		Chronic	Li et al. (2004)	Methamphetamine abuse	416 cases 435 controls	Taiwanese	Methamphetamine abusers	–	val158met (rs4680; G/A)	Val allele frequency higher in abusers
		Chronic	Lohoff et al. (2008)	Cocaine dependence	330	African–American	Cocaine dependence patients	–	val158met (rs4680; G/A)	Met allele frequency higher in abusers
		Acute	Mattay et al. (2003)	Amphetamine brain response	123	–	Healthy volunteers	Placebo, 0.25 mg/kg of body weight	val158met (rs4680; G/A)	Val/Val performance improves with amphetamine; Met/Met perform worse with amphetamine
		Chronic	Suzuki et al. (2006)	Methamphetamine-induced psychosis	143 cases 200 controls	Japanese	Methamphetamine-induced psychosis patients	–	val158met (rs4680; G/A)	Met allele frequency higher in cases with spontaneous relapse

(continued)

Table 1 (continued)

Strong Candidate Genes Gene name	Locus symbol	Administration type	Study	Phenotype	Number	Ethnicity	Group	Dose	Associated polymorphisms	Notes
Monoamine oxidase A	*MAOA*	Chronic	Nakamura et al. (2009)	Methamphetamine-induced psychosis	118 cases 199 controls	Japanese	Methamphetamine-induced psychosis patients	–	MAOA-u VNTR	4-repeat allele associated with prolonged (vs. transient) psychosis in males
Dopamine beta-hydroxylase	*DBH*	Chronic	Cubells et al. (2000)	Cocaine-induced paranoia	45	European–American	Cocaine dependence/paranoia patients	–	Del-A haplotype	Frequency higher in cases
	DBH	Acute	Kalayasiri et al. (2007)	Cocaine-induced paranoia	31	Euopean–American, African–American	Cocaine dependence patients	0, 8, 16, and 32 mg/70 kg body weight	−1021C→T (rs1611115)	T/T genotype associated with increased risk for paranoia
Tryptophan hydroxylase 2	*TPH2*	Acute	Manor et al. (2008)	Methylphenidate therapeutic response	498	–	Children with ADHD	0.3–1 mg/kg	rs1386488-rs2220330-rs1386495-rs1386494-rs6582720-rs1386492-rs4760814-rs1386497 haplotype	C–G–C–A– A–G–A–C "Yang" haplotype associated with better response to methylphenidate
Fatty acid amide hydrolase	*FAAH*	Acute	Dlugos et al. (2009b)	Amphetamine subjective response	72	Caucasian	Healthy volunteers	Placebo, 10 mg, 20 mg	rs3766246, rs2295633; rs3766246-rs324420-rs2295633 haplotypes	C/C genotype for both SNPs associated with increased arousal and decreased fatigue at 10 mg

(continued)

Table 1 (continued)

Strong Candidate Genes Gene name	Locus symbol	Administration type	Study	Phenotype	Number	Ethnicity	Group	Dose	Associated polymorphisms	Notes
Brain-derived neurotrophic factor	*BDNF*	Acute	Flanagin et al. (2006)	Amphetamine subjective response	100	66 Caucasian, 20 African–American, 12 Asian, 2 unknown	Healthy volunteers	Placebo, 10 mg, 20 mg	val66met (rs6265; G/A)	Val/Val associated with higher response at 10 mg
Casein kinase 1 epsilon	*CSNK1E*	Acute	Veenstra-VanderWeele et al. (2006)	Amphetamine subjective response	101	67 Caucasian, 20 African–American, 12 Asian, 2 unknown	Healthy volunteers	Placebo, 10 mg, 20 mg	rs135745 (C/G)	C/C associated with greater sensitivity at 10 mg
Adenosine A_{2A} receptor	*ADORA2A*	Acute	Hohoff et al. (2005)	Amphetamine subjective response	99	65 Caucasian, 20 African–American, 12 Asian, 2 unknown	Healthy volunteers	Placebo, 10 mg, 20 mg	1976C/T (rs5751876) 2592C/T ins (rs3032740)	rs5751876 & rs3032740 associated with increased anxiety at 10 & 20 mg
Cytochrome P450 2D6	*CPY2D6*	Chronic	Otani et al. (2008)	Methamphetamine dependence	202 cases 337 controls	Japanese	Methamphetamine dependence patients	–	CYP2D6*10, CYP2D6 *14	*10 and *14 alleles at lower frequency in cases

(continued)

Table 1 (continued)

Strong Candidate Genes Gene name	Locus symbol	Administration type	Study	Phenotype	Number	Ethnicity	Group	Dose	Associated polymorphisms	Notes
Glycoprotein endo-alpha-1, 2-mannosidase	*MANEA*	Chronic	Farrer et al. (2009)	Cocaine-induced paranoia	1,612 individuals for family-based; 1,921 unrelated subjects for case–control replication	Euopean–American, African–American	Cocaine dependence/ paranoia patients	–	rs9387522 and rs9387522 in all populations; rs6937479 from family based	rs9387522 A allele associated with cocaine induce paranoia in all populations

Genes are discussed in the following order: transporters, receptors, biosynthetic enzymes, and miscellaneous

Table 2 Association studies of less commonly studies genes with responses to stimulant drugs

Possible candidate genes Gene name	Locus symbol	Administration type	Study	Phenotype	Number	Ethnicity	Group	Dose	Associated polymorphisms	Notes
Glutathione S-transferase Mu 1	*GSTM1*	Chronic	Nakatome et al. (2009)	Methamphetamine abuse	100 cases 150 controls	Japanese	Methamphetamine users	–	Null allele	Null/null associated with abuse in females
Glutathione S-transferase theta-1	*GSTT1*	Chronic	Nakatome et al. (2009)	Methamphetamine abuse	100 cases 150 controls	Japanese	Methamphetamine users	–	Null allele	Higher liablity to abuse in combination with *GSTM1* null genotype
Glutathione S-transferase P	*GSTP1*	Chronic	Hashimoto et al. (2004)	Methamphetamine abuse/ psychosis	189 cases 199 controls	Japanese	Methamphetamine-induced psychosis patients	–	Ile105Val (rs947894; A/G)	G/G, A/G associated with abuse and psychosis
Prodynorphin	*PDYN*	Chronic	Nomura et al. (2006)	Methamphetamine dependence	143 cases 206 controls	Japanese	Methamphetamine dependence patients	–	Promoter VNTR	3- and 4-repeat alleles associated with increased risk
Prokineticin receptor 2	*PROKR2*	Chronic	Kishi et al. (2010)	Methamphetamine dependence	199 cases 337 controls	Japanese	Methamphetamine dependence patients	–	rs3746684, rs6085086, rs3746684 and rs17721321-rs6085086-rs3746684-rs3746682-rs4815787 haplotype	Individual SNPs and G–G–G–C–G haplotype associated with dependence
Solute carrier family 22 member 3	*SLC22A3*	Chronic	Aoyama et al. (2006)	Methamphetamine dependence	213 cases 443 controls	Japanese	Methamphetamine-induced psychosis patients	–	rs509707-rs4709426 haplotype	Associated with polysubstance abuse
Glycine transporter	*GLYT1*	Chronic	Morita et al. (2008)	Methamphetamine dependence/ psychosis	204 cases 210 controls	Japanese	Methamphetamine users	–	IVS3 + 411C > T (rs2486001); rs2486001-rs2248829 haplotype	T/T and C/T genotypes associated with methamphetamine use disorder
Alpha-synuclein	*SNCA*	Chronic	Kobayashi et al. (2004)	Methamphetamine dependence/ psychosis	170 cases 161 controls	Japanese	Methamphetamine dependence/ psychosis patients	–	rs1372520, rs3756063, rs3756059	Association only in females
Gamma-aminobutyric acid receptor subunit gamma-2	*GABRG2*	Chronic	Nishiyama et al. (2005)	Methamphetamine use disorder	178 cases 288 controls	Japanese	Methamphetamine use disorder patients	–	315 C > T-1128-99C > A haplotypes	Increased susceptibility to methamphetamine use disorder

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Table 2 (continued)

Possible candidate genes Gene name	Locus symbol	Administration type	Study	Phenotype	Number	Ethnicity	Group	Dose	Associated polymorphisms	Notes
Dystrobrevin-binding protein 1	*DTNBP1*	Chronic	Kishimoto et al. (2008a)	Methamphetamine-induced psychosis	197 cases 243 controls	Japanese	Methamphetamine-induced psychosis patients	–	rs3213207, rs2619538; rs2619539-rs3213207-rs2619538 haplotype	rs3213207 G allele, rs3213207 T allele at higher frequency in cases
Frizzled-3	*FZD3*	Chronic	Kishimoto et al. (2008b)	Methamphetamine-induced psychosis	288 cases 240 controls	Japanese	Methamphetamine-induced psychosis patients	–	rs2241802-rs2323019-rs352203-rs880481 haplotype	G–A–T–G and A–G–C–A haplotypes negative risk factors for psychosis
D-amino acid oxidase activator	*G72*	Chronic	Kotaka et al. (2009)	Methamphetamine-induced psychosis	209 cases 291 controls	Japanese	Methamphetamine-induced psychosis patients	–	rs778293 (A/G); rs3916965-rs2391191 (G-A) and rs947267-rs1421292 (T–T)	rs778293 G/G associated with Methamphetamine-induced psychosis
Glutamate receptor, metabotropic 2	*GRM2*	Chronic	Tsunoka et al. (2010)	Methamphetamine-induced psychosis	196 cases 802 controls	Japanese	Methamphetamine dependence/ psychosis patients	–	rs3821829–rs12487957–rs4687771 haplotype	C–C–A, C–T–T haplotypes associated with Methamphetamine-induced psychosis
NAD(P)H dehydrogenase, quinone 2	*NQO2*	Chronic	Ohgake et al. (2005)	Methamphetamine-induced psychosis	191 cases 207 controls	Japanese	Methamphetamine dependence/ psychosis patients	–	Promoter indel	Del/Del associated with prolonged psychosis
PRKCA-binding protein	*PICK1*	Chronic	Matsuzawa et al. (2007)	Methamphetamine-induced psychosis	208 cases 218 controls	Japanese	Methamphetamine abusers	–	rs713729, rs2076369	rs713729 methamphetamine abuse; rs713729 and rs2076369 spontaneous relapse of psychosis

(continued)

Table 2 (continued)

Possible candidate genes Gene name	Locus symbol	Administration type	Study	Phenotype	Number	Ethnicity	Group	Dose	Associated polymorphisms	Notes
Superoxide dismutase 2	*SOD2*	Chronic	Nakamura et al. (2006)	Methamphetamine-induced psychosis	116 cases 189 controls	Japanese	Methamphetamine-induced psychosis patients	–	Ala/Val exon 2 (rs4880)	Ala/Val associated with prolonged psychosis; Ala allele at higher frequency
Carboxylesterase 1	*CES1*	Sub-chronic	Nemoda et al. (2009)	Methylphenidate therapeutic response	122	Hungarian	Children with ADHD	10–30 mg (by body weight) twice daily (0.22 to 0.95 mg/kg/day)	Gly143Glu (rs71647871)	Glu/Glu, Glu/Gly associated with better treatment response

The genes here are not as well studied in relation to the phenotypes discussed in this review; they are therefore denoted 'possible candidate genes'. The associations described have primarily been performed for methamphetamine use-related phenotypes

sample from the same study, Hamidovic et al. (2010a) tested 4 additional SNPs near the 5′ end of *SLC6A3* that were not in linkage disequilibrium with the 3′-UTR VNTR, and found a significant association between the rs460000 C/C genotype and increased scores on the ARCI Euphoria and Stimulation composite scales after 10 and 20 mg amphetamine administration, when compared to A/A and A/C individuals. Interestingly, this SNP is in perfect linkage disequilibrium with rs463379, a SNP that has been associated with increased risk of ADHD (Friedel et al. 2007), which suggests that variants underlying acute response to amphetamine may also underlie disease risk. Overall, these results suggest that both the 3′-UTR VNTR and SNPs in *SLC6A3* affect acute response to amphetamine.

The 3′-UTR VNTR polymorphism has also been studied in relation to acute responses to methylphenidate in children that have been diagnosed with ADHD. In a pilot study, eight children received acute doses of methylphenidate before SPECT neuroimaging (Rohde et al. 2003). Children homozygous for the 10-repeat allele exhibited greater cerebral blood flow, which may reflect higher transporter activity, in the frontal and basal ganglia brain areas in response to methylphenidate than children who were not homozygous for the 10-repeat allele.

S*LC6A3* has also been the analyzed for its role in modulating therapeutic responses to sub-chronic (8 weeks) administration of methylphenidate. Similar to the Rohde et al. (2003) study discussed above, Cheon et al. (2005) used SPECT to measure dopamine transporter density in several brain regions (basal ganglia, right basal ganglia, and occipital cortex) of 11 children diagnosed with ADHD treated with varying doses of methylphenidate, and measured both clinical response and transporter density. Children with at least one copy of the 9-repeat allele ($n = 4$) showed a better therapeutic response to methylphenidate than 10/10 individuals (4 out of 4 responders versus 2 out of 7 responders in the 10/10 group), and significantly lower dopamine transporter density than 10/10 individuals. This suggests that 10/10 individuals may require more methylphenidate due to increased dopamine transporter density within the brain.

The association between the 3′-UTR VNTR and response to sub-chronic methylphenidate has also been examined in a larger cohort of children and adolescents with ADHD (Purper-Ouakil et al. 2008). Individuals received placebo and varying doses of methylphenidate until no further clinical improvement or limiting side effects occurred (mean dose 31.19 mg/day). They were phenotyped with the ARS, the Stroop test (Stroop 1935), the Trail Making Test (Reitan 1958), and the Continuous Performance Test (Rosvold et al. 1956). Subjects that were homozygotes for the 10-repeat allele had significantly lower treatment responses. However, the final methylphenidate doses reached did not differ across genotype group. These results suggest that the maximal response to methylphenidate may be lower in 10/10 homozygotes and cannot be overcome with larger doses. Similarly, another study of adults with ADHD found that the 10/10 genotype was associated with non-statistically significant lower therapeutic response to 3 weeks of treatment with methylphenidate as assessed by the CGI-S and ARS (Kooij et al. 2008).

Although the results discussed above suggest that the 10-repeat allele may be associated with poor treatment response to methylphenidate, other studies have

reported that therapeutic responses are poorer in patients with the 9-repeat allele. In a double-blind study, Stein et al. (2005) found that children with the 9/9 genotype showed poor response to methylphenidate treatment as measured by ARS and CGI-S when they received higher (36 and 54 mg) but not lower (placebo or 18 mg) doses of methylphenidate. These results suggest that individuals with at least one copy of the 10-repeat allele responded better when given higher doses of methylphenidate. Joober et al. (2007) also performed a double-blind, placebo-controlled fixed-dose study, in which children diagnosed with ADHD were treated with methylphenidate for two weeks (0.5 mg/kg/day) and the effect of 3′-UTR VNTR was assessed. Similar to the results of Stein et al. (2005), children with the 9/10 and 10/10 genotypes showed significant improvement in ADHD symptoms following treatment as measured by the CGI-Parents scale when compared to 9/9 children; no difference was observed between the 9/10 and 10/10 groups. The 10-repeat allele was also associated with better treatment response to methylphenidate following longer term treatment in children diagnosed with ADHD using family-based association testing (Bellgrove et al. 2005). In addition to these studies, three studies have observed no association between the 3′-UTR VNTR polymorphism and methylphenidate response (da Silva et al. 2010; McGough et al. 2006; Roman et al. 2001). Therefore, the reported effects of the 3′-UTR VNTR on treatment response are contradictory and warrant further investigation.

The dopamine transporter has also been studied in relation to stimulant drug abuse. In these studies, the exact doses of drug are unknown and presumed to be high relative to laboratory or clinical studies. A case–control study examined methamphetamine dependence and drug-induced psychosis in a cohort of individuals with methamphetamine use disorder and psychosis (Ujike et al. 2003). No associations were found between the four polymorphisms tested and methamphetamine dependence or psychosis. However, when the patients with prolonged psychosis were analyzed separately from those with transient psychosis, there was a strong association indicating that individuals with nine or fewer repeat alleles of the 3′-UTR VNTR had prolonged psychosis. The 9-repeat allele was also marginally associated with increased risk of cocaine-induced paranoia in cocaine dependent subjects when the frequency of the 9-repeat allele was compared in individuals with and without psychosis (Gelernter et al. 1994). The reasons for these associations are unclear, given the lack of information about the doses that were ingested. The findings may indicate that drug users with the 9-repeat allele of the 3′-UTR VNTR polymorphism are more sensitive to stimulant-induced psychotic phenotypes, or, alternatively, they may have ingested higher doses of the drug to achieve their desired effect, thus increasing their risk for psychosis.

Lastly, the effects of an additional polymorphism in *SLC6A3* and cocaine-related behaviors have also been examined. Guindalini et al. (2006) examined the *SLC6A3* Intron 8 VNTR (Int8 VNTR), which consists of either five or six repeats and is in moderate to low linkage disequilibrium with the 3′-UTR VNTR (Asherson et al. 2007), and found that the 6-repeat allele was associated with cocaine abuse in a case-control study of cocaine abusers. When the 5- and 6-repeat alleles were cloned into expression vectors and transfected into a dopaminergic

cell line, the 6-repeat allele showed increased *SLC6A3* expression following treatment with various stimuli (including cocaine), while the 5-repeat allele showed no change in expression. This study, along with Hamidovic et al. (2010a), suggests that polymorphisms other than the 3′-UTR VNTR may also contribute to responses to stimulant drugs.

SLC6A4

The serotonin transporter (*SLC6A4; 5-HTT*) is another direct target of stimulant drugs, and has been associated with numerous psychiatric phenotypes including obsessive-compulsive disorder (Bloch et al. 2008), autism (Huang and Santangelo 2008), and depression (Brown and Harris 2008; Kato and Serretti 2008; Risch et al. 2009). The 5-hydroxytryptamine transporter gene-linked polymorphic region (5-HTTLPR), which may be the most widely studied polymorphism in all of psychiatric genetics, has at least two common alleles: a short (S) 14-repeat and a long (L) 16-repeat allele (Nakamura et al. 2000; Rausch 2005). The 5-HTTLPR S allele has been associated with reduced gene expression (Hranilovic et al. 2004) and increased risk for psychiatric phenotypes like depression. The long allele has been further refined into two alleles (L_A and L_G) distinguished by an A→G polymorphism within the first repeat; the L_G allele is reported to have equivalent expression to the S allele (Hu et al. 2006). In additional to 5-HTTLPR, a VNTR in Intron 2 of *SLC6A4* has also been described, which consists of either a 10- or 12-repeat allele. The 12-repeat allele has been associated with increased gene expression (Hranilovic et al. 2004).

We have examined both of the *SLC6A4* polymorphisms mentioned above to determine whether they influence acute responses to amphetamine using our sample of healthy volunteers described in the previous section (Lott et al. 2006). When these two polymorphisms were analyzed separately, individuals homozygous for the 10-repeat allele of the Intron 2 VNTR showed a stronger euphoric response. When the polymorphisms were analyzed jointly, no significant association was observed, but trends in the predicted directions were observed—subjects homozygous for the low expressing alleles (S and 10-repeat) had the strongest responses to amphetamine (for the POMS Anxiety, DEQ Feel Drug, and ARCI Euphoria scales). These data identify a non-significant trend towards decreased expression of the serotonin transporter being associated with increased responses to stimulants.

The serotonin transporter has also been investigated for its role in sub-chronic methylphenidate treatment response in children diagnosed with ADHD (Thakur et al. 2010). In a 2 week trial, children received placebo and methylphenidate at varying doses. Subjects homozygous for the higher expressing L_A had the worst response to placebo but the best response to methylphenidate, heterozygotes were intermediate, and individuals homozygous for the L_S and L_G alleles exhibited the best response to placebo but deterioration with methylphenidate treatment as measured by the CGI-Parents subscale. Thus, lower expression of *SLC6A4* is associated with stronger euphoric, but weaker therapeutic responses to stimulant drugs.

The 5-HTTLPR polymorphism has also been associated with adverse responses in methamphetamine abusers. The 5-HTTLPR polymorphism was tested for association with prolonged methamphetamine-induced psychosis in a case-control study of methamphetamine abusers (Ezaki et al. 2008), utilizing the sample and methods described in the previous section (Ujike et al. 2003). *SLC6A4* was chosen as a candidate gene for this phenotype based on previous neuroimaging findings from the same group showing that methamphetamine abusers had lower serotonin transporter density than non-abusers (Sekine et al. 2006). The lower expressing S allele was significantly associated with methamphetamine psychosis, and in particular with prolonged psychosis. Thus, the S allele (and the L_G allele in the one instance where it was differentiated from the L_A allele) appears to be associated with more intense acute and chronic responses to various different stimulants. Furthermore, it appears that the lower expressing alleles of both the dopamine and the serotonin transporters are associated with greater propensity to methamphetamine-induced psychosis.

SLC6A2

The norepinephrine transporter (*SLC6A2; NET*) is a third direct target of stimulant drugs (Sulzer et al. 2005). Variants in *SLC6A2* have been associated with psychiatric phenotypes including depression (Haenisch et al. 2009; Min et al. 2009), antidepressant response (Min et al. 2009), and panic disorder (Lee et al. 2005). Using our sample of healthy adults (Dlugos et al. 2007) we found that rs36017 (C/C genotype) was associated with increased positive mood, as measured by a composite scale composed of "elation" minus "depression", following amphetamine administration (20 mg), while rs47958 (C/C genotype) was associated with increased elation. Haplotypes containing these SNPs (rs36017-rs10521329-rs3785155, G–C–C and C–C–A) were also associated with increased positive mood. A follow-up study with a larger number of individuals replicated the association between rs36017 and the POMS Elation scale, as well as with the POMS Vigor scale, and identified a new association between the A/A genotype at rs1861647 and these scales (Dlugos et al. 2009a). In addition, a different haplotype than those mentioned above, which was also constructed from rs36017, rs10521329, and rs3785155 (C–C–G), was associated with increased vigor following amphetamine administration. In sum, these studies suggest that multiple variants in *SLC6A2* influence responses to acute amphetamine administration.

5 Neurotransmitter Receptors

DRD2

The dopamine D2 receptor (*DRD2*) has been studied in relation to a variety of psychiatric traits, including schizophrenia (Allen et al. 2008), smoking cessation (David and Munafò 2008) and impulsivity (Eisenberg et al. 2007; Rodriguez-

Jimenez et al. 2006). In particular, the historically named *Taq*1A SNP (also known as rs1800497) has been widely studied. Historical nomenclature describes the A1 (T) and the A2 alleles (C). This polymorphism was initially described as being located in *DRD2*, but is now recognized to be located in a neighboring gene, *ANNK1* (Neville et al. 2004). However, this polymorphism appears to influence the expression of the *DRD2* gene and thereby alter *DRD2* function. In a study of *DRD2* polymorphisms and gene expression in postmortem human brain tissues, rs1800497 was not associated with *DRD2* expression, but the G allele of another SNP in *DRD2*, rs12364283, was found to be associated with enhanced expression (Zhang et al. 2007).

Variation in *DRD2* has been investigated in relation to amphetamine-induced impulsive behavior. Amphetamine increases behavioral inhibition, and the degree of this inhibition varies across individuals (de Wit et al. 2000). We examined the role of several SNP polymorphisms in *DRD2* and the effects of amphetamine on behavioral inhibition utilizing the sample of healthy human subjects that is described above. Individuals were phenotyped with the stop task (Logan et al. 1984), a measure of behavioral inhibition, and genotyped at 12 SNPs in *DRD2* (but not the Taq1A polymorphism). One SNP, rs12364283, was significantly associated with better performance on the stop task following 10 mg amphetamine administration in the G/G and A/G groups. This G allele of this SNP, as discussed earlier, is associated with increased *DRD2* expression (Zhang et al. 2007); increased *DRD2* expression may be related to better task performance (Cropley et al. 2006).

Variation in *DRD2* has been investigated for its effect on bupropion treatment response (David et al. 2007). David et al. (2007) found that smokers with the A2/A2 genotype at *Taq1A* who received bupropion (150 mg/day for the first 3 days, then 300 mg/day) were three times more likely to abstain from smoking at the end of the trial compared to A2/A2 subjects receiving placebo. This difference was not observed for the other genotypic groups.

Finally, *DRD2* has also been investigated for association with methamphetamine dependence and methamphetamine-induced psychosis. Šerý et al. (2001) found no association between polymorphisms in *DRD2* and methamphetamine dependence. Ujike et al. (2009) tested 3 SNPs in *DRD2*: 141C insertion/deletion (rs1799732; -/C), Ser311Cys (rs1801028; C/G) and *Taq1A*, and found that the *Taq1A* A2 (C) allele, which was associated with good response to bupropion for smoking cessation, was associated with prolonged methamphetamine psychosis (A2/A2, A1/A2 genotypes). Additionally, they found that the Del/Del and Ins/Del genotypes of 141C insertion allele (rs1799732) were associated with rapid onset of psychotic symptoms (within 3 years of initial abuse). Therefore, the *Taq1A* polymorphism, along with other polymorphisms in *DRD2*, may influence development of stimulant-induced psychosis as well as drug dependence.

DRD4

The dopamine D4 receptor (*DRD4*) has been associated with smoking behavior (Laucht et al. 2008), schizophrenia (Shi et al. 2008), novelty seeking (Munafò

et al. 2008) and impulsivity (Munafò et al. 2008), as well as responses to stimulant drugs. The exon III VNTR polymorphism of *DRD4* is the most commonly studied. This polymorphism has 8 alleles, varying from 2 to 8 and 10 repeats (Lichter et al. 1993). The 7-repeat allele has been associated with ADHD in some studies (Brookes et al. 2006; Faraone et al. 2001; Li et al. 2006), but not in all (Johansson et al. 2008). Because of its association with ADHD, the 7-repeat allele has been the focus of most studies involving stimulant drug responses.

We have investigated the effect of the exon III VNTR polymorphism and acute subjective and physiological responses to amphetamine in our sample (Lee et al. 2006), and found that individuals with a single copy of the 7-repeat allele experienced more rewarding effects of the drug, with increased scores on the POMS Friendliness, POMS Elation, and heart rate scales at 20 mg and on the DEQ More scale at 10 mg and decreased scores on the ARCI Dysphoria and POMS Anxiety scales at 20 mg when compared to individuals lacking the 7-repeat allele. Therefore, the 7-repeat allele may modulate subjective and physiological responses to acute amphetamine administration.

Variation in *DRD4* has also been tested for association with therapeutic response following sub-chronic methylphenidate administration in children diagnosed with ADHD (Hamarman et al. 2004). Children with the 7-repeat allele of the exon III polymorphism required higher doses of methylphenidate (about two times more) to achieve the same therapeutic response over a 2-week period as measured by the CGI-S. Cheon et al. (2006) undertook a similar study and found that the 4-repeat allele was associated with the best treatment responses based on the ARS and the Kiddie-Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version (K-SADS-PL; Kaufman et al. 1997). Only one individual in that study had the 7-repeat allele, and therefore the previous finding could not be examined; conversely, the 4-repeat allele was not analyzed in the Hamarman et al. (2004) study. Therefore, these two sub-chronic studies found associations with different alleles of the exon III polymorphism and different measures of methylphenidate response.

DRD4 has also been investigated for association with methamphetamine dependence. Chen et al. (2004a) reported a higher frequency of the 7-repeat exon III VNTR allele in methamphetamine abusers as compared to controls, although the association did not reach statistical significance. A subsequent study utilizing the same population examined another VNTR polymorphism in the promoter region of *DRD4*, with a long (240 bp) and short allele (120 bp) (Li et al. 2004). Although no association between methamphetamine abuse and the promoter VNTR was found, when the promoter and exon III VNTR polymorphisms were analyzed as a haplotype, there was a significant association of the 7-repeat allele exon III VNTR and short promoter VNTR allele with methamphetamine abuse. Therefore, the 7-repeat allele of the exon III VNTR increases the dose of methylphenidate needed for therapeutic effects and may also increase the risk for development of methamphetamine abuse.

OPRM1

The μ-opioid receptor, *OPRM1,* has been investigated for a role in the subjective response to acute amphetamine. Stimulation of μ-opioid receptors by endogenous beta-endorphins in the ventral tegmental area increases dopamine release (Spanagel et al. 1992); therefore, variation in *OPRM1* may influence dopamine release and therefore response to stimulants. A commonly studied coding polymorphism within *OPRM1*, Asp40Asn (A118G; rs1799971; A/G), was first described by Bergen et al. (1997) and has been associated with numerous phenotypes, including heroin addiction (Drakenberg et al. 2006), schizophrenia (Šerý et al. 2010), and naltrexone treatment response (Oroszi et al. 2009). This SNP has also been shown to alter binding of beta-endorphin to the receptor (Bond et al. 1998). We examined associations between several SNPs (including rs1799971) and the acute responses to amphetamine on the ARCI Euphoria, Energy and Stimulation scales (Dlugos et al. 2010), and found that two polymorphisms (rs510769 G/G, A/G and rs2281617 C/C) were associated with increased euphoric responses to amphetamine at 10 mg; rs510769 is in strong linkage disequilibrium with rs1799971. The results indicate that variation in *OPRM1* may be related to variation in positive, euphoric responses to amphetamine.

Rs1799971 has been associated with the duration of methamphetamine-induced psychosis in a case-control study of individuals with methamphetamine dependence/psychosis; G/G individuals were more likely to become psychotic within 3 years of their first methamphetamine intake (Ide et al. 2004). In a more recent study using the same population, the previous association did not replicate, but the G/G genotype of an additional SNP in *OPRM1* (IVS2 + G691C; rs2075572; G/C) was associated with both methamphetamine dependence and psychosis (Ide et al. 2006). These results suggest the possibility that additional variants underlie chronic methamphetamine response, although rs1799971 has been the main target of the literature in investigating acute and chronic stimulant responses.

ADORA2A

The adenosine A_{2A} receptor (*ADORA2A*) is a major target of caffeine (Daly and Fredholm 1998) and forms a heterodimer with the dopamine D_2 receptor (Fuxe et al. 2005). We investigated the effect of *ADORA2A* polymorphisms on the anxiety response to amphetamine in healthy human subjects (Hohoff et al. 2005) and found that two polymorphisms (rs5751876; T/T and rs3032740; T_{ins}/T_{ins}), were associated with increased anxiety at the 10 and 20 mg doses.

6 Biosynthetic Enzymes

COMT

Various enzymes involved in the synthesis and breakdown of neurotransmitters have also been analyzed for associations with acute response to stimulant drugs.

One major candidate gene is catechol *O*-methyl transferase (*COMT*). This gene codes for an enzyme that preferentially metabolizes dopamine in the prefrontal cortex, rather than in the limbic and striatal brain regions, where the dopamine transporter is more important for clearance (Chen et al. 2004b). *COMT* contains a *val→met* coding polymorphism (val^{158}*-met;* rs4680; G(*val*)/A(*met*)) that has been associated with a variety of phenotypes including personality, cognition, risk for psychiatric disorders (Tunbridge et al. 2006), and pain sensitivity (Andersen and Skorpen 2009). The *met* allele has been associated with 3–4 times lower activity compared to the *val* allele (Lachman et al. 1996).

Polymorphisms in *COMT* have been associated with acute amphetamine response. In a landmark study (Mattay et al. 2003), healthy volunteers completed the Wisconsin Card Sorting Test (WCST; Heaton et al. 1993) after placebo or amphetamine, and underwent fMRI while performing the N-back working memory task (Kirchner 1958). Amphetamine administration reduced prefrontal cortical activity at all working memory loads when compared to placebo in individuals homozygous for the *val* allele. This was interpreted as a more efficient physiological response; this reduction was associated with improved reaction time and no decrease in accuracy on the task. Conversely, amphetamine increased prefrontal cortical activity in the most difficult part of the working memory task in *met* homozygotes. This was interpreted as a reduction in efficiency, because increased prefrontal cortical activity was associated with increased reaction time and decreased accuracy. The authors proposed that amphetamine increased dopamine levels above an optimum level in *met/met* individuals and thus negatively impacted cortical function. In contrast, in *val/val* individuals, amphetamine increased the lower pre-drug dopamine levels so that they were closer to optimal and thus enhanced function. The WCST also showed genotypic effects, with *val/val* subjects improving following amphetamine administration and *met/met* individuals performing worse. Taken together, the results of this study suggest that an optimum level of dopamine in the prefrontal cortex is necessary for efficient prefrontal cortex function, and that this efficiency is in part mediated by val^{158}*-met* genotype. Another study (Hamidovic et al. 2010b) evaluated the effect of val^{158}*-met* on a processing speed task (Digit Symbol Substitution Test; Wechsler 1958) and a reaction time test measuring attention lapses (Deviation from the Mode; de Wit 2009) and reported that when compared to placebo, amphetamine improved DSST performance in *val* homozygotes and heterozygotes, but not in *met* homozygotes. However, *val* homozygotes and heterozygotes exhibited more lapses in attention under placebo conditions, suggesting that the drug improved a preexisting deficit in one genotypic group. Taken together, these findings suggest that individuals with the *met* allele are less sensitive to the cognitive enhancing effects of stimulant drugs.

COMT has been investigated for association with chronic stimulant drug phenotypes. The *val* allele has been associated with polysubstance abuse (Vandenbergh et al. 1997), and in a later case–control study, Li et al. (2004) found that the *val/val* genotype was significantly associated methamphetamine abuse. In addition, Lohoff et al. (2008) found that cocaine-dependent individuals possessed the lower activity *met* allele more often than controls, suggesting that this polymorphism may

play some role in dependence. These results differ from the Vandenbergh et al. (1997) and Li et al. (2004) studies described above; Lohoff et al. suggest their finding of the *met* allele association may also be due to linkage disequilibrium or population stratification.

MAOA

Monoamine oxidase A (*MAOA*) degrades monoamine neurotransmitters and has been most commonly associated with aggressive behavior (reviewed in Grigorenko et al. 2010). *MAOA* contains a 30 bp VNTR polymorphism within its promoter that consists of 3, 3.5, 4, or 5 repeats (MAOA-u VNTR); the 3.5 and 4 repeat alleles are transcribed more efficiently than the 3- or 5-repeat alleles (Sabol et al. 1998). Nakamura et al. (2009) tested the MAOA-u VNTR polymorphism for association with methamphetamine-induced psychosis, and found that in males, the 4-repeat allele was associated with having prolonged psychosis rather than transient; this effect was not seen in females.

DBH

Dopamine beta-hydroxylase (*DBH*) catalyzes the conversion of dopamine to norepinephrine (Kaufman and Friedman 1965) and has been associated with ADHD (reviewed in Banaschewski et al. 2010); additionally, a locus near *DBH* was recently associated with smoking cessation (Furberg et al. 2010). Cubells et al. (2000) investigated the effects of *DBH* polymorphisms on cocaine-induced paranoia in patients with cocaine dependence/paranoia, and identified a haplotype found more frequently in cocaine-dependent individuals reporting paranoia, that was also associated with low DBH plasma levels in normal subjects (−4784–4803del-444A→G; del-A haplotype). Individuals from the same group later sequenced *DBH* in eight individuals at the phenotypic extremes for DBH plasma levels, and identified a putative functional polymorphism (−1021C→T; rs1611115; C/T) accounting for 35–52% of phenotype variance in DBH activity (Zabetian et al. 2001); the T allele was associated with low DBH plasma levels, and found to be in positive linkage disequilibrium with the del and A alleles associated with low DBH plasma levels and paranoia in the Cubells et al. (2000) study (Zabetian et al. 2003). A controlled laboratory study was later conducted in which 31 cocaine-using volunteers acutely self-administered intravenous doses of the cocaine (0, 8, 16, and 32 mg/70 kg body weight) over four sessions (Kalayasiri et al. 2007). The previously identified −1021C→T polymorphism was tested for association with cocaine-induced paranoia, and the low DBH plasma level T/T genotype group reported higher paranoia when compared to the C/T and C/C groups.

TPH2

Tryptophan hydroxylase 2 (*TPH2*) catalyzes the rate-limiting step in the synthesis of serotonin, and *TPH2* polymorphisms have been investigated for association with depression, suicidal behavior, bipolar disorder (Zhang et al. 2006) and ADHD (Banaschewski et al. 2010; Brookes et al. 2006). Manor et al. (2008) tested for association of *TPH2* SNPs and acute therapeutic response in children diagnosed

with ADHD, and identified an 8-SNP haplotype (rs1386488, rs2220330, rs1386495, rs1386494, rs6582720, rs1386492, rs4760814, rs1386497; C–G–C–A–A–G–A–C) that was significantly associated with better acute therapeutic response following methylphenidate treatment.

FAAH

Fatty acid amide hydrolase (*FAAH*) has also been studied in relation to acute response to stimulants; FAAH degrades several endocannabinoids that bind to cannabinoid receptors (McKinney and Cravatt 2005). Recently, polymorphisms in *FAAH* have been associated with brain response to cannabis (Filbey et al. 2009) and other phenotypes such as obesity (Engeli 2008). Much of the work associating variants in *FAAH* with stimulant response has been done in animal models (e.g., Madsen et al. 2006), and has shown that response to stimulants may also be influenced by the cannabinoid system. We investigated the effect of *FAAH* polymorphisms on subjective responses to acute amphetamine, using the sample of healthy volunteers that has been previously described (Dlugos et al. 2009b). Two SNPs, rs3766246 (C/C genotype) and rs2295633 (C/C genotype), were associated with amphetamine-induced arousal and decreased fatigue at 10 mg but not 20 mg, supporting the hypothesis that the endocannabinoid system may influence the acute response to low doses of amphetamine.

7 Miscellaneous

BDNF

Brain-derived neurotrophic factor (*BDNF*) is a growth factor that is involved in developmental processes (Hyman et al. 1991) and has been implicated in depression (Kato and Serretti 2008), smoking behavior (Furberg et al. 2010), obesity (den Hoed et al. 2010), and body mass index (Shugart et al. 2009). *BDNF* contains a *val*→*met* substitution (*val*^{66}*-met;* rs6265; G/A); the *met* allele produces a protein that is improperly secreted from neurons and has been reported to affect memory and hippocampal function (Egan et al. 2003). We examined the effects of *BDNF val*^{66}*-met* genotype on subjective responses to acute amphetamine (Flanagin et al. 2006) and found that individuals homozygous for the *val* allele possessed increased feelings of arousal and energy when administered 10 mg amphetamine relative to the other genotype groups. Therefore, the *BDNF val*^{66}*-met* genotype may also contribute to subjective responses to stimulant drugs.

CSNK1E

Another enzyme showing association with acute stimulant drug responses is casein kinase 1 epsilon (*CSNK1E*). *CSNK1E* encodes an enzyme that phosphorylates dopamine and cAMP-regulated phosphoprotein (DAARP-32; PPP1R1B), a second messenger that integrates dopaminergic and glutamatergic signaling

(Greengard 2001). We have previously reported that a quantitative trait locus (QTL) for methamphetamine sensitivity co-maps with an expression QTL for *Csnk1e* in mice, suggesting that the latter might cause the former (Palmer et al. 2005). Furthermore, pharmacological inhibition of *Csnk1e* blocks the locomotor response to methamphetamine in mice (Bryant et al. 2009) and rats (unpublished data). Mice with a null allele for *Csnk1e* exhibit paradoxically higher response to methamphetamine (unpublished data). We have also investigated the effects of SNPs in *CSNK1E* on subjective amphetamine response in humans (Veenstra-VanderWeele et al. 2006). The C allele of rs135745, which is located in the 3′-UTR of the gene, was associated with the response to amphetamine at 10 mg (but not 20 mg) as measured by the DEQ Feel Drug and ARCI Euphoria scales. Interestingly, other SNPs in *CSNK1E* have been associated with both heroin addiction in a case-control study (Levran et al. 2008) and ADHD in a family-based genome-wide association study (Mick et al. 2010), suggesting another possible link between ADHD, sensitivity to stimulants and drug abuse.

CYP2D6

Cytochrome P450 2D6 (*CYP2D6*) is a p450 enzyme that metabolizes methamphetamine (Lin et al. 1997). Otani et al. (2008) investigated the effect of *CYP2D6* polymorphisms in methamphetamine dependent patients in a case-control study, and found the lower activity *CYP2D6*10* and *CYP2D6*14* alleles were underrepresented in patients, suggesting that these alleles are protective against development of methamphetamine dependence.

MANEA

An association between rs1133503, located in the 3′-UTR of glycoprotein endo-alpha-1,2-mannosidase (*MANEA)*, and cocaine-induced paranoia was the strongest result in a genome-wide scan for variants associated with cocaine dependence and cocaine-induced paranoia (Yu et al. 2008). In a later study from the same group, 11 SNPs in *MANEA* were studied further using a family-based approach in two separate populations (African-–American; AA and European–American; EA). Nine of these SNPs were at least nominally associated with cocaine-induced paranoia in the AA population, whereas six of them at least nominally associated in the EA population (Farrer et al. 2009). Additionally, the rs9400554-rs6937479-rs9387522 haplotype (T–T–A) was associated with cocaine-induced paranoia in the pooled AA/EA family-based sample, and the C–A–C haplotype was associated with decreased risk of cocaine-induced paranoia in the pooled sample. No significant associations were found for the cocaine dependence phenotype. Two separate case–control samples (EA and AA) were used for replication. The individual SNP associations from the family-based studies did not replicate in either population sample. However, two associated haplotypes in the replication study contained SNPs that were found in associated haplotypes in the family-based analysis (rs900554 and rs9387522; C–A; T–A); the C–A haplotype was associated with increased risk of cocaine-induced paranoia and cocaine dependence in EA,

and the T–A haplotype was associated with increased risk of cocaine dependence in the AA replication sample.

8 Exploratory Studies

A number of association studies have focused on genes that are not as well studied as those mentioned in the previous section; these more exploratory studies are summarized in Table 2. These studies mostly focus on methamphetamine abuse-related phenotypes. These genes include *CES1* (Nemoda et al. 2009); *DTNBP1* (Kishimoto et al. 2008a); *FZD3* (Kishimoto et al. 2008b); *G72* (Kotaka et al. 2009); *GABRG2* (Nishiyama et al. 2005); *GLYT1* (Morita et al. 2008); *GRM2* (Tsunoka et al. 2010); *GSTM1* (Nakatome et al. 2009); *GSTP1* (Hashimoto et al. 2004); *GSTT1* (Nakatome et al. 2009); *NQO2* (Ohgake et al. 2005); *PDYN* (Nomura et al. 2006); *PICK1* (Matsuzawa et al. 2007); *PROKR2* (Kishi et al. 2010); *SLC22A3* (Aoyama et al. 2006); *SNCA* (Kobayashi et al. 2004) and *SOD2* (Nakamura et al. 2006).

9 Genome-Wide Association Studies

Presently, only three GWAS has been conducted investigating responses to stimulant drugs. One study investigated the therapeutic response to methylphenidate (Mick et al. 2008). Children diagnosed with ADHD ($n = 187$), received varying doses of methylphenidate over a 5-week period, and were phenotyped with the ADHD-RS IV scale and then genotyped at about 300,000 SNPs. No associations reached genome-wide significance, and the strongest associations were not in genes examined in any previous candidate gene studies. Two studies have examined genetic variation underlying stimulant abuse. Uhl et al. (2008) used a case–control nested study to investigate genetic variants underlying methamphetamine dependence, with the goal of identifying genes with an unexpected accumulation of low *p*-values, and Yu et al. (2008) took a family-based association test (FBAT) approach and scanned evenly spaced markers for association with cocaine dependence and cocaine-induced paranoia. As previously mentioned, the association between *MANEA* SNP (rs1133503) and cocaine-induced paranoia was the most significant result in this study, but after correction for multiple testing this result was not statistically significant.

10 Closing Remarks

The main focus of this review was to investigate sources of genetic variation across a range of different phenotypes and prototypic stimulant drugs. Some of the data are specific to acute or chronic administration and therapeutic or

non-therapeutic responses. Some genes, such as *OPRM1*, were associated with both acute subjective amphetamine liking and methamphetamine dependence. Understanding how these polymorphisms influence various phenotypes has important implications for the study of drug abuse and for our understanding of the pathophysiology and treatment of disorders such as ADHD. Interestingly, several genes discussed here are implicated in both ADHD and ADHD treatment response.

Many of these studies test multiple hypotheses and in some cases underpowered to do so, therefore there is a need for replication of these results. For example, our investigation of healthy human subjects has been used to test many different genetic hypotheses, so that if corrections for multiple testing across all of these different genes were applied, several results would not be considered statistically significant. In an effort to examine the reliability of our results we now have collected almost 400 subjects and are in the process of performing replication analyses.

There is still much to be learned about the polymorphisms reviewed here. The *SLC6A3* 3′-UTR VNTR is particularly illustrative of this, since it has been associated with many phenotypes in quite a number of studies, yet the results appear inconsistent or even contradictory. Resolving these apparent inconsistencies across studies is an urgent goal to better understand the function of the 3′-UTR VNTR and its relation to drug response.

There is significant promise in future technologies that will become available shortly. Genome-wide association studies will remain important in providing unbiased answers. As whole-genome re-sequencing becomes more readily available, it will be possible to study rare variants in more sophisticated ways. Copy number variation is another relatively unexplored type of genetic variation that has been suggested to be important in pharmacogenomics (Johansson and Ingelman-Sundberg 2008). Finally, there are substantial opportunities and challenges in integrating the findings from genetic studies in humans and model organisms (Phillips et al. 2008).

Acknowledgements This work was supported by NIH grants DA02812, DA027545 and DA021336.

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