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Review

Neuroimaging in Psychiatric Pharmacogenetics Research: The Promise and Pitfalls

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The integration of research on neuroimaging and pharmacogenetics holds promise for improving treatment for neuropsychiatric conditions. Neuroimaging may provide a more sensitive early measure of treatment response in genetically defined patient groups, and could facilitate development of novel therapies based on an improved understanding of pathogenic mechanisms underlying pharmacogenetic associations. This review summarizes progress in efforts to incorporate neuroimaging into genetics and treatment research on major psychiatric disorders, such as schizophrenia, major depressive disorder, bipolar disorder, attention-deficit/hyperactivity disorder, and addiction. Methodological challenges include: performing genetic analyses in small study populations used in imaging studies; inclusion of patients with psychiatric comorbidities; and the extensive variability across studies in neuroimaging protocols, neurobehavioral task probes, and analytic strategies. Moreover, few studies use pharmacogenetic designs that permit testing of genotype × drug effects. As a result of these limitations, few findings have been fully replicated. Future studies that pre-screen participants for genetic variants selected *a priori* based on drug metabolism and targets have the greatest potential to advance the science and practice of psychiatric treatment. *Neuropsychopharmacology* (2013) **38,** 2327–2337; doi:10.1038/npp.2013.152; published online 17 July 2013

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INTRODUCTION

Approximately 25% of the population is afflicted by one or more psychiatric disorders (Kessler *et al*, 2005). Twin studies reveal a substantial heritability for psychiatric disorders, including schizophrenia and bipolar disorder (BD), major depression, and substance use disorders including nicotine dependence (McGuffin *et al*, 2003; Goldman *et al*, 2005; van Belzen and Heutink, 2006). Although pharmacotherapy represents the foundation of psychiatric treatment, most patients do not achieve a sufficient therapeutic response. To improve treatment outcomes, genetic variants that code for drug-metabolizing enzymes and pharmacodynamic targets are being examined to identify individuals most likely to benefit from alternate therapies and those at risk for adverse drug reactions (Malhotra *et al*, 2012). Despite some progress, there are a limited number of actionable findings, due in part to the low penetrance of implicated genes and a failure to capture the complexity in pathophysiological phenotypes that give rise to variable treatment outcomes.

Moving beyond simple classifications of treatment responders and nonresponders, genetic variability can be studied in the context of intermediate phenotypes related to treatment effects on brain structure, neural circuitry, and neurochemical processes (Meyer-Lindenberg and Weinberger, 2006). There are a variety of neuroimaging approaches that have substantial *potential utility* in this regard, including: blood-oxygen-level-dependent (BOLD) functional magnetic resonance imaging (fMRI) to examine neural activity associated with treatment targets such as attention, working memory, reward-related responding, emotional processing, and in the case of addiction, reactivity to drug-related cues; BOLD signal at rest to characterize spontaneous fluctuations of connectivity within and between neural circuits; and positron emission tomography (PET) to estimate receptor availability and neurotransmitter levels in the brain. Although the imaging genetics approach has been used to study underlying pathophysiological processes in psychiatric conditions (Tost *et al*, 2012), few studies have combined both genetic

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and imaging approaches to study effects of psychiatric treatment. The goal of this paper is to outline promising avenues for, and the challenges of, incorporating neuroimaging phenotypes into psychiatric pharmacogenetics research.

STATE OF THE SCIENCE

We reviewed existing literature incorporating neuroimaging phenotypes into work on genetic influences on treatment response. For each imaging phenotype, we selected studies that have the following characteristics: (a) human psychiatric patient population or healthy controls exposed to relevant drug treatment or drugs of abuse, with assessment of drug response; (b) neuroimaging assessment; and (c) genetic analysis. Studies meeting these criteria are listed by imaging phenotype in Table 1 and discussed below.

Working Memory Assessed with fMRI

Deficits in working memory have a central role in both psychiatric illness and addiction, based on its centrality to cognitive control and goal-directed behavior (Millan *et al*, 2012; Ashare *et al*, 2013). Several studies have examined genes involved in dopamine regulation for a role in working memory-related brain activity and treatment response; these studies suggest that alleles associated with reduced dopaminergic tone may enhance the cognitive effects of drug treatment. The widely studied catechol-*O*-methyltransferase (*COMT*) val158met variant (rs4680) codes for the COMT enzyme involved in dopamine degradation; the valine allele is associated with reduced prefrontal dopamine levels (Egan *et al*, 2001). With respect to schizophrenia treatment, the met allele is linked with improved working memory performance and reduced prefrontal cortical activity after 8 weeks of treatment with olanzapine (Bertolino *et al*, 2004); however, this study did not include a placebo condition for comparison. In the context of drugs of abuse that increase dopamine release, individuals with the val/val genotype show improved prefrontal efficiency (reduced activity at the same level of performance) during working memory performance following amphetamine administration (Mattay *et al*, 2003), whereas smokers with val/val genotypes show improved performance and increased prefrontal activity following nicotine exposure *vs* abstinence (Loughead *et al*, 2009). The T allele of the dopamine D2 receptor (*DRD2*) C957T variant, considered a reduced activity variant (Hirvonen *et al*, 2009), is also associated with reduced working memory and processing efficiency following nicotine administration (Jacobsen *et al*, 2006). Although it is difficult to draw conclusions from a single study of psychiatric treatment, emerging data on the effects of drugs of abuse suggest that individuals who carry putative reduced activity alleles for genes related to dopamine signaling may be more responsive to the cognitive enhancing effects of stimulating drugs. To expand the pool of pharmacogenomic markers to assess medication or drug effects on working memory or other domains of executive cognitive function, a focus on variants identified in genome-wide association studies (GWAS) for association with psychiatric conditions or neurocognitive phenotypes may be fruitful (Tost *et al*, 2012). However, despite the identification of novel molecular targets based on genomic analysis, the lack of consistency in phenotype assessment is a rate-limiting factor.

A potential area for improvement for these cognitive imaging phenotypes would be standardization of tasks across the field to facilitate comparisons between studies. Toward this end, the NIMH-funded Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) is establishing standardized batteries that measure cognitive functions most affected in schizophrenia (Carter *et al*, 2012). Proposed CNTRICS tasks probe domain-specific cognitive performance with discrete neural correlates, seeking to avoid ambiguous interpretations. For example, working memory tasks proposed by the CNTRICS initiative (Carter *et al*, 2012) are designed to probe different aspects of working memory (ie, goal maintenance, item maintenance, capacity, and interference control). Thus, the use of multiple cognitive tasks may permit investigators to distinguish genetic associations with medication effects on discrete cognitive domains *vs* generalized cognitive deficits and neurobiological changes associated with psychiatric illness. Similarly, substance abuse results in long-term neuroadaptive changes, a process that may also be influenced by genetic factors. It is therefore difficult to disentangle pre-existing risk factors from the effects of gene by drug exposure interactions in chronic drug users. Furthermore, fMRI studies of cognitive function in addiction have yet to incorporate both genotype and pharmacotherapy, and instead have focused only on effects of administration (or withdrawal) from drugs of abuse. Addiction research may benefit from adopting a similar approach to the CNTRICS initiative and establishing standardized neurocognitive batteries to evaluate genetic influences on treatment response.

Emotional Face Processing Assessed with fMRI

Through deconstructing cognition as a whole into discrete domains, one can also test seemingly non-cognitive facets of psychiatric disorders targeted by treatment, such as perception and social/emotional processing. CNTRICS suggests addressing aspects of positive and negative symptoms in schizophrenia by measuring perception and social/emotional processing (Carter *et al*, 2012), and these measures have shown some promise for predicting antidepressant treatment outcomes (Arnone *et al*, 2012; Rosenblau *et al*, 2012). Although little work has been done utilizing a pharmacogenetic approach to optimize treatment, initial studies in major depressive disorder provide one model for future research.

Although the endogenous cannabinoid system and neuropeptide Y (NPY) are not targeted directly by current anti-depressant treatments, recent work suggests that genetic variants in these systems that are associated with poor treatment outcomes contribute to impaired emotional processing. For example, the G allele of the *CNR1* variant rs1049353 is associated with poorer antidepressant response and weaker striatal and thalamic response to happy faces (Domschke *et al*, 2008), whereas a genetic variant conferring reduced expression of NPY (the rs16147 C allele) is associated with greater amygdala reactivity to emotional faces in depressed patients, and with poorer treatment

Table 1 Imaging Pharmacogenetic Studies in Psychiatric Disorders

Imaging phenotype	Gene, SNP	Treatment	Subjects and study design	Outcome	Reference
Working memory-related activity measured by BOLD fMRI	*COMT* val158met, rs4680[a]	Olanzapine	$N = 30$ schizophrenia patients, drug-free at study start, completed 8 weeks of olanzapine treatment. 20 completed fMRI scans with N-back task at 4 and 8 weeks of treatment.	Met/met (*vs* val/*) show improved performance and reduced prefrontal activation after 8 weeks of treatment; no genotype differences at 4 weeks.	Bertolino *et al* (2004)
		Amphetamine	$N = 27$ healthy adults completed two fMRI sessions with N-back task: after single 0.25 mg/kg dose of dextroamphetamine and after placebo (double-blind, order counterbalanced)	Val/val show increased prefrontal efficiency (ie, reduced BOLD signal for same level of performance) after amphetamine *vs* placebo; met/met show decreased efficiency after amphetamine *vs* placebo, but only at the highest memory load	Mattay *et al* (2003)
		Nicotine	$N = 33$ healthy smokers completed two fMRI sessions with n-back task: smoking satiety and after ~12 h/overnight abstinence (order counterbalanced)	Val/val show reduced performance and reduced BOLD signal in prefrontal cortex during nicotine abstinence *vs* smoking; no abstinence effect in met/*	Loughead *et al* (2009)
	DRD2 C957T[b]		$N = 36$ adult subjects (22 smokers and 14 nonsmokers) completed two fMRI sessions with n-back: nicotine patch and placebo patch (double-blind, order counterbalanced).	T/* (*vs* C/C) show reduced performance and processing efficiency in left anterior insula, left cerebellum, bilateral mid occipital gyrus, and right fusiform gyrus following nicotine *vs* placebo	Jacobsen *et al* (2006)
Emotional face processing during BOLD fMRI	*CNR1* rs1049353[c]	Various antidepressant treatments	$N = 256$ patients with major depression (MD) completed 6 weeks of treatment; $n = 33$ completed fMRI with emotional faces task at study start	G/* *vs* (A/A) show poorer treatment response; A/* (*vs* G/G) show stronger striatal and thalamic BOLD response to happy faces	Domschke *et al* (2008)
	NPY rs16147[d]		$N = 256$ patients with major depression completed 6 weeks of antidepressant treatment; a subset of $n = 35$ patients completed fMRI scan with emotional faces task at study start (This sample overlaps with Domschke *et al*, 2008.).	C/* (vs T/T) associated with poorer treatment response in overall sample, and stronger BOLD response in the amygdala to sad and angry faces in imaging subsample.	Domschke *et al* (2010)
Cue reactivity during BOLD fMRI or perfusion MRI	*CHRNA5* rs16969968[e]	Nicotine	$N = 24$ female smokers completed fMRI scan with visual smoking cue reactivity task	G/G (*vs* A/*) show increased cue reactivity in regions related to memory and habitual responding	Janes *et al* (2012)
	DRD4 VNTR[f]		$N = 15$ smokers completed fMRI scan with visual smoking cue reactivity task after 2 h of smoking abstinence	7-Repeat allele (*vs* <7-repeats) associated with increased cue reactivity to visual cues in reward regions; smoking cue by genotype interaction on craving	McClernon *et al* (2007)
	CYP2A6[g]		$N = 31$ smokers (fast *vs* slow nicotine metabolizers) completed fMRI scan with visual smoking cue reactivity task	Fast (*vs* slow) nicotine metabolizers show increased smoking cue reactivity in reward regions	Tang *et al* (2012)
Cue reactivity during BOLD fMRI or perfusion MRI	*DAT1* VNTR[h]	Nicotine	$N = 19$ smokers completed two perfusion fMRI scan sessions: smoking cue and neutral cue exposure, approximately 1 h apart	9-Repeat allele (*vs* 10-repeat homozygotes) associated with greater reactivity in the ventral striatal/pallidal/orbitofrontal cortex regions to visual and tactile smoking cues.	Franklin *et al* (2009)
			$N = 35$ smokers completed an attentional bias task before perfusion MRI scan with smoking cue paradigm	9-Repeat carriers (vs 10-repeat homozygotes) showed positive correlation between attentional bias to smoking cues and increased cue reactivity in the amygdala	Wetherill *et al* (2012)
			$N = 26$ smokers completed perfusion MRI with neutral and smoking cue video exposures	Presence of 9-repeat allele associated with greater reactivity in ventral striatum and medial orbitofrontal cortex	Franklin *et al* (2011)
	GABRA2 rs279871[i]	Alcohol	$N = 40$ adults (social drinkers, nondependent heavy drinkers with and without family history of alcoholism) completed two separate fMRI scans with alcohol odor cue paradigm (alcohol cue *vs* appetitive control cue): one with IV alcohol infusion and one with IV saline infusion (order randomized)	A/A (*vs* */G) show enhanced BOLD signal in response to cues in medial prefrontal cortex; reduced BOLD signal in ventral tegmental area; increased risk of dependence; and reduced 'high' during alcohol infusion	Kareken *et al* (2010)
	DRD4 VNTR[f]		$N = 73$ heavy drinkers completed fMRI scan with alcohol taste cue paradigm	Presence of 7-repeat allele associated with increased reactivity to taste cues in reward regions before alcohol priming dose; no genotype difference after the priming dose	Filbey *et al* (2008)
Cue reactivity during BOLD fMRI or perfusion MRI	*SNCA* rs2583985[j]	Alcohol	$N = 326$ heavy drinkers completed fMRI with alcohol taste cue paradigm	A/* (*vs* G/G) show increased reactivity to taste cues in caudate and paracingulate regions	Wilcox *et al* (2013)
	OPRM1 A118G, rs1799971[k]		$N = 73$ heavy drinkers completed fMRI scan with alcohol taste cue paradigm	G/* *vs* A/A show increased reactivity to taste cues in reward regions before and after alcohol priming	Filbey *et al* (2008)

Table 1 (Continued)

Imaging phenotype	Gene, SNP	Treatment	Subjects and study design	Outcome	Reference
		Alcohol/naltrexone	*N* = 74 adult AD individuals completed fMRI scan with alcohol cue paradigm on day 6 of a 7-day treatment with naltrexone or placebo (randomized, double-blind)	G/* *vs* A/A show increased cue reactivity to alcohol taste and visual cues in reward regions in placebo-treated individuals, but nominally lower cue reactivity in individuals treated with naltrexone	Schacht *et al* (2013)
	CNR1 rs2023239[l]	Cannabis	*N* = 43 marijuana users completed fMRI scan with cue reactivity paradigm following 72 h abstinence	G/A *vs* A/A show enhanced cue reactivity to tactile cues in reward regions, increased cannabis withdrawal, and increased craving	Filbey *et al* (2010)
	FAAH C385A, rs324420[m]		*N* = 43 marijuana users completed fMRI scan with cue reactivity paradigm following 72 h abstinence	C/C (*vs* A/*) show increased response to marijuana cues in reward regions. Combined number of risk alleles for *FAAH* rs324420 plus *CNR1* rs2023239 was positively correlated with cue reactivity	Filbey *et al* (2010)
CBF	*DAT1* VNTR[h]	Methylphenidate	*N* = 8 male treatment-naïve children with ADHD received methylphenidate for 4 days before SPECT imaging session	Presence of 10-repeat allele associated with higher regional CBF in medial frontal and left basal ganglia regions, and with poorer treatment response.	Rohde *et al* (2003)
CBF	*OPRM1* A118G, rs1799971[k]	Nicotine	*N* = 15 healthy smokers completed two arterial spin labeled (ASL) perfusion MRI scans: smoking as usual and overnight abstinence (order counterbalanced)	A/A (*vs* G/*) show greater increases in CBF in regions associated with cravings during nicotine abstinence *vs* satiety	Wang *et al* (2008)
	DRD2 -141C[n]			DelC/InsC (*vs* InsC/InsC) show greater increases in CBF in regions associated with cravings during nicotine abstinence *vs* satiety	
	COMT val158met, rs4680[a]			val/val (*vs* met/*) show greater increases in CBF in regions associated with cravings during nicotine abstinence *vs* satiety	
Structural abnormalities based on MRI	*AKT1* rs1130233[o]	Lithium and sodium valproate	*N* = 138 schizophrenic patients with complete pharmacological, cognitive, and structural MRI data from the Clinical Brain Disorders Branch Sibling Study	A/* genotype (*vs* G/G) associated with increased gray matter volume in the medial temporal lobe and prefrontal cortex, and reduced cognitive deterioration following treatment with mood stabilizers.	Tan *et al* (2012)
	BDNF val66met, rs6265[p]	Various antidepressant treatments	*N* = 37 adults completed structural MRI scan within 2 weeks of hospital admission for treatment of current major depressive episode	Inverse correlation between gray matter volume in right orbitofrontal cortex and time to symptom remission in met carriers, but not val/val individuals	Cardoner *et al* (2013)
		Escitalopram	*N* = 32 elderly patients with unipolar depression;2-week single-blind placebo drug-washout before MRI scan; followed by 12 weeks of treatment with escitalopram	*/met (*vs* val/val) and white matter abnormalities independently predict remission	Alexopoulos *et al* (2010)
MOR availability based on PET	*OPRM1* A118G, rs1799971[k]	Nicotine	*N* = 22 smokers completed two PET sessions after overnight abstinence: after smoking a nicotine-containing cigarette and after a placebo cigarette	A/A *vs* G/* show greater MOR availability during both sessions; no genotype × session interaction	Ray *et al* (2011)
		Alcohol, Naltrexone	*N* = 25 AD adults and 28 healthy controls. AD subjects completed PET scan on day 5, naltrexone on days 15–18, and post-treatment PET scan on day 18	A/A *vs* */G show increased MOR availability at baseline. Nonsignificant trend toward reduced availability after naltrexone in G/* *vs* A/A	Weerts *et al* (2012)
SERT occupancy based on SPECT	*5-HTTLPR*[q]	Paroxetine	*N* = 42 drug-naïve or currently drug-free depressed adults completed SPECT scan at baseline and after 6 weeks of open-label paroxetine	Higher SERT occupancy in the diencephalon associated with greater symptom improvement in L_A/* *vs* S^0/S^0; similar effect in midbrain for L_A/L_A *vs* S^0/*	Ruhe *et al* (2009)
Dopamine transporter availability or occupancy based on PET or SPECT	*DAT1* VNTR[h]	Methylphenidate	*N* = 11 drug naïve children with ADHD completed 8 weeks of MPH treatment	Homozygosity for 10-repeat allele associated with greater DAT availability in basal ganglia following treatment and poorer treatment response compared with 9R carriers	Cheon *et al* (2005)
	DAT1 VNTR[h] X *DRD4* VNTR[f]		*N* = 17 male adolescents with comorbid ADHD and substance abuse completed SPECT scans before and after 3 weeks of methylphenidate treatment	Individuals with both *DAT1* 10-repeat and *DRD4* 7-repeat genotypes show reduced blockade of DAT (less change in availability pre- to post-treatment) in the caudate and putamen	Szobot *et al* (2011)
Dopamine receptor availability based on PET	*OPRM1* A118G, rs1799971[k]	Alcohol	*N* = 28 male social drinkers completed two [^{11}C]raclopride PET scans sessions: IV alcohol infusion *vs* placebo infusion	G/* *vs* A/A show increased DA release following alcohol challenge	Ramchandani *et al* (2011)
	DAT1 VNTR[h]	Nicotine	*N* = 45 healthy smokers completed one [^{11}C]raclopride PET scans sessions during which they either smoked (*n* = 35) or did not smoke (*n* = 10) during a break in scanning	9-Repeat carriers (*vs* 10-repeat homozygotes) showed greater decreases in binding potential (ie, greater dopamine release) in the ventral caudate/nucleus accumbens after smoking a cigarette	(Brody *et al*, 2006)

Table 1 (Continued)

Imaging phenotype	Gene, SNP	Treatment	Subjects and study design	Outcome	Reference
	DRD4 VNTR[f]		$N = 45$ healthy smokers completed one [^{11}C]raclopride PET scans sessions during which they either smoked ($n = 35$) or did not smoke ($n = 10$) during a break in scanning	<7-Repeat carriers (*vs* 7-repeat homozygotes) showed greater decreases in binding potential (ie, greater dopamine release) in the ventral caudate/nucleus accumbens after smoking a cigarette	
	COMT val158met, rs4680[a]			Val/val (*vs* */met) associated with greater decreases in binding potential (ie, greater dopamine release) in the ventral caudate/nucleus accumbens after smoking a cigarette	
Axial diffusivity based on diffusion tensor imaging	*GSK3-β* rs334558[r]	Lithium	$N = 70$ bipolar patients (50 untreated, 20 treated chronically with lithium at study start) completed a single DTI scan session	*/C (*vs* T/T) genotype and long-term lithium treatment were independently associated with increased axial diffusivity in white matter tracts	Benedetti *et al* (2013)

Abbreviations: AD, alcohol dependent; CBF, cerebral blood flow; MOR, Mu-opioid receptor; SERT, serotonin transporter.
[a]Met allele codes for lower activity protein because of thermal instability; associated with higher intracellular DA levels due to decreased degradation, and typically associated with better performance on executive function tasks (Egan *et al*, 2001).
[b]T allele associated with reduced mRNA stability, lower expression of DRD2 receptors, and reduced receptor affinity (Hirvonen *et al*, 2009).
[c]Synonymous SNP; functional consequences uncertain (Domschke *et al*, 2008).
[d]C allele associated with reduced gene expression, reduced affinity for an as-yet-unknown factor. NPY is anxiolytic; C allele associated with anxiety and depressive symptoms (Sommer *et al*, 2010).
[e]A allele associated with reduced receptor sensitivity, increased risk of nicotine dependence, increased smoking quantity (Bierut *et al*, 2008).
[f]7-Repeat allele associated with reduced receptor sensitivity (Asghari *et al*, 1995).
[g]Faster nicotine metabolizers smoke more and have greater difficulty quitting (Schnoll *et al*, 2009).
[h]Homozygosity for the 10-repeat allele associated with increased DAT expression compared with 9-repeat carriers (Fuke *et al*, 2001).
[i]Functional consequences uncertain, but suspected to alter gene expression (Kareken *et al*, 2010).
[j]Functional consequences uncertain, but suspected to alter gene expression (Wilcox *et al*, 2013).
[k]G allele associated with reduced mRNA and protein levels and reduced binding affinity (Mague *et al*, 2009).
[l]Functional consequences uncertain, but may code a splice variant (Zhang *et al*, 2004).
[m]A allele associated with reduced expression and lower stability of FAAH (Chiang *et al*, 2004).
[n]DelC variant associated with increased receptor density (Jonsson *et al*, 1999).
[o]Synonymous variant; A allele associated with reduced protein expression, reduced cognitive performance *vs* */G (Blasi *et al*, 2011).
[p]Met allele inhibits activity-dependent secretion of BDNF; no effect on mature protein function. Met allele associated with worse memory performance, lower hippocampal volume/activation, impaired synaptic transmission, etc. (Egan *et al*, 2003).
[q]L allele associated with higher concentrations of SERT mRNA (increased transcription) and with twofold higher serotonin uptake (L homozygotes); S allele associated with increased anxiety-related traits and increased risk of depression following stress (Lesch and Gutknecht, 2005).
[r]Promoter region SNP; T allele associated with greater activity (Kwok *et al*, 2005).
*, Any allele.

response among a subgroup of patients with anxious depression (Domschke *et al*, 2010).

Although limbic reactivity to emotional faces may provide a useful measure to identify likely treatment responders or for early medication screening, important limitations of these studies include the combined analysis of patients taking a range of medications (eg, tricyclics, SSRIs, neuroleptics) and the lack of randomization to medication *vs* placebo. Thus, the treatment component of these studies was incidental, rather than an imaging pharmacogenetic approach. Future studies selecting genetic variants based on drug targets and metabolizing enzymes, and testing gene × treatment interactions would be a promising extension of this work.

Cue Reactivity Assessed with fMRI or Perfusion MRI

Cue-induced cravings (ie, intense, acute cravings triggered by drug-associated stimuli) contribute to addiction and relapse, and the pattern of cue-evoked neural responses (cue reactivity) in reward regions may provide a biomarker of relapse risk for addiction treatment (Sinha and Li, 2007). Cue reactivity may therefore provide an imaging phenotype for assessing individual factors, which influence treatment response. A majority of studies have focused on genetic variation in the dopamine system. For example, the 7-repeat allele of a common variable number tandem repeat (VNTR) in the dopamine D4 receptor (*DRD4)* gene, associated with decreased dopaminergic tone and increased craving (Hutchison *et al*, 2002), is associated with enhanced cue reactivity in drug reward-related regions among alcohol drinkers and regular smokers (McClernon *et al*, 2007; Filbey *et al*, 2008). The *SNCA* rs2583985 A allele, which may alter alpha synuclein expression in dopaminergic neurons, was also associated with increased cue reactivity in heavy drinkers (Wilcox *et al*, 2013). The 9-repeat allele of the dopamine transporter gene (*DAT1*, also called *SLC6A3*) VNTR is associated with increased reactivity in the ventral striatum and medial orbitofrontal cortex to smoking cues *vs* neutral cues in two independent studies (Franklin *et al*, 2009; Franklin *et al*, 2011); a positive correlation between increased activation in the amygdala and attentional bias for smoking cues was also noted in carriers of the 9-repeat allele (Wetherill *et al*, 2012).

Additional peptide and neurotransmitter systems may also have a role in cue reactivity. Alcohol increases release of endogenous opioid peptides that bind to mu-opioid receptors. The G allele of the mu-opioid receptor (*OPRM1)* A118G variant has been associated with increased alcohol cue reactivity in regular and heavy drinkers (Filbey *et al*, 2008), an effect that may be reversed following treatment with the mu-opioid receptor antagonist naltrexone (Schacht *et al*, 2013). Cannabinoid receptor signaling may mediate the effects of alcohol on dopamine release on the ventral tegmental area (VTA; Pava and Woodward, 2012), and the *CNR1* rs2023239 G allele, conferring increased cannabinoid receptor binding (*vs* A allele), is associated with enhanced drug cue reactivity in regular alcohol drinkers (Hutchison *et al*, 2008) as well as cue reactivity in regular marijuana users (Filbey *et al*, 2010). Variation in *CNR1* may also impact nicotine dependence (Chen *et al*, 2008b), although to our knowledge this has not been examined in neuroimaging cue reactivity studies in smokers.

Some genetic influences on neural cue reactivity may be specific to different drugs of abuse. Homozygosity for the gamma-aminobutyric acid receptor subunit alpha-2 gene (*GABRA2*) rs279871 A allele increases risk for developing alcohol dependence (Edenberg *et al*, 2004). Drinkers homozygous for this allele show increased reactivity to alcohol taste cues in the medial prefrontal cortex but decreased reactivity in the VTA; the apparently discordant findings across brain regions may reflect cue-evoked inhibitory responses in the VTA (Kareken *et al*, 2010). Of relevance to marijuana use, fatty acid amide hydrolase (FAAH) metabolically inactivates the endogenous cannabinoid anandamide; the A allele of the *FAAH* variant rs324420 is associated with lower risk of cannabis dependence (Tyndale *et al*, 2007) and reduced responses to marijuana tactile cues in regular cannabis users (Filbey *et al*, 2010). In the context of nicotine dependence, homozygosity for the G allele of the alpha-5 subunit of the nicotinic acetylcholine receptor gene (*CHRNA5*) rs16969968, which may increase nicotinic acetylcholine receptor activation (Bierut *et al*, 2008), is associated with enhanced cue reactivity in several cortical and subcortical brain regions in nicotine-dependent women (Janes *et al*, 2012). Enhanced cue reactivity has also been documented in faster metabolizers of nicotine (Tang *et al*, 2012), who relapse at higher rates than slower metabolizers (Lerman *et al*, 2006; Schnoll *et al*, 2009). With one notable exception (Schacht *et al*, 2013), none of these studies incorporated genetic and neuroimaging analysis of cue reactivity into clinical trials testing different therapies for addiction. However, these initial studies suggest that cue reactivity may be a promising intermediate phenotype for examining mechanisms of individual differences in substance abuse treatment response.

Regional Cerebral Blood Flow (CBF) Assessed with Perfusion MRI

Regional CBF is thought to reflect localized metabolic activity, providing an alternate neuroimaging measure for pharmacogenetic research. Although abnormalities in CBF have long been associated with psychiatric disorders (Theberge, 2008), the application of arterial spin-labeled perfusion MRI to pharmacogenetic studies is still in an early stage. Methylphenidate (MPH), the most commonly prescribed medication for the treatment of attention-deficit hyperactivity disorder (ADHD), blocks the dopamine transporter and increases dopamine release. A VNTR in *DAT1* increases DAT expression and has been linked to poorer response to MPH treatment for ADHD (Durston, 2010). In one study, the *DAT1* 10-repeat allele (10R) was associated with higher CBF in medial frontal and left basal ganglia areas among children following MPH treatment (Rohde *et al*, 2003), which may suggest greater dopamine-induced activation following treatment in children genetically predisposed to have more active dopamine reuptake. In a small preliminary study, genetic variants associated with greater risk of nicotine addiction were associated with increased CBF during nicotine withdrawal in regions associated with cravings, suggesting a possible mechanism for genetic vulnerability to addiction (Wang *et al*, 2008). However, the very small sample sizes in these studies limit interpretation of these findings.

Structural Abnormalities Assessed with MRI

Functional alterations commonly observed in psychiatric disorders may reflect underlying changes in brain structure (Michael *et al*, 2011; Kwaasteniet *et al*, 2013), suggesting an additional neuroimaging phenotype for pharmacogenetic studies. In MDD and BD, for example, volumetric differences in the amygdala and basal ganglia have been noted for patients compared with healthy controls, although the direction of alterations differs: studies of MDD typically report smaller (but hyperactive) regions, whereas BD patients exhibit enlargements (Konarski *et al*, 2008). Volumetric reductions of the prefrontal cortex are common to both disorders (Konarski *et al*, 2008), and effective treatments for these disorders appear to normalize these structural and functional abnormalities (Drevets *et al*, 2002; Chen *et al*, 2008a; Savitz *et al*, 2010; Hafeman *et al*, 2012).

Although only a few studies have investigated genetic influences on antidepressant and anti-psychotic treatment response using structural MRI, preliminary efforts support this approach and highlight the role of neuronal growth factors in antidepressant response. An investigation into the effects of a variant the gene encoding the brain-derived neurotrophic factor (*BDNF* val66met) demonstrated an inverse correlation between gray matter volume in the right orbitofrontal cortex and time to symptom remission after antidepressant treatment was observed in carriers of the *BDNF* met allele, but not in *BDNF* val homozygotes (Cardoner *et al*, 2013). In addition, the *BDNF* met allele and white matter abnormalities independently predict remission of depressive symptoms in patients with late-onset depression after treatment with escitalopram (Alexopoulos *et al*, 2010). We found only one study investigating pharmacogenetic imaging of BD. Benedetti *et al* (2013) reported overlapping effects of lithium treatment and the reduced activity C allele of the *GSK3-β* rs334558 promoter variant on measures of axial diffusivity in white matter fiber tracts in BD patients. However, the sample size for this study was too small to investigate gene by treatment interactions. In schizophrenic patients, a variant associated with reduced expression of a protein-regulating GSK3-*β* activity (the *AKT1* rs1130233 A allele)

was associated with increased gray matter volume in the medial temporal lobe and prefrontal cortex, and with reduced cognitive deterioration following treatment with lithium or sodium valproate (Tan *et al*, 2012). BDNF and GSK3-β both regulate neuronal growth and survival; relationships between these genetic variants and structural measures of treatment response support the hypothesis that antidepressant and lithium treatments may act through neurogenerative pathways, possibly simulating normal function in patients with genetic deficits in neurotrophic signaling.

Receptor Availability or Transporter Occupancy Assessed with PET/Single-Photon Emission Computed Tomography (SPECT)

Although molecular imaging techniques such as PET and SPECT may lack the temporal resolution of MRI, they offer unique advantages in elucidating pharmacological response at the receptor level. For example, VNTRs in *DAT1* and *DRD4* have been associated with increased risk of ADHD (Durston, 2010), because MPH, the most commonly prescribed medication for the treatment of ADHD, blocks the dopamine transporter and increases dopamine release, these variants are promising candidates for influencing treatment response. One SPECT study demonstrated that children homozygous for the *DAT1* 10R allele (thought to increase DAT expression and typically associated with increased risk of ADHD) had a greater increase in DAT density in the basal ganglia after MPH treatment and were less likely to experience a beneficial clinical response (Cheon *et al*, 2005). A more recent study demonstrated that a combination of the *DAT1* 10R/10R genotype with the *DRD4* VNTR 7-repeat risk allele was associated with reduced blockade of DAT by MPH in adolescents comorbid for substance abuse (Szobot *et al*, 2011). The *DRD4* 7-repeat variant results in a less sensitive receptor (Asghari *et al*, 1995). Together, these results suggest that genetic traits that result in reduced dopamine signaling may diminish the effectiveness of MPH for treating ADHD. In contrast, genes associated with lower synaptic dopamine concentrations and normal dopamine receptor and transporter function are associated with greater smoking-induced dopamine release; subjects carrying at least one *DAT1* 9R allele, $<$7-repeats of the *DRD4* VNTR, or who were homozygous for the *COMT* val allele showed a greater change in [^{11}C]raclopride-binding potential in the ventral caudate and nucleus accumbens after smoking a cigarette (Brody *et al*, 2006). Genetic variation in the mu-opioid receptor, which has downstream effects on dopamine release, is also related to dopamine release following an alcohol challenge (Ramchandani *et al*, 2011).

SPECT imaging has been used to demonstrate a modifying effect of a serotonin transporter (SERT) gene promoter variant (*5HTTLPR)* on the relationship between SERT occupancy after treatment with paroxetine (a selective serotonin reuptake inhibitor, or SSRI) and 6-week symptom relief in MDD (Ruhe *et al*, 2009). Carriers of the *5HTTLPR* L_A genotype showed positive associations between SERT occupancy in the diencephalon and improvements in scores on the Hamilton Depression Rating Scale; in the midbrain, this effect was significant only for L_A homozygotes. The L_A variant is associated with increased SERT transcription and up to twofold higher serotonin uptake (Lesch and Gutknecht, 2005); this suggests that SSRI activity may be more relevant to treatment outcome in individuals predisposed to greater SERT availability, although this finding requires replication. Unfortunately, none of these studies included a placebo condition, precluding analysis of a gene $\times$ treatment interaction.

Finally, studies of the mu-opioid receptor variant *OPRM1* A118G, which modulates receptor expression and binding affinity (Mague and Blendy, 2010), offer promising support for use of [^{11}C]carfentanil PET imaging in this context. Homozygosity for the common A allele is associated with greater receptor availability in smokers, alcohol-dependent patients and healthy controls (Ray *et al*, 2011; Weerts *et al*, 2012). However, although the A allele is associated with increased risk of nicotine addiction, the G allele is more frequently a risk factor for alcohol dependence (Ray *et al*, 2012). Thus, associations between *OPRM1* variation and molecular phenotype may depend on the specific drug of abuse (Mague and Blendy, 2010).

SOME PITFALLS

Although the findings presented above represent a major step forward in our understanding of the genetic underpinnings of aberrant neurocircuitry associated with neuropsychiatric disorders and their treatment, several issues should be considered. Although neuroimaging offers the advantage of detecting more subtle objectively measured phenotypes, the sample sizes tend to be small, due in part to the intensity and cost of these assessments. Consequently, these studies may be prone to detect spurious genetic associations; this is a particular problem with *post-hoc* genotyping of multiple candidate genes. Studies that incorporate prospective genotyping of functional variants with an *a priori* hypothesis can attenuate this problem to some extent, but replication is necessary. A focus on variants identified in GWAS of psychiatric illness is proving to be a useful approach in imaging genetic research (Tost *et al*, 2012). Moreover, integrating GWAS approaches with neuroimaging directly may lead to the identification of novel variants underlying treatment effects on brain structure and function. Although the volume of the data generated poses some challenges, appropriate correction procedures may address this (Meyer-Lindenberg *et al*, 2008). Furthermore, understanding the molecular basis of these novel variants is required to build polygenic models that accurately represent biological function.

Well-validated neuroimaging paradigms and use of standardized neurobehavioral task probes are critical to advance the field. Within fMRI, for example, there is tremendous variability in experimental paradigms and analytic approaches that contributes to false positive results (Carpentier *et al*, 2012). The issue of test-retest reliability is another consideration; some cognitive fMRI measures (such as the n-back working memory task) provide very good within-subject reproducibility, whereas others (such as the facial matching tasks) are more variable (Bennett and Miller, 2010; Plichta *et al*, 2012). Further, comorbidities in psychiatric populations can pose a significant challenge, and variability in screening criteria across studies may

limit the reproducibility of findings. For example, nicotine dependence occurs at a substantial rate in persons with mood disorders, psychosis and other forms of addiction. However, despite well-documented effects of both smoking and nicotine withdrawal on neural activation and neurotransmitter regulation, few psychiatric imaging studies control for smoking status, smoking rate, or time since last use in any rigorous way.

An added consideration for the eventual use of neuroimaging phenotypes is the increased cost compared with standard behavioral and clinical measures, which may be prohibitive for some patients and therefore requires clear demonstration of added value. However, imaging measures do provide an objective assessment that does not rely on patient self-report or clinician judgment. Imaging may also provide a more sensitive measure, enabling more rapid feedback for treatment decisions and facilitating rapid screening of new medications. Imaging measures for medication screening may reduce the necessary sample size to demonstrate an effect (or lack thereof) in early clinical development. However, to achieve the promise of these approaches, study designs that randomize patients to treatment are necessary to test a pharmacogenetic hypothesis.

CONCLUSION AND FUTURE DIRECTIONS

The emerging integration of neuroimaging into psychiatric pharmacogenetics research has the potential to accelerate psychiatric treatment development and delivery. For example, neuroimaging studies are contributing to a more refined understanding of treatment targets by elucidating the neural circuits and neurochemical processes underlying a broader range of neurobehavioral phenotypes. These include: alterations in reward learning and response to reward, executive cognitive function, decision-making and behavioral control, emotional reactivity, and social processing. Resting state functional connectivity (rsFC) studies are providing additional insight into the role of large-scale network coupling in psychiatric disorders (Menon, 2011). These studies have demonstrated genetic influences on rsFC in schizophrenia, MDD, and addiction, and suggest that rsFC may have the potential to predict treatment response (Hong *et al*, 2010; Liu *et al*, 2011; Chen *et al*, 2012; Jamadar *et al*, 2013). However, to our knowledge no studies have yet combined genetic analysis of rsFC with treatment in a psychiatric population, highlighting this as an area for further exploration. Further, neuroimaging of treatment effects on these targets can generate profiles of the effects of efficacious treatments on aberrant neural circuitry or neurochemistry, providing a biomarker of treatment response against which novel compounds can be compared and selected for future development. For example, a demonstration that tolcapone, a COMT inhibitor approved for treatment of Parkinson's disease, significantly improved cortical efficiency during tasks assessing executive function in healthy individual homozygous for the val allele of the *COMT* val158met variant (Apud *et al*, 2007) has inspired research into genotype-based tolcapone treatment of cognitive impairments in schizophrenia (Apud *et al*, 2007; Roussos *et al*, 2009). Incorporating genetics into these studies can provide an assay of individual differences in treatment response, enabling the development of medications that are targeted to particular genotypic groups. The identification of treatment responders and non-responders using a combination of genetic and neuroimaging approach may thus provide a more powerful strategy for targeted therapy than either tool alone (Ray *et al*, 2008).

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