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Dopaminergic Genetic Variation Influences Aripiprazole Effects on Alcohol Self-Administration and the Neural Response to Alcohol Cues in a Randomized Trial

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Dopamine (DA) signaling regulates many aspects of Alcohol Use Disorder (AUD). However, clinical studies of dopaminergic medications, including the DA partial agonist aripiprazole (APZ), have been inconsistent, suggesting the possibility of a pharmacogenetic interaction. This study examined whether variation in DA-related genes moderated APZ effects on reward-related AUD phenotypes. The interacting effects of APZ and a variable number tandem repeat (VNTR) polymorphism in *DAT1/SLC6A3* (the gene encoding the DA transporter (DAT)) were tested. In addition, interactions between APZ and a genetic composite comprising the *DAT1* VNTR and functional polymorphisms in catechol-*O*-methyltransferase (*COMT*), *DRD2*, and *DRD4* were evaluated. Ninety-four non-treatment-seeking individuals with AUD were genotyped for these polymorphisms, randomized to APZ (titrated to 15 mg) or placebo for 8 days, and underwent an fMRI alcohol cue-reactivity task (day 7; $n = 81$) and a bar lab paradigm (day 8). Primary outcomes were alcohol cue-elicited ventral striatal (VS) activation and the number of drinks consumed in the bar lab. *DAT1* genotype significantly moderated medication effects, such that APZ, relative to placebo, reduced VS activation and bar-lab drinking only among carriers of the *DAT1* 9-repeat allele, previously associated with lower DAT expression and greater reward-related brain activation. The genetic composite further moderated medication effects, such that APZ reduced the primary outcomes more among individuals who carried a larger number of *DAT1*, *COMT*, *DRD2*, and *DRD4* alleles associated with higher DA tone. Taken together, these data suggest that APZ may be a promising AUD treatment for individuals with a genetic predisposition to higher synaptic DA tone.

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INTRODUCTION

Dopamine (DA) signaling regulates many aspects of Alcohol Use Disorder (AUD). Alcohol cues and intravenous alcohol self-administration both increase DA release in the human ventral striatum (VS) (Boileau *et al*, 2003; Oberlin *et al*, 2013). Individuals with AUD, relative to controls, display enhanced alcohol-induced (Yoder *et al*, 2016) but blunted amphetamine-induced VS DA release (Martinez *et al*, 2005) and, unlike controls, demonstrate no association between striatal DA release and prefrontal glucose metabolism (Volkow *et al*, 2007), suggesting impaired cortical modulation of VS DA signaling. To remediate this impairment, several dopaminergic medications have been explored as AUD treatments, including the atypical antipsychotic aripiprazole (APZ) (Vergne and Anton, 2010), a high-affinity D_2, D_3, and 5-HT_{1A} partial agonist that also acts as an antagonist at 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, and 5-HT_7 receptors (Shapiro *et al*, 2003; Yokoi *et al*, 2002). Despite this relatively broad pharmacological profile, APZ is of particular interest for AUD, because its D_2 partial agonist property may stabilize dysregulated DA neurotransmission by increasing striatal DA synthesis among individuals with low basal synthesis capacity and decreasing it among individuals with high basal capacity (Ito *et al*, 2012).

APZ has been reported to reduce alcohol-induced euphoria (Kranzler *et al*, 2008), drinking in the natural environment and a bar-lab setting (Voronin *et al*, 2008), and alcohol cue-elicited VS activation (Myrick *et al*, 2010). In a large multisite AUD clinical trial, APZ did not significantly change the primary drinking outcome (percent days abstinent), but did significantly improve other outcomes, including drinks per drinking day and an alcohol consumption biomarker (Anton *et al*, 2008). As in other studies, these latter effects were highly variable, suggesting that between-subjects differences in an unknown factor might moderate APZ effects.

Given APZ's effects on DA transmission, one such between-subjects difference might be DA-related genetic variation. The DA transporter (DAT) is the primary mechanism for striatal DA clearance. A 40 bp variable number tandem repeat (VNTR) polymorphism (rs28363170) in the 3′-untranslated region of the DAT gene (*DAT1/SLC6A3*), whose most common allelic variants are 9 and 10

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repeats, may affect DAT function. The 9-repeat (9R) allele, relative to the 10-repeat (10R) allele, has been associated with reduced DAT expression (Fuke *et al*, 2001) and, among AUD individuals, lower striatal DAT availability (Heinz *et al*, 2000), potentially leading to relatively increased extrasynaptic DA tone. Consistent with these findings, individuals who carry the 9R allele, relative to 10R homozygotes, display greater VS activation during reward anticipation and receipt (Aarts *et al*, 2010; Dreher *et al*, 2009; Forbes *et al*, 2009). Further, nicotine-dependent 9R carriers display greater smoking cue-elicited VS activation (Franklin *et al*, 2009; 2011) and greater VS DA release after smoking (Brody *et al*, 2006).

Beyond the *DAT1* VNTR, polymorphisms in other genes also affect DA tone and reward-related behavior, including AUD-specific phenotypes. Multilocus genetic composite scores comprised of genotypes at the *DAT1* VNTR and polymorphisms in the genes encoding the DA-catabolizing enzyme catechol-*O*-methyltransferase (*COMT*) and the D_2 and D_4 receptors (*DRD2* and *DRD4*) have been reported to predict striatal response to reward, such that individuals who carry a larger number of alleles putatively associated with high basal DA tone display greater reward-related VS activation (Nikolova *et al*, 2011; Stice *et al*, 2012). The polymorphisms aggregated in these composites include single-nucleotide polymorphisms (SNPs) in *COMT* (rs4680/val158met) and *ANKK1* (rs1800497/Taq1A, originally believed to be in the adjacent *DRD2* promoter) and a 48 bp VNTR in *DRD4*. The *COMT* met allele has been associated with reduced COMT efficiency (Chen *et al*, 2004), likely increasing extrasynaptic DA accumulation, and with heightened DA receptor sensitivity among AUD individuals (Schellekens *et al*, 2012). The *ANKK1* Taq1A A1 allele has been associated with dysregulated DA response among AUD individuals (Schellekens *et al*, 2012) and is in high linkage disequilibrium with the *DRD2* rs1076560 T allele, which has been associated with reduced striatal expression of the short (primarily presynaptic) D_2 receptor isoform (Zhang *et al*, 2007), likely increasing extrasynaptic DA accumulation. Finally, the *DRD4* VNTR long allele has been associated with reduced *DRD4* mRNA expression (Simpson *et al*, 2010), altered intracellular signaling after D_4 binding (Asghari *et al*, 1995), and, among heavy drinkers, greater alcohol craving after consumption of a priming drink (Hutchison *et al*, 2002), greater alcohol cue-elicited striatal activation (Filbey *et al*, 2008), and less cortical activation during response inhibition (Filbey *et al*, 2011).

Individually, each of these DA-related polymorphisms may also influence dopaminergic drug effects. Evidence is strongest for the *DAT1* VNTR, which has been reported to moderate the effects of methylphenidate (Kasparbauer *et al*, 2015; Kooij *et al*, 2008), the D_2 agonist bromocriptine (van Holstein *et al*, 2011), and the D_2/D_3 agonist ropinirole (MacDonald *et al*, 2016) on cognitive function. Among AUD individuals, we previously reported an interaction between *DAT1* genotype and naltrexone, an opioid antagonist that decreases alcohol-induced striatal DA release, on alcohol cue-elicited medial prefrontal cortex activation (Schacht *et al*, 2013). Among individuals with schizophrenia, multiple studies suggest that *DRD2* rs1076560 (Blasi *et al*, 2015) and *COMT* rs4680 (Schacht, 2016) moderate antipsychotic effects on schizophrenia symptoms. Finally, among heavy drinkers and AUD individuals, the *DRD4* VNTR has been reported to moderate atypical antipsychotic (olanzapine) effects on drinking and cue-elicited alcohol craving (Hutchison *et al*, 2003, 2006), and opioid antagonist (LY2196044) effects on drinking (Wong *et al*, 2014). Taken together, these data strongly suggest the possibility of a pharmacogenetic interaction between DA-related genetic variation and dopaminergic drugs, particularly in AUD, in which DA function is dysregulated.

Given these findings, the current study investigated whether *DAT1* VNTR genotype or a broader index of DA-related genetic variation comprised of genotypes at the *DAT1* and *DRD4* VNTRs and *COMT* rs4680 and *DRD2* rs1076560 SNPs moderated APZ effects on reward-related phenotypes among non-treatment-seeking AUD individuals. Primary outcomes were alcohol cue-elicited VS activation and alcohol self-administration in a bar-lab setting. APZ has fewer adverse side effects than other atypical antipsychotics (Khanna *et al*, 2014), but its most common adverse effects are nausea, dizziness, and somnolence (Mallikaarjun *et al*, 2004); thus, adverse effect severity was a secondary outcome. APZ, relative to placebo, was hypothesized to reduce all outcomes to a greater extent among *DAT1* 9R carriers, relative to 10R homozygotes, and among individuals with a larger number of alleles associated with relatively higher basal DA tone.

MATERIALS AND METHODS

Overview

The Medical University of South Carolina (MUSC) Institutional Review Board approved the study, which was an 8-day sub-acute dosing human laboratory investigation (ClinicalTrials.gov identifier: NCT01292057) conducted at MUSC between April 2011 and December 2015. All subjects provided informed consent before participation, for which they were compensated. After randomization to study medication, subjects underwent an fMRI alcohol cue-reactivity task on day 7 of medication ingestion and a bar-lab paradigm on day 8. To maximize cue reactivity and motivation to drink, they were instructed to abstain from alcohol on the evenings of days 6 and 7. These procedures were identical to those previously published (Anton *et al*, 2012; Schacht *et al*, 2013).

Subjects

Subjects were recruited via media advertisements and were required to be ages 21–40 and to meet DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, revised 4th edition) diagnostic criteria for Alcohol Dependence, as assessed by the Structured Clinical Interview for DSM-IV (First *et al*, 2002). The upper age limit was chosen for two reasons. First, the study required alcohol administration; this can only be ethically achieved on an outpatient basis among non-treatment-seeking subjects, who tend to be younger than treatment seekers (Ray *et al*, 2017). Second, subjects were randomized to medication on the basis of a trait impulsivity measure (see below); as age and impulsivity are negatively correlated (Galvan *et al*, 2007), the upper limit was intended to ensure a sufficient number of individuals with

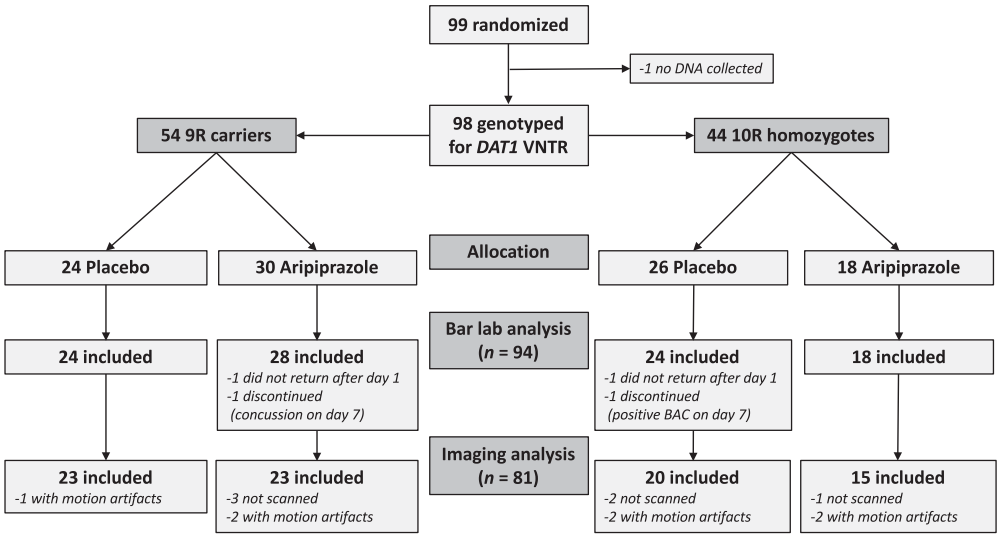

Figure 1 Subject flow through the study.

higher impulsivity. Exclusion criteria were as follows: current DSM-IV Substance Dependence for any other substance, except nicotine; current use of illicit substances or any prescription medication, as evidenced by urine drug screen and self-report; current DSM-IV Axis I diagnosis or suicidal/homicidal ideation; history of significant medical illness; and liver enzyme (ALT or AST) levels greater than three times normal. Female subjects could not be pregnant or nursing. At baseline, the Alcohol Dependence Scale (Skinner and Allen, 1982), Obsessive Compulsive Drinking Scale (OCDS) (Anton *et al*, 1996), and Timeline Follow-back (Sobell and Sobell, 1992) were used to assess AUD severity, alcohol craving, and past-90-day drinking, respectively.

Figure 1 displays subject flow through the study. Ninety-nine subjects were randomized to medication, but DNA was not collected from one subject. Of the remaining 98 subjects, 2 did not return after day 1 and 2 were discontinued from the study before completing the fMRI or bar-lab sessions, leaving 94 subjects for the bar-lab analysis (Table 1 lists demographic and severity data for these subjects). Of these individuals, 6 were not scanned, due to equipment issues ($n=2$), claustrophobia ($n=2$), and alcohol withdrawal symptoms on day 7 ($n=2$), and 7 were excluded due to motion during the scan, leaving 81 subjects for the imaging analysis. Demographic and severity characteristics for this subset of subjects did not significantly differ from the larger sample.

Genotyping

Genomic DNA was extracted from peripheral blood mononuclear cells (Gentra Puragene Blood Kit; Qiagen, Valencia, CA) and PCR-amplified. VNTR genotypes were determined using custom primers 5′-TGTGGTGTAGGGAACGGCCT-GAG-3′ and 5′-CTTCCTGGAGGTCACGGCTCAAGG-3′ (*DAT1*), and 5'-AGGACCCTCATGGCCTTG-3′ and 5′-GCGACTACGTGGTCTACTCG-3′ (*DRD4*) (Thermo Fisher Scientific, Waltham, MA). Amplified samples were electrophoresed on 2.0% agarose gels and visualized with ethidium bromide under UV light, and genotypes were scored by two raters independently. For *DAT1*, two subjects carried alleles other than 9R or 10R: one had one 8R allele and one had two 3R alleles. As alleles with <9 repeats have also been associated with reduced DAT expression relative to the 10R allele (Fuke *et al*, 2001), these alleles were categorized as 9R for analytic purposes. For *DRD4*, using the classification system most consistent in the addiction literature (McGeary, 2009), alleles were scored as "long" ($\geqslant 7$ repeats) or "short" (<7 repeats). *DRD4* genotype could not be determined for one subject. SNP genotypes were determined with a StepOne Real-Time PCR System and Taqman 5′-nuclease assays (Thermo Fisher), using allele-specific probes (Catalog 4351376 and 4362691) and three known controls for each genotype. Genotypes for all polymorphisms (Table 2) were in Hardy–Weinberg equilibrium and consistent with expected population allele frequencies (Chang *et al*, 1996; Clarke *et al*, 2014; Kang *et al*, 1999; Palmatier *et al*, 1999).

Randomization and Medication

Subjects were urn randomized (Stout *et al*, 1994) to receive APZ (day 1: 5 mg; days 2–3: 10 mg; and days 4–8: 15 mg) or placebo for 8 days, instructed to take medication each morning, and were observed to ingest the first and last doses. APZ's elimination half-life is ~60 h and peak concentration (C_{max}) for a 15 mg dose occurs ~3 h after ingestion (Mallikaarjun *et al*, 2004). Thus, medication was at C_{max} and ~90% of steady state during the experimental procedures on days 7 and 8. As subjects were non-treatment seekers who were not motivated to reduce their drinking, procedure timing was chosen to achieve near-maximal steady state while minimizing subject attrition that might have occurred by the time 100% steady state was achieved after 12–13 days of medication. Subjects and investigators were blind to both genotype and medication assignment. A parent study, described in a companion paper (Anton *et al*, 2017), hypothesized that APZ would reduce drinking more among subjects with greater trait impulsivity (briefly, data supported this hypothesis for bar-lab drinking). Thus, subjects were stratified by their baseline Barratt Impulsiveness Scale (BIS-11) (Patton *et al*, 1995) score into groups with BIS-11 scores greater vs. less than the median score of 68 observed in a previous pilot study (Voronin *et al*, 2008),

Table 1 Demographic, Severity, and Drinking Data

	***DAT1* 9R carriers**		***DAT1* 10R homozygotes**		p^a	p^b
	Placebo	**APZ**	**Placebo**	**APZ**		
N	24	28	24	18	—	—
Age	27.9 (5.4)	25.4 (4.7)	26.1 (5.2)	28.4 (6.6)	0.69	0.18
Sex (% male)	75.0	75.0	79.2	77.8	0.91	0.98
Race (% Caucasian)	75.0	82.1	83.3	83.3	0.67	0.87
Current smoker (%)	58.3	35.7	33.3	55.6	0.82	0.19
ADS score	11.3 (6.8)	13.2 (5.9)	12.0 (6.2)	12.6 (5.8)	0.29	0.72
BIS-11 score	63.8 (16.5)	67.2 (15.2)	66.7 (12.5)	64.1 (11.5)	0.80	0.78
OCDS score	16.4 (8.0)	18.0 (8.6)	16.3 (8.8)	19.2 (7.7)	0.22	0.63
Drinks per day[a]	6.2 (2.8)	8.6 (3.9)	7.2 (2.8)	7.8 (2.9)	**0.02**	**0.05**
Drinks per drinking day[a]	7.9 (3.1)	10.7 (3.4)	9.5 (3.6)	9.3 (3.4)	**0.04**	**0.04**
Heavy drinking days, %[a]	72.3(26.6)	94.4 (9.8)	80.1 (23.0)	79.5 (26.9)	**0.01**	**0.01**

Abbreviations: ADS, Alcohol Dependence Scale; APZ, aripiprazole; BIS-11, Barratt Impulsiveness Scale; OCDS, Obsessive Compulsive Drinking Scale.
Figures are means (SD) unless otherwise indicated. Current smoking was defined as smoking $\geqslant 10$ cigarettes per day. Statistics for differences between groups refer to the significance of the χ^2-statistic for sex, race, and smoking, and the *t* and *F* statistics for other variables. *P* values for significant differences ($p < 0.05$) are bolded.
p^a = test for difference between medication groups.
p^b = test for difference between all four groups.
[a]In the 90 days before medication randomization.

Table 2 Genotype Frequencies and Scoring for Each Polymorphism

Polymorphism	**Genotypes**	***n***	**Frequency**	**DA-related composite score**	
				Additive	**Dominant**
DAT1 VNTR	9/9	16	0.17	High	High
	9/10	36	0.38	Intermediate	High
	10/10	42	0.45	Low	Low
COMT rs4680	Met/met	25	0.27	High	High
	Met/val	41	0.44	Intermediate	High
	Val/val	28	0.30	Low	Low
DRD2 rs1076560	T/T	1	0.01	High	High
	T/G	27	0.29	Intermediate	High
	G/G	66	0.70	Low	Low
DRD4 VNTR	Long/long	3	0.03	High	High
	Long/short	29	0.31	Intermediate	High
	Short/short	61	0.65	Low	Low

For the DA-related genetic composite measure, two scoring models were evaluated. For the additive model, "high" genotypes (two alleles associated with higher DA tone) were scored as 2, "intermediate" genotypes as 1, and "low" genotypes as 0, and the total possible score ranged from 0 (no higher DA alleles) to 8 (all higher DA alleles). For the dominant model, homozygous "high" genotypes and heterozygous "intermediate" genotypes were each scored as 1 and "low" genotypes as 0, and the total possible score ranged from 0 (homozygous for all lower DA alleles) to 4 (homozygous or heterozygous for all higher DA alleles).

and randomization was conducted separately within each stratum. Urn variables balanced across medication groups within each stratum were sex and smoking status. Study medications were identically over-encapsulated with 100 mg riboflavin and distributed in labeled blister packs. Urinary riboflavin was measured at baseline and on day 7 with a fluorometric assay based on standard curves of weighed-in riboflavin (Anton, 1996), and samples were considered adherent if the riboflavin value was $\geqslant 1000$ ng/ml or had doubled since baseline.

Neuroimaging

On day 7, subjects were breathalyzed, assessed for alcohol withdrawal, and re-administered the OCDS. As noted above, one subject with a breath alcohol concentration (BAC) >0 and two subjects with Clinical Institute Withdrawal Assessment for Alcohol-Revised (Sullivan *et al*, 1989) scores >4 were excluded from scanning. Scans were scheduled in the afternoon or evening, to ensure medication was at C_{max}. After acquisition of a high-resolution anatomical image, subjects were given a sip (10 ml) of their preferred 80-proof liquor mixed with juice and administered a 12 m-long task

during which they passively viewed pseudorandomly interspersed blocks of alcoholic beverage images (ALC) (equally distributed between beer, wine, and liquor), non-alcoholic beverage images (BEV), blurred versions of these images that served as visual controls, and a fixation cross. Each 24 s-long block comprised only one image type and was followed by a 6 s period during which subjects were instructed to rate their urge for alcohol. Images were selected from a normative set (Stritzke *et al*, 2004), supplemented with images from advertisements, and matched for intensity, color, and complexity. This task consistently elicits robust cue-elicited VS activation among non-treatment-seeking AUD individuals (Schacht *et al*, 2011).

Functional images were acquired with a gradient echo, echo-planar imaging sequence implemented on a 3T TIM Trio scanner (Siemens, Erlangen, Germany). Acquisition parameters were as follows: repetition/echo times = 2200-/35 ms; 328 volumes; flip angle = 90°; field of view = 192 mm; matrix = 64 × 64; voxel size = 3.0 × 3.0 mm; 36 contiguous 3.0 mm-thick transverse slices. Using FEAT (fMRI Expert Analysis Tool) v. 6.00, part of FSL (FMRIB's Software Library, Oxford) (Smith *et al*, 2004), functional images were realigned to the middle volume, spatially smoothed (8 mm full width at half maximum kernel), resampled to 2 mm isotropic voxels, and registered, first to the subject's high-resolution anatomical image and subsequently to the Montreal Neurological Institute (MNI) 152-subject-average template. Based on previous findings of greater reliability (Schacht *et al*, 2011) and better prediction of medication response (Schacht *et al*, 2017) for right, vs. left, cue-elicited VS activation, analyses focused on the right VS, defined *a priori* as a 6 mm-radius sphere centered at the point (12 15 −6) in MNI space. For each subject, this sphere was reverse registered from the MNI-152 image to the subject's anatomical image and the average percentage change of the blood oxygen level-dependent signal between ALC and BEV blocks (i.e., ALC vs. BEV percent signal change) was extracted using the FSL featquery tool.

Bar-lab Paradigm

On day 8, subjects were observed to ingest the last medication dose at 1130 h. Thirty minutes later, they were provided a gender- and weight-adjusted standard caloric lunch. At 1400 h, subjects were administered a priming drink (1:3 ratio of their preferred 80-proof liquor and juice), adjusted for gender, age, and weight to produce a targeted BAC of 30 mg% (Watson, 1989), and instructed to consume it within 5 min. Forty minutes later, subjects were presented a tray of four drinks, each with a targeted BAC of 15 mg%, and told they could consume as many as they desired over the next hour. After an hour, this tray was removed and another tray of four drinks was made available over a second hour. To create a decisional balance between drinking and abstaining, subjects were given a "bar credit" of $16 with which to "purchase" drinks, at the cost of $2/drink, and were told that any money they did not spend would be given to them the following day. After the procedure, subjects were given dinner and remained until 2200 h. A BAC measurement below 20 mg% was required before departure and a friend or taxi drove subjects home.

Adverse Effects

A physical symptom checklist was used to assess the presence and severity (self-rated as none, mild, moderate, or severe) of 21 adverse effects at baseline and on day 8, immediately before the bar-lab paradigm.

Statistical Analysis

The general linear model (GLM) (SPSS 23, IBM, Armonk, NY) was used to test the interaction between medication and *DAT1* genotype on the primary outcomes (VS ALC vs. BEV activation and the number of drinks consumed in the bar lab). A model that included between-subjects factors for medication, *DAT1* genotype, and their interaction was tested for each outcome. Analyses first compared 9R carriers with 10R homozygotes and subsequently examined the additive effect of the 9R allele. By chance, baseline drinking significantly differed between groups, such that APZ-treated subjects, and specifically APZ-treated *DAT1* 9R carriers, drank more heavily (Table 1); accordingly, baseline drinks per day was covaried in all models. Significant interactions were followed up with simple effects contrasts. Effect sizes were estimated with the η_p^2 statistic, which summarizes the amount of variance in the dependent variable attributable to the interaction term or simple effect, and for which effects can be categorized as "small" ($\eta_p^2 \geqslant 0.0099$), "medium" ($\eta_p^2 \geqslant 0.0588$), or "large" ($\eta_p^2 \geqslant 0.1379$) (Cohen, 1969). VS activation was also analyzed for correlation (Pearson's *r*) with BIS scores, day 7 OCDS scores, and bar-lab drinking.

The GLM was also used to test the interaction between medication and a DA-related genetic composite on the primary outcomes. Based on previous data regarding the functional significance of each polymorphism and its consequences among AUD individuals, the *DAT1* 9R, *COMT* met, *DRD2* T, and *DRD4* long alleles were categorized as higher-DA alleles, and the total number of alleles each subject carried was calculated (Table 2). Few subjects carried more than four higher-DA alleles (four subjects had five alleles and one had seven), so these subjects were combined with those who carried four, yielding five groups of subjects with zero ($n = 7$), one ($n = 15$), two ($n = 31$), three ($n = 22$), or four or more ($n = 18$) alleles. These groups did not significantly differ on any characteristic indicated in Table 1, except race (see below). A model that included between-subjects factors for medication, the additive effect of the number of higher-DA alleles, and their interaction was tested for each outcome. To explore the contributions of each polymorphism relative to *DAT1* genotype alone, every permutation of *DAT1* genotype and the other polymorphisms (e.g., *DAT1*+*COMT*, *DAT1*+*DRD2*, *DAT1*+*COMT*+*DRD2*, etc.) was calculated, and effect sizes for the interactions between these permutations and medication on the primary outcomes were estimated. A dominant model with two groups per polymorphism, in which higher DA-allele homozygotes and heterozygotes were combined, was also tested; only three subjects had ⩾1 higher-DA allele for all four polymorphisms, so they were combined with those who carried ⩾1 allele for three polymorphisms.

For the secondary outcome (adverse effect severity), the main effect of medication on the presence/absence of each effect was first evaluated with the GLM. Insomnia, somnolence, irritability, trouble concentrating, nausea/vomiting,

dizziness, fatigue, blurry vision, and difficulty reaching orgasm were significantly more frequent ($p<0.05$) in the APZ group (see Anton *et al*, 2017 for detail). To account for the influence of these effects on the pharmacogenetic interactions evaluated above, the presence/absence of each was evaluated individually as a covariate in all models. To evaluate whether *DAT1* genotype or DA composite score affected adverse effect severity, the generalized linear model was used to test interactions between medication and *DAT1* genotype and between medication and the additive effect of the number of higher DA alleles on the severity of each effect that significantly differed between medication groups.

RESULTS

Adherence

Of the 94 subjects included in the bar-lab analysis, 36/47 (76.6%) placebo-treated and 35/47 (74.4%) APZ-treated subjects were deemed adherent by urinary riboflavin on day 7; these proportions were not significantly different ($\chi^2(1, N=94)=0.058$, $p=0.81$).

Cue-elicited VS Activation

The interaction between medication and *DAT1* genotype was significant (F(1, 76) = 4.98, $p=0.029$, $\eta_p^2=0.061$). Relative to placebo, APZ reduced VS activation among 9R carriers, but increased it among 10R homozygotes (Figure 2a). The simple effect of medication approached significance among 10R homozygotes (F(1, 76) = 2.86, $p=0.095$). Baseline drinking did not significantly affect VS activation. In additive analyses, the interaction between medication and *DAT1* genotype was also significant (F(1, 76) = 5.13, $p=0.026$, $\eta_p^2=0.063$), such that APZ, relative to placebo, reduced VS activation more among subjects with a greater number of 9R alleles. VS activation was significantly positively associated with day 7 OCDS score ($r(81)=0.26$, $p=0.018$), but not BIS-11 score or bar-lab drinking.

Bar-lab Drinking

The main effect of medication (F(1, 89) = 4.63, $p=0.034$, $\eta_p^2=0.049$) and the interaction between medication and *DAT1* genotype (F(1, 89) = 6.11, $p=0.015$, $\eta_p^2=0.064$) were significant, such that APZ, relative to placebo, reduced drinking among 9R carriers, but not 10R homozygotes (Figure 2b). The simple effect of medication was significant only among 9R carriers (F(1, 89) = 11.54, $p=0.001$, $\eta_p^2=0.115$). Baseline drinking significantly affected bar-lab drinking (F(1, 89) = 4.80, $p=0.031$), such that subjects who drank more at baseline also drank more in the bar lab. In additive analyses, the interaction between medication and *DAT1* genotype was also significant ($F(1, 89)=4.73$, $p=0.032$, $\eta_p^2=0.050$), such that APZ, relative to placebo, reduced drinking more among subjects with a greater number of 9R alleles.

DA-Related Genetic Composite Effects

The interaction between medication and the additive effect of higher DA alleles across all four polymorphisms was significant for both VS activation (F(1, 76) = 4.12, $p=0.046$, $\eta_p^2=0.051$; Figure 3a) and bar-lab drinking (F(1, 88) = 6.50, $p=0.013$, $\eta_p^2=0.069$; Figure 3b), such that APZ reduced these outcomes more among subjects with a greater number of higher DA alleles. The simple effect of medication on bar-lab drinking was significant only among subjects who carried four or more higher-DA alleles (F(1, 82) = 14.60, $p=0.0005$, $\eta_p^2=0.151$). Effect sizes for the pharmacogenetic interactions were larger for most genotype permutations than for *DAT1* alone. For all interactions, APZ effects were better among individuals with a greater number of higher DA alleles. For VS activation, the largest effect was for the permutation of *DAT1*, *DRD2*, and *DRD4* genotypes ($\eta_p^2=0.084$); for bar-lab drinking, for the permutation of *DAT1*, *COMT*, and *DRD2* genotypes ($\eta_p^2=0.10$) (Table 3). Interactions between the dominant model composite and medication were significant for both VS activation (F(1, 76) = 3.98, $p=0.050$, $\eta_p^2=0.050$) and bar-lab drinking (F(1, 88) = 5.89, $p=0.017$, $\eta_p^2=0.063$), such that APZ, relative to placebo, reduced these outcomes more among subjects with higher composite scores, with the largest effect in the '3+' group.

Impulsivity Effects

As subjects were randomized to medication on the basis of their BIS-11 scores and we previously reported that BIS-11 self-control significantly moderated APZ effects on bar-lab drinking (Anton *et al*, 2017), we evaluated whether BIS-11

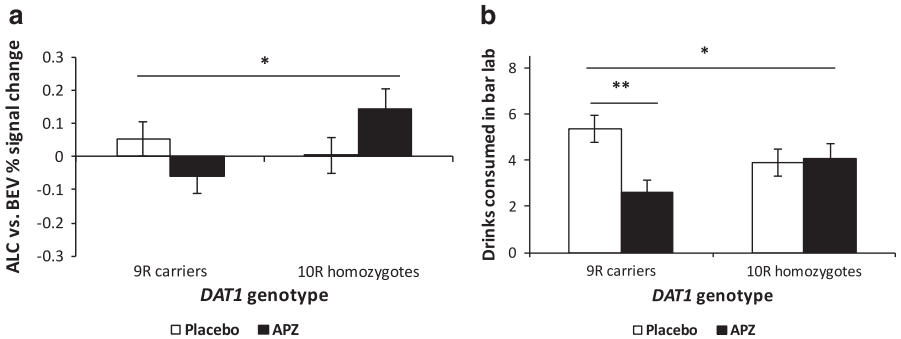

Figure 2 Effects of medication group and *DAT1* variable number tandem repeat (VNTR) genotype on (a) alcohol cue-elicited ventral striatal (VS) activation and (b) bar-lab drinking. These factors significantly interacted in their effects on both outcomes, such that aripiprazole (APZ), relative to placebo (PLA), reduced cue-elicited activation and bar-lab drinking among 9R carriers, but not among 10R homozygotes. Figures are estimated marginal means ± SE and are adjusted for baseline drinks per day. *$p<0.05$ for interaction between medication and genotype; **$p\leqslant 0.001$ for simple effect of medication among 9-repeat (9R) carriers.

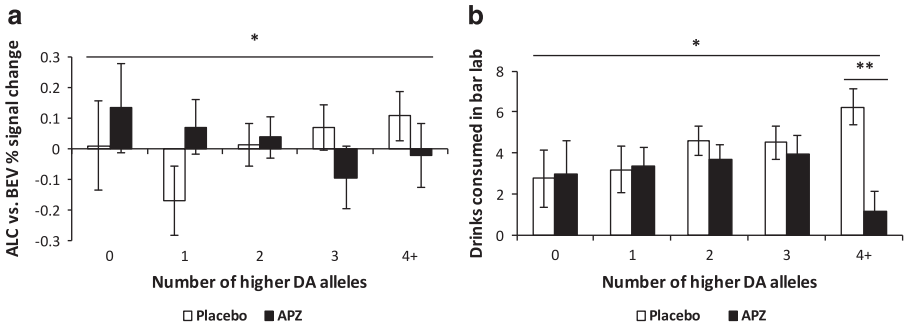

Figure 3 Effects of medication group and the additive dopamine (DA)-related genetic composite measure on (a) alcohol cue-elicited ventral striatal (VS) activation and (b) bar-lab drinking. These factors significantly interacted in their effects on both outcomes, such that aripiprazole (APZ), relative to placebo (PLA), reduced cue-elicited activation and bar-lab drinking more among subjects who carried a greater number of alleles associated with higher DA. Figures are estimated marginal means ± SE and are adjusted for baseline drinks per day. *$p < 0.05$ for interaction between medication and linear effect of number of higher DA alleles; **$p \leqslant 0.001$ for simple effect of medication among individuals with four or more higher DA alleles.

Table 3 *P*-values and Effect Sizes for Interactions Between Medication and Permutations of *DAT1* VNTR and Other DA-Related Polymorphisms

	VS activation ($n = 81$)		Bar lab drinks ($n = 94$)	
Genotype permutation	***p***	η_p^2	***p***	η_p^2
DAT1	**0.026**	0.063	**0.032**	0.050
DAT1+COMT	0.19	0.023	**0.007**	0.079
DAT1+DRD2	**0.021**	0.068	**0.006**	0.081
DAT1+DRD4	**0.014**	0.077	**0.045**	0.045
DAT1+COMT+DRD2	0.16	0.026	**0.002**	0.100
DAT1+COMT+DRD4	0.087	0.038	**0.011**	0.071
DAT1+DRD2+DRD4	**0.01**	0.084	**0.011**	0.072
DAT1+COMT+DRD2+DRD4	**0.046**	0.051	**0.013**	0.069

Statistics are for the interaction between medication (aripiprazole vs. placebo) and each permutation of genotypes (additive effect of number of *DAT1* 9R, *COMT* met, *DRD2* T, and/or *DRD4* long alleles) in a general linear model that also included baseline drinks per day and the main effects of medication and the genotype permutation. *P*-values for significant interactions ($p < 0.05$) are bolded.

total or self-control subscale scores moderated the interactions between medication and either genetic factor (*DAT1* genotype or the DA-related genetic composite) on VS activation or bar-lab drinking. In every model, the three-way interaction between the BIS-11 variable (total or self-control score), the genetic factor, and medication was not significant, whereas the two-way interactions between each genetic factor and medication remained significant. Thus, pharmacogenetic effects did not vary as a function of impulsivity and these effects were independent from our previously reported interaction between self-control and APZ.

Adverse Effects

All interactions described above remained significant when any of the adverse effects that significantly differed between medication groups was covaried. The interaction between medication and *DAT1* genotype on insomnia severity was significant (Wald $\chi^2(1, N = 94) = 7.77$, $p = 0.005$), such that 10R homozygotes who received APZ, relative to placebo, had more severe insomnia, but 9R carriers did not. The interaction between medication and *DAT1* genotype on irritability approached significance (Wald $\chi^2(1, N = 94) = 2.92$, $p = 0.088$), in the same direction as the interaction for insomnia. *DAT1* genotype did not significantly moderate the severity of any other effects that significantly differed between medication groups. There was also a significant interaction between medication and the additive effect of higher DA alleles on insomnia severity (Wald $\chi^2(1, N = 93) = 5.01$, $p = 0.025$), but not other adverse effects, such that, among subjects who received APZ, insomnia was less severe among subjects with a greater number of higher DA alleles.

Race Effects

Consistent with expected allele frequencies, subjects with self-reported Caucasian ancestry ($n = 76$ for the total sample; $n = 66$ for those with usable imaging data) were significantly more likely to have more higher DA alleles than non-Caucasian subjects ($\chi^2(1, N = 93) = 9.57$, $p = 0.048$), so all models were also evaluated among only Caucasian subjects. All effects that were statistically significant in the larger sample remained significant in this subsample, except for the interaction between medication and the genetic composite on VS activation, which was reduced to trend-level significance ($p = 0.066$).

DISCUSSION

Collectively, these data suggest a novel pharmacogenetic interaction between DA-related genetic variation and APZ response in AUD. This interaction was medium-sized, with large medication effects in the groups that responded better to APZ, and was present for both the *DAT1* VNTR and a composite measure that aggregated genotypes at this VNTR and three other putatively functional DA-related polymorphisms. In each case, individuals with genotypes associated with higher basal DA tone displayed better APZ effects. Thus, APZ may be beneficial among individuals genetically predisposed to enhanced DA effects, but ineffective among others. This mixed profile could account for previous negative AUD clinical trial results.

As hypothesized, *DAT1* 9R carriers treated with APZ, compared with placebo, displayed less cue-elicited VS

activation and alcohol self-administration, and reported less severe APZ-related insomnia, than 10R homozygotes. Given the 9R allele's association with lower DAT expression (Fuke *et al*, 2001) and enhanced reward-related VS activation (Aarts *et al*, 2010; Dreher *et al*, 2009; Forbes *et al*, 2009), these individuals might have been predisposed to greater striatal extrasynaptic DA accumulation or prolonged effects after alcohol cue exposure or the bar-lab priming drink. APZ's DA partial agonist effect might have displaced this elevated endogenous DA among these individuals, reducing DA-mediated cue reactivity or alcohol reward. As APZ, relative to placebo, also potentiated VS activation (which was associated with greater OCDS scores) among *DAT1* 10R homozygotes, its D_2 partial agonist effect might have been detrimental among these individuals, who putatively have relatively lower DA tone. APZ's serotonergic effects might also have influenced this interaction; although beyond the scope of this work, evaluation of pharmacogenetic interactions between APZ and functional polymorphisms in serotonergic genes (e.g., *SLC6A4* 5-HTTLPR) might be fruitful. Although *DAT1* genotype significantly moderated medication effects on both cue-elicited VS activation and bar-lab drinking, these outcomes were not significantly correlated, suggesting potentially dissociable effects. However, as bar-lab safety constraints limited the number of drinks available for self-administration, the upper range of this variable might have been artificially restricted, obviating correlation with (unrestricted) VS activation.

Beyond its interaction with *DAT1* genotype, APZ, as hypothesized, also more effectively reduced VS activation and alcohol self-administration, and caused less severe insomnia, among individuals with a larger number of alleles associated with higher DA tone. Effect sizes for the pharmacogenetic interactions were larger for nearly all permutations of the genetic composite than for *DAT1* alone, suggesting that the other DA-related polymorphisms accounted for additional variance in APZ effects. Individually, each of these polymorphisms has previously been reported to moderate DA partial agonist effects, with better effects noted among individuals carrying more higher-DA alleles (Blasi *et al*, 2015; Hutchison *et al*, 2003, 2006; Schacht, 2016). In contrast, an interaction in the opposite direction was reported between a similar DA-related genetic composite and the effects of the D_2/D_3 agonist ropinirole on impulsive decision-making, such that ropinirole, relative to placebo, increased impulsivity among healthy adults who carried more higher-DA alleles (MacDonald *et al*, 2016). Taken together with previous reports of greater reward-related VS activation among individuals who carried more higher DA alleles (Nikolova *et al*, 2011; Stice *et al*, 2012), these findings suggest that individuals genetically predisposed to high DA tone may be hypersensitive to reward, and that partial, but not full, DA agonists may reduce this hypersensitivity among these individuals, perhaps by normalizing DA tone.

Study strengths included low attrition and the use of well-validated alcohol cue reactivity and self-administration paradigms. However, several factors limit interpretation. First, subjects were younger, primarily male, non-treatment-seeking individuals who were compensated for participation. It is unclear whether these pharmacogenetic findings extend to individuals older than 40 years or to treatment seekers such as those examined in the multi-site APZ trial (Anton *et al*, 2008), and the number of females limited power to evaluate sex as a moderator of pharmacogenetic effects. Second, DA-related genetic variation was an exploratory aim and subjects were randomized to medication by their BIS-11 scores rather than *DAT1* or other genotypes. However, impulsivity was well balanced between groups and did not significantly moderate pharmacogenetic effects. Finally, several caveats regarding the genetic composite should be noted. This measure assumed additive, rather than interactive, effects of its constituent polymorphisms, and combined polymorphisms associated with changes in both striatal and cortical DA. Low minor allele frequencies for the *DRD2* and *DRD4* polymorphisms precluded an interactive approach, which would have allowed evaluation of epistatic effects and of striatal vs. cortical DA effects on APZ efficacy. Previous work has suggested an interaction between *COMT* and *DAT1* variation on reward-related VS activation (Dreher *et al*, 2009; Yacubian *et al*, 2007), but no two- or three-way interactions between *DAT1*, *DRD4*, and *DRD2* variation on this phenotype have been previously observed (Forbes *et al*, 2009). Previous studies of similar DA-related genetic composites have sometimes categorized "higher-DA" alleles differently for some polymorphisms. Notably, the *DAT1* 10R allele has been associated with lower DAT availability among controls and individuals with attention-deficit/hyperactivity disorder (Faraone *et al*, 2014). However, among AUD individuals, the 9R allele was associated with lower striatal DAT availability (Heinz *et al*, 2000). Nonetheless, further study of the functional consequences of these polymorphisms among AUD individuals would be valuable.

In conclusion, this study suggested that, among non-treatment-seeking young adults with AUD, polymorphisms in *DAT1* and other DA-related genes moderated APZ effects on alcohol cue-elicited striatal activation and alcohol self-administration. These findings require replication, but potentially support a precision medicine approach for APZ in AUD, in which DA-related genetic variation might be used to target this medication to individuals particularly likely to demonstrate better therapeutic effects and fewer adverse effects.

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Dr. Schacht reports that, in the past 2 years, he has consulted for Laboratorio Farmaceutico CT. Dr. Anton reports that, in the past 2 years, he has consulted for Indivior, Xenoport, and Laboratorio Farmaceutico CT, and has received grant funding from Eli Lilly. He is the Chair of the Alcohol Clinical Trials Initiative (ACTIVE), which is conducted under the auspices of the American Society for Clinical Psychopharmacology and funded (currently or in the recent past) in part by Eli Lilly, Lundbeck, Pfizer, Ethypharm, Indivior, Xenoport/Arbor, Otsuka, and Amygdala. Drs. Randall and Voronin report no biomedical financial interests or potential conflicts of interest.

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