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Pharmacogenetic associations of the type-3 metabotropic glutamate receptor (*GRM3*) gene with working memory and clinical symptom response to antipsychotics in first-episode schizophrenia

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Abstract

Rationale—Type-3 metabotropic glutamate receptor gene (*GRM3*) single nucleotide polymorphisms (SNPs) have been associated with cognitive performance and prefrontal cortex brain activity in chronically treated schizophrenia patients. Whether these SNPs are associated with cognitive and symptom response to antipsychotic therapy has not been extensively evaluated.

Objectives—The aim of the study was to examine pharmacogenetic relationships between *GRM3* and selected variants in relevant dopamine genes with changes in spatial working memory and clinical symptoms after treatment.

Methods—Sixty-one untreated first-episode schizophrenia patients were assessed before and after 6 weeks of antipsychotic pharmacotherapy, primarily consisting of risperidone. Patients' level of cognitive performance on a spatial working memory task was assessed with a translational oculomotor paradigm. Changes after treatment in cognitive and clinical measures were examined in relationship to genetic polymorphisms in the *GRM3*, *COMT*, and *DRD2/ANKK1* gene regions.

Results—Spatial working memory performance worsened after antipsychotic treatment. This worsening was associated with *GRM3* rs1468412, with the genetic subgroup of patients known to have altered glutamate activity having greater adverse changes in working memory performance after antipsychotic treatment. Negative symptom improvement was associated with *GRM3* rs6465084. There were no pharmacogenetic associations between *DRD2/ANKK1* and *COMT* with working memory changes or symptom response to treatment.

Conclusions—These findings suggest important pharmacogenetic relationships between *GRM3* variants and changes in cognition and symptom response with exposure to antipsychotics. This information may be useful in identifying patients susceptible to adverse cognitive outcomes associated with antipsychotic treatment and suggest that glutamatergic mechanisms contribute to such effects.

Keywords

Schizophrenia; Pharmacogenetics; Antipsychotic; Cognition; Glutamate; Dopamine; *GRM3*; *COMT*; *DRD2*

Introduction

There is an urgent need to improve benefit and reduce adverse effects of treatments for patients with schizophrenia. First-line pharmacological options consist of antipsychotics, which have variable effects across patients in clinical benefit, tolerability, and cognition. Pharmacogenetic strategies may be useful in identifying mechanisms and potential biomarkers of response heterogeneity in ways that are both clinically applicable and helpful in guiding drug development efforts. One significant challenge inherent in pharmacogenetic studies of schizophrenia is the confounding nature of prior treatment exposure which may alter receptor expression (Wilmot and Szczepanik 1989), cell number (Konopaske et al. 2008), brain structure (Ho et al. 2011; Keshavan et al. 1994; Ren et al. 2013), and function

(Lui et al. 2010; Ren et al. 2013). Untreated or treatment-naïve patients early in their course of illness, while challenging to recruit, arguably afford an optimal approach for ascertaining antipsychotic effects on brain and behavior, as well as untarnished relationships with molecular measures.

The cognitive and clinical consequences of schizophrenia are both important outcomes for examination in pharmacogenetic studies. To date, pharmacogenetic aspects of cognitive response to antipsychotics have not been extensively examined in first-episode patients. Cognitive deficits in schizophrenia are a primary source of persistent functional disability associated with the illness (Green 1996; Hill et al. 2013; Kalkstein et al. 2010). When cognitive performance is assessed via domain-specific neurophysiology or neuropsychological tasks over the course of antipsychotic treatment, a mixed pattern of beneficial and adverse cognitive outcomes has been observed (Hill et al. 2008; Mishara and Goldberg 2004; Reilly et al. 2005, 2006, 2007; Riedel et al. 2010). Oculomotor tasks that assess specific neurophysiological indices of cognitive function have proven to be robust and sensitive methods to assess drug effects on cognition in non-human primates (Sawaguchi and Goldman-Rakic 1994) as well as humans (Reilly et al. 2008a, b) and are therefore useful translational approaches for probing the cognitive effects of centrally acting drugs.

One adverse cognitive effect of antipsychotics that has been identified using these neurophysiology measures is a worsening of spatial working memory (SWM) performance. This effect was originally demonstrated in nonhuman primates using an oculomotor delayed response paradigm (Sawaguchi and Goldman-Rakic 1994). Similar effects using the same paradigm have been reported in schizophrenia patients (Reilly et al. 2006, 2007). Notably, in the clinical studies, some patients showed more dramatic changes after treatment than others. Because working memory deficits are predictors of poor community outcome and employment status (Green 2006; Liddle 2000), exacerbating deficits in this domain after treatment are of significant clinical interest. Thus, identifying characteristics that may predispose some individuals to experience a worsening of existing cognitive deficits as a result of antipsychotic treatment is an important aspect of optimizing treatments for patients.

Candidate gene pharmacogenetic studies are useful in testing hypotheses about neurotransmitters already known to affect neurophysiological processes supporting cognitive activity, but for which relationships with genetics modulators of these systems in the context of drug exposure are undefined. As it relates to cognitive processes, we hypothesized that gene variants influencing glutamate signaling through the type-3 metabotropic glutamate receptor are related to cognitive response to antipsychotics and tested these associations along with other variants known to influence dopamine disposition, a well-recognized factor influencing cognitive processes.

Disruptions in glutamate transmission are thought to influence symptom presentation and cognitive dysfunction in schizophrenia. Group-II metabotropic glutamate receptors (i.e., mGluR2/3) have been studied in investigations examining mechanisms of glutamate dysfunction and as targets for drug development for schizophrenia (Javitt 2007; Moghaddam 2004; Moghaddam and Jackson 2003; Moghaddam and Javitt 2012). The type-3

metabotropic glutamate receptor gene (*GRM3*) encodes the mGluR3 protein which functions to modulate signaling through *N*-methyl-D-aspartate receptors (NMDARs) in ways that may reverse NMDAR hypofunction which is believed to be an important contributor to cognitive deficits and negative symptoms in schizophrenia (Cartmell and Schoepp 2000). Preclinical studies have indicated that pharmacologically altering mGluR3 can reverse behavioral effects of dopamine dysregulation in rodent models and may also have domain-specific cognitive effects (Amitai and Markou 2010; Bespalov et al. 2007; Yoon et al. 2008). While human genetic studies of *GRM3* have identified associations with prefrontal physiology and associated cognitive processes in chronically treated patients (Egan et al. 2004), pharmacogenetic relationships with cognitive or clinical outcomes have not been examined in first-episode treatment studies.

We designed the present study to test the hypothesis that genetic variation in *GRM3* influences antipsychotic effects on working memory. First-episode patients with minimal or no prior exposure to antipsychotics were recruited to minimize effects of prior drug exposure on initial assessments. Candidate single nucleotide polymorphisms (SNPs) selected included *GRM3* variants known to be related to glutamate disposition (Egan et al. 2004; Xia et al. 2012). Recognizing that dopamine disposition in the prefrontal cortex (PFC) also influences working memory, we additionally examined the commonly studied Val158Met (rs4680) polymorphism in the catechol-o-methyltransferase (*COMT*) gene, which is a primary genetic contributor to dopamine disposition in the PFC (Lachman et al. 1996). Interactions between *GRM3* and *COMT* have been reported in studies of disease risk and cognitive performance (Nicodemus et al. 2007; Tan et al. 2007). Finally, the TaqIA (rs1800497) and the −141C ins/del (rs1799732) variants in the dopamine-2 receptor gene and ankyrin repeat and kinase domain containing 1 gene (*DRD2/ANKK1)* region that are believed to influence of striatal dopamine-2 (D2) receptor density (Arinami et al. 1997; Jonsson et al. 1999) were examined due to known physiological relationships with dopamine signaling and prior associations with aspects of clinical antipsychotic response in some populations (Bertolino et al. 2010; Lencz et al. 2006; Tunbridge et al. 2006; Zhang et al. 2010).

Methods

Participants

Sixty-one patients meeting criteria for schizophrenia or schizoaffective disorder according to the Structured Clinical Interview for DSM-IV Disorders (SCID) (First et al. 1995), verified at consensus diagnostic meetings, were enrolled from outpatient and inpatient clinics at the University of Illinois at Chicago (*n*=22) and the University of Pittsburgh Western Psychiatric Institute and Clinic (WPIC) (*n*=39). Some participants were included in previous nongenetic neurocognitive studies reported by our group (Reilly et al. 2006, 2007). Participants were predominantly antipsychotic naïve (*n*=55) but six had received minimal prior antipsychotic treatment (mean cumulative lifetime exposure of 13.7±11.7 days) (see Table 1). Those with prior antipsychotic exposure were known to be untreated for a minimum of 3 days prior to study procedures, but typically any exposure was brief and inconsistent before study enrollment. A group of 130 controls without psychiatric disorders

matched on age, sex, race, socioeconomic status, and Wide Range Achievement Test (WRAT) word reading subtest scores were assessed in parallel to characterize the level of cognitive deficit evident in the patient sample before and after treatment relative to the ability of the matched healthy controls. All participants met the following criteria: (1) age 15–45, (2) no history of neurological disease or head trauma, (3) no currently active substance or alcohol abuse or lifetime history of substance dependence, (4) WRAT Reading standard score ≥70, (5) no caffeine or nicotine for at least 1 h prior to testing, and (6) at least 20/40 far visual acuity with or without correction. Participants were free of benzodiazepines for at least 48 h prior to testing. Exclusion criteria for healthy controls included any history of Axis I disorders as assessed by the SCID and any known history of psychotic or mood disorder in first-degree relatives. The study was approved by the Institutional Review Boards of the University of Pittsburgh and the University of Illinois at Chicago and was performed in accordance with the ethical standards set forth by the 1964 Declaration of Helsinki. All participants gave their written informed consent to study participation.

Clinical assessment

Symptom severity was assessed using the Brief Psychiatric Rating Scale (BPRS) which ranks 18 items on severity levels of 1–7 (minimum score of 18; maximum severity score of 126). In addition to BPRS total scores, subscale scores for positive and negative symptoms were examined (Overall and Gorham 1961; Rhoades and Overall 1988). Depressive symptoms were assessed using the 24-item Hamilton Depression Rating Scale (Hamilton 1960). Extrapyramidal symptom ratings were evaluated using the Extrapyramidal Side Effects Scale (EPSE) (McEvoy et al. 1991) at the Pittsburgh site and the Simpson-Angus Scale (SAS) (Simpson and Angus 1970) at the Chicago site.

Eye movement assessment

Behavioral data from 6-week treatment trials was collected over the course of 15 years (1995–2010) at first-episode psychosis programs in Pittsburgh and then in Chicago. An oculomotor delayed response task assessing SWM was administered in a darkened room. Detailed descriptions of the eye movement tasks have been published previously (Reilly et al. 2006, 2007). Eye movement recordings for each trial were measured by trained personnel using software and methods developed in our laboratory. Subjects were instructed to maintain central fixation and not to look toward the brief appearance (0.1 s) of a visual target appearing unexpectedly to the left or right of center in the horizontal plane, but to remember its location over a delay period and then make an eye movement to the remembered location when the central fixation stimulus was extinguished.

The tasks used over this time frame varied in subtle task parameters such as the duration of delay periods (all averaged 4–5 s) and maximum laterality of target displacement (12–18° of visual angle). Patient-control differences did not differ across the different task conditions, and data were pooled for genetic association studies. First, performance for each subject was averaged across specific task parameters that did not differ across groups (e.g., left vs. rightward movements, different lateral extent of target displacement from center fixation). Second, to account for differences in task conditions, individuals' scores were converted to a common metric by computing each patient's standardized (i.e., *z* score) performance relative

to matched healthy controls who performed the exact same task and were recruited at the same site [(subject's score−mean control performance)/SD of controls]. The *z* score for spatial error at the resting eye position after subjects made saccades to fixate the remembered target location (distance between saccade endpoint and visual cue determined on each trial) was used as the primary outcome variable for assessing SWM. Only correctly performed trials were included (e.g., subjects did not look to the wrong direction or look to the initial appearance of the peripheral target, and saccade gain toward the correct target location was >0.15 and <1.5).

Treatment

After initial assessments, patients were treated for 6 weeks with flexibly dosed antipsychotics focusing on risperidone (*N*=47, 3.0±1.7 mg/day) as the antipsychotic of choice with other agents used as alternatives where clinically preferred [i.e., olanzapine (*N*=2, 15.0±7.1 mg/day), haloperidol (*N*= 8, 3.0±1.7 mg/day), aripiprazole (*N*=3, 13.3±2.9 mg/day), and quetiapine (*N*=1, 300 mg/day)]. Mean chlorpromazine equivalents (averaging 246±146 mg/day) were used to examine potential dose-response relationships with clinical and cognitive outcomes (Andreasen et al. 2010). While antipsychotic monotherapy was utilized for most participants, a small number were also coadministered benztropine *N*=11, an anti-depressant *N*=8, or a sedative/hypnotic *N*=3 during the 6-week follow-up period. Use of these agents was not associated with differential symptom or cognitive outcomes.

Genotyping

Genomic DNA was isolated from ethylenediaminetetraacetic acid (EDTA)-treated whole blood using the Gentra Puregene extraction kit (Qiagen Sciences, Germantown, MD), quantified, and quality checked with Picogreen (Invitrogen, Eugene, OR) and Nanodrop assays (Thermo Scientific, Wilmington, DE). Samples were genotyped for candidate SNPs within *GRM3*, *COMT*, and *DRD2* as well as a panel of ancestry informative markers (AIMs). SNP selection was designed to determine if variation in *GRM3*, that is known to be related to glutamate disposition, brain function, symptom response, or gene splicing, is related to SWM performance before and after antipsychotic treatment. We also selected known functional SNPs in *COMT* and *DRD2/ANKK1* which may also impact dopamine disposition in ways that relate to cognitive and clinical outcomes assessed here and might interact with *GRM3*-mediated effects. Sequence-validated pyrosequencing and TaqMan assays were utilized for genotyping which was done blind to behavioral data. Five SNPs in *GRM3* (rs6465084, rs274622, rs1989796, rs1468412, and rs2228595), two in *DRD2/ANKK1* [rs1799732 (−141C Ins/del) and rs1800497 (TaqIA)], and one in *COMT* [rs4680 (Val158Met)] were assessed. DNA was not available for controls. Therefore, our genetic analyses focused on treatment effects in patients, and data from control subjects was used only to assess the degree of cognitive deficit in patients at the two testing sessions. Genotyping calls were 100 % for all markers.

In addition to candidate SNPs, 105 AIMs were genotyped using the Sequenom MassARRAY platform as previously described (Giri et al. 2009; Hooker et al. 2010; Kupfer et al. 2009, 2010). Ancestry was determined for each individual for European, West African, and Native American genetic components. Individual ancestry estimates scored from 0 to

100 % for each ancestry group were obtained from the genotype results using the Bayesian Markov Chain Monte Carlo method implemented in the program STRUCTURE 2.1 (Falush et al. 2003).

Statistical analyses

Allele and genotype frequencies (Supplementary Table 1) and Hardy Weinberg Equilibrium (HWE) were assessed with PLINK software (Purcell et al. 2007). SNP positions were obtained from the UCSC Genome Browser http://genome.ucsc.edu/ (Karolchik et al. 2014). Linkage disequilibrium (LD) was assessed with Haploview version 4.2 software (Barrett et al. 2005).

Associations between genotypes and both cognitive performance and clinical ratings were examined using PLINK in which changes in SWM and symptoms after treatment were assessed as quantitative trait phenotypes. This method modeled SWM and symptoms using a linear regression approach whereby SNPs were assessed using an additive model unless prior knowledge for dominant or recessive inheritance was a better fit for the data. Covariates for SWM associations included baseline performance, task version, and self-reported race. Task version and race did not significantly affect outcomes but were forced into the model based on the a priori data analysis plan. Paired *t* tests were used to examine pre-posttreatment changes in SWM and symptoms. Univariate regression models and Pearson correlations conducted with IBM SPSS Statistics 20 (Armonk, NY) using SWM or BPRS change scores confirmed that neither demographic nor clinical variables (i.e., site, age, sex, race, education, socioeconomic status, smoking status, EPS measures, estimated WRAT IQ, antipsychotic dose or type (risperidone only, first vs second generation), other psychotropic/anticholinergic agent) were associated with changes observed over the course of treatment. The mperm feature in PLINK using 10,000 permutations was used to provide an empirical point estimate (EMP) of significance that assesses the robustness of individual genotype-phenotype associations (EMP1) and also corrects for multiple genotype comparisons while accounting for relatedness between SNPs (EMP2) (Purcell et al. 2007). Post hoc multivariate models assessed whether outcomes were influenced by genotype combinations or interactions. Additional repeated measures analyses (also including ancestry and task version in the models) were completed to generate genotype×time interaction terms. In addition to whole group analyses, we also conducted stratified analyses of self-reported race groups (White/Caucasian and Black/African American) to examine effects of population and admixture. In these stratified analyses, association studies were repeated with the additional inclusion of the percent ancestry relevant for the population (e.g., % Caucasian ancestry in the analysis of White participants, and % West African ancestry in the analysis of African American participants) (Giri et al. 2009). Cohen's $d=[(x_1-x_2)/s]$ was used to define effect sizes between case/control or genotype groups. Pearson product-moment correlation coefficient (r) was used to define the strength of linear relationships between clinical and cognitive variables. Power analyses were conducted with Quanto (Gauderman and Morrison 2006) to examine genotype-phenotype relationships at our observed allele frequencies. At the minor allele frequencies observed (≥0.25 for all SNPs but *GRM3* rs2228595) and assuming an additive inheritance model, we were

adequately powered (β=0.80, 2-sided type-I error rate=0.05) to detect genotype beta coefficients of ≥1.0 in whole group analyses, which represents R^2 values of ≥0.124.

Results

Clinical and spatial working memory changes during antipsychotic treatment

At the time of enrollment, schizophrenia patients presented with moderately severe symptoms of psychosis (mean BPRS±SD total scores of 47.3±8.6) and had impaired performance on the SWM task compared to controls ($t_{1,189}$=3.46; p<0.0001). After treatment, clinical symptoms as measured by BPRS total ($t_{1,59}$= 5.88; p<0.0001) and positive subscales ($t_{1,60}$=6.54; p<0.0001) were significantly improved. Negative symptoms were not significantly improved ($t_{1,60}$=1.03; p=0.31) in the overall sample although there was significant variability in this measure (SD change=3.1 points on the BPRS negative subscale) that was unrelated to medication type or dose. As reported previously in a subset of our patients (Reilly et al. 2006, 2007), SWM deficits approximately doubled after antipsychotic treatment (pretreatment mean±SD z scores=−0.76±1.73; post treatment z scores=−1.48±1.84; $t_{1,60}$=3.18; p=0.002). SWM performance (pretreatment as well as change after treatment) was not correlated with BPRS total scores in untreated patients (r=0.13, p=0.31) or with change in symptoms after treatment (r=0.07, p=0.61).

Genotype associations with spatial working memory performance

Variation in *GRM3*, but not *COMT* or *DRD2*, was associated with SWM performance changes after treatment. Two *GRM3* SNPs (rs274622 and rs1468412) were associated with SWM change with the rs1468412 SNP surviving adjustment for multiple comparisons (Supplementary Table 2). As highlighted in Fig. 1, the rs1468412_TT genotype group (n=11) exhibited a substantial worsening in SWM performance after treatment (genotype×time interaction p=0.001) when compared to A-allele carriers (n=50). This represented a reliable and large effect size difference between genotype groups at the 6-week time point (Cohen's d=0.75). To explore the potential effects of combinations of *GRM3* genotype groups with treatment effects, we conducted an exploratory regression analysis assessing genotype interactions and combinations. This analysis determine that both rs1468412_TT and rs6465084_AA genotypes were each associated with adverse effects on SWM (both p<0.007). Furthermore, there was a significant interaction between these SNPs (p=0.001) such that the small subgroup (n=4) of carriers of both the rs1468412_TT and rs6465084_AA genotypes had pronounced adverse changes in performance after treatment (time×TT+AA genotype group interaction p<0.0001). No associations between *DRD2* or *GRM3* genotypes with SWM performance were observed in untreated patients at baseline. Consistent with prior studies, *COMT* Met/Met carriers had an advantage in performance over Val allele carriers (Cohen's d=0.76), ($t_{1,60}$=5.28; p=0.025) in SWM performance at baseline in untreated patients. The significance of *GRM3* associations with SWM performance was not altered when controlling for *COMT* Met158Met genotype status, nor was there evidence for any *GRM3* interactions with *COMT* or *DRD2*. Self-reported race and genetic ancestry for African Americans or Caucasians were not related to SWM outcomes (AIMs p=0.65 and p=0.52 respectively) with the direction and effect of the rs1468412_TT genotype similar in both groups when assessed in stratified analyses.

Genotype associations with clinical symptoms

Two *GRM3* SNPs (rs6465084 and 1989796) were associated with changes in BPRS negative symptom scores, with the rs6465084 SNP surviving correction for multiple comparisons (Supplementary Table 3). As illustrated in Fig. 2, the rs6465084_AA genotype group (n=33) exhibited reduced negative symptom severity after treatment while G-allele carriers had minimal change or worsening in negative symptoms (time×genotype interaction p=0.046). *GRM3*, *COMT*, and *DRD2/ANKK1* genotypes were not associated with clinical ratings in untreated patients at baseline. No associations surviving multiple comparisons were observed between any SNPs and changes in BPRS total or BPRS positive symptom scales after treatment (Supplementary Tables 4 and 5). Self-reported race and genetic ancestry for African Americans or Caucasians were not related to negative symptom outcomes (AIMs p=0.12 and p=0.70, respectively) with the direction and effect of the rs6465084_AA genotype similar in both groups when assessed in stratified analyses.

Discussion

We conducted a pharmacogenetic candidate gene study to examine relationships between functional polymorphisms in the *GRM3*, *COMT*, and *DRD2/ANKK1* genes and cognitive and symptom outcomes following antipsychotic treatment (predominantly with risperidone) in untreated first-episode schizophrenia patients who had minimal or no prior antipsychotic exposure. We demonstrated that *GRM3* variants were associated with a worsening of working memory deficits and a reduction in negative symptoms after antipsychotic treatment. Consistent with many prior studies (Tunbridge et al. 2006), the *COMT* Val158Met SNP was associated with SWM, although there were no differential drug response outcomes by *COMT* genotype groups. No associations with *DRD2* SNPs were observed.

Glutamate signaling in working memory processes

To our knowledge, this is the first study to demonstrate that SNPs in *GRM3* influence the risk for adverse cognitive effects of antipsychotic treatment. Adverse effects of antipsychotics on SWM are established in nonhuman primate models (Sawaguchi and Goldman-Rakic 1994), and we have shown them in previous behavioral studies of patients with schizophrenia (Reilly et al. 2006, 2007). The present findings expand knowledge about treatment response mechanisms to include glutamate mechanisms, as well as to specify a group of genetically identified patients who may be at greatest risk for treatment-related adverse cognitive effects. This is important for advancing mechanistic understanding and also suggests that glutamatergic interventions might be an effective strategy to minimize these treatment outcomes—and possibly the deficit in this cognitive domain that is present prior to treatment.

Abnormalities in glutamate signaling are believed to be important components of the pathophysiology of schizophrenia (Moghaddam and Javitt 2012). At the genetic level, variation in *GRM3* is associated with altered excitatory amino acid transporter-2 (EAAT2) expression in postmortem brains of individuals with schizophrenia and *N*-acetylaspartate measures in the dorsolateral prefrontal cortex (Egan et al. 2004). Disruptions in glutamate

signaling have been linked to deficits in working memory performance and brain function in patients with schizophrenia as well as in rodent models of the disease (Aultman and Moghaddam 2001; Egan et al. 2004; Krystal et al. 2005).

The *GRM3* rs1468412_TT and rs6465084_AA genotypes associated with outcomes in our study have both been linked to measures of reduced glutamate signaling and cortical disposition in the brain (Egan et al. 2004; Xia et al. 2012) and neuropsychological deficits in chronically treated schizophrenia patients (Egan et al. 2004). In treated patients with *GRM3* rs1468412_TT or rs6465084_AA genotypes, prior studies identified worse performance on list learning and verbal fluency tests. Imaging studies showed lower *N*-acetylaspartate (NAA) levels in the dorsolateral prefrontal cortex (DLPFC) and inefficient brain activity during working memory tasks with one or both of these markers when examined in nonpsychiatric study samples (Egan et al. 2004). Our findings identified genotype relationships in the same direction, but only after antipsychotic treatment, suggesting that a genetic predisposition to inefficient cortical processing during executive functioning tasks is exacerbated by antipsychotics.

Based on currently available evidence, our cognitive findings are consistent with the hypothesis that patients with a genetic variation related to altered mGluR3 signaling exhibit increased sensitivity to the adverse effects of D2 antagonism from antipsychotic drugs. This may represent an indirect effect resulting from a suboptimal state of glutamate signaling to support working memory processes creating a vulnerability to adverse outcomes from antipsychotic, as opposed to a direct effect of antipsychotics on mGluR3 receptor expression or function. At the molecular level, there is evidence for antipsychotic effects on components of glutamate signaling pathways measured by RNA and protein expression studies (Fatemi et al. 2006, 2012; Fitzgerald et al. 1995) but not a direct modulation of mGluR3 (Ghose et al. 2009).

In animal studies, metabotropic glutamate antagonism, agonism, and D2 antagonism appear to have differential beneficial and adverse effects on cognition depending on the model studied and cognitive domain assessed (Amitai and Markou 2010; Young et al. 2012). Rodent studies have helped to highlight important mGluR-antipsychotic interactions in cognition whereby antipsychotics reverse phencyclidine (PCP) effects on certain memory tasks, but that pretreatment with an mGluR2/3 antagonist (LY341495) blocks the benefits of antipsychotic treatment (Grayson et al. 2007; Horiguchi et al. 2011). The results of our pharmacogenetic studies in humans build on this knowledge from preclinical work and are the first demonstration in humans that genetic variation in *GRM3* may have biological consequences resulting in adverse cognitive sequelae from antipsychotic treatment.

GRM3 variation and symptom response to antipsychotics

Ours is the third investigation to identify a relationship between *GRM3* variants and symptom response to antipsychotics (Bishop et al. 2005; Fijal et al. 2009). Prior studies did not examine the rs6465084 SNP found most highly associated with negative symptom response in the present investigation. The rs274622 (Bishop et al. 2005) or the tightly linked rs724226 SNP (Bishop et al. 2005; Fijal et al. 2009) were associated with negative and/or positive symptom response to antipsychotics in those investigations. In the present study, the

rs274622 SNP was associated with BPRS positive symptom score changes after treatment (supplementary Table 5) but this effect did not survive correction for multiple testing. Thus, our findings are in a consistent direction as previous investigations and further implicate the importance of the rs6465084 SNP which has since been more extensively studied in relation to aspects of brain function.

Understanding the effects of glutamate dysregulation on symptom presentation and the ability of D2 antagonists to reverse these effects represent active lines of psychopharmacology research. In addition to effects on cognitive processes, NMDAR hypofunction as modeled by ketamine administration causes schizophrenia-like symptoms and cognitive disturbances in healthy individuals and exacerbates these in patients with schizophrenia (Adler et al. 1998; Krystal et al. 1999; Lahti et al. 1995; Malhotra et al. 1996). D2 antagonizing antipsychotic agents can reverse behavioral markers of schizophrenia in NMDA antagonist animal models (Moghaddam and Jackson 2003). Earlier gene expression studies identified upregulation of NMDARs in the striatum in rats after chronic exposure to antipsychotics (Fitzgerald et al. 1995) which may provide a mechanism for this effect on symptoms. Additionally, mGluR2/3 antagonism by LY341495 induces behavioral phenotypes such as hyperlocomotion and reduced habituation to locomotion in exploratory activity tasks in rodent models which are reversed by antipsychotic exposure as well as mGluR2/3 agonists (Bespalov et al. 2007; Yoon et al. 2008). Thus, while altered glutamate activity in PFC may increase vulnerability to adverse cognitive effects of antipsychotics, mGluR3 alterations at presynaptic terminals that could result from *GRM3* SNPs may be reversed by antipsychotic effects in the striatum with the associated beneficial effect of negative symptom reduction. It may be helpful to further investigate these molecular hypotheses in human spectroscopy imaging studies as prior research has identified relationships between glutamate and related amino acid metabolites in the striatum and anterior cingulate and early treatment response and also treatment-resistant illness (Demjaha et al. 2014; Egerton et al. 2012).

Some limitations and other considerations of our study must be recognized. At our sample size, we were powered to detect moderate to large effect sizes but not more subtle genotype-phenotype relationships or gene-gene interactions. This limitation is to a degree balanced by the advantages that accompany an untreated first-episode sample assessed with a particularly sensitive and translational neurocognitive phenotyping strategy. Oculomotor measures of SWM are known to be considerably more sensitive to antipsychotic effects on cognition than many traditional neuropsychological tests (Hill et al. 2008). This may have contributed to our ability to detect of associations of cognitive treatment outcome with variation in *GRM3* genotype. Our study sample was one that consisted of more than one race group, which is important to consider for possible confounding aspects of population stratification. We assessed the effects of race according to both self-report and genetic determinations of ancestry and did not find evidence suggesting that they influenced our findings. Despite this, we recognize that differences in allele frequencies were observed across race groups for some SNPs and that our sample size limited our ability to comprehensively assess the influences of race and ancestry.

Conclusions

To our knowledge, this is the first study to identify relationships between variants in *GRM3* and antipsychotic treatment-related effects on a translational measure of neurocognition in humans. We identified relationships between *GRM3* SNPs with symptom response that are consistent with two prior antipsychotic treatment studies with ours being the first to characterize this effect in a first-episode study sample with minimal prior antipsychotic exposure. Collectively, these findings provide additional information on the complex interplay between glutamate and dopamine signaling in influencing beneficial and adverse outcomes of antipsychotic treatment. They may represent an important step towards the development of targeted therapeutics and identification of subgroups of patients who may be at greater risk for beneficial symptom outcomes and others for adverse cognitive effects of antipsychotic drugs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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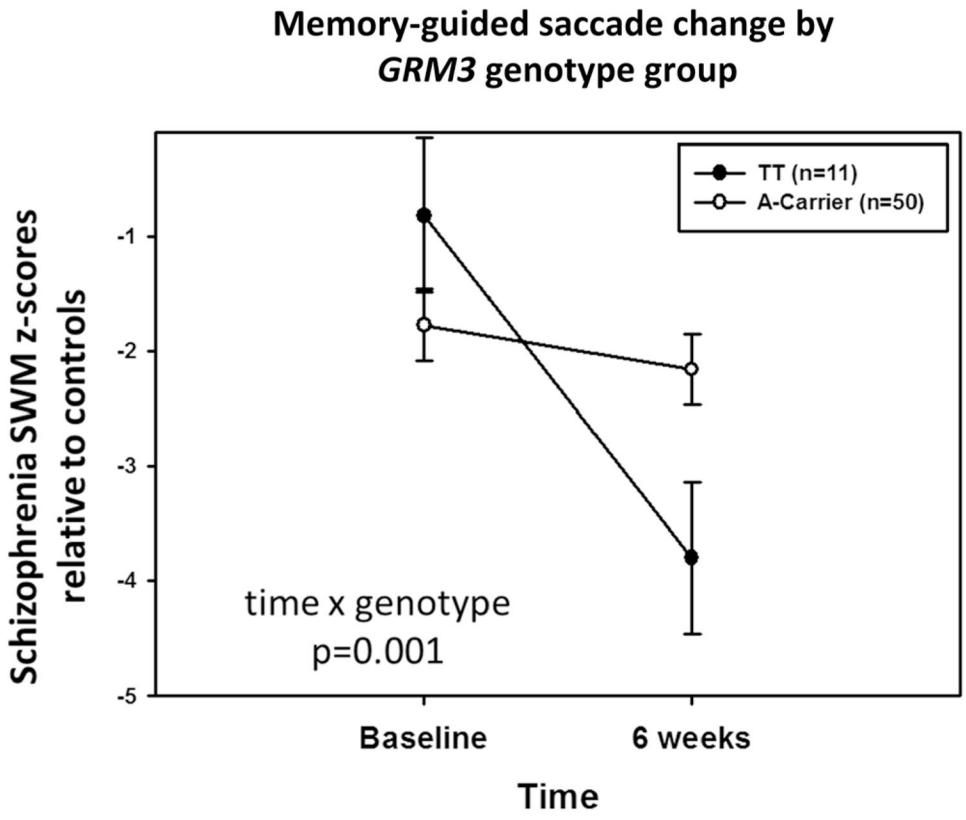

Fig. 1.

Schizophrenia subject performance on the memory-guided saccade task of spatial working memory was *z* scores relative to controls (±SE) are depicted before (baseline) and after 6 weeks of antipsychotic treatment. Prior to treatment, deficits were observed on average for both groups. After treatment, performance in the rs1468412_TT genotype group worsened while non_TT subjects did not

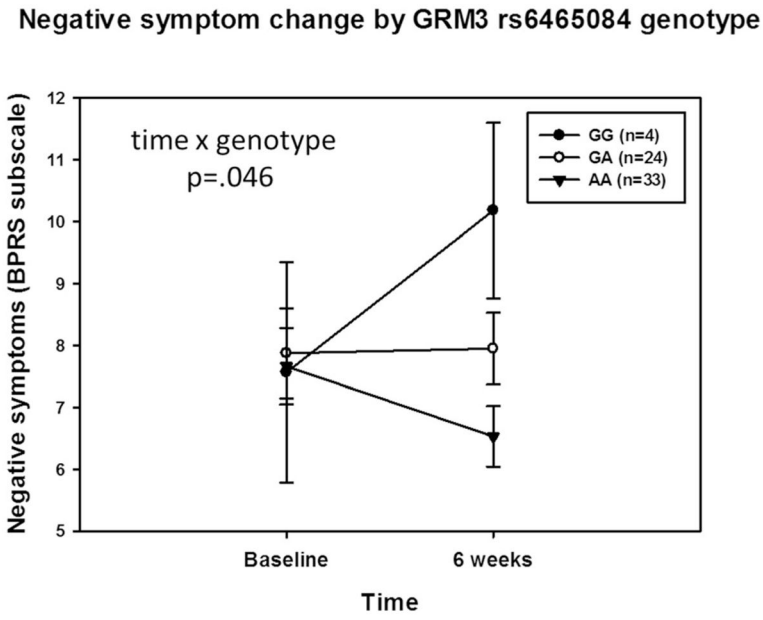

Fig. 2.

Negative symptom change by *GRM3* genotype group. Schizophrenia subject ratings on negative symptom components of the BPRS (±SD) are depicted before (baseline) and after 6 weeks of antipsychotic treatment

Table 1

Schizophrenia participant characteristics and demographics

Age	**24.3±6.2**
WRAT Reading	98.5±14
Global Assessment of Function	35.2±9.4
Brief Psychiatric Rating Scale (BPRS) Total scores	47.3±8.6
Hamilton Depression Rating Scale (HAM-D)	23.3±10.2
Total cumulative exposure (days) to all antipsychotic medications prior to testing in the 6 patients who were not antipsychotic naive	13.7±11.7
Extrapyramidal Symptoms	
EPSE[a] (Pittsburgh)	1.4±1.8
SAS[b] (Chicago)	0.64±1.5
Sex (males)	41 (67 %)
Diagnosis	
Schizophrenia	54 (88.5 %)
Schizoaffective disorder	6 (9.8 %)
Schizophreniform disorder	1 (1.6 %)
Race/ethnicity	
White, non-Hispanic	28 (45.9 %)
Black, non-Hispanic	28 (45.9 %)
Other (Hispanic/Asian)	5 (8.2 %)

[a] Extrapyramidal Side Effects Scale (scale range 0–35) (McEvoy et al 1991)

[b] Simpson-Angus Scale (scale range 0–40) (Simpson and Angus 1970)