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ORIGINAL PAPER

Association of variants in *DRD2* and *GRM3* with motor and cognitive function in first-episode psychosis

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Abstract Similar smooth pursuit eye tracking dysfunctions are present across psychotic disorders. They include pursuit initiation and maintenance deficits that implicate different functional brain systems. This candidate gene study examined psychosis-related genotypes regulating dopamine and glutamate neurotransmission in relation to these pursuit deficits. One hundred and thirty-eight untreated first-episode patients with a psychotic disorder were genotyped for four markers in *DRD2* and four markers in *GRM3*. The magnitude of eye movement abnormality in patients was defined in relation to performance of matched healthy controls ($N = 130$). Eighty three patients were followed after 6 weeks of antipsychotic treatment. At baseline, patients with a −141C deletion in *DRD2* rs1799732 had slower initiation eye velocity and longer pursuit latency than CC insertion carriers. Further, *GRM3* rs274622_CC carriers had poorer pursuit maintenance than T-carriers. Antipsychotic treatment resulted in prolonged pursuit latency in *DRD2* rs1799732_CC insertion carriers and a decline in pursuit maintenance in *GRM3* rs6465084_GG carriers. The present study demonstrates for the first time that neurophysiological measures of motor and neurocognitive deficits in patients with psychotic disorders have different associations with genes regulating dopamine and glutamate systems, respectively. Alterations in striatal D2 receptor activity through the −141C Ins/Del polymorphism could contribute to pursuit initiation deficits in psychotic disorders. Alterations in *GRM3* coding for the mGluR3 protein may impair pursuit maintenance by compromising higher perceptual and cognitive processes that depend on optimal glutamate signaling in corticocortical circuits. *DRD2* and *GRM3* genotypes also selectively modulated the severity of adverse motor and neurocognitive changes resulting from antipsychotic treatment.

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Introduction

There is considerable interest in neurophysiological intermediate phenotypes as translational biomarkers to advance gene and drug discovery in psychiatry [1, 2]. One of the best established intermediate phenotypes is a neurophysiological deficit referred to as smooth pursuit or eye tracking dysfunction that involves a reduced ability to accurately track slowly moving objects with the eyes [3, 4]. In schizophrenia, this deficit not only occurs in patients but is familial [5–8]. Consistent with multiple lines of evidence indicating shared neurobiological alterations and genetic vulnerability across schizophrenia spectrum disorders and psychotic affective disorders [4, 9–13], comparable pursuit deficits have been demonstrated in patients with psychotic affective disorders [7, 14–17] and their unaffected relatives [18]. Certain specific pursuit deficits are caused or increased by antipsychotic treatment [19–22]. However, these treatment-related effects are not consistent across patients, suggesting that there is variability which might be explained by genetic factors that moderate how antipsychotic drugs affect different functional brain systems.

In both patients with schizophrenia and patients with psychotic affective disorder, two distinct neurophysiological pursuit impairments have been identified [14–17] that implicate different functional brain systems in which neurophysiology is modulated by different neurotransmitter systems [23]. First, slowed pursuit initiation in response to the onset of target motion represents an abnormality in motor function. Dopamine modulation in the basal ganglia is crucial for motor response initiation generally and pursuit initiation specifically [24]. Second, deficits in maintaining accurate sustained pursuit reflect altered use of higher-order predictive mechanisms and perceptual analysis of performance that are dependent on corticocortical connectivity across specific well-characterized regions of association cortex [25, 26]. This integrated cortical activity is highly dependent on glutamate signaling in frontoparietal tracts [27].

Studies of genetic associations with eye tracking dysfunctions in patients with psychotic disorders differ, first, with respect to methods applied to measure and analyze pursuit performance (all studied pursuit maintenance but not initiation) and second with respect to the selection of candidate genes coding for catechol-O-methyltransferase, dopamine receptor 3 (DRD3), dopamine transporter 1 (DAT1), neuregulin-1 and neuregulin-3, RAN-binding protein, putative transmembrane palmitoyltransferase (ZDHHC8), receptor for reticulon 4 (RTN4R) or kynurenine 3-monooxygenase [28–41]. Whether distinct neurophysiological pursuit impairments are related to different specific polymorphisms has not yet been examined.

To assess how genes may regulate pursuit without potential medication confounds, we examined pursuit performance in a sample of untreated first-episode psychosis patients before and after antipsychotic treatment. We selected two candidate genes that have been implicated as risk genes for psychotic disorders and also either for motor (D2 receptor gene on chromosome 11q23, *DRD2*) or cognitive impairments (the type 3 metabotropic glutamate receptor gene on chromosome 7q21.1-q21.2, *GRM3*). Alterations in D2 receptor functions have been related to psychotic symptoms making the D2 receptor a primary target of dopamine antagonists including antipsychotic agents [42, 43]. *GRM3* polymorphisms are believed to contribute to susceptibility to psychosis, altered cognitive function, altered prefrontal cortical levels of N-acetylaspartate/creatine [44–47] and the regulation of synaptic glutamate concentrations via the effects on astrocytes [48]. Both genes have not previously been studied in relation to pursuit deficits in psychotic disorders. We predicted that pursuit initiation and maintenance would be related to genetic polymorphisms regulating dopamine and glutamate synaptic neurotransmission, respectively.

Our second interest was in the role *DRD2* and *GRM3* might modulate response to antipsychotic treatment. Undesirable side effects of D2 antagonists related to D2 receptor occupancy include motor slowing as an aspect of drug-related parkinsonism [49]. *GRM3* polymorphisms have been associated with negative symptom reduction with antipsychotic treatment in schizophrenia patients [50, 51]. While *GRM3* is associated with cognitive deficits in schizophrenia, its influence on cognitive outcome after antipsychotic treatment is yet not established.

Methods and materials

Participants

One hundred and thirty-eight first-episode psychosis patients comprising 46 women (33.3 %) from in- and outpatient services from the University of Pittsburgh and the University of Illinois at Chicago met DSM-IV criteria for a schizophrenia spectrum disorder (Schiz: schizophrenia $N = 86$, schizoaffective disorder $N = 9$, schizophreniform disorder $N = 1$), bipolar I disorder with psychosis (BDP, $N = 26$) or unipolar depression with psychosis (UDP, $N = 16$, Table 1). Diagnoses were made at consensus conferences conducted 4–8 weeks after baseline testing using all available clinical data, including results

Table 1 Patient's characteristics

	Schizophrenia spectrum disorder ($N = 96$)	Psychotic bipolar disorder ($N = 26$)	Psychotic unipolar depression ($N = 16$)
Mean age (SD), [Years]	24.5 (7.7)	24.9 (8.5)	21.4 (7.2)
Mean IQ (SD), [from WASI]	96.7 (13.9)	94.5 (13.9)	95.9 (15.3)
Mean genetic ancestry [%]*			
West African	35	37	34
European	52	54	56
Native American	13	9	10
Mean baseline BPRS (SD)**	46.2 (9.2)	36.7 (11.1)	43.5 (10.8)

BPRS Brief Psychiatric Rating Scale [53], *WASI* Wechsler Abbreviated Scale of Intelligence [54]

* as assessed by 105 ancestry informative markers (AIMs)

** $F_{(2,135)} = 9.85$, $p < 0.01$, post hoc: $p_{\text{BDPvsUDP}} = 0.03$, $p_{\text{BDPvsSchiz}} < 0.01$

from the Structured Clinical Interview for DSM [52] and ratings on the Brief Psychiatric Rating Scale (BPRS) [53]. Groups did not differ between sites with respect to age and IQ [54].

Inclusion criteria comprised (1) age between 15 and 45 years, (2) no known systemic or neurological disease, (3) no history of significant head trauma with loss of consciousness, (4) no substance dependence for at least 1 year and no substance abuse for at least 1 month, and (5) minimum of 20/40 far acuity, with or without correction. Only 28 (15 Schiz, 9 BDP, 4 UDP) of 138 patients had been treated previously in their lifetime with antipsychotic medication, typically with limited treatment adherence resulting in a median total lifetime exposure in those patients of 9 days. At time of testing, all patients were free of antipsychotic medication and had not taken benzodiazepines within 48 h of testing.

A subsample of 83 participants (63 Schiz, 11 BDP, 9 UDP) was available for re-evaluation after 6 weeks of antipsychotic medication treatment. This subsample did not differ from the full baseline sample on sociodemographic features, baseline clinical ratings and oculomotor performance. At follow-up, BPRS scores were significantly reduced compared to baseline ($F_{\text{time}}(1,79) = 54.41$, $p < 0.01$) with no difference across diagnostic groups (mean BPRS difference scores: Schiz -8.5, standard deviation (SD) = 9.1; BDP −9.6 (SD = 9.7), UDP −12.8 (SD = 7.0). Patients were treated with low to moderate doses of antipsychotics including risperidone ($N = 72$, mean dosage 3.0 mg (SD = 1.7), olanzapine ($N = 5$, mean dosage 12 mg (SD = 7.6)), haloperidol ($N = 2$ on 4 and 8 mg/day), aripiprazole ($N = 2$ on 10 and 15 mg/day) and quetiapine ($N = 2$ on 100 and 300 mg/day). Mean chlorpromazine equivalents [55] were 242 mg ± 146 with no significant difference between patient groups. Sixteen patients (9 Schiz, 7 UPD) received adjunctive treatment with antidepressants, mostly serotonin reuptake inhibitors.

To account for potential site-related effects, patient's eye movement data were referenced to data from site-specific healthy controls ($N = 130$). This procedure provided z-scores for each patient relative to the mean and standard deviation of healthy controls from their site that were used for statistical analyses of associations with genetic data. Healthy community controls were matched for age and IQ as described previously [14]. Exclusion criteria for controls, in addition to those used for patients, included any history of Axis I disorders (SCID) and any known history of psychotic or mood disorder in first-degree relatives [14]. The study was approved by the Institutional Review Boards of the University of Pittsburgh and the University of Illinois at Chicago, and all participants provided written informed consent. Data were collected from 1993 to 2011.

Eye movement assessment

Pursuit tasks have been described previously in reports of pursuit data included in the present genetic analyses [14], with recruitment starting in Pittsburgh and then continuing in Chicago. Eye movement studies were performed in a darkened black room in which participants viewed a screen with their head stabilized in a chin rest. Participants were instructed to follow a small moving target with their eyes as precisely as possible. Recording was performed using infrared sensors mounted on spectacle frames (Model 210, Applied Science Laboratories, Inc, Bedford, MA). Fixation targets were presented for 5 s at 0°, ±3°, 6°, 9°, 12° and 15° to calibrate the eye movement data.

To determine pursuit latency, we used a simple ramp task in which the target moved at an unpredictable time, direction and speed (either 4°, 8°, 16°, 24° or 32°/s) from center fixation. Each trial started with central fixation for 2–4 s. Targets were extinguished after reaching ±15° and reappeared at the central fixation position after a 1-s delay

Table 2 Means with standard deviation (SD) for eye movement parameters of interest

	Healthy controls	Psychosis patients	Patient's Z-scores relative to controls
Pursuit initiation latency at baseline [ms]	187 (25)	190 (32)	0.16 (1.34)
Pursuit initiation latency at follow-up [ms]	183 (21)	190 (33)	0.25 (1.36)
Initial eye velocity gain at baseline	0.82 (0.24)	0.67 (0.25)	−0.64 (1.07)
Initial eye velocity gain at follow-up	0.81 (0.28)	0.66 (0.25)	−0.72 (1.02)
Maintenance eye velocity gain at baseline	0.86 (0.09)	0.81 (0.11)	−0.48 (1.27)
Maintenance eye velocity gain at follow-up	0.86 (0.10)	0.81 (0.12)	−0.52 (1.41)

to begin the next trial. Target conditions were presented in a randomized order resulting in a total of 40 trials (4 repetitions × 5 speeds × 2 directions). Latency of pursuit initiation was defined as time for pursuit velocity to reach 2°/s for at least 20 ms if that preceded the first catch-up saccade.

To assess eye velocity during the pursuit initiation phase (first 100 ms) and the maintenance phase, we used a step-ramp task that was similar to the ramp task. After the initial central fixation for 2–4 s, the target stepped 3° to the left or right before continuing moving in that direction at either 4, 8, 16 or 24°/s. The task consisted of 32 trials presented in a fixed pseudorandom order. Initial open-loop eye velocity was determined during the first 100 ms after the initial catch-up saccade following the target step. Maintenance eye velocity was also measured in the remaining interval of pursuit after the first 100 ms.

Pursuit analyses

Eye movement data were digitized at 500 Hz. Data from each trial were visually inspected to eliminate blinks and other artifacts. All saccades were excluded from data before calculating pursuit eye velocity. Saccade onset was defined as the point when eye acceleration exceeded 1,000°/s^2 and saccade endpoints were identified at 25 % of peak deceleration. Both initiation and maintenance eye velocity were related to target velocity to determine initiation gain and maintenance gain. All eye movement data were scored blind to participant characteristics.

Since target speed and direction effects did not differ across groups for any of the three parameters of interest, i.e., pursuit initiation gain, latency and pursuit maintenance gain, measurements were averaged across target speed and direction. Table 2 shows means for all eye movement parameters of interest in healthy controls and patients including z-scores used in analyses.

Genotyping

Genomic DNA from patients was isolated from whole blood using standard protocols and quantified and quality checked with Picogreen (Invitrogen, Eugene, OR) and Nanodrop assays (Thermo Scientific, Wilmington, DE). Pyrosequencing assays were designed using PSQ assay design software v 1.0.6. (Qiagen, CA).

Genotyping was done blind to symptom ratings. We selected four candidate single nucleotide polymorphisms (SNPs) in each of the *DRD2* and *GRM3* gene regions based on functional consequence or prior association with disease risk, pathology, or antipsychotic treatment response [9, 44, 50, 51, 56–58]. Patients were genotyped for the *DRD2/ANKK1* gene region (rs1799732 (−141C Ins/del), rs6277 (957C > T), rs1800497 (TaqIA), rs1800498 (TaqID)) and four SNPs in the *GRM3* gene (rs6465084, rs274622, rs1989796, rs1468412). *GRM3* rs6465084 and rs1468412 genotypes were determined by TaqManSNP Genotyping Assays (C__11245618_10 for rs6465084 and C_7586401_10 for rs1468412 Applied Biosystems, CA) using a StepOne Plus Real Time PCR system (Applied Biosystems, CA). All genotype assays were validated using capillary sequencing. Additionally, approximately 10 % of samples were re-genotyped to verify assay precision which were all 100 %. Genotyping calls were 100 % for all markers.

In addition to *DRD2* and *GRM3* candidate markers, 105 ancestry informative markers (AIMs) were genotyped using the Sequenom MassARRAY platform [59, 60] as previously described [61, 62]. Ancestry was determined for each individual using AIMs for European, West African and Native American genetic ancestry [60–63]. Individual ancestry estimates were obtained from the genotype results using the Bayesian Markov Chain Monte Carlo (MCMC) method implemented in STRUCTURE 2.1 [64]. Each participant was then scored from 0 to 100 % for the probability of being in each ancestry group (Table 1).

Statistical analyses

Allele and genotype frequencies and Hardy–Weinberg equilibrium were evaluated with PLINK software in race-specific groups separately [65], as shown in Table 3. Significant deviation from Hardy–Weinberg equilibrium was observed in both Caucasians and African Americans for *DRD2* rs6277 ($p < 0.01$), which was excluded from further association tests. Linkage disequilibrium (LD) plots were created with Haploview version 4.2 software [66], as

Table 3 Allele and genotype frequencies for *DRD2* and *GRM3* polymorphisms

SNP	Position	MAF	Alleles	Genotype count AA/Aa/aa
DRD2				
rs1800497	113271078	0.319	C:T	68/52/18
rs6277	113283209	0.373	G:A	76/21/41
rs1800498	113291838	0.384	C:T	30/46/62
rs1799732	113346003	0.286	C:-	77/43/18
GRM3				
rs274622	86272690	0.319	T:C	66/56/16
rs6465084	86403225	0.304	A:G	66/60/12
rs1468412	86433201	0.42	T:A	49/62/27
rs1989796	86474063	0.339	G:A	65/51/21

Note that Hardy–Weinberg equilibrium was evaluated for each SNP and race group, i.e., African American and Caucasian, separately. For more details see supplemental material

SNP positions defined by UCSC genome browser (GRCh37/hg19) assembly

SNP single nucleotide polymorphism, *MAF* minor allele frequency

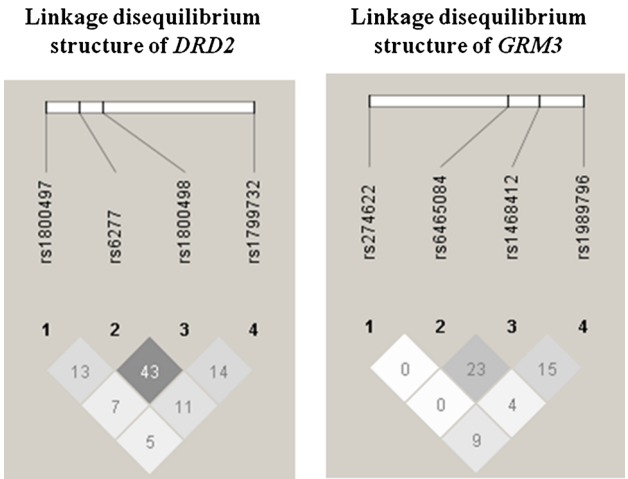

Fig. 1 Linkage disequilibrium for four SNPs in *DRD2* and four SNPs in *GRM3* displayed as R^2

shown in Fig. 1. Table 3 shows allele and genotype frequencies for DRD2 and GRM3 polymorphisms in the sample as a whole.

We used fixed-effects one-way analyses of variance (ANOVAs) with genetic ancestry data as covariates. To test for genotype-specific effects of antipsychotic treatment on pursuit parameters of interest (*interaction of genotype x time*), we used repeated-measures ANOVAs of the subsample available at both baseline and follow-up, again with genetic ancestry data as covariates. To account for multiple comparisons resulting from the seven SNPs considered in analyses, p-values from SNP-specific analyses were multiplied by seven to preserve an experiment-wise error rate of $p < 0.05$.

Evaluation of possible confounds

Baseline pursuit performance did not differ between patient groups or race-specific groups (African American ($N = 58$), Caucasian ($N = 57$) and others ($N = 23$) including Hispanic ($N = 11$), Asian ($N = 5$) and miscellaneous ($N = 5$)) nor were pursuit variables of interest correlated with age, IQ or chlorpromazine-equivalent antipsychotic dose at follow-up. There also were no significant interactions between genotypes as related to the seven markers tested and self-reported race (*genotype x race*) or site (*genotype x site*) for any eye movement parameter of interest (initial eye velocity gain, pursuit initiation latency or maintenance eye velocity gain), indicating that pursuit performance did not differ between genotypes across race groups or sites.

Results

Association of *DRD2* with pursuit initiation

Marker rs1799732 (−141C Ins/Del) was significantly associated with parameters of pursuit initiation. First, at baseline, −141C deletion carriers had lower initial eye velocity gain than patients carrying the CC insertion (*genotype:* $F_{(1,114)}8.45$, $p_{\text{corrected}} = 0.028$). This difference between genotype groups did not change after 6 weeks of treatment (*genotype x time:* $p > 0.05$), Fig. 2.

Second, the −141C Ins/Del polymorphism was also associated with a change in the latency of pursuit initiation after treatment (*genotype x time*: $F_{(1,79)}10.55$, $p_{\text{corrected}} = 0.014$). −141C deletion carriers had longer pursuit latency than CC insertion carriers at baseline (*genotype:* $F_{(1,79)}$ 12.53, $p_{\text{corrected}} = 0.0014$) but not at follow-up (*genotype:* $p > 0.05$). Post hoc analyses revealed that treatment resulted in an increase in pursuit latency in CC insertion carriers (paired $t_{(37)}$ 3.61, $p_{\text{corrected}} = 0.0056$) in contrast to a slight latency reduction in deletion carriers, Fig. 3.

There was no association between the −141C Ins/Del polymorphism and pursuit maintenance gain nor were there any associations between the *DRD2*rs1800497 (TaqIA) and *DRD2*rs1800498 (TaqID) with any of the pursuit parameters tested.

Association of *GRM3* with pursuit maintenance

GRM3 genotype was related to pursuit maintenance gain but not to either of the pursuit initiation measures. First,

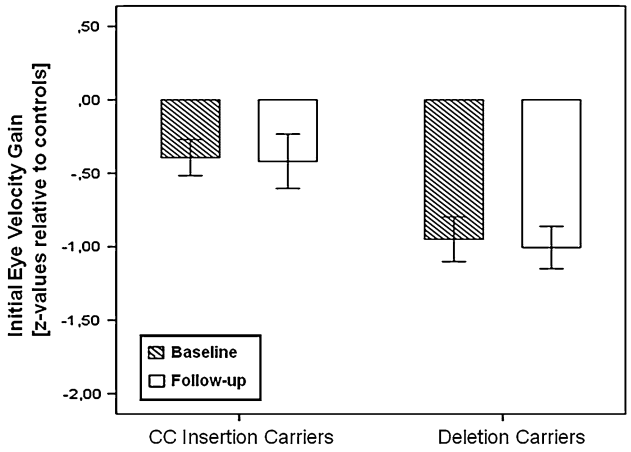

Fig. 2 Association of variants of the −141C Del/Ins polymorphism in *DRD2* with initial eye velocity gain in unmedicated patients with psychotic disorders at baseline ($N = 138$) and follow-up ($N = 83$) after six weeks of antipsychotic treatment. There was no effect of treatment on genotype differences in repeated-measures ANOVA of the follow-up sample, means with standard errors are presented, for detailed statistical results see results section

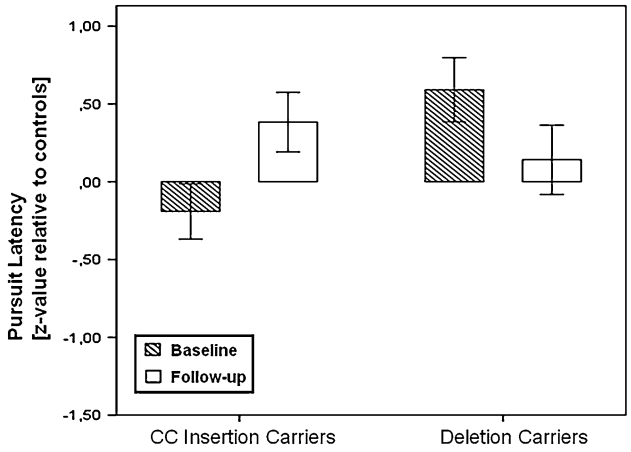

Fig. 3 Association of variants of the −141C Del/Ins polymorphism in *DRD2* with pursuit latency in a sample of 83 unmedicated patients with psychotic disorders at baseline and follow-up after 6 weeks of antipsychotic treatment. Antipsychotic treatment resulted in a reduction in pursuit latency differences between genotype groups, means with standard errors are presented, for detailed statistical results see results section

there was a significant association of rs274622 with maintenance eye velocity gain at baseline. The rs274622_CC genotype had poorer sustained pursuit maintenance than T-carriers (*genotype:* $F_{(1,134)}$ 9.80, $p_{\text{corrected}} = 0.014$). There was no differential treatment effect on sustained pursuit performance between T-carriers and the CC carriers (*genotype x time*: $p > 0.05$), Fig. 4.

With respect to *GRM3*rs6465084, GG carriers had unimpaired pursuit maintenance performance at baseline but showed a decline in performance after treatment while the baseline deficit in A-carriers did not change after

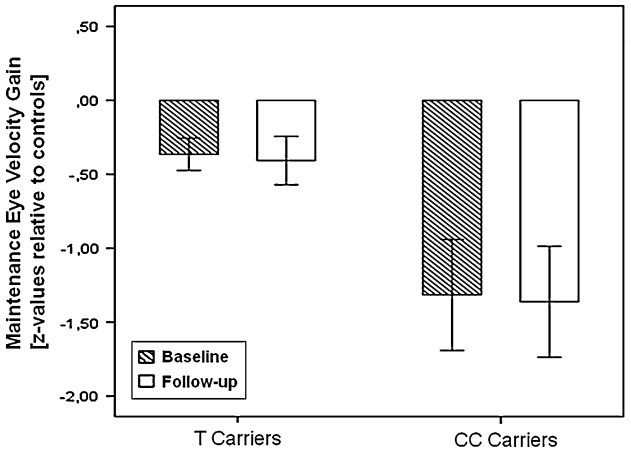

Fig. 4 Association of variants of rs274622 polymorphisms in *GRM3* with maintenance eye velocity gain in unmedicated patients with psychotic disorders at baseline ($N = 138$) and follow-up after 6 weeks of antipsychotic treatment ($N = 83$). There was no effect of treatment on genotype differences in repeated-measures ANOVA of the follow-up sample, means with standard errors are presented, for detailed statistical results see results section

treatment (*genotype x time*: $F_{(1,79)}$ 7.95, $p_{\text{corrected}} = 0.042$). No associations were observed between *GRM3*rs1989796 and *GRM3*rs1468412 with parameters of pursuit initiation or maintenance.

Discussion

In psychiatric genetics, advances are often constrained by uncertainties about how gene variants modulate specific aspects of brain function. Clarification of associations at the level of specific SNPs in genes that have been identified to mediate risk to psychosis, in relation to highly specified neurophysiological parameters, can speed understanding of illness pathophysiology and the development of novel targeted therapies. The present candidate gene study of discrete oculomotor phenotypes demonstrates for the first time that pursuit initiation and sustained pursuit maintenance have distinct associations with genes regulating dopamine and glutamate systems, respectively, in untreated patients with psychotic disorders. Specifically, *DRD2* was associated with pursuit initiation ability, consistent with the role of dopaminergic neurotransmission in the striatum, regulating speed of motor response initiation as demonstrated in preclinical studies and in patients with Parkinson's disease [24]. This association was also modulated by antipsychotic treatment highlighting the importance of studying the genotype–phenotype associations of interest in untreated patients and offering indirect support for the proposed role of D2 receptor activity and motor response initiation. Second, variants in *GRM3* were associated with the maintenance of pursuit, which requires active dynamic

interaction across corticocortical circuitry for perceptual analysis and action planning. *GRM3* codes for the type 3 metabotropic glutamate receptor (mGluR3) protein that is essential for optimal glutamate signaling in the brain, notably in prefrontal cortex as has been shown previously with other neurocognitive processes in psychotic disorders [44, 45, 47]. Together, these preliminary findings demonstrate linkage of specific neurophysiological parameters with particular functional polymorphisms that regulate brain neurochemistry in ways believed to be fundamental in the pathophysiology of psychotic disorders.

Pursuit initiation modulated by the *DRD2* promoter region

Pursuit initiation was impaired in patients carrying a deletion of cytosine at position-141 in the 5' promoter region of *DRD2* compared to carriers of a CC insertion at that position. In healthy subjects, this polymorphism has been related to altered *DRD2* promoter expression in vitro [67] and changes in D2 receptor density of the striatum [68]. In schizophrenia, variants of the −141C Ins/Del polymorphism have been associated with disease risk in some studies [42, 67, 69–71]. A recent meta-analysis of six studies suggested association of the Del allele with poorer antipsychotic drug response compared to the CC genotype [43].

Our present findings indicate that the −141C Ins/Del polymorphism affects pursuit initiation in first-episode psychosis patients, the more motor component of pursuit, in two different ways. First, the −141C deletion was associated with reduced initial eye velocity compared to the CC genotype. This association was not affected by antipsychotic treatment initiation, suggesting that it represents a stable genotype–intermediate phenotype association in psychotic disorders. Second, unmedicated −141C Del carriers also needed longer time to start pursuit of a moving target, i.e., their pursuit latency was prolonged compared to the CC genotype. This association was modulated by antipsychotic treatment resulting in reduced response latency in −141C deletion carriers after treatment but increased latencies in CC insertion carriers. Together, these findings suggest that altered D2 receptors in striatum due to a −141C deletion reduce the ability to use retinal motion signals to quickly initiate a pursuit motor response in patients.

During the pursuit initiation phase, there is not yet time for feedback about performance to influence pursuit velocity; thus, eye velocity directly depends on sensory input. Such a link between striatal activation during pursuit and visual motion processing area V5 has been established in healthy individuals [72]. In contrast, this effect was not seen in untreated patients with schizophrenia [72], which is consistent with the idea that a reduced ability for sensory input to drive striatal activity and motor response initiation occurs in psychotic disorders. An alteration in dopamine physiology is a likely cause of this disturbance, and our findings of an association with D2 genes offer new support for the more general model that disturbances in striatal output represent an important component in the neurobiology of psychotic disorders.

Pursuit maintenance modulated by *GRM3*

Type 3 metabotropic glutamate receptors mediate signal transduction through G-protein second messenger systems inhibiting cAMP accumulation [73]. *GRM3* has been associated with prefrontal and hippocampal physiology during cognitive function in healthy individuals. It has also been associated with risk for schizophrenia in some studies [44–46, 74] as well as with risk for psychosis in bipolar I disorder [75]. Consistent with a potential role in modulating function in higher cortical function, the rs274622 polymorphism that we found to be associated with pursuit maintenance has been implicated in modulation of the auditory cortical response to phoneme change that can be impaired in schizophrenia [76]. We found that patients carrying the *GRM3* rs274622_T allele demonstrated better pursuit maintenance than the CC genotype, a difference that did not change after antipsychotic treatment. Analysis of the *GRM3* promoter region has shown that this polymorphism may exist in a TATA sequence representing a potential transcription factor binding site [77]. The rs274622_C allele would disrupt this sequence, potentially reducing mGluR3 expression and thereby dysregulating glutamate transmission. This could explain our findings of better sustained pursuit performance in the rs274622_T allele carriers. In line with this, a previous Japanese case–control study suggested that haplotypes including the rs274622_T allele may confer protection against schizophrenia [78].

Secondly, our data suggest an association of the *GRM3* rs6465084 polymorphism with changes in pursuit maintenance after antipsychotic treatment. A-carriers had impaired pursuit maintenance at baseline that did not change after treatment, while pursuit maintenance in GG carriers was not impaired at baseline but declined after treatment. The finding of a stable pursuit maintenance deficit in patients carrying the A_allele is consistent with studies, suggesting that the rs6465084_A allele represents a risk allele for schizophrenia and a modifying marker for the severity of illness-associated cognitive deficits [79, 80]. In healthy individuals, AA homozygotes have been shown to have lower prefrontal N-acetylaspartate levels in vivo indicating altered synaptic activity and tissue glutamate [27]. Furthermore, lower mRNA levels of the glial

glutamate transporter EAAT2 have been found in postmortem prefrontal cortex of healthy AA homozygotes, a protein regulated by *GRM3* that modulates synaptic glutamate [44]. Healthy AA homozygotes also show heightened activation of dorsolateral prefrontal cortex (DLPFC) during a working memory task [44], which has been interpreted as reflecting inefficient cortical processing. A similar activation pattern of DLPFC has been reported in patients with schizophrenia and their healthy siblings [81]. Notably, two independent fMRI studies revealed increased DLPFC and frontal eye field activation during pursuit maintenance in patients with schizophrenia, consistent with the view that altered glutamate signaling in higher-order cortical networks disrupts pursuit control in psychotic disorders [72, 82].

Limitations and future perspectives

While our findings are novel and potentially heuristically valuable, there are also limitations. Studies of unmedicated patients with psychosis have the advantage of examining distinct neurophysiological alterations without confounds of antipsychotic treatment; however, clinical realities limit the sample size for such investigations. Thus, although our sample size must be regarded as large compared to other eye movement studies in unmedicated first-episode psychosis patients, it is still small for a genetic study. To enhance the statistical power, we combined patients with three psychotic disorders based on the knowledge that previous studies demonstrated comparable pursuit initiation and maintenance impairments in schizophrenia spectrum disorders, psychotic bipolar disorder and psychotic major depression [7, 14, 16, 18, 72]. Consistent with this, exploratory analyses of our data did not identify significantly different genotype–phenotype association in the individual patient groups. Still, further research is needed to examine potential disorder-specific effects. With the small sample of untreated early-course patients, we may have lacked the statistical power to detect associations with some candidate markers included in this study (rs1800497 (TaqIA) and rs1800498 (TaqID) in *DRD2* and rs1989796 and rs1468412 in *GRM3*) and to examine the effects of other genes in modulating the phenotypes of interest in the framework of a GWAS analysis. Furthermore, our findings with respect to antipsychotic-related effects in the follow-up sample must also be regarded as exploratory due to the small sample size. Last, lacking DNA samples in the matched controls, we cannot determine whether the genotype–phenotype associations are limited to or are stronger in psychotic patients than in the general population.

Despite these limitations, our findings with a rare and relatively large sample of untreated psychotic patients demonstrate one of the first direct associations of illness-related genotypes that regulate dopamine and glutamate transmission with specific neurophysiological abnormalities of brain function. They offer a promising approach for advancing pathophysiological models and understanding discrete components of the complex multifactorial risks for psychosis. From a pharmacogenetic perspective, the data underline the notion that genetic variation influences heterogeneous treatment outcomes following antipsychotic treatment and that neurophysiological biomarkers may be useful for tracking variability in treatment response across individuals.

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Conflict of interest Dr Sweeney is a consultant to Roche, Pfizer, Takeda, Bristol-Myers Squibb and Eli Lilly. Dr. Bishop has received research support from Ortho-McNeil Janssen. Drs Lencer, Harris, Reilly, Patel, Kittles, Prasad, Nimgaonkar and Keshavan report no biomedical financial interests or potential conflicts of interest.

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