



## BDNF and COMT, but not APOE, alleles are associated with psychiatric symptoms in refractory epilepsy

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### ABSTRACT

**Objective:** The objective of this study was to determine whether three common genetic polymorphisms [apolipoprotein (APOE) ε4 (rs42938 and rs7412), brain derived neurotrophic factor (BDNF) Met (rs6265), and catechol-O-methyltransferase (COMT) Val (rs4680)] are associated with increased psychiatric symptomatology in individuals with pharmacoresistant epilepsy.

**Methods:** One hundred forty-eight adults ( $M_{age} = 38$  years; 53% female) with refractory epilepsy completed self-report measures of mood, anxiety, and/or personality/psychopathology. Mann-Whitney *U*, *t*-tests, and Fisher's exact tests were used to determine if APOE4, BDNF Val66Met, or COMT Val158Met are associated with increased psychiatric symptomatology in people with epilepsy.

**Results:** As a group, BDNF Met carriers reported greater symptoms of depression on the Personality Assessment Inventory (PAI) than those without a Met allele ( $p = 0.004$ ); COMT Val carriers reported greater symptoms on the PAI Schizophrenia ( $p = 0.007$ ), Antisocial Features ( $p = 0.04$ ), and Alcohol Problems ( $p = 0.03$ ) scales than noncarriers. On the individual level, a significantly greater proportion of BDNF Met carriers demonstrated elevated PAI Depression scores compared to those without a Met allele ( $p = 0.046$ ). There was also a larger proportion of COMT Val carriers with elevated PAI Anxiety scores as compared to those without a Val allele ( $p = 0.036$ ).

**Significance:** This retrospective cross-sectional study provides preliminary evidence for a genetic basis of psychiatric comorbidities in epilepsy and suggests that BDNF and COMT may play an important role in the pathophysiology of mental health problems in this vulnerable population.

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### 1. Introduction

Psychiatric comorbidities affect up to 70% of people with pharmacoresistant epilepsy and significantly impact quality of life [1]. Psychiatric comorbidities in epilepsy have been thought to be due to psychosocial stress. However, recent evidence suggests a more complex pathogenesis. Not only are individuals with epilepsy two times more likely to develop depression, but also individuals

with depression are 2.5 times more likely to develop epilepsy [2]. Individuals with psychiatric comorbidities show greater abnormalities on neuroimaging [3] [1] and have a poorer seizure prognosis [4] and an increased risk of sudden death [5]. This suggests that there may be genetic differences in patients with epilepsy and psychiatric comorbidities.

Genetic factors play a significant role in psychiatric disorders with heritability estimates of up to 75% [6,7]. Apolipoprotein E (APOE), brain-derived neurotrophic factor (BDNF), and catechol-O-methyltransferase (COMT) polymorphisms have been studied as candidate genes in a number of psychiatric conditions. APOE4 has been variably associated with depression and bipolar disorder [8], and BDNF Val66Met has been reliably associated with stress-induced depression [9]. The COMT Val158Met has been associated with obsessive compulsive and bipolar disorders, and the COMT Val allele has been associated with schizophrenia and panic

**Abbreviations:** APOE, apolipoprotein E; BDNF, brain-derived neurotrophic factor; COMT, catechol-O-methyltransferase.

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disorder [10,11]. Despite this knowledge and the high prevalence of psychiatric disorders in individuals with epilepsy [12], genetic associations with psychiatric comorbidities in patients with epilepsy have remained largely unexplored. The aim of the current study was to determine whether these three common genetic polymorphisms are associated with increased psychiatric symptomatology in people with pharmacoresistant epilepsy.

## 2. Methods

### 2.1. Standard protocol approvals, registrations, and patient consents

This study involved an institutional review board (IRB)-approved, retrospective investigation of previously collected and archived data from 148 patients with pharmacoresistant epilepsy who were evaluated in the Cleveland Clinic Epilepsy Center.

### 2.2. Participants

The sample included patients with medically refractory epilepsy who underwent a comprehensive neuropsychological evaluation to evaluate candidacy for epilepsy surgery. Patients were included in the study if they completed at least one self-report measure of psychiatric symptomatology and had genotyping results available for *APOE*, *BDNF*, or *COMT*.

### 2.3. Measures

All patients in the study completed at least one of the following self-report measures: Beck Depression Inventory-Second Edition (BDI-II) [13], Beck Anxiety Inventory (BAI) [14], and/or Personality Assessment Inventory (PAI) [15]. The BDI-II is a self-report measure of recent (last two weeks) depressive symptoms assessed with 21 items, each consisting of 4 statements arranged in increasing symptom severity. The BAI is a similar self-report measure designed to assess recent (last two weeks) symptoms of anxiety. It also consists of 21 symptom items, the severity of which is rated on a 4-point Likert scale ranging from "not at all" to "severely." The PAI is a 344-item inventory used to screen for psychopathology and/or aid clinical diagnosis/treatment planning. The following 10 clinical scales generated by this measure were included in this study: Somatic Concerns, Anxiety, Depression, Mania, Paranoia, Schizophrenia, Borderline Features, Antisocial Features, Alcohol Problems, and Drug Problems.

### 2.4. DNA genotyping

Genomic deoxyribonucleic acid (DNA) from peripheral blood was processed by the Genomic Medicine Biorepository at Cleveland Clinic. For samples where DNA was unavailable from peripheral blood, DNA was isolated from resected brain tissue using GeneJET Genomic DNA Purification Kit (Thermo Fisher Scientific Inc., Waltham, MA) according to manufacturer's protocol. The *BDNF* genotyping was performed with AmpliTaq Gold DNA Polymerase (Thermo Fisher Scientific Inc., Waltham, MA) using the forward primer 5'-AAGCAAACATCCGAGG ACAA-3' and reverse primer 5'-GAGGCTCCAAAGGCACT-3' at 95 °C for 10 min, followed by 37 cycles of 95 °C for 30 s, 62 °C for 30 s, 72 °C for 30 s, and a final extension of 72 °C for 10 min. The *COMT* genotyping was performed with LightScanner Master Mix (BioFire Defense, Salt Lake City, UT) using the forward primer 5'-ACCCAGCGGATGGTGGATT T-3' and reverse primer 5'-ATGCCCTCCCTGCCACAG-3' at 95 °C for 2 min, followed by 53 cycles of 94 °C for 30 s, 69.9 °C for 30 s, and a final 95 °C for 30 s and 25 °C for 30 s. The *BDNF* and *COMT* amplicons were subjected to Exonuclease and Shrimp Alkaline Phosphatase treatment and finally Sanger sequenced for single nucleotide polymorphism (SNP) calls. The *APOE* genotyping was performed with LightScanner Master Mix (BioFire Defense, Salt Lake City, UT) using

the forward primer 5'-ACGCGGGCACGGCTGTCCAAGG-3', reverse primer 5'-GGCGCTCGGGATGGCGCTGA-3', forward probe 5'-TGGG CGCGCACATGAGGAGGTGTGCGCCCGCCTGGTGGAGTACC-3', and reverse probe 5'-GCGGCTCTCCGCGATGCCGATGACCTGCAGAAGCG CCTGGC-3' at 95 °C for 80 s, followed by 55 cycles of 95 °C for 30 s, 75 °C for 30 s, 77 °C for 30 s, and a final 95 °C for 30 s and 28 °C for 30 s. Results were analyzed with LightScanner instrument and Analysis Software v.2.0.0.1331.

Table 1 summarizes the genotype and allele frequencies for each of the three genes under study, which were consistent with those observed in the general population and did not differ from Hardy-Weinberg equilibrium [16]. For statistical analyses, patients were categorized into one of two groups based on carrier status for each gene: *APOE*  $\epsilon 4+$  or  $\epsilon 4-$ , *COMT* Val+ or Val-, and *BDNF* Met+ or Met-.

### 2.5. Analyses

Student's *t*-tests (normally distributed continuous variables), Mann-Whitney *U* tests (skewed continuous variables), and Fisher's Exact tests (categorical variables) were used to examine differences between the genotype groups on demographic and disease variables and on self-report questionnaires. Demographic and/or disease variables that were significantly different between the groups and also significantly associated with the outcome variable were included as covariates in primary analyses. Outcomes of interest were compared as a function of carrier status, while controlling for covariates as necessary, using Student's *t*-tests, two-way analysis of variance (when including categorical covariates) or analysis of covariance (when including continuous covariates). Outcomes were log-transformed if warranted prior to analysis.

Finally, to examine clinically relevant differences at the individual level that are obscured when analyzing group data, we classified the score for each patient as clinically elevated/not elevated on each measure/scale using the cutoffs recommended in the technical manuals (i.e., BDI-II raw score > 13, BAI raw score > 7, and PAI *t*-score > 59). We then performed Fisher's exact tests to examine differences in the proportion of patients with elevated psychiatric symptoms as a function of genotype.

All statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) version 24.0. All tests for statistical significance were two-sided. An alpha level of  $p < 0.05$  was considered significant for the detection of group differences. Effect sizes were interpreted based on the value of partial eta squared (small = 0.010, medium = 0.059, and large = 0.138) [17] or Cramer's *V* (small = 0.1, medium = 0.3, and large = 0.5) [18]. Given the exploratory nature of this study and the nonindependence of certain outcome variables, we did not correct for multiple comparisons.

**Table 1**  
Frequencies of Genotypes and Alleles.

Genotype	Frequency, n (%)	Allele	Frequency, n (%)
<i>APOE</i>			
$\epsilon 2/\epsilon 2$	1 (1)	$\epsilon 2$	22 (7)
$\epsilon 2/\epsilon 3$	20 (13)	$\epsilon 3$	241 (82)
$\epsilon 3/\epsilon 3$	96 (65)	$\epsilon 4$	33 (11)
$\epsilon 3/\epsilon 4$	29 (20)		
$\epsilon 4/\epsilon 4$	2 (1)		
$\epsilon 2/\epsilon 4$	0 (0)		
<i>BDNF</i>			
Val/Val	101 (69)	Val	244 (82)
Val/Met	42 (28)	Met	52 (18)
Met/Met	5 (3)		
<i>COMT</i>			
Val/Val	45 (30)	Val	155 (52)
Val/Met	65 (44)	Met	141 (48)
Met/Met	38 (26)		

2.6. Data availability statement

The datasets analyzed in the current study are not publicly available because of restricted access, but further information about the datasets is available from the corresponding author on reasonable request.

3. Results

A total of 148 patients met all inclusion criteria. Patients were taking an average of 2.36 (SD = 0.96) antiepileptic drugs (AEDs) at the time of their neuropsychological evaluation. These medications were categorized with respect to potential psychiatric side effects based on the current literature [19–21]. Seventy-four percent of participants were taking at least one AED with favorable psychotropic effects (i.e., carbamazepine, oxycarbazepine, lamotrigine, pregabalin, gabapentin, and valproic acid), and 64% of participants were taking at least one AED with unfavorable psychotropic effects (i.e., phenobarbital, primidone, levetiracetam, zonisamide, and topiramate). Forty-three percent were taking at least one drug from each category. A summary of the sample characteristics is provided in Table 2.

There were no significant differences in demographic or disease characteristics between *APOE* ε4+ and ε4− groups or between *BDNF* Met+ and Met− groups. The *COMT* Val+ group had a higher proportion of nonwhite individuals (13.7% vs. 0%) and a lower mean education (13.1 vs. 14.0) than the Val− group. The observed difference in race is consistent with population data showing a higher frequency of the Val allele in the African and Hispanic populations [22].

3.1. Group analyses

The group analyses are presented in Table 3. At the group level, *BDNF* Met+ individuals reported greater symptoms of depression on the PAI than those with Met−. Mean Depression scores were approximately 8 points higher in *BDNF* Met carriers with a medium range effect size. Scores on the Schizophrenia, Antisocial Features, and Alcohol Problems scales from the PAI were significantly higher in the *COMT* Val+ patients compared with that in the Val− patients. The greatest difference was observed on the Schizophrenia scale, with Val+ patients having a mean score 6-points higher than the Val− group and a medium effect size. Val+ patients had median Antisocial Features and Alcohol

**Table 2**  
Demographic, seizure, and medication data for study patients.

	Mean (SD) or Median (IQR)
Age	38.0 (13.8)
Education	13.3 (2.4)
Age at Seizure Onset	19 (11–32)
Duration of Epilepsy	12 (6–22)
Sex – Female	n (%) 78 (53)
Race – White	133 (90)
Seizure Side	
Left	77 (52)
Right	61 (41)
Bilateral	7 (5)
Generalized	3 (2)
Seizure Site	
Temporal	91 (61)
Parietal	4 (3)
Frontal	19 (13)
Multilobar	31 (21)
Generalized	3 (2)
≥ 1 Psychotropic Meds	57 (39)
≥ 1 Mood (+) AED	109 (74)
≥ 1 Mood (−) AED	95 (64)

SD = standard deviation; IQR = interquartile range;  
Mood (+) = favorable psychotropic effects.  
Mood (−) = unfavorable psychotropic effects.

**Table 3**  
Self-report mood, anxiety, and personality scores as a function of carrier status.

Gene: <i>APOE</i>	ε4+ n = 31	ε4− n = 117	p	η <sup>2</sup> <sub>p</sub>
Beck				
Depression (BDI-II)	11.0 (3.0–20.0)	12.0 (5.5–20.5)	0.627	0.003
Anxiety (BAI) <sup>*</sup>	11.0 (2.0–19.0)	10.0 (4.0–18.0)	0.875	0.000
PAI <sup>±</sup>				
Somatic Concerns	63.2 (8.8)	62.6 (8.8)	0.231	0.017
Anxiety	55.9 (10.2)	55.6 (10.2)	0.572	0.004
Depression	57.5 (11.0)	57.4 (11.3)	0.948	0.000
Mania	45.2 (7.6)	44.6 (7.6)	0.117	0.029
Paranoia	49.0 (43.3–59.0)	46.0 (40.0–56.0)	0.361	0.009
Schizophrenia	51.3 (9.0)	51.6 (9.3)	0.569	0.004
Borderline Features	50.7 (9.1)	50.5 (9.2)	0.634	0.003
Antisocial Features	48.5 (40.8–54.0)	45.0 (41.0–52.0)	0.466	0.010
Alcohol Problems	47.0 (41.0–47.8)	45.0 (41.0–50.0)	0.834	0.000
Drug Problems	48.0 (42.0–52.5)	48.0 (45.0–54.0)	0.418	0.005
* n = 129; ε4+ 28, ε4−101 ± n = 87; ε4+ 18, ε4−69				
Gene: <i>BDNF</i>	Met+ n = 47	Met− n = 101	p	η <sup>2</sup> <sub>p</sub>
Beck				
Depression (BDI-II)	15.5 (6.0–21.0)	12.0 (5.0–21.0)	0.196	0.004
Anxiety (BAI) <sup>*</sup>	12.5 (5.8–19.0)	9.0 (3.0–17.0)	0.184	0.006
PAI <sup>±</sup>				
Somatic Concerns	64.2 (8.8)	62.8 (8.8)	0.552	0.004
Anxiety	59.6 (9.6)	54.7 (10.2)	0.050	0.045
Depression	<b>63.3 (10.2)</b>	<b>55.5 (10.7)</b>	<b>0.004</b>	<b>0.095**</b>
Mania	45.1 (8.4)	45.2 (7.4)	0.954	0.000
Paranoia	50.0 (45.0–56.5)	45.0 (40.0–57.0)	0.132	0.020
Schizophrenia	52.4 (7.3)	51.0 (9.5)	0.529	0.005
Borderline Features	53.5 (9.1)	49.8 (9.0)	0.108	0.030
Antisocial Features	45.5 (40.8–53.3)	45.0 (41.0–52.0)	0.910	0.001
Alcohol Problems	47.0 (41.0–50.0)	45.0 (41.0–48.0)	0.467	0.002
Drug Problems	48.0 (42.0–51.0)	48.0 (45.0–55.0)	0.137	0.031
* n = 129; Met+ 42, Met− 87 ± n = 87; Met+ 22, Met− 65				
Gene: <i>COMT</i>	Val+ n = 110	Val− n = 38	p	η <sup>2</sup> <sub>p</sub>
Beck				
Depression (BDI-II)	14.5 (6.0–21.3)	10.0 (4.0–17.0)	0.087	0.022
Anxiety (BAI) <sup>*</sup>	11.0 (5.0–19.0)	5.0 (2.0–15.0)	0.081	0.027
PAI <sup>±</sup>				
Somatic Concerns	63.7 (9.4)	61.8 (9.2)	0.760	0.001
Anxiety	57.2 (10.4)	52.3 (8.8)	0.054	0.043
Depression	58.6 (10.8)	54.1 (11.1)	0.245	0.016
Mania	44.6 (7.2)	47.1 (8.6)	0.183	0.021
Paranoia	49.0 (40.5–58.0)	44.5 (37.8–51.8)	0.097	0.027
Schizophrenia	<b>52.8 (9.2)</b>	<b>46.8 (7.0)</b>	<b>0.007</b>	<b>0.083**</b>
Borderline Features	51.7 (9.2)	48.0 (8.4)	0.292	0.013
Antisocial Features	<b>48.0 (42.0–53.0)</b>	<b>42.0 (38.0–51.3)</b>	<b>0.038</b>	<b>0.039</b>
Alcohol Problems	<b>47.0 (41.0–50.0)</b>	<b>42.0 (41.0–47.0)</b>	<b>0.031</b>	<b>0.033</b>
Drug Problems	48.0 (46.0–54.0)	48.0 (42.0–54.0)	0.379	0.007

Note: BDI-II and BAI scores are reported as raw scores; PAI scores are reported as *t*-scores (M = 50, SD = 10).

Values reported as mean (SD) for normally distributed variables and median (IQR) reported for skewed variables.

Bold values represent significant findings at *p* < 0.05.

\* n = 129; Val+ 102, Val− 27.

\*\* η<sup>2</sup><sub>p</sub> ≥ 0.059.

± n = 87; Val+ 65, Met− 22.

Problems scores 6 and 5 points higher respectively than Val− patients. There were no significant mean differences between carrier groups on any other scale/measure. Education was included as a covariate when

examining Somatic Concerns, Depression, and Borderline Features scores as a function of *COMT* (Val +, Val –) carrier status. Race was included as a covariate when examining BDI-II and BAI scores as a function of *COMT* (Val +, Val –) carrier status.

### 3.2. Individual analyses

Close to half of the patients in our study had clinically elevated BDI-II scores, and almost 60% had clinically elevated BAI scores. [Table 4](#)

**Table 4**  
Proportion of Patients with Clinically Elevated Scores on Self-Report Measures.

Gene: <i>APOE</i>	$\epsilon 4+$ n = 31	$\epsilon 4-$ n = 117	p	Cramer's V
Beck				
Depression (BDI-II)	14 (45)	56 (48)	0.842	0.022
Anxiety (BAI)*	16 (57)	59 (59)	1.000	0.011
PAI $\pm$				
Somatic Concerns	13 (72)	38 (55)	0.283	0.141
Anxiety	8 (44)	20 (29)	0.260	0.134
Depression	6 (33)	29 (42)	0.595	0.072
Mania	2 (11)	7 (10)	1.000	0.013
Paranoia	4 (22)	9 (13)	0.456	0.104
Schizophrenia	2 (11)	14 (20)	0.506	0.096
Borderline Features	2 (11)	11 (16)	1.000	0.055
Antisocial Features	2 (11)	4 (6)	0.599	0.085
Alcohol Problems	1 (6)	2 (3)	0.506	0.059
Drug Problems	3 (17)	11 (16)	1.000	0.008
* n = 129; $\epsilon 4+$ 28, $\epsilon 4-$ 101				
$\pm$ n = 87; $\epsilon 4+$ 18, $\epsilon 4-$ 69				
Gene: <i>BDNF</i>	Met + n = 47	Met – n = 101	p	Cramer's V
Beck				
Depression (BDI-II)	27 (57)	43 (43)	0.112	0.139
Anxiety (BAI)*	28 (67)	47 (54)	0.188	0.120
PAI $\pm$				
Somatic Concerns	14 (64)	37 (57)	0.625	0.059
Anxiety	10 (46)	18 (28)	0.186	0.165
Depression	<b>13 (59)</b>	<b>22 (34)</b>	<b>0.046</b>	<b>0.224</b>
Mania	6 (9)	3 (14)	0.686	0.063
Paranoia	3 (14)	10 (15)	1.000	0.021
Schizophrenia	3 (14)	13 (20)	0.751	0.071
Borderline Features	4 (18)	9 (14)	0.731	0.053
Antisocial Features	3 (14)	3 (5)	0.167	0.155
Alcohol Problems	0 (0)	3 (5)	0.568	0.110
Drug Problems	1 (5)	13 (20)	0.106	0.183
* n = 129; Met + 42, Met – 87				
$\pm$ n = 87; Met + 22, Met – 65				
Gene: <i>COMT</i>	Val + n = 110	Val – n = 38	p	Cramer's V or OR**
Beck				
Depression (BDI-II)	58 (53)	12 (32)	0.209	0.612**
Anxiety (BAI)*	64 (63)	11 (41)	0.097	0.476**
PAI $\pm$				
Somatic Concerns	39 (60)	12 (55)	0.997	1.002**
Anxiety	<b>25 (39)</b>	<b>3 (14)</b>	<b>0.036</b>	<b>0.231</b>
Depression	28 (43)	7 (32)	0.487	0.689**
Mania	6 (9)	3 (14)	0.686	0.063
Paranoia	2 (9)	11 (17)	0.502	0.095
Schizophrenia	15 (23)	1 (5)	0.061	0.208
Borderline Features	2 (9)	11 (17)	0.641	0.675**
Antisocial Features	5 (8)	1 (5)	1.000	0.054
Alcohol Problems	1 (5)	2 (3)	1.000	0.035
Drug Problems	10 (15)	4 (18)	0.745	0.033

BDI-II = Beck Depression Inventory – Second Edition; BAI = Beck Anxiety Inventory; OR = odds ratio Exp(B)

Values reported as n (%).

Bold values represent significant findings at  $p < 0.05$ .

\* n = 129; Val + 102, Val – 27

\*\* Cramer's V  $\geq 0.3$ .

$\pm$  n = 87; Val + 65, Met – 22

illustrates that, at the individual level, a significantly greater proportion of *BDNF* Met + patients demonstrated clinically elevated Depression scores on the PAI as compared to Met – patients. There was also a larger proportion of *COMT* Val carriers with clinically elevated symptoms of Anxiety on the PAI as compared to those without a Val allele.

### 4. Discussion

We examined the relationship between *APOE*, *BDNF*, and *COMT* polymorphisms and psychiatric symptomatology in people with pharmacoresistant epilepsy. The strongest relationship was observed between *BDNF* alleles and the PAI Depression scale. The *BDNF* Met carriers showed greater depressive symptoms on this scale than those without a Met allele. Further, at the individual level, a larger proportion of Met carriers had clinically elevated symptoms of depression on this measure (59% of carriers versus 34% of noncarriers). These findings are consistent with existing literature in healthy individuals and other patient populations that have shown *BDNF* Met carriers have an increased susceptibility to depression [9,23,24].

The functional consequences of *BDNF* polymorphisms inform how this might contribute to the pathogenesis of both depression and epilepsy. The *BDNF* Val66Met polymorphism results in decreased secretion of the protein, BDNF. This protein is highly expressed in the CNS and is a key modulator of neuronal plasticity and synaptogenesis [25]. Serum BDNF levels are decreased in patients with depression and normalize with antidepressant treatment [26]. Additionally, individuals with epilepsy who have more frequent seizures have lower BDNF levels than those with less frequent seizures, independent of depressive symptoms [27]. This may help to account for the high incidence of depression in patients with epilepsy. This mechanism has treatment ramifications for both seizure control and depression symptoms. First, patients treated with selective serotonin reuptake inhibitors (SSRIs) have increased serum BDNF levels and decreased seizure frequency [28]. Second, animal studies have demonstrated that the development of depression following epilepsy onset can be prevented through treatment with a BDNF analog [29].

The *BDNF* Val66Met polymorphism is also associated with decreased dendritic arborization and impaired long-term potentiation [25]. This is particularly important for the hippocampus, and healthy individuals with a *BDNF* Val66Met allele have decreased hippocampal volumes [30]. Hippocampal atrophy is common in epilepsy [31] and is observed in individuals exposed to significant prolonged stress [32], which is a model for depression. Individuals with epilepsy who carry the *BDNF* Val66Met allele may have an increased vulnerability to depression because of epilepsy and genotype-related reduction in the volume and/or plasticity in these structures.

Interestingly, depression symptoms as reported on the BDI-II were not related to *BDNF* genotype. This may be due to the short time frame referenced on this measure; the BDI-II assesses acute depressive symptoms within the last two weeks, whereas the PAI assesses more stable, longstanding personality traits. The duration of mental health symptoms is relevant to the natural history of seizure disorders. Prior research in epilepsy has demonstrated that individuals with a lifetime history of a psychiatric diagnosis, including depression, are more likely to have poor seizure outcomes with pharmacotherapy [33] and following anterior temporal lobectomy [34–37], and are at increased risk for sudden unexplained death in epilepsy (SUDEP) [5].

Our results also suggest a relationship between the *COMT* rs4680 polymorphism and psychiatric symptomatology in epilepsy. As a group, Val carriers had higher scores on the Schizophrenia, Antisocial Features, and Alcohol Problems scales of the PAI than those without a Val allele. The Val allele has previously been variably associated with schizophrenia [38], antisocial behavior [39], and alcoholism [40]. Results of the current study suggest a similar association with psychiatric symptomatology in people with epilepsy. While differences in group mean/median scores were statistically significant, it is important to

note that mean/median scores on these measures were within the normal range for both genotype groups, and there was no difference in the proportion of patients with elevated scores on these measures at the individual patient level. At the individual level, a larger proportion of *COMT* Val carriers endorsed clinically elevated anxiety symptoms on the PAI scale.

Again, the functional role of *COMT* Val is informative in understanding the potential mechanism underlying the range of psychiatric symptoms associated with its presence. Catechol-*O*-methyltransferase is an enzyme responsible for dopamine degradation. The Val allele confers higher enzymatic activity resulting in lower synaptic dopamine in the prefrontal cortex [41]. This is consistent with studies reporting that patients with drug-resistant temporal lobe epilepsy and psychiatric comorbidities exhibited a decrease in D2 receptor neurotransmission, compared to those without psychiatric comorbidities [42,43]. Notably, administration of D2 agonists reverses depression-like behavior in rats with genetic absence epilepsy [44]. Dysregulation of dopaminergic signaling has been implicated in the development of various psychiatric disorders [38,45]. The association of the Val allele with schizophrenia has been hypothesized to be due to the selective decrease of dopamine within the prefrontal cortex [41]. However, dopaminergic signaling in the brain also influences many aspects of cognitive functioning including motivation, emotion, reward, attention, and decision-making. The Val allele has been reliably associated with impaired cognitive functioning [46], so it is possible that the cognitive symptoms included in the Schizophrenia PAI scale may be driving the observed differences between the genotype groups. Regardless, our results provide further evidence for the role of aberrant dopaminergic signaling in the etiology of psychiatric comorbidities in epilepsy.

Studies indicate that *COMT* Val carriers tend to have a poorer treatment response with antidepressant/anxiolytic therapy [47–49]. In our cohort, Val carriers were taking significantly more psychotropic medications than those without a Val allele. It is possible that the variation in the proportion of patients with clinically elevated scores was due to differences in treatment response, rather than differences in predisposition to anxiety. Further studies will be needed to clarify whether the *COMT* Val allele influences risk for anxiety, treatment response, or both, in individuals with epilepsy.

We did not find any significant associations between *APOE* genotype and BDI-II, BAI, or PAI clinical scale scores. Our results indicate that *APOE* is not likely to play a major role in psychiatric comorbidities in epilepsy. This is in line with studies in the general population, which have not found a consistent association between the *APOE*  $\epsilon$ 4 allele and psychiatric disorders such as depression, bipolar disorder, and schizophrenia [8].

Some limitations should be considered when interpreting the results of our study. We examined the relationship between these genes and self-reported psychiatric symptomatology, not formal clinical Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) diagnoses. However, the BDI-II, BAI, and PAI are well-validated and highly sensitive and specific, making them appropriate tools for the exploratory nature of our study. Another limitation is the complexity in taking into account psychiatric effects of AEDs. The evidence for classifying AEDs as having favorable versus unfavorable psychiatric effects is not homogenous or complete. Furthermore, it is difficult to assess potential effects of polytherapy. Nevertheless, psychiatric side effects of AEDs represent a potentially important confounding factor, so we examined this in our analysis. Finally, all patients in our cohort are from a single specialized center and have treatment-refractory epilepsy, potentially limiting the generalizability of our results to the larger epilepsy community.

#### 4.1. Conclusions

Identifying the factors underlying mental health problems in people with epilepsy is a key part of effective medical care. Mood disorders have a greater impact on quality of life in people with epilepsy than

seizure frequency or severity [1]. Furthermore, psychiatric comorbidities are associated with poorer seizure prognosis [4] and increased risk of death from SUDEP [5] and other causes [50]. Here, we examined the associations between genetic variants and self-reported psychological symptoms in people with epilepsy. Our study provides preliminary evidence for a genetic contribution to psychiatric comorbidities in epilepsy and suggests that *BDNF* and *COMT* may play an important role in the pathophysiology of mental health problems in this vulnerable population.

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