BDNF Val66Met Polymorphism, Antidepressant Use, and Cognitive Performance: A Moderation Analysis in Patients with Psychotic Disorders

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Background:

- Brain-derived neurotrophic factor (BDNF) is a neuropeptide essential for neuronal development and plasticity. It is suggested to be a mediator of antidepressant efficacy in depression, and more broadly has been associated with cognitive performance.
- Antidepressants may be used to treat depressive symptoms in psychotic disorders, however, with unclear benefits for cognitive symptoms.
- The *BDNF* Val66Met (rs6265) polymorphism may affect the expression and stability of BDNF, but its relationship with cognitive performance in the context of antidepressant medications in psychosis has not been examined.

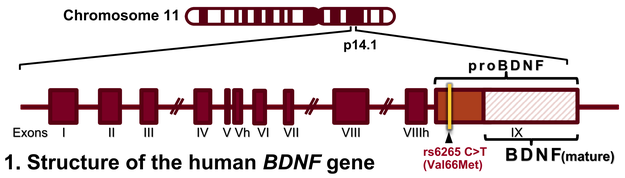


Figure 1. Structure of the human *BDNF* gene

Objective:

- This study investigated the moderation of *BDNF* Val66Met genotype on the relationship between antidepressant use and cognitive performance in clinically stable patients with psychotic disorders.

Methods

❑ **Participants**
- Participants (total N=640) diagnosed with schizophrenia spectrum disorder (N=428) and psychotic bipolar disorder (N=212) from the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) study[1] were examined.

❑ **Inclusion Criteria**
- 15-65 years of age
- WRAT-IV Reading >70
- No history of medical condition known to significantly impact cognition
- Clinically stable with no recent medication changes (6wks)
- Available detailed medication information

❑ **Neuropsychological Performance**
- Brief Assessment of Cognition in Schizophrenia (BACS) adjusted for sex and age

❑ **Genotyping**
- Participants genotyped using the Illumina PsychChip followed by imputation using the 1000 Genomes reference panel
- The *BDNF* single nucleotide polymorphism Val66Met (rs6265) was examined

❑ **Statistical Analysis**
- Participants stratified by genotype and by diagnoses for analyses
- Regression-based moderation analyses conducted to investigate interactions between Val66Met genotype and antidepressant use in relation to BACS controlling for: symptom severity (Positive and Negative Syndrome Scale (PANSS) Total score) & race
- Significant interactions probed through the pick-a-point approach using Hayes' PROCESS Model 1[2]

Table 1. Demographic and Clinical Characteristics

Variable	Schizophrenia Spectrum Disorder (N=428)	Psychotic Bipolar Disorder (N=212)	Test statistic (*p-value*)
	Mean (S.D.) or n (%)	Mean (S.D.) or n (%)	
Age	36.33 (12.54)	36.00 (12.7)	t=-0.31, 638df (0.761)
Male	243 (56.8%)	80 (37.7%)	χ^2=20.56, 1df (≤0.001)
Race			χ^2=39.10, 2df (≤0.001)
Caucasian	216 (50.5%)	160 (75.5%)	
African American	194 (45.3%)	43 (20.3%)	
Other	18 (4.2%)	9 (4.2%)	
MADRS Total score	10.46 (9.31)	9.60 (9.10)	t=-1.10, 638df (0.270)
PANSS Total score	66.08 (16.80)	52.62 (13.97)	t=-10.07, 638df (≤0.001)
BACS composite score	-1.38 (1.26)	-0.89 (1.16)	t=4.79, 638df (≤0.001)
BACS subtest score			
Verbal Memory	-0.84 (1.26)	-0.41 (1.14)	t=4.26, 638df (≤0.001)
Digit Sequencing	-0.79 (1.05)	-0.52 (1.03)	t=3.11, 638df (0.002)
Token Motor	-1.16 (1.12)	-0.84 (1.15)	t=3.38, 638df (0.001)
Verbal Fluency	-0.72 (1.09)	-0.45 (1.13)	t=2.96, 638df (0.003)
Symbol Coding	-1.37 (1.18)	-1.08 (1.12)	t=2.95, 638df (0.003)
Tower of London	-0.58 (1.23)	-0.23 (1.08)	t=3.49, 638df (0.001)
Medications			
Total Number of Psychotropic Medications	2.53 (1.44)	2.72. (1.38)	t=1.61, 638df (0.109)
Antidepressant User	202 (47.2%)	100 (47.2%)	χ^2=0.00, 1df (0.995)
SSRIs/SNRIs	131 (30.6%)	52 (24.5%)	χ^2=2.57, 1df (0.109)
Tricyclics	3 (0.7%)	7 (3.3%)	χ^2=6.24, 1df (0.013)
Miscellaneous	68 (15.9%)	41 (19.3%)	χ^2=1.37, 1df (0.241)

Figure 2. Moderation of *BDNF* Val66Met polymorphism on the effect of antidepressant use on cognitive performance, depicted as a conceptual diagram (2A) and a statistical diagram (2B)

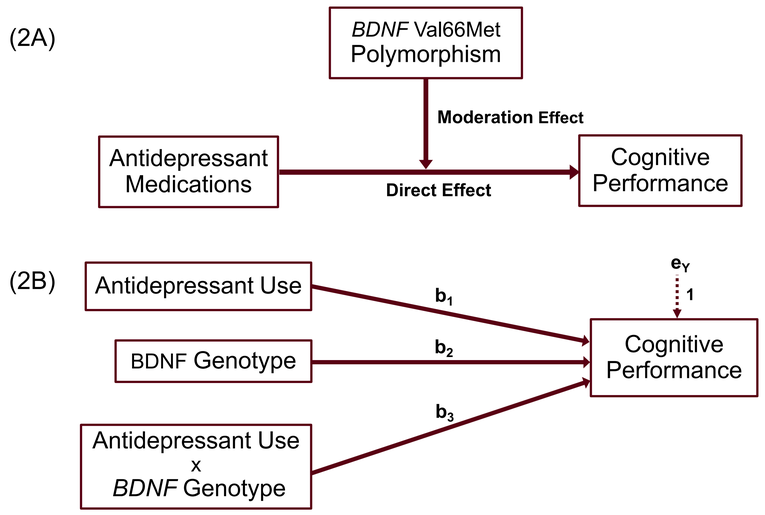
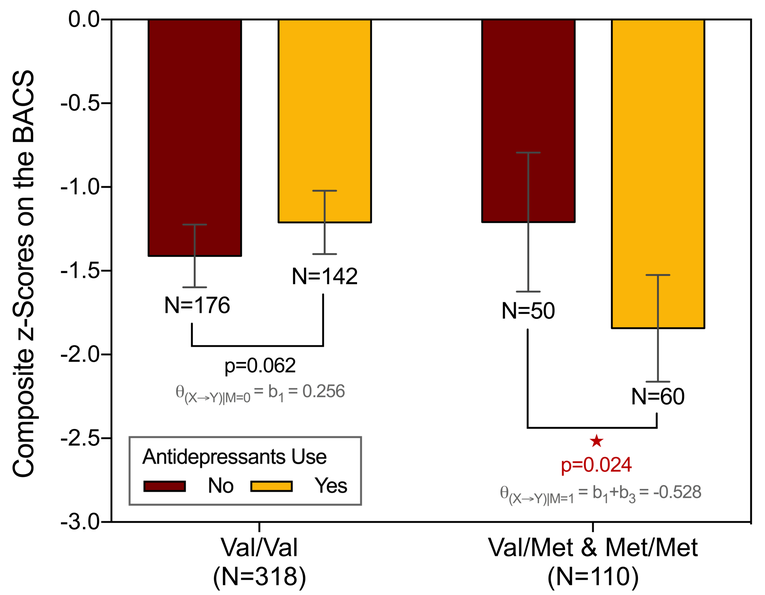


Figure 3. Visual representation of the *BDNF* Val66Met genotype moderation (M) of the antidepressant effect (X) on composite BACS scores (Y) in schizophrenia spectrum disorder



The statistical model of linear moderation estimated by allowing X, Y to be a linear function of M:

$$\widehat{Y} = i_1 + (b_1 + b_3 M)X + b_2 M = i_1 + b_1 X + b_2 M + b_3 XM$$

In this model, the conditional effect of X on Y:

$$\theta_{X \to Y} = b_1 + b_3$$

Figure 4. Visual representation of the *BDNF* Val66Met genotype moderation of the antidepressant effect on Verbal Memory (4A) & Digit Sequencing (4B) in schizophrenia spectrum disorder

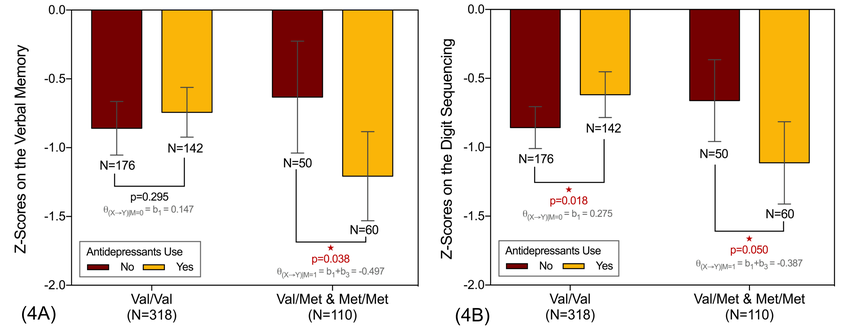


Table 2. Unstandardized coefficients of *BDNF* Val66Met Genotype x antidepressant use interaction predicting BACS scores controlling for current symptom severity (PANSS Total score) and race

	BDNF Val66Met Genotype x antidepressant use interaction			
	Schizophrenia spectrum disorder (N=428)		Psychotic bipolar disorder (N=212)	
	Unstandardized coefficient	*Test statistic (p-Value)*	*Unstandardized coefficient*	*Test statistic (p-Value)*
Composite BACS	-0.784	t=-2.903, 422df (0.004)	0.225	t=0.616, 422df (0.538)
Verbal Memory	-0.644	t=-2.331, 422df (0.020)	-0.090	t=-0.252, 422df (0.801)
Digit Sequencing	-0.662	t=-2.899, 422df (0.004)	0.141	t=0.439, 422df (0.661)
Token Motor	-0.430	t=-1.771, 422df (0.077)	0.129	t=0.358, 422df (0.721)
Verbal Fluency	-0.409	t=-1.711, 422df (0.088)	0.380	t=1.053, 422df (0.294)
Symbol Coding	-0.497	t=-1.921, 422df (0.055)	0.303	t=0.875, 422df (0.382)
Tower of London	-0.328	t=-1.192, 422df (0.234)	0.010	t=0.029, 422df (0.977)

Primary Findings

- ❖ In participants with schizophrenia spectrum disorders, Val66Met genotype significantly moderated the relationship between antidepressant use and composite BACS scores [F(1, 422)=8.426, p=0.004], whereby there was no association between antidepressant use and composite BACS scores in Val/Val genotype groups while among Met allele carriers, a lower composite BACS score was associated with antidepressant use.
- ❖ Among BACS subtests, Verbal Memory and Digit Sequencing were most associated with antidepressants moderated by Val66Met genotype.
- ❖ Examining the influence of depression (MADRS) or psychosis (PANSS) symptoms did not change these findings.
- ❖ This relationship was not detected in psychotic bipolar disorder.

Conclusion/Discussion

- ❖ The Val66Met polymorphism known to influence *BDNF* gene expression and stability may moderate the impact of antidepressant use on cognitive performance in patients with schizophrenia spectrum disorders.
- ❖ These findings indicate that genetic factors related to neuroplasticity may be important determinants of drug action, and explain interpatient differences that have been previously observed in antidepressant effects on cognitive performance.
- ❖ **Future Direction:** to investigate the association of BDNF serum level and *BDNF* genotype related to cognitive performance in the context of antidepressant exposure

Acknowledgment and Disclosure:
Research reported in this publication was supported in part by funding from the National Institute of Mental Health (MH083888 to J.R.B., MH072767 to S.K.H., MH083126 to J.L.R., MH077851 to C.A.T., MH078113 to M.S.K., MH077945 to G.P., MH077852 to G.T., MH077862 to J.A.S.). R.S.E.K has received royalties for the BACS. L.Z. has received 2019 Defining the Future Research Grant from CPNP Foundation and 2018 Melendy Summer Research Scholarship from College of Pharmacy, University of Minnesota.

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