**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=460) diagnosed with schizophrenia spectrum disorder (N=409) and psychotic bipolar disorder (N=12) from the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNP) study were examined.

- **Inclusion Criteria:**
  - 16 years of age.
  - WRAT-IV reading > 70.
  - No history of medical condition known to significantly impact cognition.
  - Clinically stable with no recent medication changes.
  - Available detailed medication information.
  - Brief Assessment of Cognition in Schizophrenia (BACS) adapted 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 (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 symptoms severity (Positive and Negative Symptom Scale (PANSS) Total score), age, and race.

- **Neuropsychological Performance:**
  - Significant interactions probed through the pick-a-point approach using Hayes PROCESS Model Y*.

### Table 1. Demographic and Clinical Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Schizophrenia Spectrum Disorder (N=409)</th>
<th>Psychotic Bipolar Disorder (N=12)</th>
<th>Test statistic (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Mean 36.5 (SD 12.24)</td>
<td>Mean 36.5 (SD 12.24)</td>
<td>t=0.31, ESMB (0.761)</td>
</tr>
<tr>
<td>Male</td>
<td>243 (59.5%)</td>
<td>79 (6.6%)</td>
<td>t=20.68, 6.52 (0.001)</td>
</tr>
<tr>
<td>Race</td>
<td>180 (44.3%)</td>
<td>33 (27.5%)</td>
<td>t=39.10, 29 (0.001)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>218 (54.5%)</td>
<td>82 (67.7%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>19 (4.6%)</td>
<td>16 (12.5%)</td>
<td></td>
</tr>
<tr>
<td>BACS Total Score</td>
<td>50.26 (3.34)</td>
<td>55.32 (2.33)</td>
<td>t=3.49, 6.38 (0.001)</td>
</tr>
<tr>
<td>PAnSS Total Score</td>
<td>56.16 (5.68)</td>
<td>42.13 (2.47)</td>
<td>t=1.05, 6.97 (0.298)</td>
</tr>
<tr>
<td>BACS subtest score</td>
<td>-1.86 (1.07)</td>
<td>-1.71 (0.95)</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2. Unstandardized coefficients of BDNF Val66Met Genotype x antidepressant use interaction

- **BDNF Val66Met Genotype**
  - Significant moderations related to antidepressant use and composite BACS scores (93.2% of variance).
  - There was no association between antidepressant use and BACS composite scores in Val66Met genotype groups.

### 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 neuropsychology may be important determinants of drug action, and explain interpatient differences that have been previously observed in antidepressant effects on cognitive performance.**

- **Future research:**
  - To investigate the association of BDNF gene level and BDNF genotype-related cognitive performance in the context of antidepressant exposure.

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### Primary Findings

- In participants with schizophrenia spectrum disorders, Val66Met genotype significantly moderated the relationship between antidepressant use and composite BACS scores (F(1, 428) = 4.26, p = 0.04), whereas there was no association between antidepressant use and BACS composite scores in Val66Met genotype groups, and among Val66Met carriers, a lower composite BACS score was associated with antidepressant use.

- Among BACS subtests, Verbal Memory and Digit Sequencing were most associated with antidepressant use moderated by Val66Met genotype.

- Examining the influence of depression (HDRS) or psychosis (PANSS) symptoms did not change these findings.

- This relationship was not detected in psychotic bipolar disorder.