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Supplementary Material

Article Title: Baseline Cognition Is Not Associated With Depression Outcomes in Vortioxetine for Major Depressive Disorder: Findings From Placebo-Controlled Trials

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LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

DISCLAIMER

Supplementary Materials

Analysis of additional cognitive variables. In addition to the DSST, several other neurocognitive tests were administered in three of the studies[31, 32, 33]. Studies included the Trail-Making Test, parts A and B (TMT-A, TMT-B), which are often referred to as measures of attention and speed (TMT-A), and mental flexibility (TMT-B); the Stroop Color/Word Test (SCW; congruent and incongruent conditions), a test of response inhibition and cognitive control; Simple Reaction Time (SRT), a measure of simple attention and processing speed; and Choice Reaction Time (CRT), a measure of complex attention and processing speed. Primary measures included time to completion (TMT-A, TMT-B, Stroop Congruent and Stroop Incongruent) and mean response times (SRT, CRT). The same two-stage modeling approach used for the primary analysis was applied here as well. We also examined the relationship between baseline cognitive performance and baseline depression severity and whether there was a differential relationship between baseline cognitive performance and change in cognitive performance.

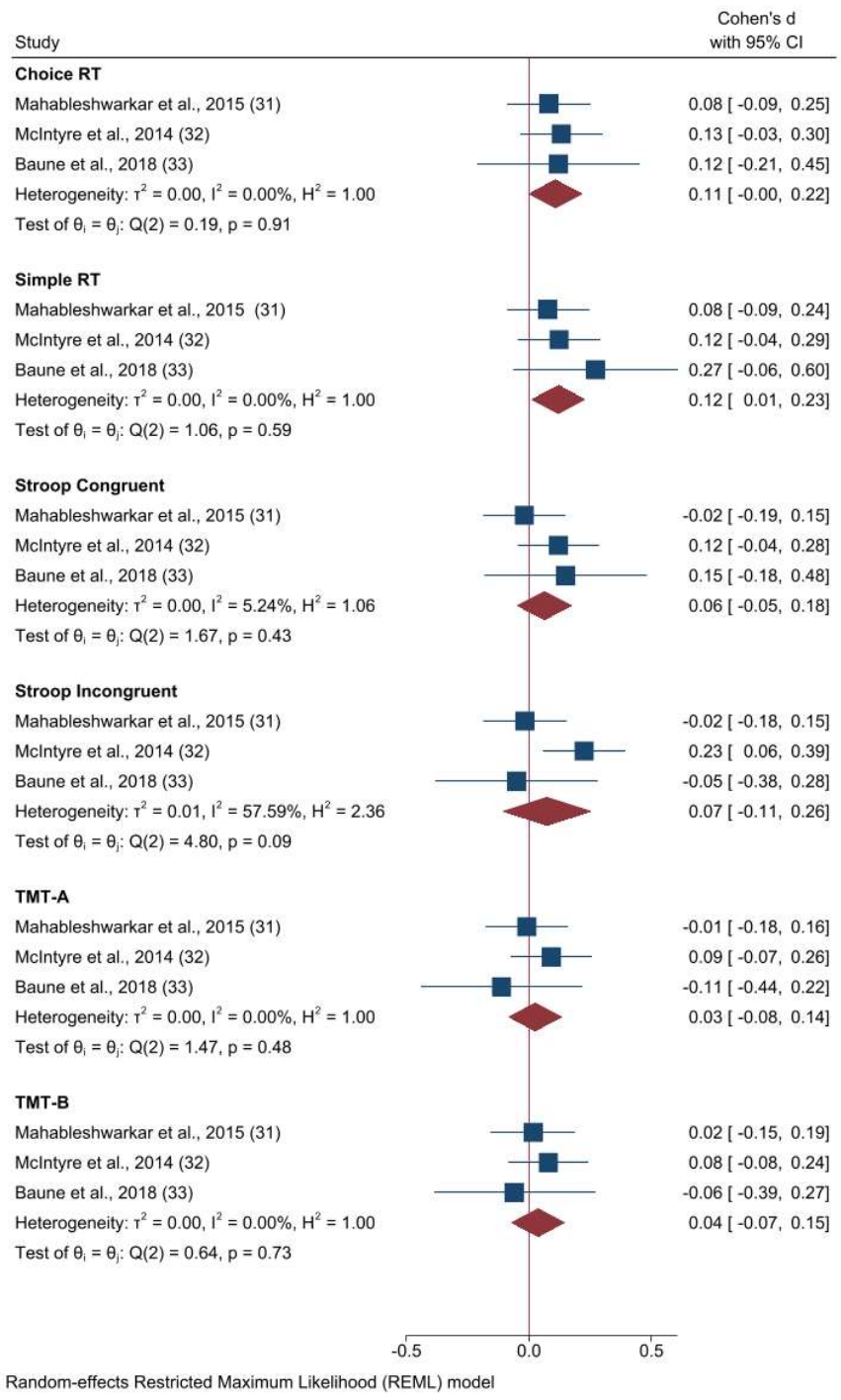
Several other neurocognitive tests were administered in one trial but not the other; analyses therefore only come from one study. The study by Mahableshwarkar et al.[31] included the Groton Maze Learning Task (GMLT), which measures visual learning, memory, and error monitoring; and the One-Back Test (OBT), which measures working memory. Total errors were used as the primary outcome for the GMLT; speed of performance was used for the OBT. In the other study by McIntyre et al.[32], the Rey Auditory Verbal Learning Test (RAVLT) was used to evaluate verbal learning and memory. Several metrics were used to evaluate performance, including acquisition (sum of learning trials), short delayed and long delayed recall, a general memory composite score (which equally weights acquisition and recall[28]), and several process measures, including forgetting (delayed recall minus words recalled on the last learning trial), and the Learning Efficiency Index (LEI), Delayed Recall Index (DRI), and Percent Retention Index (PRI[50]). Additional analyses were also conducted to compare duloxetine to vortioxetine and placebo. A False Discovery Rate (FDR) was applied to control for Type I error.

Relationship between baseline cognition and depression outcome. There was no relationship between baseline cognitive measures and baseline depression severity (all 95% confidence intervals contained zero). There were no significant differences in the relationship between baseline cognition and depression outcome between vortioxetine and placebo on any cognitive measures (see Supplementary Figure 1). For measures only included in Mahableshwarkar et al.[31], there was no relationship between baseline cognition and baseline depression severity on the GMLT (r = -0.01, p = 0.730) or OBT (r = -0.08, p = 0.052). Regarding differences in the relationship between cognition and outcome between vortioxetine and placebo, there were no differences on the GMLT (Cohen's d = -0.06, p = 0.494) and OBT (Cohen's d = 0.07, p = 0.398).

In terms of the RAVLT in the study published by McIntyre et al.[32], there was an association between acquisition and baseline depression severity (r = -0.10, p = 0.015) but not on any other measure (all $r \geq$ -0.08, all $p \geq 0.056$). Regarding differences in the relationship between cognition and outcome between vortioxetine and placebo, there was no differences observed in acquisition (Cohen's d = 0.14, p = 0.087), learning efficiency (Cohen's d = 0.13, p = 0.110), short delay recall (Cohen's d = 0.16, p = 0.055), long delay recall (Cohen's d = 0.12, p = 0.146), delayed recall index (Cohen's d = 0.14, p = 0.090), percent retention index (Cohen's d = 0.09, p = 0.304), or in the memory composite (Cohen's d = 0.14, p = 0.093).

In terms of duloxetine, there was no significant difference in slopes with vortioxetine across all cognitive measures (all $d \leq |0.10|$, all $p \geq 0.256$). There was no difference in slopes between duloxetine and placebo for all cognitive measures (all $d \leq |0.15|$, all $p \geq 0.079$), with the exception of CRT for continuous outcomes (d = 0.18, p = 0.036); however, it was not significant with FDR correction. Paroxetine observed a difference in slopes with vortioxetine on CRT (d = 0.43, p = 0.012); however, it was not significant with FDR correction. There was no difference in slopes between paroxetine and placebo for all cognitive measures (all $d \leq 0.32$, all $p \geq 0.059$).

Supplementary Figure 1. Differences in the relationship between baseline cognition and change in depressive symptoms for vortioxetine versus placebo.



Note. Positive values indicate a stronger association between baseline cognition and change in depression severity for vortioxetine.