September 23, 2016

John H. Krystal, M.D.

Yale University School of Medicine

VA Connecticut Healthcare System

West Haven, CT, USA

Dear Dr. Krystal:

Enclosed please find our manuscript entitled, “Depression modulates brain activity during conceptual source memory retrieval*”*, which I am submitting for consideration as an Archival Report in *Biological Psychiatry*.

Our manuscript represents an initial effort to fill an important hole in the literature. Specifically, although behavioral research on unipolar depression has consistently revealed episodic memory deficits with key implications for treatment, functional studies of this topic are surprisingly rare. Thus, we conducted an event-related potential (ERP) investigation of source memory retrieval in unmedicated adults with Major Depressive Disorder (MDD) and healthy controls.

We report two main findings, which are informed by extensive work in healthy adults linking successful episodic retrieval with a positive ERP deflection over left parietal cortex. First, we found a significant (and visually obvious) reduction in this ERP from 400-800 ms in our MDD group, highlighting a neural mechanism that could underlie the episodic memory deficit in depression. Second, we found that depressed adults were exquisitely sensitive to the match between encoding task and retrieval cue. Specifically, although depressed adults were generally less accurate and less confident than controls, they were extremely accurate when cued to retrieve words from a deep encoding condition, and this corresponded to sustained activation of the same sector of left parietal cortex. In other words, depressed adults performed worse than controls except when engaged in conceptual source retrieval, and the variation in their memory accuracy was linked to an ERP that is known to reflect activity in parieto-hippocampal circuits that supports recollection.

This is one of the first functional studies of source memory in MDD. Given the clinical importance of memory deficits in depression and the dearth of neuroscientific studies on this topic, I think the manuscript would appeal to readers of *Biological Psychiatry*; I hope its publication in the journal would spur additional imaging, molecular, and translational research on this critical topic. On the next page I list six well-qualified reviewers. Thank you for your time, and I look forward to hearing from you.

Sincerely,



Dan Dillon, Ph.D.

Director, Motivated Learning & Memory Laboratory

Center for Depression, Anxiety & Stress Research, McLean Hospital

**Suggested Reviewers**

Ian Dobbins

Jutta Joormann

Greg Hajcak

Dan Foti

Paula Hertel

JP Hamilton