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June 25, 2021

Dear Dr. Martin and Editors at *Current Biology*,

Following your response to our presubmission inquiry (date received 6/24/2021), we are submitting our manuscript entitled "*Neural reinstatement reveals divided organization of fear and extinction memories in the human brain*" for review at *Current Biology*. We are excited about this project and believe it is a good candidate for consideration for the broad readership of *Current Biology*. We'll briefly explain what this project is about and the major findings.

The most exciting advance in the neuroscience of fear learning in the past decade has been the discovery of stable and separate memory traces of fear and extinction in the rodent brain. State-of-the-art activity-dependent labeling is used to tag neurons in rodents that are active during the encoding and retrieval of emotional information. This has revealed a divided neural organization of these memories. Yet translating these advances to human neuroimaging has remained a methodological and conceptual challenge.

In this project, we present a new approach to successfully translate essential findings from animal neuroscience to the human brain using multivariate pattern analysis (MVPA) of fMRI data. We developed a hybrid Pavlovian conditioning paradigm with an episodic memory component that allows us to "tag-and-track" distinct memory representation across days in the same individual. Specifically, we use MVPA to isolate spatially distributed patterns of overlapping brain activity unique to the encoding and retrieval of fear versus extinction memories. We then compare these neural signatures between healthy adults and individuals with post-traumatic stress disorder (PTSD) symptoms, for which the ability to organize separable fear and extinction memories is presumably abnormal.

Our major finding is that fear and extinction memories have a divided organization across the medial prefrontal cortex and long-axis of the hippocampus in the healthy adult brain. We found a double dissociation such that neural patterns unique to the encoding and retrieval of fear were represented in the dorsal anterior cingulate cortex and posterior hippocampus, whereas patterns unique to the encoding and retrieval of safety were represented in the ventromedial prefrontal cortex and the anterior hippocampus. We also report dynamic interactions between these regions that provide a plausible mechanism for gating the retrieval of fear and extinction memories. Remarkably, in individuals with PTSD there was a misallocation of extinction memories to regions typically involved in encoding fear. These data reveal a striking explanation for safety learning deficits in PTSD

– experiences that should be encoded separately from fear memories are instead lumped together with them.

Altogether, we are excited about these data and have received very positive feedback from our colleagues across multiple disciplines, including experts on animal models of learning and memory, cognitive neuroscience of memory and emotion, and clinical translational neuroscience. This project bridges increasing evidence from rodent neurophysiology for the divided organization of opposing associative memories, and it provides new insights into how disorganization in these neural representations may contribute to psychiatric disease. This work also provides a new experimental and analytical approach for the study of emotional memory organization in humans that we believe may be adopted by the cognitive neuroscience community more broadly.

Thank you for your time.

Sincerely,

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