Modifying Memory: The Neural Mechanisms of Adaptive Memory Updating

Background: Memories are readily distorted. Although false memories may seem maladaptive, malleability can be a beneficial way to update memories with relevant new information. Through the process of *reconsolidation*, memories can be destabilized by a reminder, modified, and then stabilized again[1]. However, rodent neuroscience research has shown that memory traces are *not* destabilized when the reminder perfectly matches the original learning circumstances. One explanation is that *prediction error*, a form of surprise, triggers memory destabilization[2]. Intuitively, a prediction error mechanism seems adaptive; memories would be modified only when new information necessitates updating.

In humans, evidence from functional magnetic resonance imaging (fMRI) has implicated dopaminergic pathways and the hippocampus in prediction error calculation, signaling discrepancies between expectation and reality[3]. Moreover, surprising feedback about semantic information elicits striatal prediction errors that drive subsequent memory updating[4]. Behaviourally, incomplete reminders of learned associations make memories susceptible to interference[5]. However, it remains an open question whether, and how, prediction error influences naturalistic episodic memories in humans.

Methodology: How are complex, real-world memories modified in the brain? In my past honours thesis research[6], I synthesized evidence from rodent and human reconsolidation research to develop a novel behavioural paradigm to modulate episodic memory in humans. As a PhD student, I will extend this research to investigate the neural correlates of prediction error and memory updating. Young adult participants (N=48, equal number male and female) will be recruited from the ethnically-diverse Duke University community, and randomly assigned to either the *Reconsolidation* or *Control* group. On Day 1, participants will view 70 video clips (*M*=30s), each depicting a salient narrative event. On Day 2, participants will view the video clips again in a pseudorandom order, but half of the videos will be surprisingly interrupted before the narrative conclusion. Reconsolidation group participants will be scanned with fMRI during memory reactivation, whereas Control group participants will undergo the same procedure in a behavioural testing room. Lastly, participants will complete a verbal cued recall test, either after 24-hours (Reconsolidation group), or at the end of the Day 2 session (Control group).

Behaviourally, I expect that interrupting the video clips on Day 2 (i.e., reactivating memories with a prediction error) will allow memories to be updated with interfering information from the other stimulus videos, thus increasing subsequent false memories. However, prediction error will only influence memory in the Reconsolidation group, because the reconsolidation process is delay-dependent. Using an event-related design, I will analyze neural activity *after* the offset of each video. I will contrast within-subjects neural responses to interrupted and complete videos (i.e., memory reactivation with and without prediction error). I hypothesize that interrupted videos will elicit prediction error signals in the striatum and hippocampus[3,4]. Moreover, on a single-trial basis, activation within these regions will predict subsequent false memories. Lastly, I predict that videos that are rated to be more surprising when interrupted (as determined by an independent sample) will parametrically enhance memory distortion.

Implications: With unprecedented ecological validity, the proposed research will cast light on the fundamental mechanisms that allow naturalistic human memories to be changed. By uncovering the ways in which memories can be adaptively updated with new information, this research can inspire new treatments for post-traumatic stress disorder[7], inform practices for eyewitness testimony, and improve learning in educational settings. The proposed research will examine novel, naturalistic human memory phenomena, and draw on prediction error theory to critically address controversial and discrepant findings that have recently emerged in the reconsolidation literature[8]. Broadly, this research both illustrates the fragility of memory fidelity and highlights the advantageous side of memory distortion.

References: **1.** Nader et al. (2000). *Nature,* 406**,** 722–726. **2.** Exton-Mcguinness et al. (2015). *Behav. Brain Res.*, 278**,** 375–384. **3.** Kumaran & Maguire (2007). *J. Neurosci.*, 27, 8517–8524. **4.** Pine et al. (2018). *Nat. Commun.* 9:1673, 1-14. **5.** Forcato et al. (2009). *Neurobiol. Learn. Mem.,* 91, 50–57. **6.** Sinclair & Barense (2018). *Learn. Mem.,* 25, 369-381. **7.** Beckers & Kindt (2017). *Annu. Rev. Clin. Psychol.,* 13, 99–121. **8.** Hardwicke et al. (2016). *Proc. Natl. Acad. Sci. U. S. A.* **113,** 5206–11.

Part I. Contributions to Research and Development

*All contributions described below resulted from undergraduate research at the University of Toronto.

A. Articles published or accepted in peer-reviewed journals

1. **Sinclair, A. H.** & Barense, M. D. (2018). Surprise and destabilize: Prediction error influences episodic memory reconsolidation. *Learning & Memory*, *25*(8), 369-381.

B. Articles submitted to peer-reviewed journals (provide submission number)

2. **Sinclair, A. H**. & Barense, M. D. (revision requested). Changing memories: How prediction error drives adaptive updating. *WIREs Cognitive Science*, # COGSCI-654, 1-27.

C. Other peer-reviewed contributions

3. **Sinclair, A. H.*** & Barense, M.D. (2018, May). Prediction error influences episodic memory reconsolidation. Talk presented at the *Ontario Psychology Undergraduate Thesis Conference* at Ryerson University, Toronto, ON. *Designated *Notable Presentation.*
4. **Sinclair, A. H.*** & Barense, M.D. (2018, April). Surprise and destabilize: Prediction error influences episodic memory reconsolidation. Talk presented at the *NeuroXchange Conference* at McMaster University, Hamilton, ON.
5. **Sinclair, A. H.*** & Barense, M. D. (2017, Nov). Surprise and destabilize: Prediction error triggers episodic memory updating. Poster presented at the *Society for Neuroscience Conference*, Washington, D.C.
6. **Sinclair, A. H.*** & Barense, M. D. (2017, April). Prediction errors in episodic memory reconsolidation. Poster presented at the *NeuroXchange Conference* at McMaster University, Hamilton, ON. *Awarded *Outstanding Poster Presentation.*
7. **Sinclair, A. H.** (2018). Pathologizing the mind: The validity of mental illness diagnoses. *Inkblot: The Undergraduate Journal of Psychology*, *7*, 54-62.
8. **Sinclair, A. H.,** Brunec, I. K., & Barense, M. D. (2017). Navigating space and time: Memory for temporal intervals during spatial navigation, *Inkblot: The Undergraduate Journal of Psychology*, *6*, 48-56.

D. Non-peer-reviewed contributions

9. **Sinclair, A. H.*** & Barense, M. D. (2017, Sept). Surprise destabilizes episodic memories. Talk presented at the *Ebbinghaus Empire Series* at the University of Toronto, Toronto, ON.
10. **Sinclair, A. H.*,** Brunec, I. K., & Barense, M. D. (2016, March). Navigating space and time: Temporal memory during spatial navigation. Poster session presented at the *Undergraduate Research Forum* at the University of Toronto, Toronto, ON.

Part II. Most Significant Contributions to Research and Development

Citation #1 (see Part I): In this publication, I report findings from the original program of research that I conducted as my undergraduate honours thesis. I proposed and designed each of the three studies that are reported in the paper. I programmed experiments, collected and analyzed data, and drafted the manuscript. Throughout this research process, I collaborated with Dr. Barense, graduate students in her lab, and undergraduate mentees. Dr. Barense and I published our findings in the peer-reviewed journal *Learning & Memory*, an ideal platform because of its interdisciplinary character and broad audience. My research extended evidence from rodent behavioral neuroscience to uncover novel phenomena about human episodic memory. Through this publication, I disseminated impactful findings about the reconsolidation of naturalistic memories, targeting a broad community of memory scientists.

Citation #5 (See Part I): At the 2017 *Society for Neuroscience* Conference (SfN), the largest neuroscience conference in the world, I joined a community of over 30,000 attendees and presented my undergraduate thesis research. Throughout a four-hour poster session, I had the privilege of communicating my findings to peers, postdoctoral scholars, and principal investigators– many of whom I had studied and cited. With the support of my mentors in the honours thesis program, I prepared and practiced talks on my thesis research, enabling me to present at several conferences (see also citations 3

and 4). While attending SfN, I networked with potential advisors for graduate school. Thus, I both broadened the impact of my research and advanced my professional development.

Citation #2 (See Part I): In May 2017, I attended the Toronto Area Memory Group conference, and earned the Moscovitch Award for Outstanding Contributions to Discussion. In recognition of my aptitude for scientific discourse, I was invited to contribute a paper to the peer-reviewed Wiley Reviews journal *WIREs Cognitive Science.* This paper (revision requested) reviews evidence that prediction error modulates memory updating in humans, drawing on both cognitive and computational neuroscience. I bridge evidence from multiple theoretical frameworks, and highlight the breadth of memory updating phenomena, ranging from classical conditioning to naturalistic episodes.

Part III. Applicant's Statement

Research Experience: I excelled as a Research Specialist in Psychology at the University of Toronto (UofT), earning the Governor General's Silver Medal upon graduation. Throughout my undergraduate career, I demonstrated my aptitude for posing research questions and designing original experimental paradigms. In my honours thesis research under the supervision of Prof. Morgan Barense, I tested novel predictions about episodic memory reconsolidation in humans. Through a program of three behavioural studies, we synthesized theory from rodent and human memory research, and demonstrated for the first time that prediction error allows naturalistic memories to be updated with new information. Additionally, as a member of Prof. William Cunningham's lab, I conducted original research in social cognitive neuroscience, exploring topics such as stereotype formation, the neural correlates of recalled and imagined episodes, and the overlapping neural representations of social and physical pain.

In addition to my proven success with experimental design, I have also programmed and run experiments, administered neuropsychological assessments, and analyzed behavioural, eyetracking, and fMRI data. Moreover, I gained interdisciplinary research experience by working in five psychology and neuroscience labs. Presently, I am beginning my PhD studies at Duke University, working with Prof. R. Alison Adcock to explore how dopamine influences memory updating through expectation and surprise. I have actively facilitated new international collaborations among my mentors at Duke and UofT.

Relevant Activities: I have effectively communicated my research findings by writing and publishing papers, giving talks, and presenting first-author posters at several conferences. At the *Toronto Area Memory Group Conference*, I earned the Moscovitch award for critical contributions to discussion, demonstrating my aptitude for constructive scientific discourse. I also received the Outstanding Poster Presentation award at the *NeuroXchange Conference*, reflecting my speaking abilities.

I have also had the pleasure of mentoring students of diverse ages and backgrounds. As a private tutor in Toronto, my pupils ranged from an Argentinian-Canadian high school student aspiring to attend university in the United States, to a new Irish immigrant struggling to complete an online Master's degree in Psychology while raising a newborn. I also gained valuable mentoring experience by serving as a peer mentor, and later, as a Teaching Assistant (TA), in a selective first-year seminar program for the life sciences. As a TA, I consulted with students, marked papers, and gave a guest lecture on open science and replication. Moreover, I volunteered as an editor for The Inkblot, an undergraduate psychology journal. I reviewed, revised, and showcased the work of student researchers.

In my graduate studies, I will serve as a volunteer science coach with the Building Opportunities and Overtures in Science and Technology program (BOOST), an outreach initiative that partners with local middle schools to offer scientific enrichment to girls and children from underrepresented racial and socioeconomic groups. On campus, I will mentor aspiring graduate students through the Graduate-Undergraduate Lunch program, work as a Teaching Assistant, and participate in community events such as the annual Brain Awareness Week. Through these outreach activities, I endeavour to draw on my own research on human memory to communicate concrete, applicable advice for academic success.