STUDY PROTOCOL
Social Behavioral Template

Influence of stress on learning and memory

Protocol Number
Protocol Number

Protocol Version
Version Date: 11/21/23
Version # 1

Clinical Trials Registration Number (if applicable)
NCT05920161

Confidentiality Statement:

We, the researchers on the project *Influence of stress on learning and memory*, will have access to data which contains confidential information that respondents generally perceive as personal and private. We understand that access to this confidential information and data carries with it responsibility to guard against unauthorized use and to abide by the data security plan. To treat information as confidential means to not divulge it or make it accessible to anyone who is not a project member. Such a disclosure would violate the confidentiality promised to participants and would violate University ethics policies.

We agree to fulfill my responsibilities on this project in accordance with the following

1. We agree to not permit non-project personnel access to the data, either electronically, in hard copy or orally.
2. We agree to not attempt to identify individuals except in those cases where it is necessary in accordance with my role on the research project.
3. We agree that in the event we inadvertently uncover the identity of an individual, we will maintain the highest level of confidentiality of this information, make no use of the knowledge and inform the study's Principal Investigator.

Synopsis

Purpose The purpose of this study is to understand how stress impacts different forms of learning and memory. Stress is a significant public health issue, and by understanding stress effects on different types of learning, the research may help to inform optimized treatment of stress-related psychopathology.
Objectives The objective of this study is to leverage novel behavioral and neuroimaging assays to determine how stress modulates distinct hippocampal learning processes in humans. Using a between-subjects design, we will investigate whether exposure to a mild laboratory stressor changes the formation of different types of memories; specifically, storing individual experiences (episodic encoding) and learning environmental regularities (statistical learning). Our central hypothesis is that stress will modulate hippocampal responses and connectivity to enhance statistical learning while impairing episodic encoding. The following specific aims will be addressed: **Aim 1.** Characterize how acute stress affects the relative expression of statistical learning and episodic encoding. **Aim 2.** Identify the neural mechanisms by which stress influences statistical learning and episodic encoding. As a secondary objective, we will determine whether individual variability in the magnitude of the stress response influences the effects of stress on hippocampal learning.
Study Population Participants in this study will be healthy individuals aged 18-45. We aim to study this healthy cohort in order to understand the baseline relationship between stress and memory in neurotypical individuals.
Number of Participants Approximately five-hundred participants will be enrolled in the study. We plan to run between two and four behavioral studies (N = 46-138 each, depending on the exact parameters of the study) and one fMRI study (N = 100). These numbers are based on power analyses from similar behavioral and fMRI studies (Sherman & Turk-Browne, 2020).
Study Design In this two-day study, participants will be exposed to a series of displays (e.g., scene images) and subsequently be tested on their memory for these displays. Some participants may undergo a stress manipulation, known as the cold pressor test (described below). Some participants may also undergo fMRI, so we can analyze how brain response patterns associated with learning and memory change as a function of stress exposure. Please see sections 4 and 6 for more detailed information about the study design and methodology.
Study Duration We expect the total duration of the study to last 2-3 years. Each participant will participate in two sessions. The first session will take 1-2 hours and the second session will take 0.5-1 hour.
Outcome Variables

The primary outcome variables will be performance on the behavioral learning and memory tasks. Additionally, we will examine cortisol and alpha-amylase responses to stress. In the fMRI study, we will additionally examine neural correlates of learning and memory.
Locations/Facilities Some behavioral studies will take place in Sheffield-Sterling-Strathcona (SSS) Hall (1 Prospect Street) or 100 College Street and some will be run online (on mTurk or Prolific). The fMRI studies will take place in the FAS Brain Imaging Center in Dunham Lab (10 Hillhouse Avenue) or BrainWorks at 100 College Street.

Abbreviations

Abbreviation	Explanation
fMRI	Functional Magnetic Resonance Imaging: a non-invasive brain imaging method
CPT	Cold Pressor Task: a validated and safe method for inducing stress in a laboratory setting
BIC	FAS Brain Imaging Center
BOLD	Blood-oxygenation-level-dependent signal: the outcome measure of fMRI data
TSP	Trisynaptic pathway: the hippocampal pathway hypothesized to be involved in episodic memory
MSP	Monosynaptic pathway: the hippocampal pathway hypothesized to be involved in statistical learning

Glossary of Terms

Glossary	Explanation
Hippocampus	A brain region involved in multiple kinds of learning and memory, which we expect to be impacted by stress
Episodic Memory	A kind of memory which holds rich and detailed information for specific events
Statistical Learning	A kind of memory which is more generalized and abstract, allowing for prediction of future events
Acute stress	A form of stress that is short-term (i.e., as induced in our study); as opposed to chronic stress
Alpha-amylase/adrenergic	The adrenergic system is activated upon exposure to acute stress. It can be measured through alpha-amylase concentrations in saliva.
Cortisol/glucocorticoid	The release of glucocorticoids (cortisol in humans) is the end product of the hypothalamic-pituitary-adrenal axis response to stress. It can be measured through cortisol concentrations in saliva.
Milgram	Yale's HIPAA-aligned computer cluster, managed by the Yale Center for Research Computing

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APPROVED BY THE YALE UNIVERSITY IRB 12/6/2023

Protocol Revision History

Version Date	Summary of Substantial Changes
8/25/2021	Adding online testing; video recording during CPT

1 Background

1.1 Background

Stress is a serious and escalating public health issue, with average stress levels in 2020 significantly increasing in the US for the first time since national assessments began in 2007 (APA, 2020). High stress levels are linked to increased risk of adverse physical (Richardson et al., 2012; Booth et al., 2015; Gianaros et al., 2015) and mental (Sinha, 2001; Gruber et al., 2020; Vinkers et al., 2014) health outcomes spanning diagnostic categories. Although the influence of stress on the hippocampus, an important hub for learning, has been posited to play a crucial role in mental health outcomes (Goldfarb & Sinha, 2018; Lee et al., 2002), this target mechanism remains poorly understood.

Advances in nonhuman animal research have revealed distinct stress effects across hippocampal subregions (Gould et al., 1998; Pavlides et al., 1993; Sapolsky et al., 1990; Chen et al., 2010; Ghosh et al., 2013; Gerges et al., 2001; McLaughlin et al., 2005; Pu et al., 2007). Intriguingly, these discrepancies map onto the trisynaptic (TSP) and monosynaptic (MSP) pathways of hippocampal transmission, with stress impairing the subregions involved in the TSP and sparing the subregions involved in the MSP. This suggests the novel hypothesis that stress will differentially impact learning processes supported by these pathways, impairing TSP-dependent while enhancing MSP-dependent functions. Recent work shows that these pathways make distinct contributions to different forms of learning, providing a unique opportunity to test stress effects across hippocampal pathways in humans.

Specifically, a neural network model of the hippocampus (Schapiro et al., 2017) demonstrates that these two different pathways are associated with two fundamentally different kinds of learning. The TSP may support *episodic encoding*, a kind of memory which allows for the memory of specific experiences (e.g., your most recent birthday). The MSP, on the other hand, may support *statistical learning*, a kind of memory which allows for the abstraction or generalization across many experiences (e.g., what a birthday tends to be like). Recent empirical work from the Turk-Browne lab shows that forming predictions about an upcoming experience (via statistical learning) impairs episodic encoding of the current experience (Sherman & Turk-Browne, 2020), suggesting that stress may both influence these learning systems separately and drive competition between them. Thus, in this study, we aim to understand how stress differentially influences episodic memory and statistical learning, and whether this is reflected in how stress influences hippocampal pathway function, as measured with fMRI.

1.2 Prior Experience (if applicable)

Please see background section about for relevant prior work from our labs in these domains. In addition, we have extensive experience administering the laboratory stress induction described here (e.g., Goldfarb, Mendelevich & Phelps 2017; Goldfarb et al 2017; Goldfarb et al 2019).

2 Rationale/Significance

2.1 Rationale and Study Significance

Stress is a serious and escalating public health issue, with average stress levels in 2020 significantly increasing in the US for the first time since national assessments began in 2007 (APA, 2020). High stress levels are linked to increased risk of adverse physical and mental health outcomes spanning diagnostic categories. Although the influence of stress on the hippocampus, an important hub for learning, has been posited to play a crucial role in mental health outcomes, this target mechanism remains poorly understood. In particular, it is unclear how stress affects learning computations supported by different hippocampal pathways. This study proposes to develop and validate behavioral and neuroimaging techniques to test novel hypotheses disentangling stress effects across hippocampal learning processes in humans.

2.2 Risks

Cold pressor test. The Cold Pressor Test (CPT) procedure has been used successfully with both children and adults without reported adverse effects (Von Baeyer et al., 2005; Kowalcyzk et al., 2006; Siegrist et al., 2006; Silverthorn and Michael, 2013; Goldfarb et al 2017a,b; Goldfarb et al 2019). Participants may experience some discomfort during this task (submerging their hand in a bucket of water). Participants will be able to withdraw from the experiment at any time without loss of compensation (prorated to the length of participation), and will have time to rest after completion of the CPT. Participants will be given a paper towel to wipe their arm after the stressor is over, and they will be given time to rest.

MRI environment. There are no known risks in the use of MRI per se and 3-T scanners are FDA-approved for all ages. However, there are some potential areas of concern. The first is the possibility of the static magnetic field attracting ferromagnetic objects toward the bore, which includes internal devices. The second is the loud noise made by the gradients during imaging. Finally, participants may feel dizzy, get an upset stomach, have a metallic taste, or feel tingling sensations or muscle twitches. These concerns exist for all MRI studies and routine exams and are not increased by the proposed research.
All studies will follow guidelines set by the FDA with regard to specific absorption ratio, limits on gradient slew rate (dB/dt), and acoustic noise. We will use a 3-T scanner that conforms to FDA safety guidelines. Such scanners are available for research and clinical studies at most major medical centers and research universities and have been used for a number of years. Safety procedures will be rigorously enforced. Members of the research team receive intensive safety training and periodic re-training.

Subjects will be screened for contraindications to scanning, including moderate or severe claustrophobia, and a history or possible history of intra-ocular, intracranial, intrathorax, or intra-abdominal metal or cardiac pacemakers. Although there are no known risks to a fetus, if the participant is female and there is any chance they could be pregnant, the safety concerns will be explained to the participant and they will be excluded.

Participants and researchers are instructed to remove all metal objects before entering the scanner room, which is verified with the walkthrough and wand-based metal detectors. The risk of noise exposure is minimized by hearing protection, bringing the sound pressure level below FDA limits. Feeling dizzy, getting an upset stomach, having a metallic taste, or feeling tingling sensations or muscle twitches are known potential effects of MRI and usually go away quickly. Researchers will alert participants to this possibility and request that they inform the researchers if they are experiencing any of these effects.

During scanning sessions, participants will be made as comfortable as possible, with the option of a pad to rest their legs on or a sheet to cover them. The researcher will be in communication with the participant between runs throughout the scanning session. Participants will be instructed to signal to the researcher in the scanner room if they need to stop at any time, by pressing the squeeze ball or button.

We are always willing to adapt our scanning protocol to any changes in the laws or guidelines set forth by the BIC, BrainWorks, the Yale New Haven Hospital, Yale University, or the FDA. Furthermore, we make all scanner-related risks clear to the participant during the screening and consent so that the participant can make a well informed decision about participating.

Incidental findings. This study is not in any way a healthcare examination of the brain, the images we collect are not designed to find abnormalities, and the researchers are not qualified to interpret the images medically. However, a worrisome finding may be seen incidentally during the course of the study. If a worrisome finding is seen incidentally on a participant's scan during the course of the study, the principal investigator will contact the participant, inform them of the finding, and recommend that they seek medical advice as a precautionary measure. The decision for additional examination or treatment is up to the participant and their physician.

Privacy. A loss of confidentiality is a risk of any research study. MRI data can contain data of medical importance and also identifying information. This could affect the confidentiality of the participants.

All participant data will be anonymized at the earliest convenience and given a de-identified participant ID. Only the PIs and members of the research team will be able to link the participant ID with identifiable details of the participant. This link will be stored in password-protected files on encrypted and password-protected computers, housed in locked laboratory space. We will plan to share anonymized data with collaborators and post them in data repositories required by our grant funding and by scientific journals. MRI data will be directly transferred from the scanner to HIPAA-aligned Yale servers. Other data on computers in the control room (e.g., behavioral responses, eye-tracking images) will either also be transferred securely over the network or get transferred manually onto an encrypted, passcode protected flash drive.

2.3 Anticipated Benefits

This project integrates translational stress neurobiology with the cognitive neuroscience of memory to test novel mechanistic hypotheses regarding stress effects on clinically meaningful functions in humans. Building upon the recent development of behaviors that map onto different hippocampal mechanisms, we can systematically examine stress effects across forms of learning centered on a single brain region. These results will enable a fine-grained analysis of hippocampal function and its modulation by stress. By revealing the susceptibility of different types of learning to stress, these findings have the potential to uncover fundamental distinctions between these learning systems that can be leveraged to optimize neural network models and generate novel predictions regarding hippocampal function. Elucidating this transdiagnostic mechanism also promises significant clinical implications, ultimately facilitating the development of targeted pharmacological and behavioral therapeutic interventions to combat risks for stress-related psychopathology.

3 Study Purpose and Objectives

3.1 Purpose

Stress presents a serious public health problem that has significantly increased during the COVID-19 pandemic. One powerful effect of stress is to modulate the structure and function of the hippocampus, a crucial brain structure for learning. This modulation may contribute to the etiology and maintenance of mental health problems including posttraumatic stress disorder and addiction. However, the effects of stress are complex: across species, stress both enhances and impairs hippocampal learning. Furthermore, although elegant work in rodent models demonstrates distinct stress actions across hippocampal subregions, the measures of learning used in humans make translation challenging. To determine the mechanisms by which stress alters learning, and to design interventions for negative stress effects, there is an urgent need to understand how stress modulates measures of human learning that disentangle contributions of hippocampal subregions. Our goal is to determine how acute stress enhances and impairs hippocampal learning, providing a basis for optimizing treatment of stress-related psychopathology and harnessing the adaptive potential of stress in everyday life.

3.2 Hypothesis

In this study, we will test the hypothesis that acute stress will have divergent effects on two hippocampal learning processes: *episodic encoding* will be *impaired* by acute stress, whereas *statistical learning* will be *enhanced* by acute stress.

3.3 Objectives

The objective of this study is to leverage novel behavioral and neuroimaging assays to determine how stress modulates distinct hippocampal learning processes in humans. Using a between-subjects design, we will investigate whether exposure to a mild laboratory stressor changes the formation of different types of memories; specifically, storing individual experiences (episodic encoding) and learning environmental regularities (statistical learning). Our central hypothesis is that stress will modulate hippocampal responses and connectivity to enhance statistical learning while impairing episodic encoding. The following specific aims will be addressed:

Aim 1. Characterize how acute stress affects the relative expression of statistical learning and episodic encoding.

Aim 2. Identify the neural mechanisms by which stress influences statistical learning and episodic encoding.

As a secondary objective, we will determine whether individual variability in the magnitude of the stress response influences the effects of stress on hippocampal learning.

4 Study Design

Overview
The in-lab experiments will consist of two testing sessions on two consecutive days. Sessions will occur between 12:00-6:00pm to account for circadian fluctuations in cortisol (Lupien et al., 2007). On Day 1, participants will be exposed to a stress or control manipulation followed by a learning task. On Day 2, participants will be tested for their memory. At the end of the experiment, the experimenter will answer any remaining questions from the participant.

Participants will provide multiple salivary samples over the course of the experiment. Saliva will be collected using salivettes, which participants will be instructed to hold under their tongue for two minutes. These will be stored in sterile tubes in a -20 freezer. The samples will be exclusively analyzed for cortisol and alpha-amylase concentrations.

Both behavioral and fMRI studies will follow the same overall design, which is described below.

Online studies will follow a similar procedure, excluding the Cold Pressor Test and saliva samples (i.e., they will answer intake questionnaires and perform the learning and memory tests). Online studies may follow the two day procedure as described below, or all procedures may be done in a single session. Additionally, online participants will not be assigned to stress or control groups; we will examine how individual differences in stress (as measured via questionnaire data) influence learning and memory.

Day 1
Intake Procedures
After providing written informed consent, participants will be asked about their demographic information, medical and psychiatric conditions using self-report forms through Yale's HIPAA-aligned instantiation of Qualtrics (providing data on age, education, menstrual cycle, and significant medical history). We will also assess subjective stress, affective state, and substance use. These questions will be taken from standardized instruments such as: Alcohol Use Disorders Identification Test (Saunders, Aasland, Babor, de la Fuente, & Grant, 1993); the Positive and Negative Affect Schedule (Watson, Clark, & Tellegen, 1988); Perceived Stress Scale (Cohen, Kamarck, & Mermelstein, 1983); Difficulties in Emotion Regulation Scale (Gratz & Roemer, 2004); Trier Inventory of Chronic Stress (Petrowski et al 2020); and Life Events Checklist (Gray, Litz, Hsu & Lombardo 2004); and Menstrual Cycle Questionnaire. Participants in fMRI experiments will also complete the MRI safety screening form.

Each participant will be randomly assigned to a stress or control group. The procedures of the experiment will be identical for both sets of subjects, with the only difference being whether they experience the ice cold water or warm water arm bath (see Cold Pressor Task below). See the flowchart below for the general procedure.

Cold Pressor Test
To induce stress, we will use the Cold Pressor Test (CPT), a widely used procedure to provoke mild to moderate pain and stress in both adults and children. It has been used in many studies of autonomic reactivity, and hormonal stress responses. The CPT has been used successfully with both children and adults without reported adverse effects (Von Baeyer et al., 2005; Kowalcyzk et al., 2006; Siegrist et al., 2006; Silverthorn and Michael,

2013; Goldfarb et al 2017a,b; Goldfarb et al 2019). The CPT involves participants submerging their fingertip to elbow in a bucket of ice cold water placed (0-2 deg C). The water exposure is terminated when the experimenter instructs the participant that the test has ended (after 3 minutes). This increases the uncontrollable characteristics of the stress exposure. Participants will not be told how much time is remaining during the water exposure, and use of wrist watches or other time-pieces is not permitted. Prior to the CPT, participants may be informed by the experimenter that they will be video recorded during the test. This information has demonstrated to induce social stress (Schwabe & Schächinger, 2018). Although the participants will be video recorded during the CPT, the video data will be discarded without being looked at by the experimenter, as the video recording is merely for the purpose of further inducing stress. As a control condition, participants follow the same procedure but submerge their arm in warm water (37-40C). Participants in the control condition will not be video recorded. The experimenter will read a standardized script with a neutral affect (neither encouraging nor intimidating) to inform the participant of the procedure. Immediately upon removing their arm from the cold/warm water, ratings of subjective stress will be assessed.

Learning Task
Our tasks involve responding to visual or auditory stimuli presented on a screen or tablet. The stimuli may differ across experiments. For example, participants may view/hear characters, shapes, photographs (e.g., faces, scenes, objects, abstract images), fractals, tones, artificial speech, and videos. The stimuli may be neutral in affect, or may be emotional (i.e, images from the IAPS picture dataset). The stimuli will be presented as a sequence, with certain kinds of stimuli reliably following other kinds of stimuli (allowing for participants to learn features of the sequence). Participants are typically required to make an immediate judgment about the stimuli, such as detection, naming, or memorization of a target stimulus. Responses are typically made by pressing a key on a keyboard or a button on a button box. All of our experiments are divided into blocks of trials, and participants are encouraged to take breaks between blocks to minimize fatigue.

Eye tracking
In the studies involving fMRI, eye gaze and pupil dilation will be acquired throughout the scan using an MR-compatible SR Eyelink system at BIC or BrainWorks.

fMRI Scanning
In the studies involving fMRI, participants will perform the learning task while being scanned with fMRI. Prior to entering the MRI scanner, participants will walk through a metal-detecting gate in the hall. Before entering the scanner room, we will pass a high-sensitivity metal detecting wand over the body of the participant.

Participants will be provided with earplugs to protect their hearing from scanner noise. When we will be delivering auditory stimuli in some experiments, we will use either earbud headphones embedded in earplugs or over-the-ear headphones over earplugs. They will also be given a squeeze button or ball and informed that they can squeeze it to communicate with the researchers in the event that they feel uncomfortable or need to stop at any point. Participants will be given an MRI-compatible button box which can be used to provide responses.

Brain images will be collected using a Siemens Prisma 3T scanner at the BIC or BrainWorks with the 64-channel head/neck coil. Structural images will be collected to measure the participant's brain anatomy. Functional images will be collected to provide information about brain activity while the participant performs tasks. We plan to use the following types of sequences (though we may adjust parameters slightly as needed):

Scout (auto-align localizer): slices = 128, matrix = 256, FOV = 250 mm, resolution = 0.5 x 0.5 x 7 mm, TR = 8.6 ms, TE = 4 ms, flip angle = 20°, time = 0:14

EPI (functional scans): slices = 90, matrix = 128, FOV = 192 mm, resolution = 1.5 mm iso, TR = 1500 ms, TE = 32.6 ms, flip angle = 55°, multiband factor = 6, time = variable

MPRAGE (T1 structural scan): slices = 192, matrix = 256, FOV = 256 mm, resolution = 1 mm iso, TR = 2300 ms, TE = 2.27 ms, TI = 900 ms, flip angle = 8°, iPAT = 3, time = 3:54

TSE (T2 structural scan, partial volume for hippocampal segmentation): slices = 54, matrix = 384, FOV = 168 mm, resolution = 0.44 x 0.44 x 1.5 mm, TR = 11390 ms, TE = 90 ms, flip angle = 150°, time = 3:49

We may also collect images with the same slice parameters as the EPI using a FLASH structural sequence (to improve alignment) and two spin echo field map sequences with reversed A-P phase encoding direction (to correct distortions).

After the scan, the researcher will debrief the participant, thank them, compensate them for their participation (if they are not coming back for a second session), and escort them out of the facility.

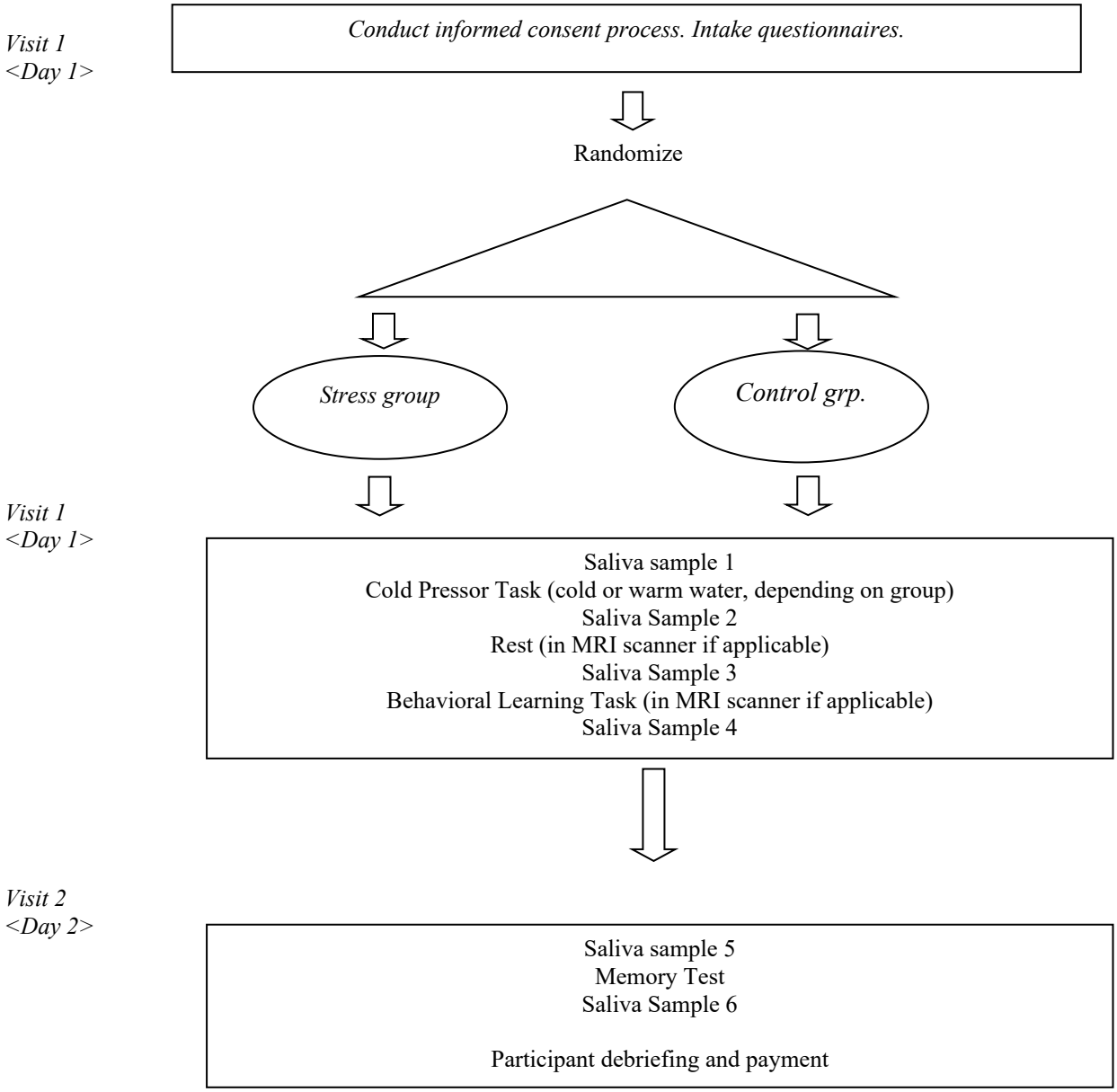
If upcoming fMRI sessions have been booked, all participants will be given the opportunity to be booked as a “back-up”. “Back-up” participants arrive at the scan center for the same appointment time as an already-booked participant. They then review and sign the consent form. If the already-booked participant *does not* attend the appointment, the “back-up” participant will complete the full experimental protocol at that time. If the already-booked participant *does* attend, the “back-up” will be compensated $10, and be scheduled to complete the protocol at a later date.

Day 2

Memory Tasks

Participants will be asked to complete memory tests near the end of the experiment. This might include recognition, in which a subject has to indicate whether the stimulus was seen before or not, or recall, in which a subject has to provide missing details about the stimulus such as the context it was seen in or an associated item that it was paired with. As on Day 1, participants will be asked to respond to visual or auditory stimuli presented on a screen or tablet, with responses made by pressing a key on a keyboard or a button on a button box. Experiments are divided into blocks of trials, and participants are encouraged to take breaks between blocks to minimize fatigue.

Study procedures



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4.1 Study Duration

Each participant will complete 2 sessions. The first session will take 1-2 hours and the second session will take 0.5-1 hour. We expect the entire study to last 3 years (including data analysis).

4.2 Outcome Variables/Endpoints

Behavioral measures of learning: during the learning task, participants will make responses to the stimuli viewed on the computer screen. Responses will be analyzed to assess learning-related effects (e.g., faster responses for predictable displays).

Behavioral measures of memory: during the memory task, participants will make judgments about whether they remember specific displays or sequences of displays. We will analyze their accuracy on these tasks to create a memory score.

Cortisol response: Saliva samples will be collected at multiple timepoints throughout the experiment. These samples will be assayed to quantify levels of the stress hormone cortisol, which will be used to assess basal levels per participant and determine the efficacy of our stress induction.

Alpha-amylase response: Saliva samples will be collected at multiple timepoints throughout the experiment. These samples will be assayed to quantify levels of salivary alpha-amylase, a proxy for the adrenergic stress response. These will be used to assess basal levels per participant and determine the efficacy of our stress induction.

Subjective measures of stress: Subjective ratings of stress will be collected after the stress manipulation to assess individual differences in subjective stress responses.

fMRI BOLD response: For the fMRI experiment, we will be collecting BOLD data for the entire brain during the learning task. Various analyses will be performed on these data to assess neural correlates related to learning and memory.

Gaze/pupil dilation: For the fMRI experiment, we may also collect eye-tracking data during the learning task. Various analyses will be performed on these data to assess proxies for noradrenergic responses and signals related to learning and memory.

Questionnaire responses: Questionnaires such as the Perceived Stress Scale will be scored to assess participants' individual differences in baseline stress levels and determine whether they influence learning and interact with acute stress.

4.2.1 Primary Outcome Variables/Endpoints

To characterize how acute stress affects the relative expression of different kinds of memory, we will measure statistical learning and episodic memory. Statistical learning will be assessed using responses/response times during the learning task, as well as from memory tests (see above). Episodic memory will be assessed by recognition memory performance. We hypothesize that measures of statistical learning will be enhanced following acute stress (as measured, e.g., by greater response time benefits during learning) and that measures of episodic memory (e.g., later recognition) will be diminished following acute stress.

To identify the neural mechanisms by which stress influences these different kinds of memory, we will focus on hippocampal responses measured during fMRI scanning. We hypothesize that measures of functional connectivity between hippocampal subregions CA1 and CA3 will be lower following acute stress (consistent with poorer episodic memory),

whereas functional connectivity between subregion CA1 and the entorhinal cortex will be higher following acute stress (consistent with better statistical learning).

4.2.2 Secondary and Exploratory Outcome Variables/Endpoints (if applicable)

To assess whether individual differences in the magnitude of the stress response predict the effect of stress on memory, we will leverage both objective and subjective measures of the stress response. We will test whether the change in cortisol and alpha-amylase from pre- to post-stress induction and subjective measures of stress – in addition to baseline levels of stress as measured through questionnaire data – predict the influence of acute stress on our neural and behavioral measures of learning and memory. We will also assess whether anticipatory noradrenergic responses (via pupil dilation) differ with stress and correspond to facilitated learning.

5 Study Participants

5.1 Study Population

Participants in this study will be healthy individuals aged 18-45. We aim to study this healthy, young cohort in order to understand the baseline relationship between stress and memory in neurotypical individuals.

5.2 Number of Participants

Approximately five-hundred participants will be enrolled in the experiments. We plan to run between two and four behavioral studies (N = 46-138 each, depending on the exact parameters of the study) and one fMRI study (N = 100). These numbers were determined based on power analyses from past studies of statistical learning and episodic encoding (Sherman & Turk-Browne 2020) and acute stress effects on memory (Goldfarb et al 2019).

Participants who do not meet our eligibility criteria as confirmed during recruitment (i.e., self-reporting that they are out of the age range or ineligible for MRI studies) will not be included in the participant count. For each participant who is excluded after their participation (i.e., due to responses on an intake questionnaire), we will recruit an additional participant so that the total number of usable participants matched the above-stated desired Ns.

5.3 Eligibility Criteria

In order to be eligible for inclusion in the study, and individual must meet all of the following criteria: (1) 18-45 years old, (2) fluent in English, (3) BMI between 18-35.

Any individual who meets any of the following criteria will be excluded from participation in this study: (1) meeting current DSM-V criteria for any substance use disorder (except caffeine), (2) having current significant medical conditions or psychiatric symptoms requiring medication, (3) current use of medications/drugs that interfere with physiological stress responses, (4) peri and post-menopausal women, pregnant or lactating women, and those with hysterectomies, (5) metal in body (for MRI safety). Menstrual cycle status and detailed history will be assessed for female participants.

5.4 Recruitment Procedures

Participants will be identified by responding to flyers (see Appendix 1 & Appendix 2), to a web or social media posting, or by filling out a form on our lab website. Prospective participants will be contacted via e-mail and/or a phone call to confirm their interest and eligibility and schedule a session. Only study personnel listed in this protocol will recruit participants.

We will send prospective MRI participants the MRI safety screening and consent forms via Yale's HIPAA-aligned instantiation of Qualtrics. Prior to scheduling an fMRI session, we will ask the participant if they would have to indicate "yes" to any of the exclusions on the screening form. If so, we will ask follow-up questions about this item to determine whether they are eligible to participate. This advance screening is intended to avoid scheduling fMRI sessions for participants who will be ineligible. Participants will be told that it is optional for them to respond to these questions over email or phone, and that we can schedule an in-person (non-fMRI) session to review the forms instead. All participants will fill out and sign the forms via Qualtrics when they come in for a session. For individuals who are deemed ineligible, all information will be destroyed immediately.

Eligible participants will be offered the option of being a "back-up" participant, in which case they would arrive at the same time as an already-scheduled participant, in addition to directly

booking their appointments. All participants will provide consent upon arrival at their first scheduled study visit.

5.5 Consent/Assent Procedures/HIPAA Authorization

Only study personnel listed in this protocol will obtain consent. During the session (upon arrival to the study site), participants will receive and sign the consent form via Yale's HIPAA-aligned instantiation of Qualtrics.

Consent forms will describe in detail the study intervention, study procedures, and risks. Written documentation of informed consent is required prior to starting any study procedures. Consent forms will be IRB-approved and the participant will be asked to read and review the document. Back-up participants will be given a separate consent form explaining the procedures and compensation.

The person obtaining consent will ensure that the potential subject is able to read and comprehend the consent. Comprehension will be assessed throughout the consent process and the participant will be given multiple opportunities to ask questions. The investigator will not enroll any participants who are determined to have limited decision-making capacity. They will have the opportunity to ask questions before and during the session. It will be stressed that any participation is voluntary and that consent can be withdrawn at any time. The conversation will take place in a private room to assure the participant's privacy. To avoid coercion, financial incentives for participation will be in line with standard subject payments. A copy of the informed consent document will be given to the participants for their records.

For online studies, participants will be presented with an online version of the consent form. They will be given as much time as they need to read the procedures, and they will indicate their consent by clicking an "I consent" button.

6 Study Methods/Procedures

6.1 Study Procedures

Each experiment will take place across two sessions on two consecutive days. The two sessions will occur 24h apart and will each be conducted between 12-6pm to control for circadian fluctuations in cortisol levels (Lupien et al 2007). Participants will be recruited via the procedures described in 5.4.

On Day 1, participants will be greeted by a member of the study personnel and consent will be obtained. Participants will be randomly assigned to either the Stress group or the Control group. Participants will become acclimated to the study environment and complete intake questionnaires. Participants will then provide a saliva sample (#1) to determine basal levels of cortisol and alpha-amylase. Participants randomly assigned to the Stress group will then undergo the cold pressor test (arm submerged in 0-2C cold water for 3 minutes), while participants in the Control group will have their arm submerged in warm water (37-40 C) for 3 minutes. Participants in the Stress group may be informed that they will be video recorded during the task. Then, a second saliva sample (#2) will be acquired.

Participants will then undergo a brief rest period to allow for the cortisol stress response to emerge (Shields et al., 2017). The duration of this rest period may differ across experiments so that we can assess the influence on the delay between stress and learning on subsequent outcomes. Participants will sit silently or watch a neutral video during this period. If participants are enrolled in the MRI study, we may collect anatomical and resting state fMRI scans during this time.

Following this rest period, an additional saliva sample will be taken (#3), and participants will complete the behavioral learning task. Participants will be exposed to a series of displays on the computer screen (see section 4) and be asked to make responses on a computer interface. After they complete the behavioral task, they will give one more saliva sample (#4), and then be dismissed for Day 1.

Day 2 will take place 24 hours later. Participants will again be greeted by a member of the study personnel. After giving another saliva sample (#5), they will then complete a series of memory tests. Following the test, they will give a final saliva sample (#6). The procedures of the study will then be explained to the participant, and the participant will be given the opportunity to ask questions about the study design. The participant will then be compensated for their participation.

Research staff will be responsible for implementing the interventions and collecting participant data. All study personnel will complete required human research protections training prior to the initiation of participant recruitment, and be trained on study protocols, recruitment and consenting, intervention and/or data collection procedures, and data handling and confidentiality. A Standard Operating Procedures manual will be developed to guide the conduct of the study and used in training. The PIs will supervise junior staff and provide re-training in the study protocol as needed.

Online studies will follow a similar procedure, excluding the Cold Pressor Test and saliva samples (i.e., they will answer intake questionnaires and perform the learning and memory tests). Online studies may follow the two day procedure as described above, or all procedures may be done in a single session. Additionally, online participants will not be assigned to stress or control groups; we will examine how individual differences in stress (as measured via questionnaire data) influence learning and memory.

Visit Schedule Table

	Recruitment (Pre-consent)	*Visit 1 Day 1*	*Visit 2 Day 2*
Review Eligibility	*X*		
Informed Consent		*X*	
Demographics		*X*	
Questionnaires		*X*	X
Saliva Samples		*X*	*X*
Behavioral Tasks		*X*	X
fMRI Scanning and eyetracking (if applicable)		*X*	
Randomization		*X*	
Adverse Events Reporting (if applicable)		*X*	*X*

APPROVED BY THE YALE UNIVERSITY IRB 12/6/2023

6.1.1 Data Collection

Questionnaire and demographic data will be collected using Yale's HIPAA-aligned instantiation of Qualtrics. Please see section 4 (*Intake Procedures*) for a list of the validated questionnaires that will be used. Licensure/training is not required for the administration of these questionnaires.

Behavioral responses will be made on a computer and responses will be recorded with custom experiment programming software designed through Matlab's Psychtoolbox (Brainard, 1997) or Python's Psychopy (Peirce, 2007), programs widely used in psychological research. MRI data will be acquired on the Siemen's 3T Prisma Scanner at the BIC or BrainWorks. Data for online studies will be completed on participants' personal computers, and will be accessed through the Prolific or mTurk interface. Responses will be recorded with custom experiment programming software designed through Javascript.

All data will be coded in a de-identified manner and stored in password-protected computer files accessible only to the research team. fMRI data will be stored on the secured and HIPAA-aligned Milgram computer cluster managed and certified for compliance by the Yale Center for Research Computing. Backups of the fMRI data may be burned to DVDs at the scanner and locked in a cabinet in the Turk-Browne lab space. Behavioral data (e.g., button presses, verbal reports, eye-tracking images) will either be recorded on computers secured in the control room and transferred on an encrypted and passcode-protected flash drive to computers in the Turk-Browne lab or on a password-protected laptop computer with full disk encryption, which will otherwise be kept locked in the Turk-Browne lab space. All video data collected during the behavioral task will be discarded without being looked at within seven days of a participant's participation.

Correspondence with study participants and a spreadsheet linking participant ID codes with identifiable information will be kept on a password-protected desktop computer with full disk encryption in the locked research coordinator office in the Turk-Browne lab space. Paper consent forms will be stored separately from any data and in a locked cabinet in the Turk-Browne lab space. Electronic consent forms and demographic forms will be stored on the secure Yale Qualtrics server, a HIPAA-aligned tool for survey data collection.

6.2 Method of Assignment/Randomization (if applicable)

Participants will be pseudo-randomly assigned to the experimental groups such that the groups do not differ in age and sex. There will be no blinding procedures, as both the experimenter and participant will be aware of whether they are receiving the cold or warm water treatment.

6.3 Adverse Events Definition and Reporting

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related.

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, or a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.

This protocol presents minimal risks to the subjects and Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs), including adverse events, are not anticipated. In the unlikely event that such events occur, Reportable Events (which are events that are serious or life-threatening and unanticipated (or anticipated but occurring with a greater frequency than expected) and possibly, probably, or definitely related) or Unanticipated Problems Involving Risks to Subjects or Others that may require a temporary or permanent interruption of study activities will be reported immediately (if possible), followed by a written report within 5 calendar days of the Principal Investigator becoming aware of the event to the IRB (using the appropriate forms from the website) and any appropriate funding and regulatory agencies. The investigator will apprise fellow investigators and study personnel of all UPIRSOs and adverse events that occur during the conduct of this research project through regular study meetings.

6.4 Reaction Management

The stress induction procedure used in this minimal risk study is a physiological stressor, which disrupts the body's homeostasis via exposure to cold water. It is not designed to induce emotional stress responses and is unlikely to lead to adverse stress reactions in healthy populations, such as the one studied here. In the case of an emergency, psychologists at the Yale Stress Center (including PI Dr. Goldfarb) may be contacted to speak to the participant.

6.5 Withdrawal Procedures

Participants who withdraw from the study before completion will be given the opportunity to ask questions about the study. The data collected from these participants will not be analyzed.

6.6 Locations/Facilities

Some behavioral studies will take place in Sheffield-Sterling-Strathcona (SSS) Hall (1 Prospect Street) or 100 College Street and some will be conducted online, on mTurk or Prolific.
The fMRI studies will take place in the FAS Brain Imaging Center in Dunham Lab (10 Hillhouse Avenue) or BrainWorks (100 College Street).

7 Statistical Design

The general statistical approach involves examining differences in our outcome measures as a function of stress condition (i.e., whether participants experience acute stress prior to the learning task or not). Analyses will primarily be conducted with repeated-measures ANOVAs (rmANOVA) and t-tests where appropriate.

7.1 Sample Size Considerations

For the behavioral studies, we aim for an N = 46 per condition. This is consistent with the sample size of the study on which this behavioral experiment is based (Sherman & Turk-Browne, 2020).

To determine the sample size for the fMRI study, we conducted power analyses based on our previous work demonstrating evidence of statistical learning in the hippocampus (Sherman et al., 2020). These results indicate that we would need N = 40 participants per group to detect neural effects (d = .45, 80% power). Thus, we will recruit 80 participants and randomly assign them to Stress (N = 40) or No Stress (N = 40) conditions.

7.2 Planned Analyses

We will test the hypotheses that: (1) stress enhances statistical learning (rmANOVA; facilitated reaction time for predictable items during learning in the Stress vs No Stress group); (2) stress enhances retention of statistical learning (*t*-test; better discrimination of *AB* category pairs in the Stress vs No Stress group); and (3) stress impairs episodic memory (*t*-test; overall lower exemplar recognition memory in the Stress vs No Stress group). Although there may be a global effect of worse episodic memory in the Stress group, we expect such deficits to be driven in part by an interaction with category type (*A*, *B*, or *X*). That is, if Stress potentiates statistical learning, these participants would quickly learn to anticipate the *B* category while viewing the preceding *A* category item. Thus, rather than focusing on encoding the *A* category item, they would be predicting the *B* category, leading to greater competition between encoding and statistical learning (rmANOVA; greater deficits in memory for *A* relative to *X* items in the Stress group).

For the fMRI experiment, we will investigate the neural mechanisms underlying stress effects on different forms of learning using a combination of *connectivity*, *multivariate*, and *univariate* approaches. Specifically, we will test the working hypothesis that stress will have opposite effects on neural processes supporting episodic encoding and statistical learning. Based on rodent models, we hypothesize that stress will facilitate the function of subregions and connections associated with the monosynaptic pathway (MSP) while impairing or sparing the function of the trisynaptic pathway (TSP).

We will test whether *stress induces state-level changes in TSP and MSP connectivity* by comparing background connectivity (Al-Aidroos et al., 2012) from CA1-entorhinal cortex (MSP) and CA1-CA2/3/DG (TSP) in Stress vs. No Stress participants. If state-level changes are not detected, we will use a different connectivity approach to separate connectivity patterns during different trial types. To probe the functional significance of connectivity changes, we will perform our recently developed seed connectome-based predictive modeling analysis (Goldfarb et al., 2020), using whole-brain CA1 connectivity during encoding to predict subsequent memory performance in Stress and No Stress participants. To test *whether stress amplifies neural signatures of statistical learning*, we will use multivariate approaches to characterize neural evidence of prediction. Following prior work (Sherman & Turk-Browne, 2020), we will train a classifier in the hippocampus (using a linear support vector machine implemented in Python's scikit-learn module) to distinguish between

different scene categories. By training the classifier on voxel patterns in the hippocampus from the localizer run (in which no statistical regularities are present) to distinguish amongst *B* categories, we can derive a signature of *B* category to apply to learning runs. The extent to which *B* can correctly be classified during the preceding *A* item (when *B* has not yet been presented) serves as a neural measure of prediction. If stress amplifies neural signatures of statistical learning, we expect to see greater evidence for the predicted category in the Stress, relative to No Stress, group. Finally, univariate whole-brain analyses will include subsequent memory analyses (Wagner et al., 1998) (contrasting Remembered with Forgotten trials from conditions A/B/X) to *test how whole brain processes supporting memory differ* in Stress vs No Stress participants.

7.2.1 Secondary Objective Analyses (if applicable)

Further exploratory analyses will investigate whether stress-induced changes in learning and memory are associated with the magnitude of the stress-induced cortisol and adrenergic response by using these measures as covariates in the above analyses. We hypothesize that larger stress-induced increases in cortisol are associated with stronger benefits for statistical learning and impairments for episodic encoding. In the fMRI study, we will test whether stress exposure modulates stimulus-evoked and ITI-evoked pupil dilation, processes previously been shown to be modulated by stress exposure and associated with subsequent episodic memory (Henckens et al 2009; Qin et al 2012), although the role of pupil reactivity in statistical learning is unclear.

7.2.2 Analysis of Subject Characteristics (if applicable)

N/A

Interim Analysis (if applicable)

N/A

7.3 Data Relevance

By examining differences in behavioral and neural measures of hippocampal learning as a function of acute stress exposure, we can test our hypothesis that stress has distinct effects different forms of hippocampal learning.

7.4 Data Coding

N/A

7.5 Data Analysis Tools

Behavioral data will be analyzed using R. fMRI data will be analyzed using a combination of FSL, AFNI and Python.

7.6 Data Monitoring

The PIs are responsible for monitoring the data, assuring protocol compliance, and conducting quarterly safety reviews.

7.7 Handling of Missing Data

All data will be collected and stored electronically. Data will be missing only in the case of a technological failure (e.g., a computer error). Participants with incomplete datasets will be excluded from the analyses and replaced.

8 Data/Specimen Handling and Record Keeping

8.1 Subject Data Confidentiality

Participant confidentiality and privacy is strictly held in confidence by the participating investigators, their staff, and the sponsor(s)/funding agency. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. All research activities will be conducted in as private a setting as possible. Representatives of the Institutional Review Board (IRB), regulatory agencies or study sponsor/funding agency may inspect all documents and records required to be maintained by the investigator for the participants in this study. The study site will permit access to such records.

The study participant's contact information will be securely stored at each study site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, regulatory, or sponsor/funding agency requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored on encrypted and password-protected computers. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used will be secured and password protected. At the end of the study, all study databases will be de-identified and archived on the Yale Milgram server. All video data collected will be stored on a password-protected computer and be discarded without being looked at within seven days of a participant's participation.

8.2 Data Quality Assurance

To ensure data quality, all study personnel will undergo comprehensive training to ensure that the study procedures are consistent for all participants. A standard operating procedure for the study will be written as a reference for all study personnel. Within each session, participants will undergo practice trials prior to the learning task and will be able to ask questions to ensure they understand the task.

8.3 Data or Specimen Storage/Security

All data will be coded in a de-identified manner and stored in password-protected computer files accessible only to the research team. fMRI data will be stored on the secured and HIPAA-aligned Milgram computer cluster managed and certified for compliance by the Yale Center for Research Computing. Saliva samples will not be marked with any identifiable information and will exclusively be analyzed for levels of cortisol and alpha-amylase.

8.4 Study Records

All Qualtrics-based consent forms and questionnaires will be stored in the Investigator's Qualtrics account, which can only be accessed by the Investigator through their credentials. Paper-based consent forms will be stored in a locked cabinet in the Turk-Browne lab.

8.5 Access to Source

All questionnaires will be Qualtrics-based and will be stored in the Investigator's Qualtrics account, which can only be accessed by the Investigator through their credentials. No other clinical or observational data will be collected.

8.6 Retention of Records

Upon completion of study and data analysis, a professional information protection, storage, and disposal company will be retained to dispose of research files and informed consent documentation. These data will be destroyed, after being kept for 5 years after the completion of the study.

8.7 Data and Safety Monitoring Plan

The principal investigators are responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews quarterly. During the review process the principal investigators will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment.

The principal investigators, the Institutional Review Board (IRB), the Brain Imaging Center (BIC), or BrainWorks have the authority to stop or suspend the study or require modifications.

This protocol presents minimal risks to the subjects and Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs), including adverse events, are not anticipated. In the unlikely event that such events occur, Reportable Events (which are events that are serious or life-threatening and unanticipated (or anticipated but occurring with a greater frequency than expected) and possibly, probably, or definitely related) or Unanticipated Problems Involving Risks to Subjects or Others that may require a temporary or permanent interruption of study activities will be reported immediately (if possible), followed by a written report within 5 calendar days of the Principal Investigators becoming aware of the event to the IRB (using the appropriate forms from the website) and any appropriate funding and regulatory agencies. The investigators will apprise fellow study personnel of all UPIRSOs and adverse events that occur during the conduct of this research project through regular lab meetings or via email, as they are reviewed by the PIs. The protocol's research monitor(s), BIC, BrainWorks, study sponsors, funding and regulatory agencies, and regulatory and decision-making bodies will be informed of adverse events such as injury within 5 days of the event becoming known to the principal investigators.

9 Study Considerations

9.1 Institutional Review Board (IRB) Review

The protocol will be submitted to the IRB for review and approval. Approval of the protocol must be obtained before initiating any research activity. Any change to the protocol will require an approved IRB amendment before implementation. The IRB will have final determination whether informed consent and HIPAA authorization are required.
Study closure will be submitted to the IRB after all research activities have been completed.
Other study events (e.g. data breaches, protocol deviations) will be submitted per Yale policies.

9.2 Research Personnel Training

All study personnel will complete required human research protections training prior to the initiation of participant recruitment, and be trained on study protocols, recruitment and consenting, intervention and/or data collection procedures, and data handling and confidentiality. A Standard Operating Procedures manual will be developed to guide the conduct of the study and used in training. The PIs will supervise junior staff and provide re-training in the study protocol as needed.

9.3 Study Monitoring

The PIs are responsible for monitoring the data, assuring protocol compliance, and conducting quarterly safety reviews. During the review process the PIs will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment.

9.4 Unanticipated Problems and Protocol Deviations

A protocol deviation is any noncompliance with the protocol. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.
It is the responsibility of the site investigator to identify and report deviations within 5 working days of identification of the protocol deviation. All deviations must be addressed in study source documents, reported to the study sponsor, and the reviewing Institutional Review Board (IRB) per their policies.
Unanticipated problems involving risks to participants or others include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

If the study team becomes aware of an unanticipated problem (e.g. data breach, protocol deviation), the event will be reported to the IRB by e-mail.
The UP report will include the following information:
Protocol identifying information: protocol title and number, PI's name, and the IRB project number;

- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs will be reported to the IRB within 5 days of the investigator becoming aware of the event.

9.5 Study Discontinuation

We do not anticipate any circumstances under which the study may be discontinued. This is a minimal risk study, and both the Turk-Browne and Goldfarb labs have successfully conducted many similar studies.

9.6 Study Completion

The study is expected to take approximately 2-3 years to complete. The IRB will be notified through the IRES system and a closure request will be submitted.

9.7 Conflict of Interest Management Plan

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership in conjunction with the appropriate conflict of interest review committee has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

All investigators will follow the applicable conflict of interest policies.

9.8 Funding Source

We are applying for NIH funding for this study. In the meantime, the study is being funded internally by Nick Turk-Browne and Elizabeth Goldfarb's labs.

9.9 Publication Plan

After data collection and analysis is complete, decisions will be made about the publication process. The PIs Goldfarb and Turk-Browne will hold primary responsibility for publishing the study results.

10 Appendices

Appendix #	Title	Section	Topic
1	**Behavioral Study Flyer**	**Recruitment**	**Recruitment Flyer**
2	**fMRI Study Flyer**	**Recruitment**	**Recruitment Flyer**

11 List of Tables