**Project working title: Comparing reinforced versus non-reinforced effects of behavioral change**

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**A. Hypotheses**

Despite the critical need for ways to change people’s value-based decision making to be healthier and adaptive, most current interventions rely on cognitive effort or external reinforcement, and fail to last in the long term (Christiansen, Bruun, Madsen, & Richelsen, 2007; Higgins, 1995; Jeffery, 2000; Judith J. Prochaska, Kevin Delucchi, 2004; Pan S. Li C., Zhao M., 2012; Wing, R. R., Venditti, E., Jakicic, J. M., Polley, B. A., & Lang, 1998).

Recently, a novel method employing non-reinforced learning was presented (Schonberg et al., 2014). This method, named the Cue Approach Task (CAT), is composed of three main parts: 1. A WTP procedure, in order to obtain participants’ subjective rating (Becker, G. M., DeGroot, M. H., & Marschak, 1964) 2. A training phase, in which all the items are presented one by one, some of them consistently coupled with a cue (‘go’ items). Participants are instructed to press a button once they detect the cue. 3. A probe phase, in which the change in preferences due to the training is examined via controlled pre-task equal valued comparisons between the ‘go’ items and the items that appeared in the training phase without a cue (‘no-go’ items). This task shows promise for long-term maintenance of behavioral change, with effects lasting up to 6 mouths so far (Salomon et al., 2017), and calls for further examination.

Here, we propose to investigate the behavioral and neural impacts of using reinforced versus non-reinforced cues in behavioral change towards snack food items, both immediately and up to one year after the experimental intervention.

We hypothesize that the effect of non-reinforced learning will decay slightly over time, but will still last in the long-term, while the effect of the reinforced training will be similar to the non-reinforced training immediately after training, but will decay sharply over time due to the removal of the reinforcing reward.

**B. Methods**

1. ***Participants***

Sixty participants will participate in each group (120 overall). We predict ~15% dropout rate over the year, thus expect ~55 participants in each group for the final one year follow-up.

1. ***Apparatus***

Stimulus presentation will be done using Matlab and Psychtoolbox 3 ([Brainard, 1997](#_ENREF_7); [Pelli, 1997](#_ENREF_53)).

1. ***Stimuli***

The stimuli data set is composed of 80 Israeli snack food items, presented on a black background. All snacks are available at main marketing stores in Israel and cost no more than 10 NIS (equal to 2.7$).

1. ***Procedure***

We will perform the CAT procedure while participants are inside the MRI scanner. The experiment will include five imaging sessions across one year. Participants will be randomly divided into two groups: non-externally reinforced (CAT) and externally reinforced group (Pavlovian cue CAT: PC-CAT). In the first session, Participants will undergo the full CAT experiment (Schonberg et al., 2014). The only difference between the two groups will be the cue during the training phase. For the PC-CAT group, the cue will be a number from the range of 21-24 (i.e.: “+21”, “+23”.) Participants will be informed that at the end of the experiment one trial will be selected and they will win the amount shown (21-24 NIS equal to 5.7-6.5$) as a bonus. The cue for the regular CAT group will be “\*\*”. After 1, 3, 9 and 12 months, we will invite all participants for a follow-up imaging session, and perform the probe phase followed by a memory task, in order to see if the effect of the CAT or the pavlovian cue had lasted.

* 1. ***Experiment***

All sessions will be held in the imaging center at Tel-Aviv University.

**Session 1:** full CAT experiment

1. BDM: ~15 minutes, outside the scanner

In order to obtain the participant initial subjective preference for 60 snacks, we will use the BDM procedure (Becker, G. M., DeGroot, M. H., & Marschak, 1964). Each snack will be presented and rated once, with no time limit for each trial. The sorted ratings will be used to determine the rank of the snacks.

--Starting imaging scan, the subject will enter the scanner--

2. Response to snacks ~6 minutes

Forty snacks will be chosen from the BDM, according to their subjective ratings (items 3-22, 39-58 from the sorted-by-preference ranking list of each subject). All items will be presented once in a random order, concluding 40 trials overall. The purpose of this task is to record the neural activation while the participant passively views the snacks. To ensure that the participant is indeed awake and perceives the items, participants will be instructed to look at the items and count how many were single or plural. Each item will be presented for 2s, followed by jittered ITI of ~7s.

3. Training: ~35 minutes

All items will be presented one by one. Some of the items will be coupled with a cue (‘go’ items). Participants will be instructed to press a button once they detect the cue. Of the forty items in the training, 12 will be ‘go’ items, thus the ratio of ‘go’ and ‘nogo’ items is 0.3. The training will have 640 trials, divided to 16 runs of 40 items each. Each item will be presented for 1s, followed by jittered ITI of ~2s. The timing for the cue appearance after the item presentation will be calculated by a step-wise procedure, in order to obtain 75% of successful button presses during the 1.5s from item onset.

4. Repeated response to snacks ~6 minutes

As explained above in ‘b.’

5. Anatomical scans: ~7 minutes

MPRAGE, FLAIR

6. Probe: ~15 minutes

Similar-valued comparisons between the ‘go’ items and the items that appeared in the training phase without visual cue (‘no-go’ items) will be presented. 36 high value and 36 for low value comparisons will be presented twice, concluding to 144 trials, separated to two runs. Each binary choice will be presented for 1.5s, followed by ITI fixation of jittered ~3.5s. The participant’s response will be indicated by a green square around the chosen item, for 1.5s minus RT. If the subject did not respond in time, the writing “You must respond faster!” will appear for 0.5s, followed by ITI fixation of jittered ~2.5s.

--Finishing imaging scan, the subject will exit the scanner--

7. Memory: ~5 minutes

Twenty-four snacks from the probe (12 ‘go’ + 12 ‘nogo’) and twenty-four ‘new’ snacks (which did not appear in the experiment until now) will be shown one by one. The participant will rate on a scale of 1-5 if that item appeared in the experiment, and if it was associated with a cue. This part will include 96 trials (24 ‘old’ + 24 ‘new’ snacks, 48 trials for each question). Each question will be presented for 3s. Participants’ responses will be indicated by a green square around the chosen answer, for 3 seconds minus reaction time. If the participant did not respond in time, the writing “You must respond faster!” will appear for 0.5s.

**Sessions 2 to 5:** follow-up experiments

These sessions will include imaging scans of a. **response to snacks (2)** b. **probe (6)**,**)** and c. **anatomical scans (5).** Then, outside the scanner, the participant will perform d. memory (8) and e. BDM (1). The procedures are explained above.

**Figure 1. Sequence of Events – please indicate clearly what’s inside and what’s outside the scanner**

1. ***Critical measures***
2. Dependent variables:
   1. Proportion choices of ‘go’ or ‘nogo’ item in the probe.
   2. Remembering if an item appeared in the experiment: accuracy and RT
   3. Remembering if an item was associated with a cue: accuracy and RT
   4. Imaging: BOLD response
3. Independent variables:
   1. Experimental group (2 levels: CAT, Classic; between subject)
   2. Session number (5 levels: 1-5 session; within subject)
   3. Item’s bid (the index of each item after sorting the BDM bids; within subject)
   4. Item’s type (2 levels: ‘go’, ‘nogo’; within subject)
   5. Item’s value group (2 levels: ‘high, ‘low’; within subject)
4. ***Planned sample***
5. 100 valid participants (100 in each group), which meet our exclusion criteria (see below).
6. The data will be collected at Tel Aviv University in the imaging center, by Shiran Oren. Participants will participate in the experiment for payment.

We will stop collecting data once reaching 120 valid participants. We will analyze data for presentations in conferences.

1. ***Exclusion criteria***
2. We will exclude participants from the analysis if they meet one of the following criteria: BDM: gave less than 1 NIS to more than 40 snacks. This refers only to the first BDM in the first session.
3. Different font, please fix: Participant will be excluded based on the following behavior patterns during training (indicating task disengagement):
   1. False alarm > 5%.
      1. False alarm is defined as response for a NoGo item during the training phase.
   2. Miss > 10%.
      1. Miss is defined as a Go trial when the participant didn’t respond at all (1.5 seconds after image onset).
4. If at any time during the training phase, the ladder dropped below 200ms.
   1. Ladder – any time the participant fails to respond during the one second image onset of a Go trial, the ladder will drop, each time by 50 ms (starting at 750ms). Each successful Go trial will increase the ladder by 16.67ms. Reaching a ladder below 200ms is an indication that the participant did not respond in many successive trials.
5. Participants will be excluded from participating in the experiment if they do not follow the next conditions:
   1. Aged 18-40
   2. Right handed
   3. Understands Hebrew
   4. Did not participate in other Schonberg lab’s experiments
   5. Normal or corrected to normal vision
   6. Like snacks, no special dietary restriction (i.e. vegan)
   7. Compatible to participate in MRI experiment (i.e. no metal in the body, not claustrophobic, no medical condition or regular drugs that affect blood flow (such as SSRI, diabetics), no tattoos in the head region etc.)
6. ***Analysis plan***
7. Hypothesis:

We hypothesize that preference change will be influenced by an interaction between group (CAT, PC) and time (0, 1, 3, 9, 12). Specifically, we hypothesize that for the CAT group, the effect of preference change will be significant through all sessions, and will show a moderate-define ? trend of decay over time. For the PC group, the effect of preference change will be significant in the first two sessions, similar to or higher than the CAT group’s effect. However, it will decay more sharply over time up to non-significance in the last session.

We consider the effect of preference change to be reflected in the following measurements:

1. During **probe**: higher probability of choosing Go over NoGo items.
2. During **memory** tasks: Shorter RTs and higher accuracy for Go over NoGo items.
3. **Neural** activity: stronger response for Go over NoGo items in these regions:
   1. CAT group: Attention-related regions: dorsal parietal cortex (DPC), including the intra-parietal sulcus (IPS) and the superior parietal lobule (SPL).
   2. PC group: Reward-related regions: striatum, amygdala, dopaminergic midbrain (see O’Doherty 2004).
   3. Both groups: Value related region: vmPFC.
4. Planned analyses

**Behavioral data:**

Probe

* + - * *Will participants choose Go items more then NoGo items?* 
        + Repeated logistic regression predicting choices of Go over NoGo items, with group and time (and their interaction) and HV/LV items as independent factors.
        + To interpret the group\*time interaction, a repeated logistic regression predicting choices of Go over NoGo items, with item value (high and low) as independent factor for each session and each group separately.

BDM

* + - * *Will the rating of items be different for Go vs. NoGo?*
        + Regression of the change in WTP (BDM[2-5]-BDM1) between Go and NoGo items as dependent, with group, session and item value (high and low) as independent factors.
        + To interpret the group\*time interaction, a regression of the change in WTP (BDM[2-5]-BDM1) between Go and NoGo items as dependent, with item value (high and low) as independent factor, for each session and each group separately.

Memory task

* + - * *Will Go items be remembered more then NoGo items?*
        + Accuracy:

Logistic regression for predicting accuracy, with by group and time (and their interaction), item association (Go and NoGo) and item value (high and low) as independent factors.

To interpret the group\*time interaction, a Logistic regression for predicting accuracy, item association (Go and NoGo) and item value (high and low) as independent factors, for each session and each group separately.

* + - * + RT:

Regression for predicting response times, with group and time (and their interaction), item association (Go and NoGo) and item value (high and low) as independent factors.

To interpret the group\*time interaction, a Regression for response times, item association (Go and NoGo) and item value (high and low) as independent factors, for each session and each group separately.

Memory & probe

* + - * *Will better memory for items correlate with choices during probe?*
        + Logistic regression for predicting choosing the Go item in probe by **accuracy** for the Go item and inverse accuracy for the NoGo item in the recognition task. Separately for each time point and each group.
        + Logistic regression for predicting choosing the Go item in probe by **RT** in the recognition task (for the NoGo item minus Go item). Only for correctly identified items in the recognition task. Separately for each time point and each group.
        + Logistic regression for predicting choosing the Go item in probe by **RT** in the **first** recognition task (for the NoGo item minus Go item). Only for correctly identified items in the recognition task. Separately for each time point and each group.

**Eye tracking data:**

* + - * *Will participant look more at Go items vs. NoGo items?*
        + Regression for predicting gaze time per item during probe, with item association (Go and NoGo) and item value (high and low) as independent factors, for each session and each group separately.
      * *Will Go items draw more attention than NoGo items?*
        + Logistic regression for whether the first saccades was towards the Go item during the probe, with item value (high and low) as independent factor, for each session and each group separately.

**fMRI data:**

Response to snacks:

**Univariate analysis**

* *Will training change neural response while viewing Go vs. NoGo items? Will it be different between the groups?*
* First-level GLM analysis on each of the response to snacks runs with feat, second level GLM analysis on the after (response to snacks [2-6] minus before (response to snacks 1)) images of each subject with feat, and then:
* For each group, analyze using one-sample permutations t-test with FSL's randomize on the results of the second level.
* Comparing the change of activations between the CAT and Classic groups using two-sample permutations t-test with FSL's randomize on the results of the second level.
* *Will neural response correlate with the initial value of items?*
* GLM on the response to snacks run before training (response to snacks 1), with WTP from BDM 1 as a regressor, for both group together (since the experiment is identical between the two groups before training)

**MVPA**

* *Will differences in neural response while viewing Go vs. NoGo items dissociate between groups?*
* Training the algorithm to distinguish between the PC and CAT groups images of the change of response to snacks for Go items vs. for NoGo items (difference of response to snacks [2-6] minus before (response to snacks 1).
* *Will differences in neural response while viewing Go vs. NoGo items dissociate between learners and non-learners participants?*
* Training the algorithm to distinguish between participants above and below the median of proportion choices of ‘go’ or ‘nogo’ item in the probe, by images of the change of response to snacks for Go items vs. for NoGo items (difference of response to snacks [2-6] minus before (response to snacks 1).
* *Will neural response while viewing the items dissociates Go vs. NoGo items?*
* Training the algorithm to distinguish between images of the change of response to snacks (difference of response to snacks [2-6] minus before (response to snacks 1)) for Go items vs. for NoGo items.
* Will neural response *while viewing the items* dissociates between items that were subsequently chosen?
* Dissociate choosing Go: training the algorithm to distinguish between neural response during response to snacks towards items that were subsequently chosen vs. not chosen during probe. Separately for each time point and for each group.
* *Are there distinct neural responses for items that were chosen vs. items that were trained?* 
  + *Training two classifiers, to predict 1)* Go vs. NoGo items and 2) chosen vs. non-chosen items. These two are intrinsically dependent since Go items are chosen more than NoGo items. Their convergence will indicate if they rely on similar neural systems.
* *Will neural response while viewing the items in the first session predict subsequent choices in subsequent sessions?*
  + Dissociate choosing Go: training the algorithm to distinguish between neural response during response to snacks [after minus before training] towards items that were subsequently chosen vs. not chosen during probe [2-5]. Separately for each time point and for each group.

**gPPI**

* + - * *Which functional connectivity patterns are associated with CAT?* 
        + Connectivity of change of response to snacks after training (difference of response to snacks [2-6] minus before (response to snacks 1)) for Go items. Seed regions: pre-hypothesized regions & significant regions from the GLM analysis.

Training

**Univariate analysis**

* *Will neural response change with the progress in training? Will it be different between the groups?*
* First-level GLM analysis on each of the 8 training runs (each with 2 training repetitions) with feat.
  + - * + Contrast the time variable in second level GLM analysis on the mean of these 8 runs to model the time difference in each subject:

Last 2 runs > First 2 runs

Linear trend model for the 8 runs [-4, -3, -2, -1, 1, 2, 3, 4]

* + - * + Group analysis using one-sample permutations test with randomize on the results of the second level for each group separately.
        + Then compare the differences between groups using two-sample permutations test with randomize
* *Will neural response during training predict subsequent choices?*
  + - * + In the above GLM analysis add a regressor with parametric modulations of choice proportion during probe, in order to identify regions in which activity levels were predictive of future behavior.

**MVPA**

* *Will neural response during training predict subsequent choices?*
  + - * + Dissociate choosing Go: training the algorithm to distinguish between neural response during training towards items that were subsequently chosen vs. not chosen during probe. Separately for each time point and for each group.

Probe

**Univariate analysis**

* *Will neural response correlate with choosing Go over NoGo items?*
  + - * + First-level GLM analysis on each of the 4 short-term probe runs with feat, second level GLM analysis on the mean of these four runs for each participant, and then:

Group analysis using one-sample permutations t-test with FSL's randomize on the results of the second level. Separately for each time point and for each group.

Comparing differences between the CAT and Classic groups using two-sample permutations t-test with FSL's randomize on the results of the second level. Separately for each time point.

**MVPA**

* *Will neural response predict choosing Go over NoGo items?*
  + - * + Training the algorithm to distinguish between trials in which the Go item was chosen vs. trials in which the NoGo item was chosen. Separately for each time point and for each group.

**gPPI**

* + - * *Which functional connectivity patterns are associated with choosing Go over NoGo items?* 
        + Connectivity on each probe (probe [1 -5]), following the above described GLM. Seed regions: pre-hypothesized regions & significant regions from the GLM analysis.

Resting state

* + - * Analyzing 'classical' analysis of resting state, and their stability / reliability within subject over time
      * ?

General note: We will use permutation tests following Eklund et al. (Eklund, A., Nichols, T. E., & Knutsson, H. (2016). Cluster failure: why fMRI inferences for spatial extent have inflated false-positive rates. Proceedings of the National Academy of Sciences, 201602413.)

In case we will not obtain results with the randomise tool, we will execute another group analysis with feat (flame1). Feat might yield better results in case our data will have within group variance, which can be better modeled by FSL's flame.We will start with z=3.1 and move to z=2.3

Overall it’s fine – I just think we don’t have a good plan for the longitudinal analyses and also maybe take ROIs from Rotem and Tom….or say we will use what they find.

What about running a snack vs. objects localizer ? So that we can restrict our analyses on a specific network like TomSa is doing ?