Reactivation of populations of ventral tegmental area neurons in the rat

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1. Introduction

• During the resting period immediately after a learning task, sub-population of neurons in hippocampus, neocortex and striatum replay their patterns of activity, a phenomenon called reactivation.

• Reactivation occurs primarily during a quiet awake state and during slow wave sleep. It has been proposed as a physiological substrate for the process of memory consolidation.

• Most experimental paradigms used to evaluate reactivation involve the delivery of rewards. The replay of task-dependent information also involves the replay of reward information in nucleus accumbens (Lansik et. al. 2008). The Ventral Tegmental Area (VTA) is a key afferent structure containing reward sensitive neurons.

• We hypothesized that the VTA contains neurons that respond differentially to different types of rewards. We also hypothesize that subpopulations of VTA neurons will reactivate depending on the type of task they were involved in.

2. Methods

Subjects: Three adult male Brown Norway/Fischer 344 hybrid rats (350-400g) were used. Animals were stereotaxically implanted with a hyperdrive consisting of 12 independently movable tetrodes (fig. 1A). Two additional electrodes were implanted in the contra-lateral dorsal hippocampus (-3.1mm from bregma, 2 mm lateral and 3 mm in depth) to obtain an EEG signal. Another two electrodes were implanted in the neck muscle to obtain an EMG signal.

Task and apparatus: Rats ran 3 tasks (fig. 1B):
- **FP**: Rats were kept in a holding pot and ate different kinds of rewards,(20mg regular food, sugar or quinine pellets), randomly delivered with a pair of tweezers.
- **FFF**: Animals were trained to forage for the same rewards dispersed on a 5 feet circular open field arena.
- **FNF**: Animals were required to forage on the arena but no reward was present.

Histology: After the recording was completed an electrolytic lesion was made by passing current (5μA for 10 seconds) on every electrode. The position of the tip of each tetrode was determined by Nissl staining and immunohistochemistry for Tyrosine-Hydroxylase (fig. 1C).

Data Analyses: Spikes were cut with Mclust (Redish D.) Reactivation was measured with the explained variance method (Kudrimoti et al, 1999).
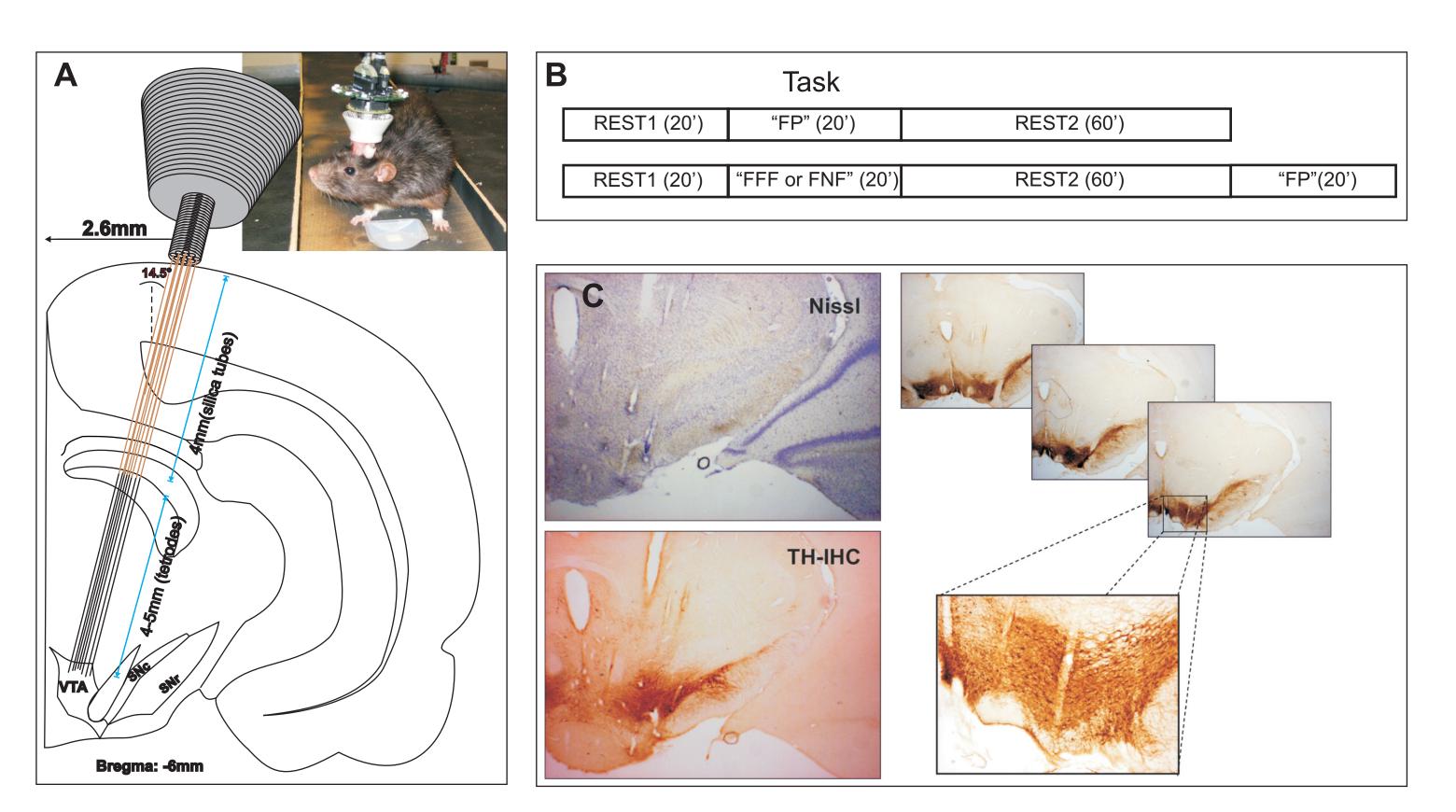

Figure 1: Methods summary. A Stereotaxic coordinates used to implant the hyperdrive targeted to VTA. **B** Time line for the different experimental conditions (time is in minutes). **C** Nissl and Tyrosine Hydroxylase staining for histological reconstruction of the tetrode positions. VTA: ventral tegmental area; SNc: Substantia Nigra pars compacta; SNr: Substantia Nigra pars reticulata.
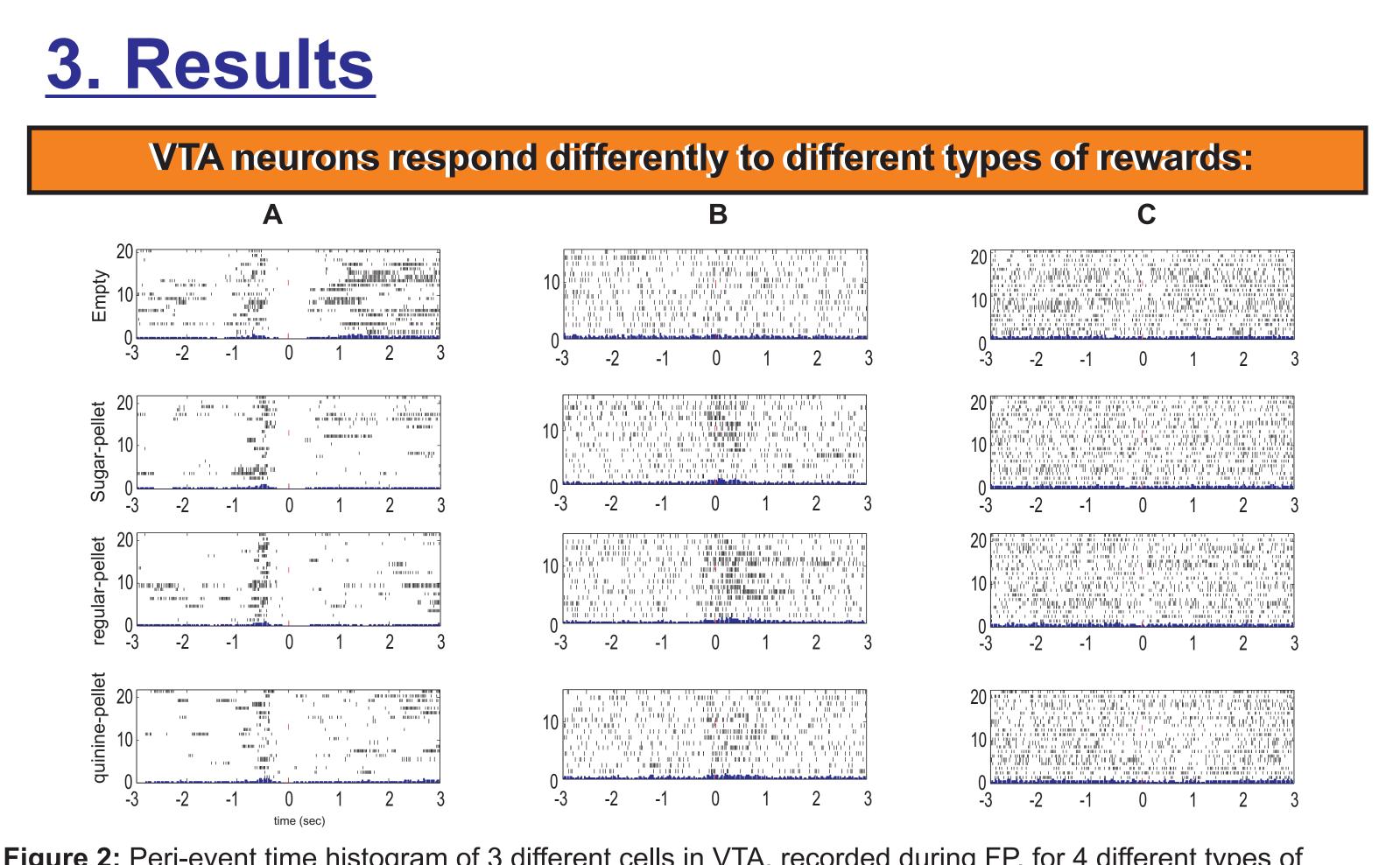
3. Results

VTA neurons respond differently to different types of rewards:

Figure 2: Peri-event time histogram of 3 different cells in VTA, recorded during FP, for 4 different types of events. **A)** neuron that responds maximally after the delivery of a reward is omitted. **B)** neuron that responds maximally after a regular food pellet. **C)** neuron that doesn't respond to any event. A and B neurons are reward sensitive neurons and C is not.

Spontaneous activity of reward sensitive VTA neurons during the resting period after the task:
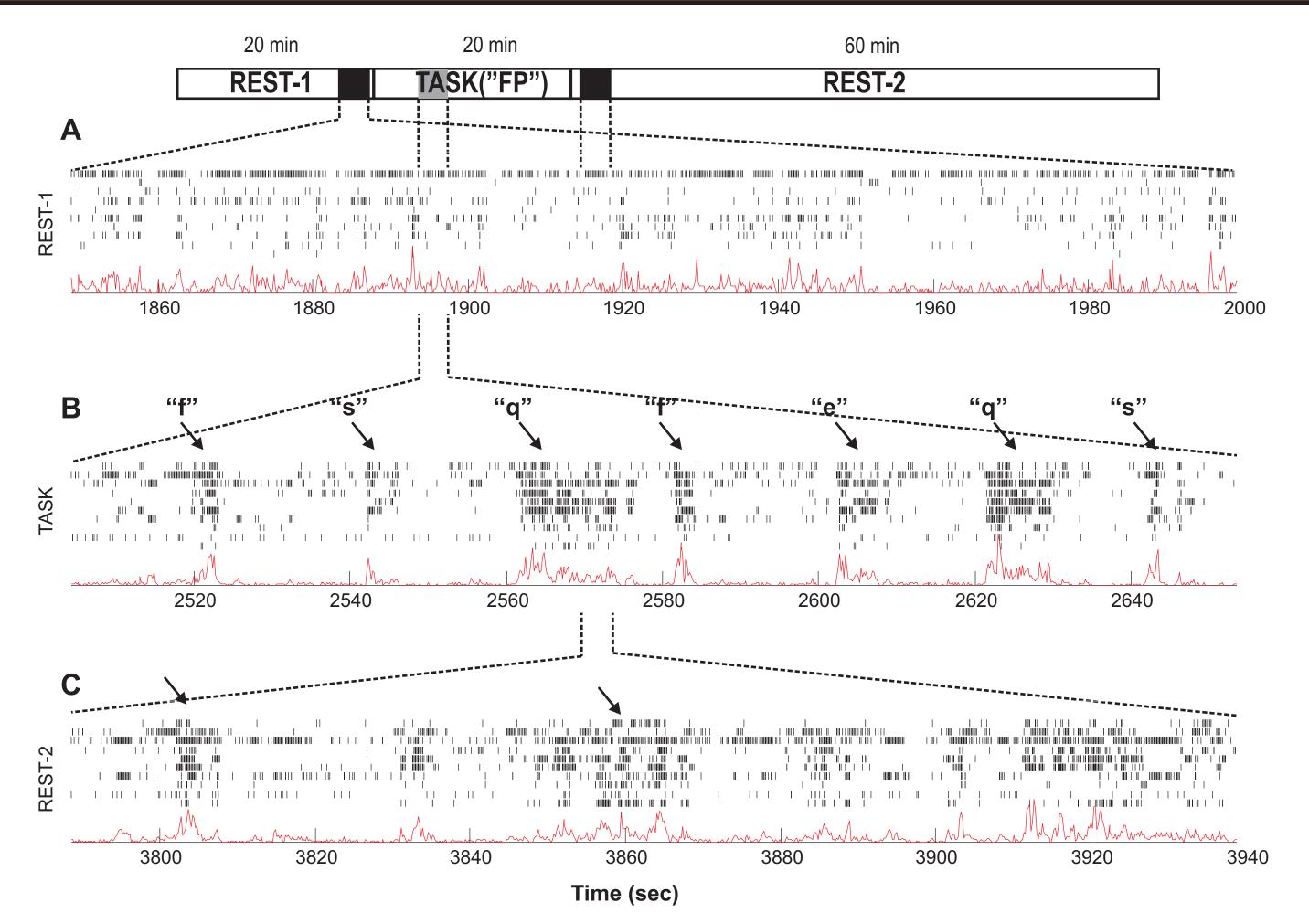

Figure 3: Raster of 10 reward sensitive neurons simultaneously recorded during different epochs of a "FP" experimental session. **A)** 3 minutes of recording during the resting period preceding the task. **B)** 3 minutes during the task and **C)** 3 minutes during the resting period after the task. The arrows in B mark the occurrence of events (f, regular food pellet; s, sugar pellet; q, quinine pellet; e empty tweezers). The arrows in C point to spontaneous neuronal activity patterns during the resting period. Some of these patterns are very similar to that exhibited during the task. No such activity patterns were observed in the resting period before the task (A).

Cross-correlations between reward sensitive neurons during the task are also found during the resting period after the task:
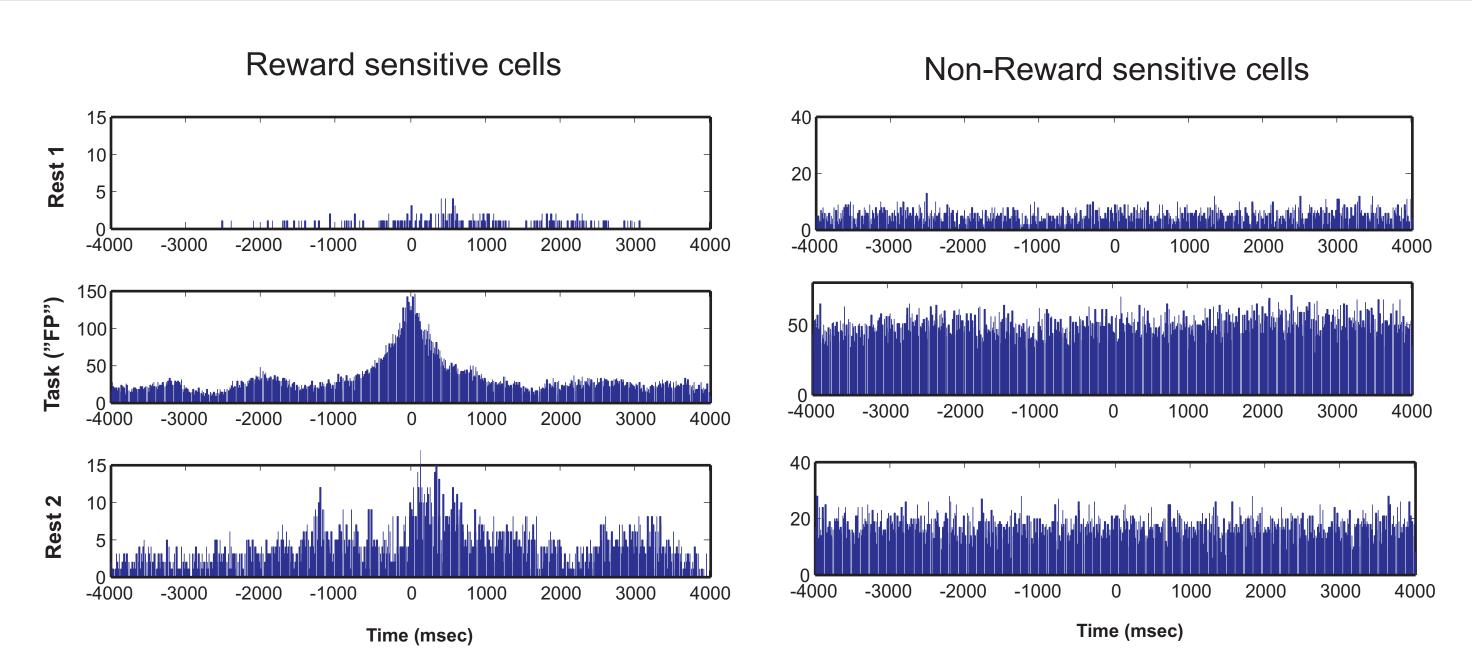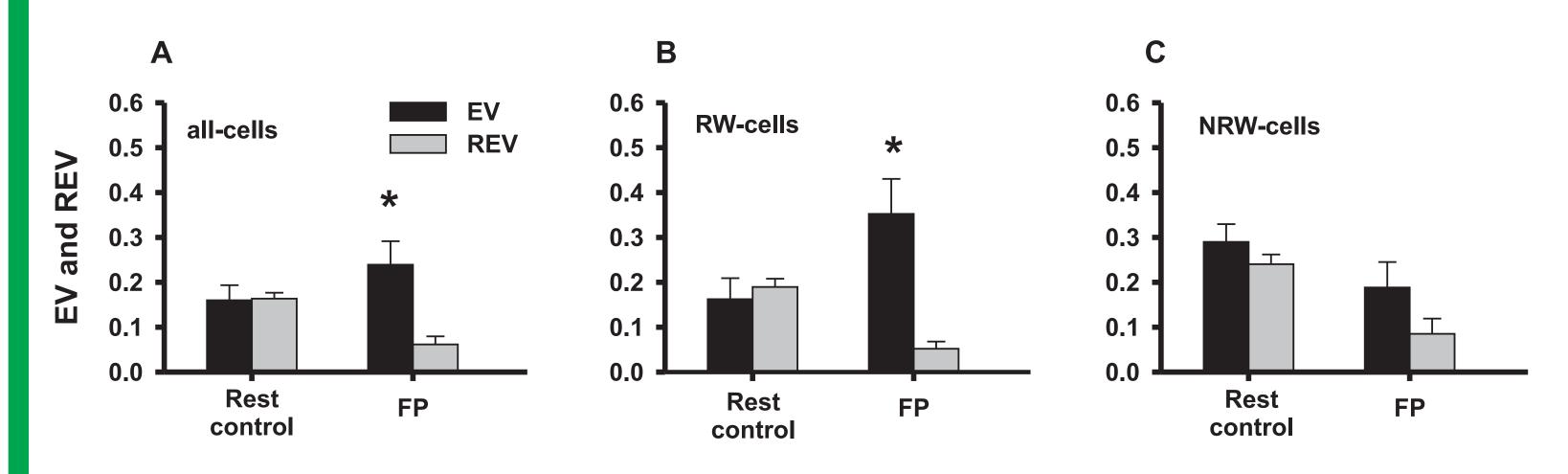

Figure 4: Cross-correlation between reward sensitive and Non-Reward sensitive cells, during the three epochs of the task ("FP"). In both cases, the cells were simultaneously recorded on different tetrodes.

4. Results

Reactivation of populations of VTA cells during a FP task:

Non-Reward sensitive neurons — Reward sensitive neurons

EV: 0.0137 REV: 0.044
EV: 0.58 REV: 0.06
EV: 0.0379 REV: 0.002

Figure 5: Examples of cross-correlation patterns in three different VTA neural populations during three different FP tasks (left: non reward sensitive neurons only, middle and right: reward sensitive neurons only). The explained variance (EV) and reverse explained variance (REV) are indicated under each neural population.

Reward sensitive neurons reactivate after a simple rewarded task, but Non-Reward sensitive neurons do not.

Figure 6: Explained and reverse explained variance for the "FP" task using **A)** the entire population of neurons, **B)** the Reward sensitive neurons (RW) only, or **C)** the Non-Reward sensitive neurons (NRW) only. The control task consisted in a continuous rest session of the same length as FP ("Rest control"). The values correspond to the mean ± SEM across all animals and all sessions. * p<0.05, Mann-Whitney test.

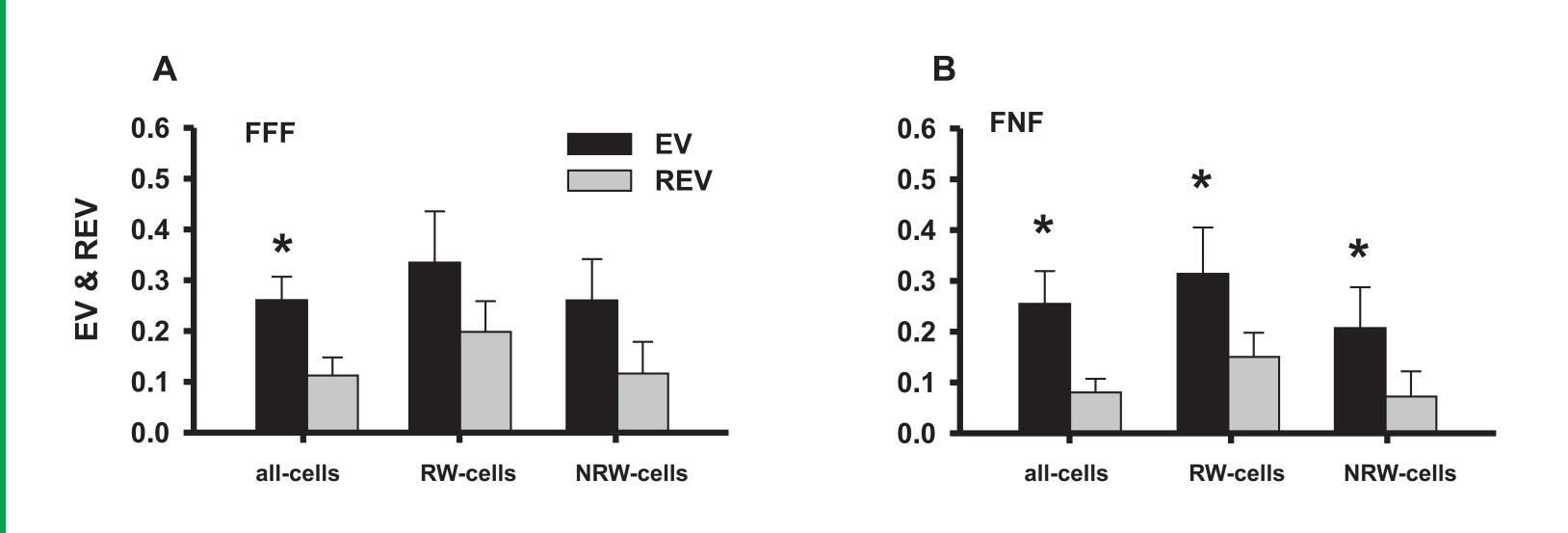### Non-Reward sensitive neurons reactivate after foraging tasks:

Figure 7: Explained and reverse explained variance for the different VTA neural populations **A)** for the "FFF" task and **B)** for the "FNF" task. In the "FFF" task reactivation is detected only if all cells are included in the analysis. During FNF both Reward sensitive and Non-Reward sensitive populations reactivated separately. The values correspond to the mean ± SEM across all animals and all sessions. * p<0.05, Mann-Whitney test.
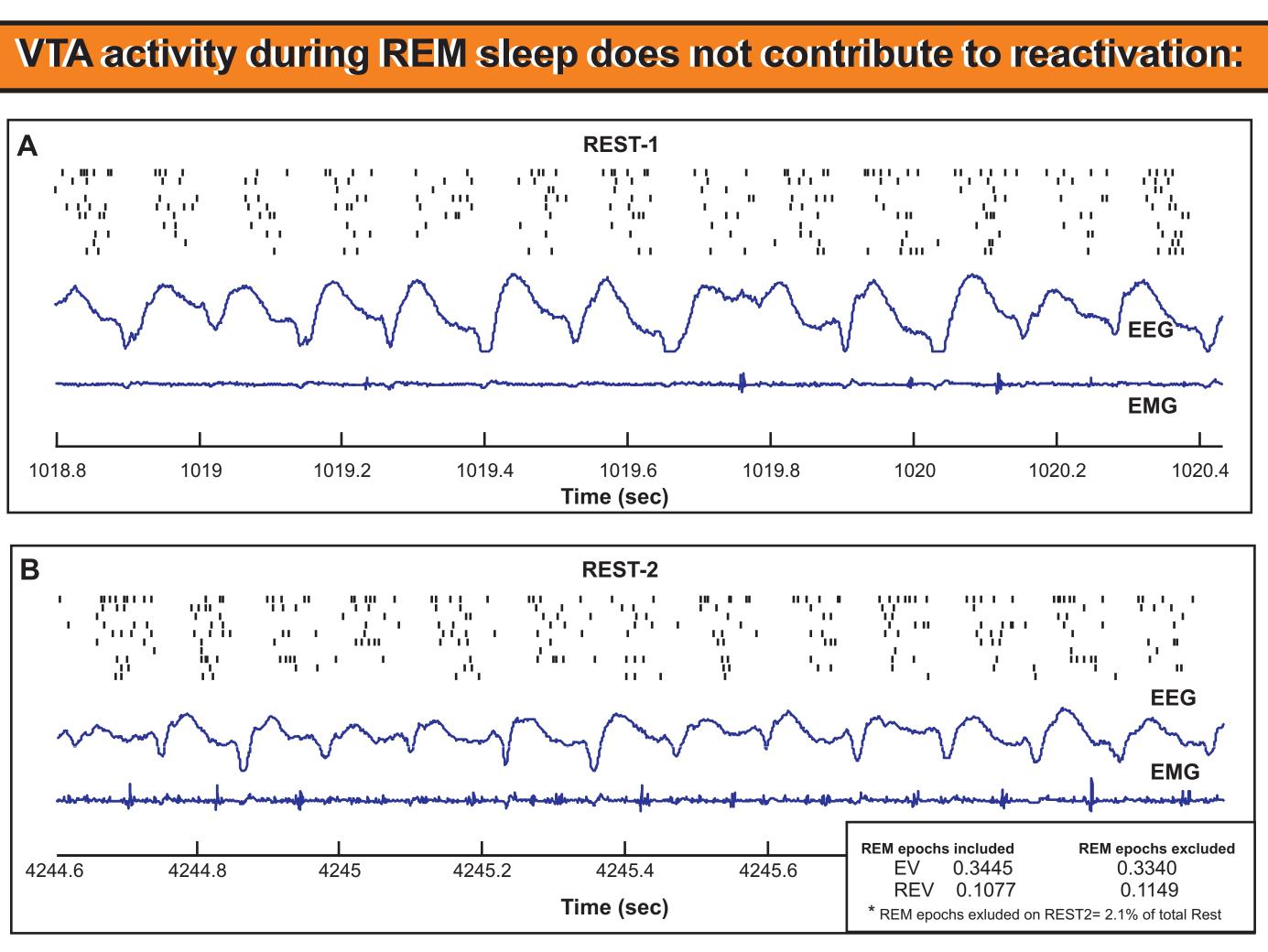
5. Results

VTA activity during REM sleep does not contribute to reactivation:

Figure 8: Patterns of REM neural activity of 10 VTA neurons (6 Reward sensitive, 4 Non-Reward sensitive) obtained **(A)** during a resting period before a "FP" task and **(B)** during a resting period after the task. EV and REV were computed with the inclusion or exclusion of the REM sleep epoch (inset in **B**).
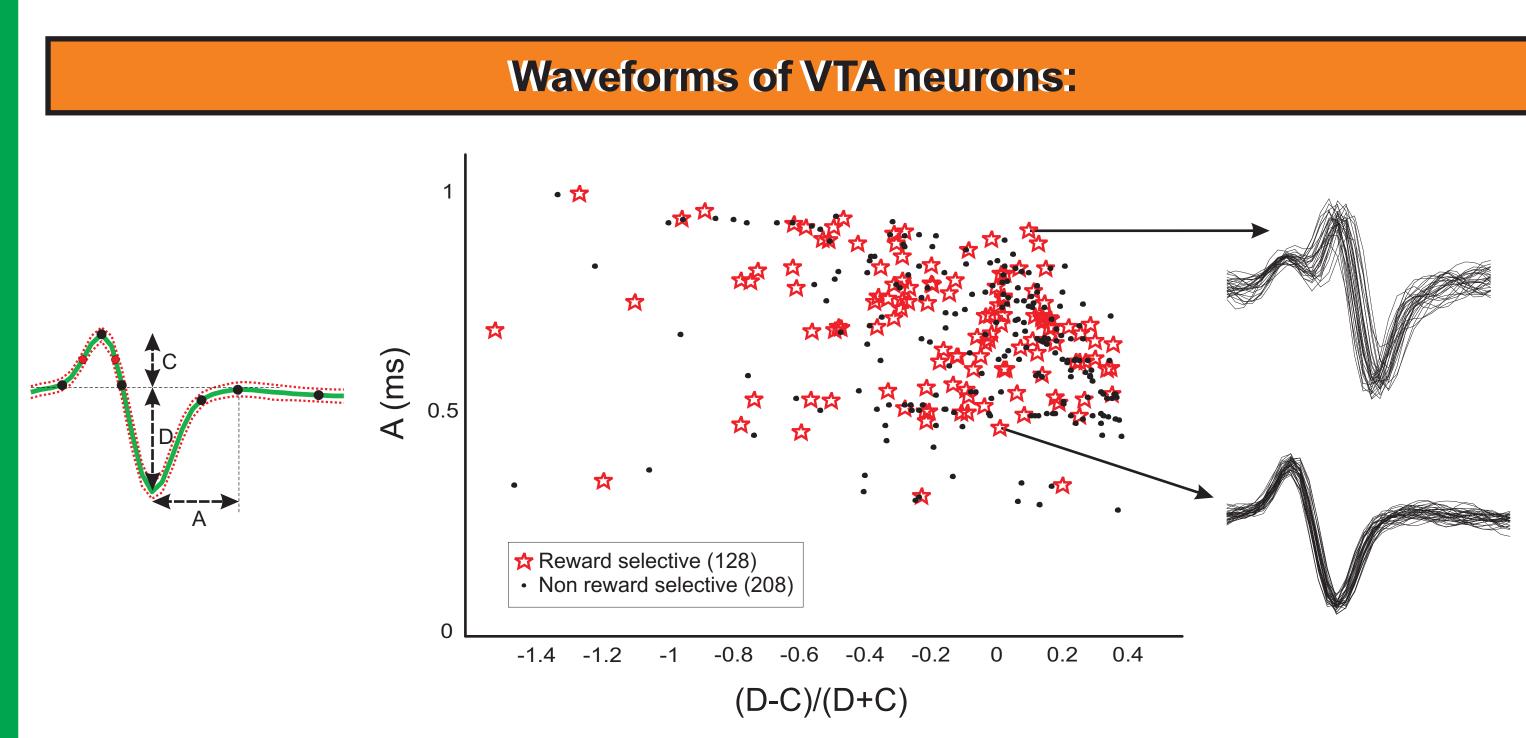
Waveforms of VTA neurons:

Figure 9: Reward sensitive cells and Non-Reward sensitive cells cannot be segregated by their waveforms alone using the Roesch et al. (2007) clustering technique. Some waveforms are however typical of extracellularly recorded dopamine cells.

6. Conclusions

• We found 2 different VTA neural population separable on the basis of their responses to food rewards.
• The 2 neural populations reactivate during sleep. In a rewarded non-spatial task, non-reward sensitive cells do not reactivate significantly but reactivate during foraging where motor activity is involved. Reward sensitive cells reactivate if the task involves rewards, or expectation of rewards.
• VTA neurons may be phase locked to theta oscillations during REM-sleep. This synchronous activity does not contribute significantly to the EV or REV measures of reactivation.
• We did not find any significant correlation between the waveform of VTA neurons and their responses to rewards.

7. References

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8. Acknowledgments