Are you good at “Spot The Difference” games?
Understanding the neural substrates controlling behavioral pattern separation

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Behavioral pattern separation is the ability to distinguish between two very similar situations or stimuli. Dependent upon hippocampal function (especially the dentate gyrus, DG), this ability wanes with age and certain psychiatric/neuropsychiatric disorders. It is critical to understand the neural substrates required for behavioral pattern separation in order to treat these individuals. Previous studies report that inhibitory function of DG interneurons is beneficial for behavioral pattern separation. To test this hypothesis, we investigated whether inhibition of DG interneurons decreases pattern separation in mice. We found that inhibition of DG interneurons decreases pattern separation in mice. This suggests that DG interneurons play a role in behavioral pattern separation.

**QUESTIONS**
- Does increasing memory load (more similar object locations) make novel object location discrimination harder?
- Does inhibition of an interneuron in the dentate gyrus (DG) decrease behavioral pattern separation?

**RESULTS**
- Control group similarly discriminates novel object location regardless of various memory loads.
- Inhibited DG somatostatin cells allow discrimination of dissimilar object location, but impair discrimination of similar object location.

**IMPLICATIONS**
- DG interneurons could play a role in pattern separation abilities.
- DG interneurons can be targeted for individuals with impaired pattern separation due to aging or psychological disorders.

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**REFERENCES**

**ABSTRACT**
Behavioral pattern separation is the ability to distinguish between two very similar situations or stimuli. Depending upon hippocampal function (especially the dentate gyrus, DG), this ability wanes with age and certain psychiatric/neuropsychiatric disorders. It is critical to understand the neural substrates required for behavioral pattern separation in order to treat these individuals. Previous studies report that inhibitory function of DG interneurons is beneficial for behavioral pattern separation. To test this hypothesis, we investigated whether inhibition of DG interneurons decreases pattern separation in mice. We found that inhibition of DG interneurons decreases pattern separation in mice. This suggests that DG interneurons play a role in behavioral pattern separation.

**SPOT THE DIFFERENCE: BEHAVIORAL PATTERN SEPARATION (BPS)**
A cognitive function to differentiate between very similar experiences/memories
- Impaired in individuals with age, depression, AD, or PTSD
- DG has a crucial role
- Underlying mechanism involves DG interneurons inhibiting DG granule cells

**CHEMOGENETICS: MANIPULATION OF INTERNEURON ACTIVITY**

**ACTIVITY**
- Compound 21 Injection
- AAVV Virus Injection

**RESULTS**
- AAVV-6-hyn-DIO-hM4D-mCherry (n=10) and AAVV-6-hsyn-DIO-mCherry (n=7)
- hM4Di = DREADD (Designer Receptors Exclusively Activated by Designer Drugs)
- Inhibitory cells in the dentate gyrus (DG) decrease behavioral pattern separation

**IMPLICATIONS**
- DG interneurons could play a role in pattern separation abilities
- DG interneurons can be targeted for individuals with impaired pattern separation due to aging or psychological disorders

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**REFERENCES**

**ASSESSING BPS IN MICE: SPONTANEOUS LOCATION RECOGNITION (SLR) TEST**
Test relies on a mouse’s innate interest in novelty.
- BENEFITS
  - minimal training
  - easier to distinguish between different memory processes
- MEMORY LOADS
  - low = dissimilar object location (d-SLR)
  - medium = similar object location (s-SLR)
  - high = extra similar object location (x-SLR)

- Excluding data points and suitability of various memory loads

- ONGOING/FUTURE DIRECTIONS
  - Assess if inhibition is targeted to DG, if not remove those mice from their respective groups and reanalyze the data.
  - Test with increased subject number (N)
  - Additionally, since the DG does not function in isolation. It is important to examine the broader neuronal circuit affecting behavioral pattern separation. The entorhinal cortex is of particular interest.
  - Does stimulation/inhibition of the entorhinal cortex that provides direct input to the DG affect behavioral pattern separation?