Review of: "Social Reactivation of Fear Engrams Enhances Memory Recall"

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Finkelstein et al in this interesting study explored the influence of social information on the activity of fear engrams that are induced by contextual fear conditioning (CFC). Briefly, they have examined the effect of a variety of social or non-social stimuli that was applied in mice after CFC training on CFC recall. They found that fear memory was enhanced when grouped housed mice, which received similar CFC training, were exposed to a recently shocked cagemate through a 1-way mirror (only the recently shocked cagemate can see the others). In addition, exposing CFC trained mice with a juvenile mouse also enhanced CFC recall. Nonetheless, exposing mice with the recently shocked mouse directly (full interaction), through an opaque mirror, or under a social buffer paradigm (1-way mirror, recently shocked mouse + a cagemate) had no effect on CFC recall. Exposing to physical stress through restraint or to the restraint apparatus alone also did not affect CFC recall. These effects of social stimuli on CFC recall were found in male mice only. Using a TetTag approach, they found that CFC related engrams in both the dorsal dentate gyrus (dDG) and the amygdala were reactivated more strongly by the 1-way mirror and the juvenile mouse than other social and non-social stimuli. Lasting, when they used optogenetic to activate dDG or amygdala neurons that were labeled during 1-way mirror or restraint, they found an increase in freezing after dDG activation only. Together, they concluded that social encounters can reactivate pre-existing dDG engrams and strengthen discrete memories.

The study is interesting for a few reasons. The role of social buffering in reducing stress and fear has been examined by many studies. However, how social information affects the recall of fear memory is not clear. This group has used a variety of original experimental designs to dissect the influence of different facets of social information on fear recall. Sex differences were also examined. The techniques used for targeting and manipulating engrams are state of the art.

Weaknesses of this study is related to the need of additional clarification of experimental design. More control experiments are likely needed for supporting their conclusion:

- The use of all 4 cagemates in many parts of behavioral training and testing (e.g. exposure to social stimuli, CFC recall) is innovative. However, it is unclear if the presence of cagemates affect the performance of mouse in these tasks. For instance, have the authors tried to compare freezing in mice when they were tested individually vs. having all 4 cagemates together? In some testing paradigm, one of the cagemates was shocked and sacrificed right after social exposure (e.g. 1-way mirror). Would the effect of having 3 cagemates instead of 4 affect CFC recall?
- Light that was applied in the 1-way mirror testing (Fig. S1) is likely stressful. Was light applied in other social paradigms

as well (e.g. full interaction)? Would the effect of 1-way mirror be reduced by removing this stressor?

- Although the comparison between the opaque mirror group and the one way mirror group is intriguing, it is not clear the purpose of the opaque mirror. Do the authors suggest that the recently shocked cagemate would behave differently if he/her can see his/her cagemates? To compare the impact of a stressed cagemate on CFC recall, an alternative control would be a non-shocked cagemate through the one way mirror.
- Both a recently shocked cagemate and a juvenile mouse could increase CFC recall. However, they are quite different stimuli. In particular, the juvenile mouse is socially novel to the test mouse. Could social novelty be responsible for the increased CFC recall? It would be interesting to know the impact of the exposure to a familiar juvenile mouse on CFC recall to reveal the impact of social novelty.

Other points:

- n size is low for some engram studies. For instance, the immediate shocks group in Fig. 2, and the BLA restraint data in Fig. 3 have a n size of 4 only.
- More data will be needed to show that light can increase freezing from base to the first ON in Fig. 4E.
- Some panels of Fig. S3 (S3E & S3F) are missing.