Time-Place Learning in Mice: A circadian system dependent learning and memory task

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Abstract

Time-Place Learning (TPL) is the process in which animals link biological significant events (e.g. encountering predators, food, mates) with the location and time of occurrence in the environment. This allows animals to anticipate which locations to visit or avoid based on previous experience and knowledge of the current time of day. Recent advances have increased our knowledge on establishing TPL in a laboratory setting, leading to the developed a now well established TPL paradigm in a three-arm maze for mice [1, 2], see Figure 1. This paradigm reflects the natural situation in which foraging animals have to evaluate risks connected with different feeding locations, which may be safe or unsafe to visit depending on the time of day.

Figure 1: The TPL maze. Mice are food deprived to 85% of ad libitum feeding weight, but can find food at the end of each of the maze arms, behind a small metal grid. In each of the 3 daily sessions (lasting maximally 10 min per mouse), mice have to learn to avoid 1 of the 3 feeding locations, depending on the time of day (i.e., session). On visiting a 'wrong' location, mice receive a mild but aversive foot shock (<1 s).

Using this paradigm, we previously demonstrated that, rather than using external cue based strategies, mice use an internal clock for TPL. This finding has made TPL an interesting research topic from several perspectives: 1: TPL is a suitable task to study the role of the circadian system in associative memory formation (with time of day as a discriminative contextual cue). 2: TPL enables the investigation of circadian clock components on a functional behavioral level. First studies have shown that TPL is *Cry* clock gene dependent, but independent of *Per* clock genes [3]. 3: TPL offers the possibility to study the functional interaction between learning/memory and the circadian system with aging. First results have shown that old mice (>17 months) use external cues instead of an internal clock for TPL. We found no significant aging effect in a spatial memory test (spontaneous alternation), but found significant aging effects in circadian system behavioral parameters. These data suggest that at old age, the circadian system is too weak for TPL and mice are forced to use an alternative (suboptimal) strategy [4]. Finally, the pros and cons of this paradigm to measure timing behavior in mice will be discussed, as well the development of an automated TPL set up.

References

1. Mulder, C.K., Gerkema, M.P., Van der Zee, E.A. (2013). Circadian clocks and memory: time-place learning. *Front Mol. Neurosci* **6**, 8.
2. Van der Zee, E.A., Havekes, R., Barf, R.P., Hut, R.A., Nijholt, I.M., Jacobs, E.H., Gerkema, M.P. (2008). Circadian time-place learning in mice depends on Cry genes. *Curr. Biol.* **18**, 844-848.
3. Mulder, C.K., Van der Zee, E.A., Hut, R.A., Gerkema, M.P. (2013). Time-place learning and memory persist in mice lacking functional per1 and per2 clock genes. *J. Biol Rhythms* **28**, 367-379.
4. Mulder, C.K., Gerkema, M.P., Van der Zee, E.A. (2013). Individual differences in time-place learning: comparison of life-long training with first-time training at old age. *20th international KNDV Zoology conference on individual differences* (Groningen, 1-3 November 2013), poster presentation.