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Interpreting Neural Representations of Aged Animals

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It is becoming more clear that normal age-related cognitive decline is characterized not so much by significant cell loss in memory-related brain structures like the hippocampus, but rather by a change in the functional organization of information processing of its neural elements. Consequently, investigations of the changes in neural plastic abilities of the aged brain represent an approach that could reasonably be expected to result in important advances in our understanding of age-related cognitive decline. To this end, the recent findings reported by Tanila et al. (1997) and Barnes et al. (1997) move the field forward in significant respects. The data presented in Tanila et al. (1997) suggest that hippocampal place fields of aged rats are remarkably stable across different environments, while Barnes et al. (1997) showed that a subset of hippocampal place fields of old rats represent spatial locations less reliably when animals are repeatedly tested across familiar environments. At first glance, these results appear in conflict. The recent commentary on this apparent discrepancy by Peter Rapp (1998) suggests the interesting possibility that in old rats there is greater interference between similar cues that were used in the different test situations of Barnes et al. (1997), and that such interference was not present in the Tanila et al. (1997) study. The results of both the Tanila and Barnes group suggest that aged animals show a change in hippocampal representational plasticity.

Additional issues deserve to be emphasized in the context of the above debate. The first issue concerns the behavioral interpretation of the observed unit correlates, and the second issue deals with age-related compensation of function and its relationship to neural representation within and outside of hippocampus. Regarding the first issue, there is even more converging behavioral and neurophysiological evidence that old rats and their place cells have difficulty when using familiar spatial information in different behavioral contexts. Barnes et al.'s data are entirely consistent with recent behavioral data (Mizumori et al., 1996) showing that aged animals are significantly slower at acquiring a spatial working memory task on a radial maze than young rats when acquisition training occurs in a spatial environment that is familiar to the rat (room A). In contrast, and parallel to the Tanila data, the *rate* of learning a spatial memory task in a novel environment (room B) was similar across ages even though the number of errors was greater for old animals. In both spatial learning conditions of the Mizumori et al. (1996) study, rats previously received extensive training on a (non-memory) forced choice task in room A. Thus, the behavioral experience was the same across all groups of animals. While old rats may have difficulty separating similar spatial contexts, they *can* learn about new spatial environments, albeit with a different, perhaps less efficient, strategy.

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Although intriguing, the unit-behavior relationships of Tanila and Barnes, as well as those just described, remain somewhat tentative in that comparisons are made across animals, laboratories, and tasks. Similarly, with specific regard to the Tanila et al. and Barnes et al. studies, it is not clear how performance of stereotyped behaviors (the condition under which their place cells were recorded) relates to age-related deficits in spatial learning. This is not a trivial issue as it has been shown that in old rats, place cell properties recorded when rats perform a more stereotyped task (forced choice task) are different from place cells recorded when the same old rats perform a spatial memory task (Mizumori et al., 1996). Moreover, this age-related change can be subregion (i.e., CA1 vs. CA3) dependent. Future studies should perform more detailed behavioral analyses on animals in which place units are being recorded so that we may gain a more complete appreciation of the functional relevance of the neurophysiological results.

When attempting to relate neurophysiological results to behavior, especially during the aged condition in which multiple structures experience altered function, the second issue of this commentary needs to be considered: Do the observed age-related hippocampal responses reflect changes in plasticity of hippocampal neurons, or changes in afferent information, or both. To address this issue, it is essential to evaluate not only age effects in hippocampus but also in afferent structures. In the case of hippocampal place cells, age changes in the medial septal or entorhinal input could lead to enhanced or reduced flexibility of spatial representation. Indeed, fiber sparing lesions of the medial septum significantly reduce hippocampal place field plasticity in young animals with an intact hippocampus (Leutgeb and Mizumori, 1997, unpublished data; Ikonen et al., 1998). Functionally, this relative inflexibility could reflect use of a different cognitive strategy for solving spatial tasks (something that old rats have been shown to do; Barnes et al., 1980) rather than less efficient spatial processing by hippocampal neurons per se.

Related to the issue of how to interpret spatial representations of old animals, we have shown that memory-*intact* rats show representational reorganization in hippocampus, while memory-impaired rats do not (Mizumori and Kalyani, 1997). The important point here is that it may not always be the case that memory-impaired rats

show the most dramatic age-related change in place field firing (or any other neurobiological marker for that matter). Old rats may perform as well as young either because their brains have not undergone extensive neurological decline, or because the old animals have learned to compensate for a more accelerated decline in neural function by adopting alternate neurocognitive strategies.

Understanding age-related compensations in function is directly relevant to the apparent discrepancy between the Tanila et al. (1997) and Barnes et al. (1997) studies. It is known that there is less information available to hippocampus via its perforant path afferent system. The consequences of this deafferentation could be compounded by age-changes in septal input, leading to a situation in which partial associations that define a particular spatial environment are not sufficient to result in flexible relational representation. Consequently, one observes an apparent independence of hippocampal representation from the current context. This, in turn, may result in opposite responses to environmental manipulation, depending on whether we expect the animal to recognize a context as the same or different. This interpretation provides an alternative view from the one expressed by Redish et al. (1998) who argued that the recurrent collaterals are not sufficiently strong in aged animals to sustain a stable representation of familiar environments.

In summary, then, while the hippocampal data from the Tanila and Barnes groups are very exciting and provocative, one must carefully consider these data within a broad, and perhaps more dynamic *neural context* in which hippocampus likely operates. In addition, it would be prudent to consider the *cognitive context* in which behaviors are performed so that more direct functional interpretations can be made of neurophysiological results. After all, it is likely that both neural and cognitive contexts ultimately define the hippocampal contribution to age-related changes in performance.

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