The Effects of Reproductive Experiences on Age-related Neural and Behavioral Changes in Female Rats

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The experiences of motherhood, pregnancy, birth and postnatal care, are associated with neural and behavioral changes. Female rats undergoing multiple bouts of motherhood (multiparous) have been shown in some, but not all studies, to have a dampened HPA axis stress response resulting in reduced anxiety, better performance on spatial memory tasks and changes in some hormone levels and stress responsivity compared to age matched females who have not given birth (nulliparous). Moreover, some of these changes extend into old age, approximately 24 months old. Thus, parous rats provide a unique, physiological model in which to investigate neural and hormonal factors that may contribute to cognitive decline and other changes with aging. Fisher 344 (F344) female rats were used for both studies. In the first study, we found that multiparous females, aged 10-12 months, performed better than middle-aged nulliparous females, aged 10-12 months, and similarly to the young nulliparous females, aged 2 months, in the spatial memory task of object placement. No differences in anxiety between any groups were noted on the elevated plus maze (EPM). Thus, multi-parity may have long lasting effects on spatial memory, but not on anxiety. Possible mechanisms underlying these behavioral effects were investigated by measuring dendritic spine density in the hippocampus, the prefrontal cortex and the amygdala. In addition, serum oxytocin levels were assessed since oxytocin is known to contribute to maternal behavior and to mood, and levels are increased during pregnancy and lactation. Apical and basal spine density in CA1 pyramidal cells of young virgins and multiparous females was higher density than the middle-aged nulliparous females. In the prefrontal cortex, apical spine density showed a similar pattern as the hippocampus, but no significant differences were present in basal spines. There were no significant differences in spine density in the medial amygdala and oxytocin levels did not differ between groups. Thus, reproductive experience attenuates some aspects of cognitive aging that are long lasting, but it did not alter anxiety.

Because olfaction is a necessary component of maternal behavior and the olfactory bulb shares connections with memory and emotion centers the same three groups of female rats were assessed for olfactory behavior, middle-aged multiparous and nulliparous females were slightly older, 11-12 months old, than in the first experiment. Olfactory abilities were tested using an olfactory acuity task and an
olfactory habituation/dis-habituation task to assess olfactory acuity and sensitivity, respectively. Anxiety was further investigated by testing closer to weaning of the last litter, using additional anxiety measures and assessing before other behavior test. As in the first study, no difference among groups was found on the EPM. In addition, the latency to approach an object was not different among groups. In contrast, rearing and wall climbing behaviors were significantly different between the middle-aged and young nulliparous females and corticosterone was lower in multiparous versus nulliparous middle-aged females. For the habituation/dis-habituation task, all groups were able to do the task successfully, but on the test trial, multiparous middle-aged females did not spend as much time with the novel scent as the other two groups. No differences among groups were found in the olfactory acuity task. These results suggest that multiparous females are impaired in distinguishing old and new odors compared to middle-aged and young nulliparous females. In addition, parity does not seem to exert long lasting effects on anxiety. In addition, there were no differences in spine density of the semi-lunar cells in layer II/III of the piriform cortex which was inconsistent with the multiparous females' poor olfactory sensitivity ability.

These results show that parity mitigates the spatial memory decline that accompanies aging. Thus, the motherhood experience confers some neuro-protective effects that attenuate the negative aspects of cognitive aging associated with memory. Parity also preserves the spine density loss in the hippocampus and prefrontal cortex that occurs with aging. The benefits of parity do not appear to extend to the amygdalar or semi-lunar cells of the piriform cortex. Long term effects of parity on olfactory behavior need further investigation because the current results were inconclusive. Overall, these results indicate that multi-parity influences some behavioral and neural changes associated with aging in females. Parous females therefore may offer valuable insights into the aging process for females and could serve as a unique and useful model for studying aging and understanding how reproductive experiences can attenuate some of the negative aspects of female aging.