The authors are most appreciative of this opportunity to comment on the commentaries. Dr. Morrison is certainly correct in urging the very careful and thorough use of animals to study the aging brain. But, as is well known, old dogs and monkeys do get amyloid laden plaques [1,2], so microscopic caution would be essential in the interpretation of the results. Our application of anti-synaptophysin in the current study is relevant to his call for analysis of synaptic proteins, since synaptophysin is a major protein constituent of the membrane of synaptic vesicles. Have experiments shown that the synapse can function without synaptophysin? It would seem probable that a functionless presynaptic terminal could exist without vesicles.

Dr. Morrison calls attention to his own animal work (1997) showing that neurons are not lost in the aging cerebral cortex. Our own prior (1987) cell counts on normal aged human neocortex were done by computerised image analysis, and demonstrated that while neuron number was preserved, there was also very significant shrinkage of large pyramids [3]. That loss of perikaryon size must include a loss of some of the metabolic machinery required by an affected cell to maintain its entire terminal arbor. This would lead to pruning of some of its synapses.

The critical issue raised by Price et al is whether the synapse loss reported by Masliah et al [4] might be attributed to the inclusion of a few subjects in an early stage of AD. We do not think so. As noted by Masliah et al, the neocortical plaques observed in the brain tissue of nine of the subjects were very sparse, averaging only about 3/mm2, and “most were diffuse plaques” [4]. The reviewers, in their 1996 report on the neuropathologic changes in individuals with a CDR of 0.5 [5], found that the number of diffuse and neuritic plaques was sufficient to meet the 1985 criteria for the diagnosis of Alzheimer disease [6]. None of our normal subjects approached those criteria.

Price et al also question our finding a loss of neocortical synapses in normal aging, and cite two papers (their references 2 and 7). Curiously their reference 2 does not deal with aging. Their reference 7 utilized 21 specimens with post-mortem times up to 36 hours and identified synapses in electron micrographs by their having been stained with phosphotungstic acid–hematoxylin and reported a slight but statistically significant drop in synapse number after age 70.

The reviewers state that “it has been difficult to confirm cognitive decline other than physical and cognitive reaction speed in non demented individuals.” The decline in processing speed with age is one of the most robust and long established findings in the neurology of aging [7], and involves not only the central processing of reaction time, but also standardized timed tests as diverse as Trails A, crossing out tasks, and the unquestionably abstract neocortical function, digit symbol substitution, as reported by the reviewers in their own longitudinal study [8]. Neocortical synapse loss might be a reasonable candidate for the neural change underlying these decremental phenomena.

Price et al emphasize the diagnostic and functional significance of tangles in AD, but Alzheimer’s second case [9] and our more than a dozen [10] equally demented patients lacked neocortical tangles.

Our major point remains: as a function of normal aging, neocortical synapses are being lost in the absence of significant amyloid and/or neurofibrillary tangles. This synaptic loss might well lead to primary senile dementia if life span is significantly increased.

References


