out, this concept may help explain the intriguing observation that those brain sites prone to accumulating extracellular Aβ deposits with age and in Alzheimer disease overlap with regions of so-called 'default activity,' that is, cortical areas that have high basal rates of metabolic activity (as determined by functional magnetic resonance imaging and positron emission tomography) when an individual is not performing a specific mental task (for example, 'daydreaming')[5].

The innovative approach of Cirrito *et al.* could now allow one to address experimentally whether specific mental activity (for example, during recall of a complex learned task) leads to less "default activity" and thus decreased Aβ release. A positive result might help explain impressions in the lay and even medical communities that persistently engaging in mental activity can help stave off Alzheimer disease–type cognitive loss. One could also use this technique to see whether rote motor (or sensory) activity not requiring special cognitive effort does not elevate Aβ levels in the corresponding primary cortices, regions that are known to be relatively spared from deposition of Aβ in aged humans. Another interesting question is whether several other protein substrates processed sequentially by the β- and γ-secretases (for example, the β2 subunit of the voltage-gated sodium channel)[6] yield stable Aβ-like peptides whose release is also enhanced by some forms of neuronal activity. A general mechanism for the neural regulation of heretofore unrecognized small hydrophobic peptides could emerge. Based on the results of Kamenetz *et al.*, decreased neuronal activity might be expected to increase local levels of APPs-α and the related p3 peptide, as well as the analogous products of other substrates undergoing sequential α- and γ-secretase processing. However, earlier work suggested that electrical depolarization of neurons increases rather than decreases APPs-α release[7].

Perhaps most important for current and future patients with Alzheimer disease is the concept that exploiting *in vivo* brain microdialysis to measure interstitial levels of Aβ peptides in APP mouse models could provide powerful preclinical discrimination among various different agents intended to decrease the production or enhance the clearance of Aβ[8]. The use of alternative *in vivo* methods in humans[9] could bring quantitative brain monitoring of Aβ-lowering therapeutics to clinical trial patients themselves.

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The author's perspective

Since publication of this work, we have been exploring whether physiological changes in neuronal and synaptic activity dynamically alter levels of amyloid-β (Aβ) in the brain, as well as the cellular mechanisms underlying these effects. In addition, we are assessing the acute effects of a variety of neurotransmitter and neurotransmitter receptor modulators on brain Aβ levels. Our published and unpublished data continue to show that synaptic activity has an important role in regulating extracellular levels of Aβ. Since publication of this paper along with work from the lab of Roberto Malinow, other groups are increasingly beginning to explore the role that a variety of neuronal activity modulators have on levels of Aβ. It may be, for example, that a variety of compounds that were thought to have only symptomatic effects on cognition may also modulate disease by affecting metabolism of Aβ.

I think it is noteworthy that the location of Aβ deposition in humans overlaps with areas of the brain that seem to be the most synaptically active when an individual is not performing a specific mental task, the so-called 'default network.' Our work suggests that the reason these regions are vulnerable to developing Aβ deposition and Alzheimer disease pathology is that, averaged over the course of a lifetime, they are the most synaptically active areas of the brain. Perhaps one of several reasons that education and other cognitive activity is protective against Alzheimer disease is that they result in less activity in these otherwise vulnerable brain regions. This is a hypothesis that can be tested. Although the Aβ microdialysis technique was challenging to develop, particularly in combination with *in vivo* electrophysiology, John Cirrito in my lab has now taught other lab members and other labs this method, and it is proving to be an incredibly useful technique to begin to unravel a variety of key questions in the field of Aβ metabolism.

David M. Holtzman, Washington University School of Medicine

Highly cited research papers on Alzheimer disease published in 2005[a]

Reference	Times cited
Petkova, A.T. *et al.* Self-propagating, molecular-level polymorphism in Alzheimer's β-amyloid fibrils. *Science* **307**, 262–265	59
Cleary, J.P. *et al.* Natural oligomers of the amyloid-β protein specifically disrupt cognitive function. *Nat. Neurosci.* **8**, 79–84	53
Lazarov, O. *et al.* Environmental enrichment reduces Aβ levels and amyloid deposition in transgenic mice. *Cell* **120**, 701–713	37
Stokin, G.B. *et al.* Axonopathy and transport deficits early in the pathogenesis of Alzheimer's disease. *Science* **307**, 1282–1288	36
Yang, F. *et al.* Curcumin inhibits formation of amyloid β oligomers and fibrils, binds plaques, and reduces amyloid *in vivo*. *J. Biol. Chem.* **280**, 5892–5901	31
Billings, L.M. *et al.* Intraneuronal Aβ causes the onset of early Alzheimer's disease-related cognitive deficits in transgenic mice. *Neuron* **45**, 675–688	29
SantaCruz, K. *et al.* Tau suppression in a neurodegenerative mouse model improves memory function. *Science* **309**, 476–481	29
Klyubin, I. *et al.* Amyloid β protein immunotherapy neutralizes Aβ oligomers that disrupt synaptic plasticity *in vivo*. *Nat. Med.* **11**, 556–561	28
Kukar, T. *et al.* Diverse compounds mimic Alzheimer disease-causing mutations by augmenting Aβ42 production. *Nat. Med.* **11**, 545–550	25

[a]Number of citations as of 13 June 2006. Table includes all primary research articles that have the terms 'Alzheimer' or 'Alzheimer's' in their title, abstract or keywords, and that have been cited at least 25 times. Table does not include reviews. Data source: *Scopus*