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PERSPECTIVE

Does synaptic hypometabolism or synaptic dysfunction, originate cognitive loss? Analysis of the evidence

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Abstract

Elderly persons with currently normal cognition who have cerebral hypometabolism as shown by low uptake of ^{18}fluorine-fluorodeoxyglucose (^{18}F-FDG), are at risk of future loss of cognition and, thus, of future Alzheimer's dementia (AD). Reduction of either ^{18}F-FDG or cognition is assumed to reflect synaptic dysfunction, since synapses account for the majority of glucose use by the brain and cognition depends upon accurate synaptic function. The chronology of the connection between reduced cerebral synaptic function and hypometabolism is, therefore, a critical question, because if synaptic dysfunction came first, then correcting the hypometabolism would likely not benefit synaptic function; but if hypometabolism came first, then correcting the hypometabolism probably would benefit synaptic function. That correction might prevent initiation of the cognitive loss that eventuates in AD and, thereby, would benefit the vast numbers of persons in their eighth to tenth decades of life who are at risk for AD. Among the many citations reviewed in this presentation, seven show hypometabolism that precedes synaptic dysfunction, and two show the reverse. Thus the preponderance of evidence, 78%, suggests that the initiating event is synaptic hypometabolism and that it is 3.5-fold less likely that synaptic dysfunction is the initiator. In addition, it is inherently unlikely that synaptic dysfunction causes hypometabolism. This conclusion could be tested by a clinical trial whose primary objective would be to assess the benefit to cognition of improving synaptic metabolism in patients who are at risk for cognitive loss.

KEYWORDS
cognition, elderly persons, ^{18}F-FDG, hypometabolism, initiating cause, prevention, synaptic dysfunction, treatment

1 | INTRODUCTION

It is well-established that in patients with Alzheimer's dementia (AD) there is cerebral hypometabolism as shown by low uptake of ^{18}F-FDG (fluorodeoxyglucose), and that those elderly persons with currently normal cognition who have cerebral hypometabolism are at risk of future loss of cognition and, thus, of future AD. Reduction of either ^{18}F-FDG or cognition is assumed to reflect synaptic dysfunction, since synapses account for the majority of glucose use by the brain and cognition depends upon accurate synaptic function.

The chronology of the connection between reduced cerebral synaptic function and hypometabolism is a critical question, because if synaptic dysfunction came first, then correcting the hypometabolism would likely not benefit cognition. If, to the contrary, hypometabolism came first, then correcting the hypometabolism would probably benefit synaptic function, thus cognition, if directed at a sufficiently early stage. That correction might prevent initiation of the cognitive loss that eventuates in AD and, thereby, would benefit vast numbers of persons in their eighth to tenth decades of life.

One approach to answering this important question was to assess the effect of experimentally caused cerebral lesions upon ^{18}F-FDG uptake.[1–3] However, a lesioned area that has poor local ^{18}F-FDG uptake is hardly a surprising finding, and it is not unexpected that a few months after making those lesions, about 15% of lesioned areas might continue to show low uptake of ^{18}F-FDG. A better approach involves follow-up studies in elderly persons thought to have normal cognition at baseline, although assessing this can be problematic. What is required is to show whether synaptic dysfunction follows or precedes low energy uptake; or, alternatively, do the two events occur in parallel? The following addresses those questions by examining the evidence concerning the chronological connection between glucose uptake as measured by ^{18}F-FDG and cognition.

In each of the following 10 sections different aspects of the problem are tackled. Part of the difficulty in untangling the data lies in the fact that synaptic dysfunction is inferred from a reduction in either cognitive function itself because that depends upon synaptic connections, or upon ^{18}F-FDG uptake because synapses consume the majority of energy used by the brain. Furthermore, many sections are interrelated, which necessitates that studies be mentioned more than once, in which event the reader is referred to a prior section for fuller details. The end of this essay has a summation of the presented evidence, in order to attempt a tentative answer to the question posed by the title.

2 | REVIEW OF THE EVIDENCE

2.1 | Broad background: many studies show a connection between synaptic activity and metabolism, and between hypometabolism and either present or future cognitive loss

Some early studies set the stage. Rangaraju et al demonstrated that at steady state there are $\approx 10^6$ free ATP molecules per nerve terminal but that, despite this large reservoir, action potentials, which require synaptic function, place additional burdens on the presynaptic reservoir.[4] When glycolysis was interrupted by introduction of its inhibitor, 2-deoxyglucose, there was a decline in presynaptic ATP, showing that synaptic formation of ATP requires an adequate rate of glucose consumption. Mosconi et al reported 77 subjects aged 50 to 80 with normal cognition at baseline, who received longitudinal clinical examinations over a mean of 7.3 years per person; all had a baseline FDG-PET scan.[5] Eight years after baseline, six had AD and 19 had MCI. As compared with those who remained cognitively normal, baseline hippocampal cerebral metabolic rate of glucose (CRMglc) in those who had developed AD was 26% reduced ($P = .002$), and was 15% reduced ($P = .01$) in those who had developed mild cognitive impairment (MCI). These effects remained significant after correcting for partial volume effects, showing that the early CMRglc reductions are independent of tissue (ie, mainly neuronal) loss and represent a reduction of glucose consumption, presumably by synapses. Terry et al also described imaging studies that demonstrate decreases in synaptic density in the very earliest stage of preclinical AD when there is not yet dementia.[6] Furthermore, those imaging studies showed a strong correlation ($r = .76$) between results of cognition tests and mid-frontal synaptic density.

A study of 115 subjects by Ng et al involved 60 subjects who were asymptomatic but at risk of AD, 33 with preclinical AD, and 22 healthy controls, all in their mid-70s and with closely similar Mini-Mental State Examination (MMSE) scores.[7] The healthy controls had no amyloid or tau pathology present; those asymptomatic but at risk for AD had either amyloid or tau pathology present; and those with preclinical AD had both amyloid and tau pathologies. By the 2 years of follow-up, those with preclinical AD had developed a mean ^{18}F-FDG uptake in the posterior cingulate cortex that was lower (95% confidence interval [CI]) than the mean for healthy controls.

Two groups of subjects at known risk for cognitive loss provided data that are useful in the present context. They are persons who are currently asymptomatic members of families that have a high rate of AD (ie, familial AD), or are either homozygous or heterozygous for the apolipoprotein E (*APOE*) ε4 gene. In the first such group, asymptomatic carriers of the genetic factor, mutant presenilin-1, were shown to have a synaptic abnormality by Mosconi et al, who applied FDG-PET (positron emission tomography) and magnetic resonance imaging (MRI).[8] The seven at-risk subjects were from three unrelated Italian families, and were examined an average of 13 years prior to the estimated age at disease onset in their affected relatives. The controls were subjects who were matched to at-risk subjects by age, sex, and education; three were siblings of the at-risk individuals but did not carry the genetic mutations, and four were derived from a database of healthy volunteers. The data showed that the medial temporal lobe (MTL) is hypometabolic in presymptomatic Familial Alzheimer's Dementia (FAD), and that CMRglc reductions exceed tissue loss in these individuals. They compared CMRglc and volumes in several brain regions, including the hippocampus, entorhinal cortex (EC), posterior cingulate cortex (PCC), parietal and temporal cortices, and the whole brain, between patients with FAD and the age-matched non-carriers. Whereas volume reductions were seen only in the parietal cortex, CMRglc reductions on FDG-PET were observed in every region examined, and remained significant even after corrections for MRI-observed regional volumes. Volume-corrected CMRglc reductions ranged from 13% (whole brain) to 21% (PCC), reflecting true reductions of brain glucose use per unit of brain volume. CMRglc was reduced 12% in the hippocampus and 20% in the EC. Overall, preclinical, familial AD patients showed generalized and widespread CMRglc reductions in the same brain regions as those that are typically hypometabolic in late-onset AD, and these reductions primarily reflect synapse loss rather than neuron loss.[8] Kennedy et al examined 24 asymptomatic persons

who also were from families with AD; their MMSE scores did not differ significantly from those of 16 age-matched controls, and their global CMRglc was reduced by 12% ($P < .02$).[9]

The second such group of subjects are either homozygous or heterozygous for the *APOE* ε4 gene At the time of their baseline scans, cognitively normal *APOE* ε4 heterozygotes at 20 to 39 years of age and cognitively normal *APOE* ε4 homozygotes and heterozygotes at 50 to 65 years of age were seen by Reiman et al to have abnormally low CMRglc bilaterally in the posterior cingulate, and parietal, temporal, and prefrontal cortex.[10] Among persons who had at least two relatives with AD, Small et al studied 12 with and 19 without *APOE* ε4; all subjects had mild memory complaints but normal cognitive performance in objective tests (but see Section 7 below), and the two groups did not differ in mean age (56.4 vs 55.5 years) or in neuropsychological performance (mean MMSE score, 28.8 vs 29.3).[11] ^{18}F-FDG scans showed that parietal metabolism was significantly lower and left-right parietal asymmetry was significantly higher in at-risk subjects with than in those without *APOE* ε4.

2.2 | A low uptake of FDG reflects subsequent cognitive loss; and an increased uptake occurred reduced cognitive loss

Jagust et al performed ^{18}F-FDG scans in 60 cognitively normal subjects with a mean age 69.5 years, who were followed for a mean of 3.8 years, with approximately annual evaluations of global cognition by MMSE and of episodic memory that was tested by using a 15-word list with 5 learning trials and a delayed recall condition that followed reading a distractor list.[12] Five subjects developed cognitive impairment without dementia and one developed AD. There was a significant association between decline in ^{18}F-FDG uptake and decline in MMSE score ($P < .001$) and a near-significant ($P = .07$) association between decline in ^{18}F-FDG uptake and decline in delayed recall. In the right and left angular gyri, the left mid-temporal and left mid-frontal gyri. Lower glucose metabolism at baseline was associated with faster, future cognitive decline as shown in the results of the MMSE and delayed recall tests. This supports the likelihood that hypometabolism might be the primary event. In a small, 24-week, double-blind, placebo-controlled, randomized clinical trial of memantine, Wang et al observed that those using memantine had less decline in both ^{18}F-FDG uptake and cognition than the controls.[13] Because memantine provides benefits to synapses,[14] these results offer weak support to the possibility that it is hypometabolism that drives synaptic dysfunction and not vice versa.

2.3 | Utilization of glucose by synapses requires transport of glucose into the cell, which is performed by GLUTs and shows that hypometabolism probably precedes synaptic dysfunction

Glucose transporters (GLUTs) move glucose into cells. Of their several isoforms, GLUT1 is present in brain and transports D-glucose, not L-glucose.[15] Cytochalasin B binds to GLUT, and was used by Kalaria and Harik to identify the location of GLUT.[16] They showed that the density of binding sites for GLUT in cerebral microvessels of AD patients was reduced by 52%; hippocampal, temporal cortex, and frontal cortex microvessels were 45% to 57% reduced but in putamen and cerebellum (largely unaffected by AD) there were no reductions. Those data do not untangle whether hypometabolism or cognitive loss comes first, because it is not known whether GLUT binding sites are already reduced in those cognitively normal persons who subsequently develop cognitive loss, or if there is no reduction in those who do not develop cognitive loss. A very small study by Skoog et al (see Section 6 for fuller details) showed that four women with normal cognition but disrupted blood-brain barrier (BBB), later developed AD, which was not the case for three men with normal cognition but disrupted BBB.[17]

2.4 | Uptake of FDG reflects levels of GLUT1

Utilization of glucose by synapses requires transport of glucose into the cell, which is performed in the brain by GLUT1. By using radiogold-labeled nano particles and electron microscopy, Cornford et al showed the deposition of GLUT in the capillary basement membrane.[18] Examining 13 different areas of rat brains, Zeller et al used a specific glut1 antibody, the deposition of which was assessed by an ^{35}S-labeled secondary antibody: and they measured glucose uptake by quantitative autoradiographic 2-deoxyglucose.[19] There was a strong correlation ($r = 0.81$, $P < .01$) between the levels of glut1 and glucose uptake, for the 13 brain regions, confirming their close relationship. Similar studies from the same laboratory showed a close correlation ($r = 0.78$, $P < .01$) between the two isoforms of GLUT (GLUT 1 and GLUT 3) and FDG uptake,[20] although GLUT3 has minor levels in the brain. Several studies show disrupted BBB in AD (for citations see ref[21]). In a study reported by Yang et al, sonification was used to induce disruption of the BBB in rats, which resulted in immediate reduction of FDG uptake and a 44% ($P < .05$) concomitant reduction of GLUT1, indicating a role for the BBB in regulating GLUT1.[22] AD patients having *APOE* ε4 were demonstrated by Montagne et al (see Section 6 for fuller details) to have a leaky BBB and cognitive decline[23] (Montagne EN OK). Together, the above findings show the connections between BBB, GLUT, and FDG (via GLUT).

2.5 | FDG uptake reflects synaptic activity

A measure of synaptic activity is given by the level of synaptophysin, because it is a presynaptic vesicle protein, and its level is related to the number of presynaptic vesicles and their contained neurotransmitter. Because the number of vesicles is related to neurotransmitter release, it is also a measure of synaptic activity. Consequently, synaptophysin levels represent synaptic density. In baboons, Rocher et al investigated the relationships between CMRglc measured by ^{18}F-FDG in the resting state and levels of synaptophysin in seven brain regions.[24] A significant, positive correlation was found between CMRglc values

and synaptophysin levels across the seven analyzed brain regions ($r = 0.61$, $P < 0.0001$). Nudo and Masterson studied the 2-deoxyglucose (2-DG) uptake in the superior olive of the cat's auditory system.[25] Afferents from the ipsilateral ear are stimulatory but from the contralateral ear are inhibitory. Autoradiographs showed clear 2-DG labeling in the vicinity of the activated inhibitory synapses. The medial superior olive was specially prepared so that it could be stimulated antidromically without synaptic activity and without concurrent orthodromic stimulation. The autoradiographs showed only minor (4.2%) elevations in 2-DG labeling of the antidromically stimulated nucleus over its unstimulated contralateral control despite heavy labeling of nearby orthodromically stimulated nuclei. These results show that [^{14}C]2-DG labeling, and by extension ^{18}F-FDG uptake, is evidence of synaptic activity whether excitatory or inhibitory, and that absent ^{18}F-FDG uptake is evidence of absent synaptic activity; one may infer that present but reduced ^{18}F-FDG uptake is evidence of hypometabolism.

2.6 | Disruption of the BBB occurs at baseline in persons who develop subsequent dementia, also in those with current cognitive loss or AD

Skoog et al followed 65 persons who were 85-years-old from a population-based sample, who received neuropsychological tests, a telephone interview by a psychiatrist, and brain computed tomography (CT); 29 had dementia at age 85, and during the next 3 years, 7 others developed dementia.[17] The cerebrospinal fluid (CSF)-to-serum ratio of albumin was used as a measure of BBB function and was 6.5 in the 29 who remained without dementia and 8.3 in the 7 who developed dementia ($P = .065$); three of those seven were men whose ratio was 6.7 ($P = .55$) and four were women whose ratio was 10.4 ($P = .007$). For comparison, the 13 with AD at baseline had a CSF-to-serum ratio of albumin that was 8.9 ($P < .05$). This study showed that in apparently healthy, 85-year-old women, the presence of a disrupted BBB, which reduces GLUT1 and therefore FDG uptake, presages eventual AD. This relates to the present topic because the BBB is the location of GLUT1.

Montagne et al evaluated 146 *APOE4* carriers and *APOE3* homozygotes who had cognitive exams at 2-year intervals up to 4.5 years from baseline, and found that accelerated cognitive decline, even after controlling for amyloid beta (Aβ) and tau status, was correlated with increased activity of the BBB-degrading cyclophilin A-matrix metalloproteinase-9 pathway in cerebrospinal fluid[23]. Their findings suggest that breakdown of the BBB contributes, via reduced GLUT1, to *APOE* ε4–associated cognitive decline independently of AD pathology.

2.7 | Hypometabolism shown by either reduced uptake of FDG or disrupted BBB and reduced GLUT, presages cognitive loss or subsequent AD

As noted in Section 3 above, the glucose transporter GLUT1 is greatly reduced in the cerebral microvessels of the AD brain. A study by Jagust et al (see Section 2 for fuller details) showed a significant association between decline in the baseline ^{18}F-FDG uptake and subsequent decline in MMSE score ($P < .001$) and a near-significant ($P = .07$) association between decline in ^{18}F-FDG uptake and decline in delayed recall, which occurred in 12.7% and the median slope of that decline was −0.13 points/year.[12]

Persons who are currently asymptomatic members of families that have a high rate of AD (ie, familial AD), or who are either homozygous or heterozygous for the *APOE* ε4 gene, provide useful information. In the first such group, Mosconi et al studied at-risk but asymptomatic members of families with genes for mutant presenilin-1 (see Section 1 for details).[8] Their data showed that the pre-symptomatic members of FAD families had generalized and widespread, reduced uptake of FDG in the same brain regions as those that are typically hypometabolic in late-onset AD. In addition, Kennedy et al examined asymptomatic persons from families with AD (see Section 1 for fuller details); their brain uptake of FDG was reduced by 12% ($P < .02$).[9] In the second such group, Reiman et al studied subjects who were either homozygous or heterozygous for the *APOE* ε4 gene (see Section 1 for fuller details) and showed that cognitively normal *APOE* ε4 homozygotes and heterozygotes at 50 to 65 years of age had low FDG uptake in the posterior cingulate, and parietal, temporal, and prefrontal cortex.[10]

2.8 | Caveat: normal FDG uptake at rest may not be normal after stimulation

Glucose utilization that is normal at rest may be revealed as decreased by applying a sensory stimulus. This is shown by reports from Pietrini et al, whose details are worth noting.[26,27] They reported eight younger (mean age = 35 years) and eight older (mean age = 50) healthy, nondemented adults with trisomy 21 (Down syndrome).[26] Older persons with trisomy 21 are at substantial risk of future AD. Levels of general intellectual functioning and compliance were similar in the two groups. At rest, the two groups showed no difference in glucose metabolism in any cerebral region. In contrast, during audiovisual stimulation the older subjects now showed significantly lower glucose metabolic rates in the parietal and temporal cortical areas. In neuropsychological tests, the older subjects also performed less well than the younger ones in all seven tests: the Stanford Binet Intelligence scale, Peabody Picture Vocabulary Test, Down Syndrome Mental Status Examination, Recent Memory Score, Immediate Memory Span Score, Language Score, and Visuospatial Construction Score. A two-sample *t* test comparing all results for each group showed a significant, 16.4% ($P = .0002$), aggregate decrease in the older group. This is instructive because it shows that even though individual scores do not show cognitive impairment, the aggregate of cognitive function test results may do so; and, importantly, a normal uptake of FDG was reduced only after a visual stimulus was introduced. A previous report from the same group had also demonstrated that glucose utilization that is normal at rest may be revealed as decreased by applying a sensory stimulus.[27] In brief, these reports by Pietrini et al serve to remind us of Hippocrates' warning: *δὲ κρίσις χαλεπή* (judgment is difficult).

2.9 | Weak support is gained from subjects who currently have subjective but only minimal objective, memory loss; some had worse loss at follow-up

Of course, if subjects at baseline already have even the mildest degree of cognitive impairment, they are not ideal witnesses. Yet, one might argue, who among the elderly does not have occasional memory lapses or, even, subjective but not objective, memory loss—so, pragmatically, an ideal group of subjects might be unavailable. For this reason, the following reports contribute to the evidence. Some reports showed hypometabolism and memory loss with follow-up data, other reports had no follow-up data. Among persons who had at least two relatives with AD, Small et al studied persons with and without *APOE* ε4; all subjects had mild memory complaints but normal cognitive performance (fuller details are in Section 1).[11] ^{18}F-FDG scans showed that parietal metabolism was significantly lower in the *APOE* ε4+ than in the *APOE* ε4− subjects. Haxby et al provided results from 10 persons with mild AD who differed from age-matched controls only on tests of memory but did not differ from controls on any test of non-memory language and visuospatial functions.[28] They had significant reductions in ^{18}F-FDG uptake in the parietal cortex. Hunt et al measured ^{18}F-FDG in patients with "aging-associated cognitive decline," who also had significantly reduced glucose metabolism in various brain areas; those who subsequently converted to AD showed more extended changes.[29] Giordani et al also reported 10 subjects, who had isolated memory impairment and baseline reduction of ^{18}F-FDG uptake in the parietal cortex; 7 of the 10 converted to AD over the following 3 years.[30] Nestor et al described 10 subjects, mean age 63.3 years, with a mean MMSE score of 28.4.[31] The cases had memory complaints of insidious onset and neuropsychological testing showed delayed recall that was ≥1.5 standard deviation (SD) below the mean for elderly controls but they did not have impaired attention, visuospatial, semantic, or executive function. All 10 cases had retrosplenial hypometabolism in the ^{18}F-FDG scans. During the 19.3 months of follow-up, their MMSE mean score fell to 26, and two cases developed AD.

2.10 | Glut1 is localized to the blood brain barrier (BBB); its level falls when the BBB is disrupted but may be regulated by an uncertain component present in brain that is yet to be identified

Partridge et al prepared the BBB membranes from bovine brain microvessels and a second preparation containing membranes that were microvessel-depleted.[32] The microvessel-depleted preparation would have contained membranes from glial cells but not from endothelial cells. They then used probes corresponding to nucleotides 385-932 of GLUT-1 cDNA, and showed that hybridization occurred over the microvascular endothelium but not over the synaptosomal membranes that excluded endothelial cells but included glial cells. Thus they concluded that there was no expression of GLUT-1 in glial cells. Boado et al noted that GLUT-1 is down-regulated in cultured bovine brain capillary endothelial cells, but a bovine brain homogenate induced a significant increase in their GLUT-1 levels.[33] Knowing the component(s) that regulated that increase might identify therapy that would address the cause of hypometabolism, which is the focus of this essay. The candidates for the component(s) include connexins, which influence gap junction channels that enable direct cell-cell transfer of metabolic, biochemical, and electric signals.[34] In addition, beyond their role in direct intercellular communication, connexins also form unapposed, non-junctional hemichannels in the plasma membrane that allow the passage of several paracrine messengers, complementing direct gap-junction communication. Connexins are expressed in vascular endothelial cells, including those that form the BBB, and are present in astrocytes, especially at their end-foot processes that wrap around cerebral microvessels. The extracellular matrix is another brain component that may be involved, because extracellular matrix from both astrocytes and pericytes, improved the appositional tightness of cerebral endothelial cells,[35] and astrocytes have long been considered as a source of BBB-inducing signals.[36] Other contributors might include pericytes, which are necessary for the formation and regulation of the BBB[23]; and it is also possible that, to some extent, all cells of the neurovascular unit contribute to the maintenance of the BBB.

3 | SUMMATION OF THE EVIDENCE

3.1 | Hypometabolism precedes synaptic dysfunction

From Section 1. With normal cognition at baseline, after 8 years, 6 had AD and 19 had MCI. As compared with those who remained cognitively normal, baseline hippocampal CMRglc in those who had developed AD was 26% reduced ($P = .002$), and was 15% reduced ($P = .01$) in those who had developed MCI.[5] Overall, preclinical, familial AD patients showed generalized and widespread CMRglc reductions in the same brain regions as those that are typically hypometabolic in late onset AD, and these reductions primarily reflect synapse loss rather than neuron loss.[8] In asymptomatic persons from families with AD who had MMSE scores that were not significantly different from those of age-matched controls, their global CMRglc was reduced by 12% (($P < .02$).[9] Cognitively normal *APOE* ε4 homozygotes and heterozygotes at 50 to 65 years of age had abnormally low CMRglc bilaterally in the posterior cingulate, and parietal, temporal, and prefrontal cortex.[10]

From Section 2. Lower glucose metabolism at baseline was associated with faster, future cognitive decline as shown in the results of the MMSE and delayed recall tests.[12]

From Section 3. Four women with normal cognition but disrupted BBB (implying low GLUT1, thus reduced uptake of FDG), later developed AD.[17]

From Section 5. [^{14}C]2-DG labeling, and by extension ^{18}F-FDG uptake, is evidence of synaptic activity whether excitatory or inhibitory; so, absent ^{18}F-FDG uptake is evidence of absent synaptic activity. One may infer that present but reduced ^{18}F-FDG uptake is evidence of hypometabolism affecting synaptic activity.[25]

3.2 | Synaptic dysfunction precedes hypometabolism

From Section 1. At 2 years of follow-up, those with preclinical AD had developed a mean ^{18}F-FDG uptake in the posterior cingulate cortex that was lower (95% CI) than the mean for healthy controls.[7]

From Section 2. Those using memantine had less decline in both ^{18}F-FDG uptake and cognition than the controls; because memantine provides benefits to synapses, these results offer some support to the possibility that it is synaptic dysfunction that drives hypometabolism and not vice versa.[13]

4 | CONCLUSIONS

For the above summation, results from nine reports were selected from among the 36 listed citations as showing findings that provide the best evidence regarding the question posed by this essay. Seven of these favor synaptic hypometabolism as preceding synaptic dysfunction. Thus the weight of evidence, 78%, suggests that the initiating event is synaptic hypometabolism and that it is 3.5-fold less likely that synaptic dysfunction is the initiator. This conclusion could be tested by a clinical trial whose primary objective would be to assess the benefit to cognition, of improving synaptic metabolism in subjects at risk for cognitive loss.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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