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Fact, Fiction, or Evolution: Mechanism Hypothesis of Alzheimer's Disease

José V. Pardo

Abstract

The metabolism hypothesis of Alzheimer's disease (AD) was first proposed in 1975. In normal aging and very mild AD, the cerebral metabolic rate for oxygen (CMRO2) and cerebral blood flow (CBF) remained approximately constant, but the metabolism of glucose (CMRglu) declined markedly. This decline in CMRglu identified a specific and primary metabolic defect that triggered downstream cellular cascades evolving into AD and its characteristic neuropathological lesions. These findings led research about AD into the role of insulin resistance that foresaw modern trials of insulin for AD treatment. The metabolism hypothesis evolved over subsequent decades with improved in-vivo measurement of metabolic parameters and AD biomarkers in humans. A more recent model highlights the interrelationships between the default mode network (DMN) and biomarkers such as CMRglu, amyloid, and tau. In other words, metabolic conditions related to sustained cortical activity during aging throughout the lifetime are conducive to the deposition of amyloid. This activity is thought to underlie the "autobiographical self." These ideas and findings motivate aging and AD-research focus on the biochemistry and cell biology of cerebral metabolism.

Keywords: dementia, amyloid, tau, cerebral metabolism, default mode networks, cerebral energetics, aerobic glycolysis, cognitive aging, functional connectivity

1. Introduction

Hoyer et al. proposed the metabolism hypothesis of AD based on observations of normal aging and early AD focusing on the relationships between CMRglu, CMRO, and CBF [1–3]. This hypothesis has both weak and strong versions. The weak version, not of interest here, suggests that amyloid deposition is an epiphenomenon, potentially unrelated to AD; the causative pathophysiology must lay elsewhere—perhaps a primary mitochondrial failure. The more interesting hypothesis relies on a stronger version: neural activity sustained during resting and introspection (i.e., wakefulness [4]) over a lifetime (i.e., the "autobiographical self") drives AD pathology.

A more recent model of the strong version posited sustained metabolic activity in the default mode network (DMN) is a substrate for amyloid deposition through the mediation of some process related to neural activity [5]. CMRglu declined with aging. Since oxidative metabolism was largely preserved, a primary abnormality in

the handling of glucose was posited with the observation that aerobic glycolysis (AG) declined precipitously during normal aging [6, 7]. Concomitantly, molecular imaging of critical biomarkers in AD identified for the first time the distribution of proteins such as fibrillar amyloid and tau in the brain, both in asymptomatic healthy elderly and in patients with various neurodegenerative disorders including AD [8–10].

Such progress led to the definition and characterization of preclinical and clinical AD based on biomarkers for staging [11–14]. To understand the pathophysiology of the hypothesized metabolic dysfunction, understanding the relationships between brain metabolism and these neuropathological biomarkers became critical during both normal aging and AD. These advances detail the evolution of imaging biomarkers along with their relationship to the brain's structural, metabolic, and cognitive dysfunction.

Here, recent findings relevant to aging and AD are reviewed briefly as background. Current understanding of the development and ontogenesis of biomarkers for AD are summarized. Data are integrated with advances in neuroimaging and brain metabolism as well as in preclinical models mostly focusing on the resting state. These results bear on the metabolism hypothesis of AD. Notable gaps in this hypothesis and its relationship to cognitive aging highlight avenues requiring further research for progress in the field.

2. Amyloid and tau in aging and AD

Several studies of patients developing dementia (both early and late-onset sporadic AD; familial AD) as well as Down's syndrome show amyloid deposition begins decades before overt symptoms of dementia arise [11, 15, 16]. Amyloid deposition of plaques, particularly the diffuse type, in AD begins in inferior neocortex with spread to other neocortical regions including precuneus, lateral parietal, and frontal association neocortices [17, 18]. Amyloid positivity predicts past and future progressive cognitive decline [19]. Glucose metabolism tends to decline where amyloid localizes; it is first seen in preclinical AD, mild cognitive impairment (MCI), and early AD using fluorodeoxyglucose (FDG) positron emission tomography (PET) in the posterior cingulate cortex (PCC) followed by biparietal involvement [20–22]. The steepest increases in amyloid deposition during healthy aging according to amyloid PET, thought to measure fibrillar amyloid or neuritic plaques, occurs in anterior cingulate cortex (ACC), PCC, precuneus, and temporal cortices [23]. The earliest detectable amyloid deposits by PET localize to precuneus, PCC, and medial orbitofrontal cortex; these deposits were not associated with atrophy or hypometabolism despite changes in functional connectivity [24].

Although there is some overlap between amyloid deposition and cortical hypometabolism [22], other factors such as APOE genotype and tau deposition affect the distribution of amyloid. Whole-brain amyloid positivity appears a greater determinant of gross cognitive dysfunction compared to the precise areal distribution; however, measures of non-crystallized intelligence (e.g., executive functions, reasoning, problem solving) are sensitive to the amount deposited [19]. It is not unusual to find a dissociation between amyloid deposition and metabolic hypometabolism or between amyloid deposition and cortical thinning [25–27]. As discussed below (Section 6.1), while clinically normal elders can show significant correlation between thinning and amyloid deposition in the PCC, they do not show a significant association between these biomarkers in the ACC [28]. Amyloid deposition although predictive of future cognitive decline correlates poorly with actual cognitive status: the number of neurofibrillary tangles (NFTs), not senile amyloid plaques, correlates with cognitive status before death [29]. Classically, amyloid

is necessary but not sufficient for the diagnosis of AD; tau with neurofibrillary changes is also required [30, 31]. However, over one-third of patients with clinically diagnosed mild to moderate AD who do not carry an APOE4 allele show minimal amyloid yet extensive neurofibrillary degeneration on autopsy [32]. Whether this group is pathophysiologically an AD variant or a tauopathy remains unclear [32, 33].

Deposits of tau generally follow amyloid. Immunohistochemical studies of tau and neuroimaging of humans using tau radiotracers converge on tau's more restricted involvement in the temporal lobe in early AD [17, 34, 35]. Tau does not follow the global miliary pattern of amyloid neocortical involvement with disease progression. Tau's presence more directly correlates with cognitive dysfunction and cortical thinning than does amyloid [14, 36]. These changes reflect presumably the final stages of neurodegeneration. Unlike amyloid deposition, the localization of tau mirrors the clinical and neuroanatomical phenotypic variability of AD [37, 38]. Longitudinal data of both amyloid and tau have enabled assessment of directionality of biomarker spread as well as potential relationships with gene expression [39]. APOE played a central role in the lipid interactome affecting both Aß and tau spread, while tau- and Aß-risk genes differentially contributed to the specific spread of each biomarker.

3. The default mode network (DMN)

The distribution of amyloid has been noted to overlap with the neural system related to the default mode of brain function [5]. The observation has prompted hypotheses about the relationship of neural activity, the default mode network, and AD that continue to evolve.

PET studies have shown a broad region of relative deactivation in resting states compared to active states with greatest deactivation within the ventromedial prefrontal cortex (VMPFC) with peak minimum at Brodmann area 10 (BA10; **Figure 1**) [40]. Additional regions showing deactivations localized bilaterally to the inferior and superior frontal cortex, PCC/precuneus, prefrontal cortex, inferior parietal cortex, and several temporal areas.

The deactivation in the VMPFC during rest was shown not to reflect a relative activation as the OEF did not change significantly from whole-brain (e.g., **Figure 1**;
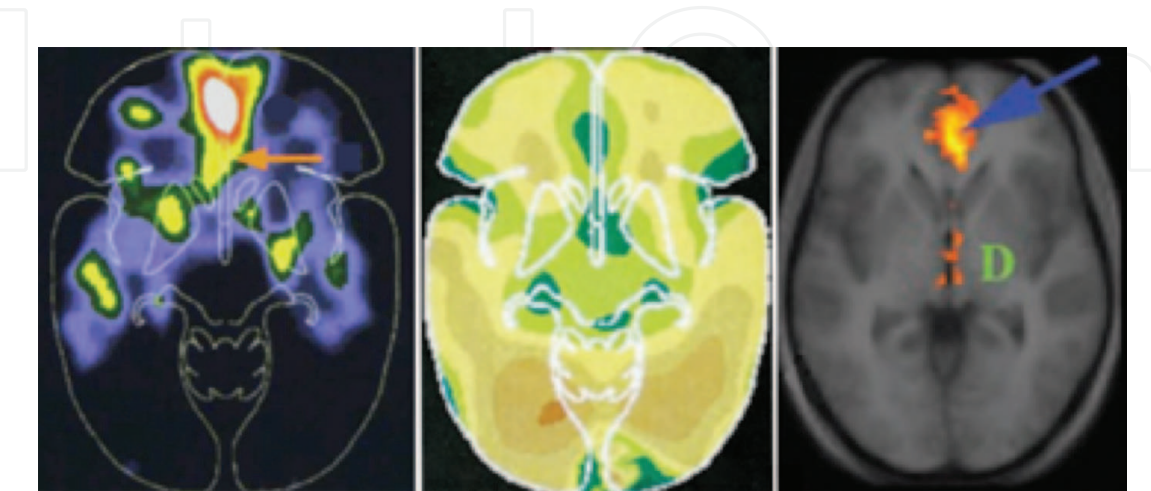
Figure 1.
Transverse sections (z = −6) of stereotactically normalized parametric data showing convergence across studies between CBF change and FC as well as relative stability of OEF. Left: Region of common relative CBF deactivation (VMPFC) in mega image contrast between active scans and passive scans (peak Z-score − 7.7; modified from [40]); middle: Default mode oxygen extraction fraction during rest with eyes closed; uniform OEF; no OEF increase in VMPFC [41]. Right: Resting state FC of the VMPFC with the DMN [49]. Middle & left: Copyright (2003) National Academy of Sciences, U.S.A.

Raichle et al. [41]). If the VMPFC were activated, it should show increased OEF (as some regions in the visual cortices, see red color). The activated network during passive tasks was hypothesized instead to reflect a return to baseline or default mode network (DMN) that was interrupted by active tasks. The regional specificity of the DMN suggested some ill-defined brain function.

The DMN can be detected even in the presence of deep anesthesia suggesting a degree of invariance with respect to consciousness possibly reflecting intrinsic brain organization such as anatomical connectivity [42]. The VMPFC becomes more active not only at rest relative to other active task states (e.g., attentional) but also during a variety of other conditions where attention is directed away from the external environment. Such states include introspection, "mind wandering" [43], self-appraisal or introspection [44], stimulus independent thought [45], episodic future simulation, trait emotional self-awareness [46], and interoceptive tasks (e.g., recall of visceral information) [47]. As this book notes, these are reflections of the "autobiographical self."

Previous work in the mid to late 1990s observed physiological fluctuations occurring during active states and even during rest in the MR blood oxygen level dependent (BOLD) signal in humans and in CBF in rodents that were correlated at low frequency (0.1 Hz) across regions known to have anatomical and functional relatedness [48]. However, it remained unclear how these temporal signals related to the DMN as defined from PET studies.

Remarkably, when the VMPFC region in the DMN (showing relative deactivation during active tasks using PET) was used as a seed region to correlate BOLD signals throughout the brain, a network surface based on interregional temporal coherence of the BOLD MR signal that was visually superimposable on the DMN. Use of a spiral MR pulse sequence avoiding signal dropout in ventral prefrontal regions enabled good signal recovery within VMPFC (**Figure 1** [49]). Subsequent fMRI studies examining resting state networks displayed a more variable pattern in the medial prefrontal regions frequently showing more dorsal localization [50–52]. The significance of this disparity is unclear but may relate to low signal recovery with fMRI in ventral brain regions or other subnetworks (see below).

The analysis of BOLD data from the resting state using independent component analysis of FC identified numerous subnetworks showing both anatomical (known afferent and efferent anatomical projections) and functional (coactivation during tasks) architecture converging with other datasets (**Figure 2**) [53]. The four principal RSNs are the dorsal attention network (DAN), DMN (as above), salience network (SAL; also termed cingulo-opercular), and bilateral frontoparietal control network (FPC). The latter is sometimes segmented to dorsal and ventral systems [54].

The precise components of these RSNs need further refinement. For example, how does the "anterior medial prefrontal cortex" relate to VMPFC, pgACC, dACC, and medial superior frontal gyrus? What elementary cognitive operations do these different areas serve? Similarly, how does the "PCC/precuneus" relate to the various medial parietal subregions, and what functions do they serve? In this regard, preliminary dissection divides the PCC into dorsal and ventral regions, each with two additional subregions that in turn connect with other differing cortical projection regions [55].

These four major networks based on data averaged across individuals only hint at the complexity on a more fine-grained analysis. ICA can produce many more networks, and the Human Connectome Project points to 180 parcels per hemisphere [56]. When resting BOLD is collected over many hours for one individual, much more complex, interdigitated, parallel, distributed networks become apparent without the blurring caused by inter-subject averaging [57].
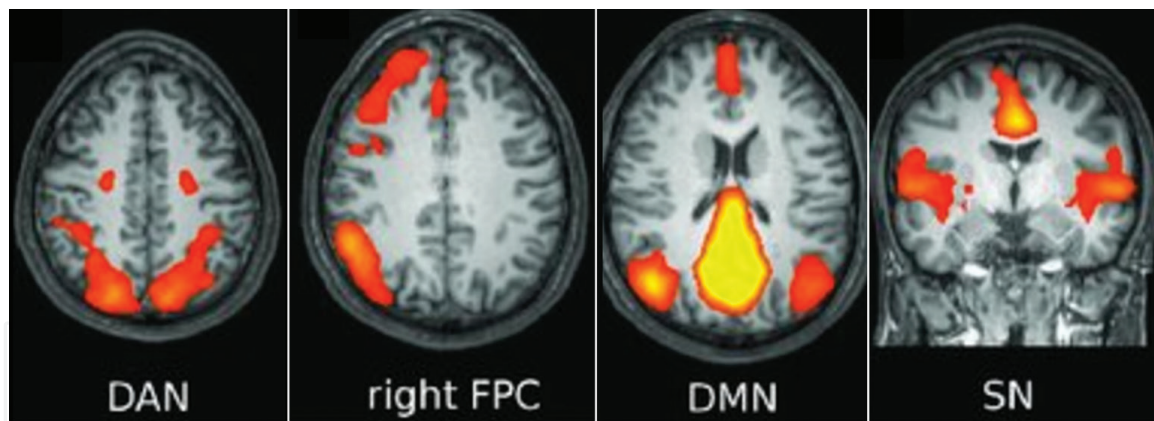
Figure 2.
Four major RSNs revealed by ICA: DAN, dorsal attention network; DMN, default mode network; SN, salience network (also called cingulo-opercular network); right FPC, frontoparietal control network. Modified from [54].

Data on the effects of aging and amyloid/tau deposition on these subnetworks continue to accrue, but there appears differential vulnerability of different subnetworks. For example, amyloid decreased the FC of the DMN subnetworks relevant to episodic memory (PCC, angular gyrus, VMPFC) while increasing FC in dorsolateral and anterior medial prefrontal cortices as well as lateral temporal regions [58]. The latter regions were interpreted as reflecting compensatory responses to the amyloid-related dysfunction in the memory subnetworks. Furthermore, the mere presence of biomarkers such as amyloid in preclinical AD can confound FC findings within and across RSNs. Cognitively normal subjects without vs. with amyloid positivity show small vs. large age-related changes in RSN functional, respectively [59].

The DMN shares considerable connectivity with the hippocampus [60, 61]. The DMN couples with different sectors of the hippocampus [62] through the parahippocampal gyrus depending on task context during rest [63]; spontaneous, unconstrained thought (e.g., thinking about one's past or future [64]); episodic memory retrieval [65]; and associative episodic memory encoding [63]. This network becomes disrupted early occurring both in preclinical and early AD (see Section 6, below) [60, 66].

4. Cerebral energetics

The energetic balance sheet indicates a large part of oxidative metabolism maintains the resting state [67–69]. The classic work of Seymour Kety showed oxygen consumption in the brain differed little across a wide variety of abnormal mental states such as in psychosis, whether in schizophrenic decompensation or acute drug intoxication [70]. In response to external stimulation, the brain only increases oxygen consumption by 5% [71]. Similarly, few differences in oxygen consumption occur between sleep vs. wakefulness [72]. Although the bulk of brain work at rest and on activation derives from oxidative phosphorylation [71], the metabolism hypothesis of AD focuses on a specific metabolic pathway: AG (i.e., glycolysis in the presence of adequate levels of oxygen; i.e., nonoxidative metabolism of glucose [73]).

Regions high in oxidative phosphorylation do not necessarily have high rates of AG. As an example, the visual cortex has very high glucose metabolism; high cerebral blood flow (CBF); high oxidative metabolism (cerebral metabolic rate for oxygen) with high levels of cytochrome oxidase; but low AG [73]. The focus on AG follows from the visual cortex having relative resistance to amyloid deposition and being one of the regions showing little decrease in metabolism with aging. In contrast, the PCC has high flow, oxidative metabolism, glucose metabolism, and high

AG [73]. As summarized above, the PCC is very susceptible to amyloid deposition and is among the earliest dysfunctional regions in AD. These observations further refined the metabolism hypothesis of AD.

In a group of mostly cognitively intact elders, those globally without amyloid did not have tau accumulation in areas prone toward tau deposits (precuneus, amygdala, entorhinal, inferior temporal, inferior and superior parietal, fusiform, and lateral occipital cortices) and did not have decreased CMRO or AG [69]. They showed a positive correlation between AG and CMRglu; no correlations surfaced between CMRO, CMRglu, or tau deposition. In contrast, those who were amyloid positive globally showed an inverse relationship between tau and AG but not between tau and CMRO or CMRglu. These data suggest the loss of AG in tau-prone regions with tau accumulation leads to decreased plasticity and decreased neuroprotection (i.e., decreased redox buffering) leading to accelerated tauopathy.

5. Role of DMN and amyloid

The default network shows overlap with brain regions high in AG which in turn show overlap with areas of amyloid deposition in AD [74]. Unlike oxidative phosphorylation used to generate energy, AG proceeds less efficiently energetically (2 ATP vs. 38 ATP per glucose molecule) but more suitably for reduction of biomolecules for anabolism [75]. Anabolism that appears to play a much greater role in early human development could also provide, albeit to a lesser extent, the substrates for plasticity related to learning and memory in adults [76, 77]. The metabolism hypothesis is important because it motivates the search for AD pathophysiology beyond amyloid deposition to some aspect of cerebral metabolism particularly AG. Normal aging is associated with the loss of AG in regions which sustain higher levels of AG in youth; these are the very regions showing susceptibility to amyloid deposition [7]. The metabolism hypothesis could help explain why the frequency of AD rises relentlessly with aging and oxidative stress.

Several lines of evidence support the metabolism hypothesis of AD through altered processing of Aß [78]. The processing pathways include both increased production and decreased clearance. Most AD-causing dominant mutations in APP, PSEN1, and PSEN2 increase Aß production [79]. One mutation that is protective for AD occurs near the APP BACE1 cleavage site impairing γ cleavage; it is associated in vitro with decreased amyloidogenic peptides [80]. Likewise, vibrissal stimulation of APP transgenic mice increases Aß in interstitial CSF and amyloid plaques while decreasing lactate, a proxy for neural activity [81]. In-vitro mouse slice preparations show based on microdialysis rapid increases in Aß correlated with synaptic activity [82]. In cognitively normal older adults, greater hippocampal activity during encoding at baseline correlates with longitudinal amyloid deposition and diminished cognitive performance [83]. APOE, the major risk locus for AD, plays a key role in Aß aggregation, fibrillogenesis, and maturation of neuritic plaques [84]. AD patients relative to controls have decreased clearance of CSF Aß with normal rate of Aß production [85].

6. Gaps in the metabolism hypothesis

Here, issues informing discussions about the amyloid hypothesis of AD and relationships to cerebral metabolism are outlined. These raise questions about the strong version of the metabolism hypothesis and its implications, or at least suggest a need for revision. Significant circumstantial evidence centers on several

observations: (1) normal cognitive aging; (2) familial AD; (3) healthy individuals at very high risk of AD (*APOE*E4* homozygotes); (4) the evolving role of tau in AD; (5) interrelationships between amyloid and tau in AD pathology; and (6) the implications for cognitive function in "real time."

6.1 The metabolism hypothesis and cognitive aging

The metabolism hypothesis suggests that if chronically elevated levels of resting brain activity over the lifetime drive Aß deposition with attendant cognitive dysfunction leading to AD, there should be amyloid deposition during healthy aging as well. Based on this mechanism, the PCC region should show major hypometabolism, atrophy, and amyloid deposition as seen in early AD [21, 86–88].

Yet, this phenomenon is not observed. The PCC in normal aging shows relative preservation (**Figure 3**). Among the regions showing the least decline in metabolism with aging is the PCC. Older healthy adults show minimal PCC atrophy rates over 12 months [89]. Older healthy adults, especially E4 non-carriers, do not show amyloid deposition in the PCC [90–92]. Young adult E4 carriers with positive family history of AD and at high risk of future AD already show PCC hypometabolism implying DMN hyperactivity related to AD must have occurred before then [93]. Of note, older healthy E4 non-carriers begin to show amyloid positivity at around 71 years of age, while the E4 carriers develop amyloid positivity about 20 years earlier. Interestingly, when separating the independent effects of aging vs. E4 load, amyloid deposition shows a more frontal involvement. Of note, the effects of aging and E4 load interact: the peak hazard ratio occurs ~60 years of age and declines thereafter; E4 is a risk factor for AD even for younger adults (<65 years) [94]. Furthermore, resting connectivity of the PCC/precuneus region to the ACC is reduced in older healthy adults who carry E4 even in the absence of detectable fibrillar amyloid or decreased CSF Aß42 suggesting both Aß-dependent and Aß-independent aging-related mechanisms [95].

The principal locus of declining metabolism in healthy elders does not map to the PCC but localizes instead to the ACC (**Figure 3**) [96–101]. ACC hypometabolism correlates also with aging-related decline in cognitive function [99]. Whereas
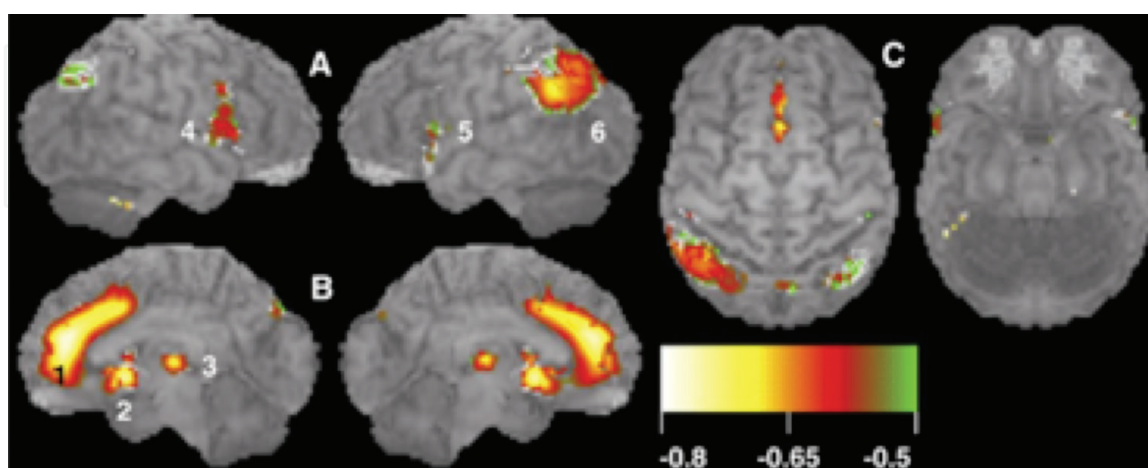
Figure 3.
Decline of brain activity with aging in healthy volunteers. Voxel-wise Pearson correlation (r) map of glucose uptake vs. age in stereotactically normalized brain (3D-SSP; S. Minoshima, University of Utah). A, lateral; B, medial; C, dorsal (left)/ventral (right). Color scale shows peak r = −0.8. Note the greatest decline in glucose uptake with age localizes to the ACC (BA 32/9; region 1). A midline circuit (regions 1-3) includes dorsomedial thalamus and basal forebrain/subgenual cingulate; the metabolism in this circuit correlates with declining executive function (verbal fluency). Other regions with lower correlations are not associated with cognitive performance. Reprinted from Neuroimage, Vol 35(3), Pardo JV et al., Where the brain grows old: Decline in anterior cingulate and medial prefrontal function with normal aging. Copyright (2007), with permission from Elsevier.

AG localizes to ACC, PCC, and parietal regions, loss of regions high in AG during youth appears to occur in all three regions without selectivity for any one of these regions [76]. So, unless AD per se involves hyperactivity of the DMN beyond that in normal elders for which there is no evidence, the hypothesis does not address the inconsistency between mechanisms of cognitive aging versus AD to account for the observed dissociation between ACC and PCC findings.

Several observations related to cognitive aging need reconciliation with the metabolism hypothesis. Healthy elders free from amyloid deposition show a remarkable disconnection between the anterior and posterior default networks (i.e., ACC and PCC) [102]. Yet, nothing about the metabolism hypothesis explains why DMN regions with high AG, where amyloid will be deposited as AD develops, should disconnect—both regions should show aging-related hypometabolism as a result of white matter damage. Similarly, cognitively normal elders not at high risk for AD (no E4) show increases and decreases within anterior DMN connectivity, while showing only decreases in posterior DMN FC [103]. Cognitively intact elders with minimal amyloid deposition without E4 have greater connectivity of the ACC to the precuneus than those with E4 [95]. The aging-related anterior vs. posterior dissociations in connectivity within DMN networks remain theoretically difficult to predict based solely on the metabolism hypothesis.

The ACC also has high glucose metabolism, flow, oxygen consumption, and AG; yet, the ACC does not show amyloid deposition akin to the PCC with healthy aging (those >60 years without amyloid positive scans [23]). Thus, chronic neural activity along with AG during the lifespan per se is not sufficient to lay down amyloid. Just as PCC hypometabolism marks focal atrophy early in AD, the region of ACC hypometabolism with aging should likewise display cortical thinning. However, several large studies do not support the prediction [104, 105], although not all findings are convergent [106]. Additionally, recent studies of tau deposition in preclinical AD show early deposition in the PCC but not in the ACC [107]. Those elders with cognitive function akin to much younger subjects (i.e., "SuperAgers") show thickening of the ACC and increased spindle cells suggestive of plasticity with aging; or alternatively, "SuperAgers" may be endowed with ACC thickening before aging [108, 109]. Also, age can confound years of education; the latter is associated with increased ACC thickness and metabolism [110, 111]. However, studies of the effects of aerobic fitness exercise on cognition and cortex show ACC thickening in older adults in support of the potential for plasticity in this region [112].

A clear dissociation can arise also between amyloid deposition and FDG metabolism in the ACC in AD that is difficult to explain with the metabolism hypothesis. Patients who initially had mild AD, as confirmed with metabolic and amyloid biomarkers, were followed for 2 years along with a matched, amyloid negative control group. Despite extensive amyloid deposition in the ACC of the AD patients, no hypometabolism colocalized in the ACC during follow-up [22]. The aging-related ACC hypometabolism noted previously likely led to a floor effect across groups. Likewise, aging-related ACC hypometabolism would tend to spare amyloid deposition in patients appearing inconsistent with the metabolism hypothesis given extensive amyloid involvement of the ACC in AD.

6.2 The metabolism hypothesis and autosomal dominant AD

A corollary of the metabolism hypothesis suggests those with familial AD would show similar patterns of hypometabolism and amyloid deposition to late-onset, sporadic AD. However, those with mutations (APP, PSEN1, PSEN2) show greatest amyloid deposition in the basal ganglia, a site that only becomes involved late in typical sporadic AD [113–115]. However, the specific pattern of

amyloid deposition may depend to some extent on the specific mutation. For example, the PS1 mutation, E280A, shows amyloid deposition more like late-onset sporadic AD than many other mutations with early onset. This variability may not surprise given the complexity of the underlying biology of different mutations in PS1 [116].

6.3 Role of APOE genotype in the metabolism hypothesis

If regional brain activity drives amyloid deposition in the pattern seen in AD, then the AD metabolic pattern should arise in those at highest risk for the future development of AD—asymptomatic *APOE*E4* homozygotes, who have a 12-fold increased risk of LOAD. So far, there are seven such individuals in the Alzheimer's Disease Neuroimaging Initiative's (ADNI) database. Their pattern of amyloid deposition highlights bilateral lenticular nuclei and the ACC/medial prefrontal involvement with the PCC notably unaffected (see **Figure 3**). In fact, the deposition of amyloid in the homozygotes is reminiscent of that seen in Down's syndrome and most mutations found in autosomal dominantly inherited forms of AD arising in APP, PS1, or PS2 [113–115, 117]. This pattern of amyloid deposition in E4 homozygotes is consistent with findings reported previously in an independent group of eight homozygotes [91].

6.4 Role of tau in the metabolism hypothesis

Another difficulty with the metabolism hypothesis of AD is the notable absence of tau involvement in this theory. The role of tau, its modifications, and its etiologic role in neurodegeneration in AD has been reviewed previously [118]. Although the metabolism hypothesis of AD focuses on amyloid deposition, there is increasing evidence that tau plays at least as great if not greater etiopathological role. Of interest in this context, recent studies show tau deposition during preclinical AD in the PCC; the metabolism hypothesis cannot explain this dissociation between PCC and ACC [107].

AD cases with neurofibrillary changes (neuritic plaques, neurofibrillary tangles, neurofibrillary threads, tau tangles) typically show extensive amyloid deposition. However, not all cases with extensive amyloid deposition show neurofibrillary changes [17]. Amyloid deposits and neuritic plaques vary widely across individuals both temporally and regionally; so, they do not provide useful biomarkers for staging of AD [17]. In contrast, the distribution of tau is consistent across individuals and provides useful staging of disease progression [17].

Hyper-phosphorylated intraneuronal tau ("pretangle") has been reported even in young adults in the absence of amyloid particularly in subcortical nuclei such as the locus coeruleus [119]. The significance of these findings in the context of AD remains uncertain as the pretangle material may be transient, related incidentally to other processes (e.g., traumatic brain injury), or the earliest manifestations of AD. Furthermore, studies of transgenic mice with APOE isoform knock-in and APOE knock-out show that even in the absence of amyloid, E4 is particularly neurotoxic in mice with mutant tau transgenes, and this toxicity is in part mediated by neuroinflammation via the innate immune system produced by microglia and type A1 astrocytes [120].

A recent study identified the significant role of tau in the context of amyloid deposition [121]. High resolution fMRI of cerebral blood volume (CBV), coupled to regional metabolism, mapped the earliest changes in preclinical AD to lateral entorhinal (LEC), transentorhinal, and perirhinal cortices, as predicted from neuropathological studies [17]. The former region's CBV correlated significantly with a test of delayed retention. Three lines of mice were generated with differential expression in entorhinal cortex of pathological human APP, tau, or both transgenes.

Mice with mutant entorhinal tau alone, but not mutant APP alone, had diminished CBV in LEC with aging [121]. The double mutant had decreased LEC CBV with aging compared to the single mutants and other controls thereby demonstrating that APP increased tau-related metabolic dysfunction. Decreased CBV in aged double mutant spread even to posterior parietal cortex, a pattern reminiscent of human AD. APP immunohistochemistry of older mice showed no changes between mutant APP and double mutant mice; the label localized mostly to entorhinal cortex. However, tau immunohistochemistry of older mice showed increased signal in the double mutants with the suggestion of relocalization of phospho-tau from neuropil to the somatodendritic compartment.

The differing roles of amyloid and tau in the evolution of AD were recently highlighted in cognitively intact elders [58]. Those positive for amyloid (Aß+) showed hyperconnectivity within DMN and SN when tau deposits were low. In contrast, the Aß + subjects showed decreased FC with increasing tau deposition. Thus, the effects of PET biomarkers on FC appear complex and likely involve multiple neuropathological processes.

These data make clear that tau cannot be ignored in understanding the ontogenesis of AD. The metabolism hypothesis needs modification for relevance beyond amyloid deposition to AD pathophysiology.

6.5 Cognitive processing in "real time"

The biomarkers discussed so far are not dynamic in terms of real time. These scans, even when measured during rest, probe parameters over many minutes—totally divorced from cognitive processes that occur at the scale of milliseconds to seconds. Recent studies hint that the metabolism hypothesis has relevance to the latter time scale.

As mentioned in Section 5, lactate is a proxy for neural activation and through regulation of NADH/NAD$^+$ becomes a modulator of rCBF in response to activation [122]. Astrocytes on activation show a metabolic switch toward AG shifting oxygenation from astrocytes to neurons [123]. In turn, lactate produced through AG is critical for memory formation [124]. Because AG can provide reducing equivalents for biosynthesis of macromolecules for plasticity, learning tasks demonstrate focal increases in AG on-line with experience-dependent plasticity [77]. The elevation in AG can persist for many minutes after an activation task [125]. How amyloid impacts real-time learning through changes in AG remains to be elucidated.

Preliminary studies have examined using magnetoencephalography (MEG) oscillatory power in real time in cognitively normal elders either with amyloid deposition ("preclinical AD") or without amyloid deposition [126]. Increases in power in the alpha range in the amyloid-positive preclinical cases at rest localized over the ACC and correlated with increased glucose metabolism. These metabolic changes did not yet correlate with structural atrophy or cognitive decline. The findings begin to define the earliest on-line physiological changes in preclinical AD. Similarly, increased functional connectivity at rest localized to the ACC. Proposed hypotheses include cognitive compensation (i.e., cognitive reserve) or amyloid-related hyper-excitability in preclinical AD [58, 127].

7. Concluding remarks about the metabolism hypothesis

The observations reviewed above argue that even if chronic neural activity in the DMN biases Aß production and clearance toward amyloid deposition, different mechanisms participate in Aß localization in normal elderly, E4 homozygotes,

familial dominant AD, and sporadic AD. Further, tau has reached a new level of significance in AD pathophysiology. The cellular and molecular mechanisms of human Aß deposition and the relationship to AD appear pleiomorphic and complex defy so far simplistic explanations for a complex disease. However, given the recent advances in multimodal molecular imaging (amyloid, tau, neuroinflammation, etc.), the story is likely to evolve quickly.

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Conflict of interest

The author declares no conflict of interest.

Author details

José V. Pardo[1,2]

1 Department of Psychiatry, University of Minnesota, Minneapolis, USA

2 Cognitive Neuroimaging Unit, Mental Health Service Line, Minneapolis Veterans Health Care System, Minneapolis, USA

*Address all correspondence to: jvpardo@umn.edu

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