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Regional variability in Alzheimer's disease biomarkers

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The amyloid cascade hypothesis predicts pathological processes in Alzheimer's disease (AD) begin with an alteration in the balance between the clearance and production of amyloid precursor protein. The disruption of this balance leads to the formation of β -amyloid ($A\beta$) plaques, aggregation of phosphorylated tau into neurofibrillary tangles (NFTs), neuronal dysfunction and death, and finally dementia [1,2]. These processes are not ubiquitous throughout the brain; rather the strength [3] and timing [4] of each pathology varies between brain regions. Understanding the underlying physiological properties that allow some cortical structures to be resistant to pathology may lead to new strategies for treating and preventing AD.

With the advancement of imaging techniques over the last decade, *in vivo* mapping of AD pathology is possible. Amyloid deposition can be measured using Pittsburgh compound B positron emission tomography (PiB PET) [5] or similar amyloid tracers; glucose metabolism can be imaged with fluoro-deoxyglucose PET (FDG PET); and structural atrophy can be assessed by volumetric analyses of magnetic resonance imaging (MRI). PET tracers for tau are only now being introduced [6].

Early post-mortem examinations in humans found a relatively diffuse distribution of $A\beta$ plaques throughout the brain and across subjects [7]. Amyloid imaging, primarily with PiB and other radioligands, has affirmed that $A\beta$ is widely deposited in both cortical and subcortical brain structures [3,4,8] but has demonstrated that there is a discernable spatial pattern to these depositions. As measured with PET, there is both an anterior locus of high plaque depositions encompassing the anterior cingulate, orbitofrontal, medial frontal, and lateral frontal cortices as well as a posterior locus consisting of the precuneus and posterior cingulate [3,4,8] (see Figure 1a). Primary sensory, motor areas, as well as the medial temporal lobes show relatively low levels of plaque pathology. Although often overlooked, there are significant subcortical deposition of amyloid, particularly in the basal ganglia and thalamus [4,9]

In addition to the formation of $A\beta$ plaques and tau NFTs, the amyloid cascade theory predicts metabolic disruption. FDG PET is a measure of glucose metabolism, which in turn

indexes neuronal health and functioning. There is hypometabolism of glucose in individuals at-risk for developing AD [2,4] as well as those with AD [2,4,10,11]. The most prominent locus of hypometabolism is located in the posterior cingulate cortex and the precuneus [3,4,10,11] (see Figure 1b). To a lesser degree, altered glucose metabolism is also present in the hippocampus, lateral temporal areas, as well as the intersection of lateral parietal and temporal areas.

Post-mortem work with humans characterized the progression of NFTs into distinct stages [7]. The initial tau aggregation appears in transentorhinal regions before moving into entorhinal cortex proper. The pathology expands to include the hippocampus and parahippocampus before spreading through the medial temporal lobe and into medial prefrontal, posterior parietal, and lateral temporal regions [7,12]. Although traditionally examined post-mortem, preliminary work with tau PET tracers is consistent with this trajectory [6]. Levels of tau pathology are strongly associated with cell death [13], and a similar spatial pattern can be seen in studies examining grey matter atrophy with MRI. Research comparing age-matched controls to both preclinical and AD patients [4,14,15] consistently shows pronounced atrophy in the medial temporal lobes, particularly the entorhinal cortex and hippocampus. A large body of work in the literature finds additional volume loss in the posterior cingulate, precuneus, and parietal areas (see Figure 1c). These declines are above and beyond that occurring in normal aging.

Resting state functional MRI has been used to isolate intrinsically organized functional networks in the brain including the “default mode” network (DMN) [16]. The DMN is highly replicable across diverse populations, and the nodes of this network represent the most globally interconnected hubs in the cerebral cortex. This network can be seen as broadly delineating the typical regions sensitive to AD as assessed with amyloid imaging, FDG PET, and volumetric analyses (e.g. [17]). Regional levels of amyloid, hypometabolism, and atrophy from within this network are considered so indicative of AD that they are used to classify individuals as having “preclinical” AD, and have been suggested as biomarkers for the evaluation of interventional treatments. The presence of a spatially selective pattern of pathology is critically useful when discriminating AD from other common dementias such as frontotemporal, vascular, and Lewy Body dementia [10,15,18].

While there is a general spatial concordance across these three measures, there are discrepancies that must be addressed. Examining multi-modal results, there are three profiles to be considered [3]. The medial temporal lobe demonstrates robust atrophy along with significant reductions in glucose metabolism, but relatively low levels of A β . Frontal regions, including the anterior cingulate, orbitofrontal cortex, and lateral and medial prefrontal cortices, have high levels of A β deposition along with either low or non-significant levels of hypometabolism and atrophy. Finally a posterior collection of association areas, including the posterior cingulate, precuneus, lateral temporal, and lateral parietal areas, have high levels of A β , hypometabolism, as well as atrophy. While often consider a solitary network, the DMN can be fractionated into different sub-networks roughly pertaining to an anterior and posterior component [19] while the hippocampus is simultaneously becoming disconnected from both [20]. This parallels the tripartite groupings

seen when comparing A β load, hypometabolism, and atrophy, suggesting a functional separation of the regions detrimentally affected by AD.

AD is not a static disorder, rather a continual accumulation and acceleration of pathological processes. The disease should not simply be modeled at one time point, but rather dynamically across time. This can be done in sporadic AD by following individuals longitudinally over time. The resources needed to acquire imaging data on large populations over decades of time limit the feasibility of such studies. An alternative approach utilizes autosomal dominant Alzheimer's Disease to model the temporal ordering of AD biomarkers [2,4]. In this manner it is possible to see elevated levels of A β in the precuneus fifteen years before, hypometabolism ten years before, and volumetric decline five years before the estimated onset of dementia. Observing high levels of PiB in medial prefrontal areas without hypometabolism or atrophy may not be indicative of an absence of these processes, but rather be due to a more delayed emergence of these pathological effects relative to a region such as the precuneus. The presence or absence of a given biomarker in an anatomical region should not be viewed as an absolute, but rather a pattern only at one moment that could later evolve.

The hippocampus demonstrates relatively small increases in A β but massive cell death, atrophy, and hypometabolism. The posterior cingulate and ventromedial prefrontal cortices both show large increases in A β yet the posterior cingulate has accompanying hypometabolism and atrophy while the ventromedial prefrontal cortex does not. These results suggest that relative to the precuneus, detrimental declines are triggered quite easily in the hippocampus, while the ventromedial prefrontal cortex is more resistant. Whether this is due to truly different pathological process or differences in timing, both interpretations suggest variation in regional sensitivity to pathology. This may be due to a number of factors including differences in the tissue at a cellular level, functional interactions between regions of the brain, and local compensatory biochemical and functional changes. Perhaps the largest omission in the literature is the lack of information in regards to the distribution of NFTs in the brain. As levels of tau pathology are more related to cell death than that of A β [13], this may provide the missing link needed to understand these discrepancies.

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Figure 1.

Regions demonstrating elevated levels of amyloid deposition, hypometabolism and atrophy in Alzheimer's patients compared with nondemented controls. (A) Amyloid deposition, (B) hypometabolism and (C) atrophy. FDG: Fluorodeoxyglucose; PiB: Pittsburgh compound B.