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Understanding cognitive deficits in Alzheimer's disease based on neuroimaging findings

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Abstract

Brain amyloid can be measured using positron emission tomography. There are mixed reports as to whether amyloid measures are correlated with measures of cognition (in particular memory) depending on the cohorts and cognitive domains assessed. In Alzheimer's disease (AD) patients and those at heightened risk for AD, cognitive performance may be related to the level and extent of classical AD pathology (amyloid plaques and neurofibrillary angles), but it is also influenced by neurodegeneration, neurocognitive reserve, and vascular health. We discuss what recent neuroimaging research has discovered about cognitive deficits in AD, and offer suggestions for future research.

Keywords

dementia; mild cognitive impairment; MRI; PET; memory; executive function

Introduction

In recent years, there has been a vast increase of brain imaging studies focusing on Alzheimer's disease (AD). Some neuroimaging studies evaluate disease progression; others attempt to predict or better understand cognitive decline. Here we review what brain imaging has revealed about cognitive deficits in AD, focusing on developments from the last five years.

Structural magnetic resonance imaging (MRI) is the mainstay of AD imaging research. Many studies explore how regional brain volumes relate to various cognitive functions in control, mild cognitive impairment (MCI) and AD cohorts. Correlations between brain structure and cognition are easiest to detect in cohorts that include AD and MCI, as the disease process promotes brain atrophy as well as cognitive decline. In such cohorts, memory performance is highly correlated with measures of temporal lobe structures affected

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early in the disease process, including the hippocampus and entorhinal cortex. Executive function and global cognition typically show significant associations with broader measures: whole brain atrophy, ventricular enlargement, and cortical thickness across multiple brain regions [57-60]. Performance on executive function tasks and the brain regions that support them may also contribute to episodic memory ability [61].

The hallmarks of AD pathology include amyloid plaques and neurofibrillary tangles, which spread throughout the brain in stereotypical patterns [5]. Related changes in MRI and PET signal mark AD progression, but active debate exists about which neuroimaging biomarkers best detect the earliest changes [62, 63]. A correlation between cognition and imaging biomarkers should be strongest when, during the disease stage assessed, the biomarker shows decline-related variability in a region essential to the cognitive function being evaluated. Cognitive performance depends on the level of neurodegeneration due to AD pathology, as well as co-morbid conditions and lifestyle choices. Additionally, the link between disease burden and cognition depends on how well the brain can successfully compensate for that degeneration (based on redundancy, plasticity, or other mechanisms promoting neurocognitive reserve).

Here, we discuss how brain imaging elucidates relationships between cognitive changes and AD-related pathological changes. We focus on brain biomarkers that relate most directly to AD processes, either through links to known pathology, or through examination of longitudinal cognitive changes. Where possible, we emphasize prodromal AD, when specific types of cognitive changes may be easier to isolate from others. Many papers explore brain structure and cognition in those with certain AD risk factors (such as apolipoprotein E allele 4 (*APOE*4). As brain differences associated with genotype may arise from factors unrelated to AD risk, we focus here on amyloid biomarkers and longitudinal changes to identify increased AD risk.

Direct relationships between brain amyloid and cognition

Brain amyloid - assessed using PET scanning (Box 1) - may relate directly to cognition in AD patients and those at increased risk for AD. Some studies reported significant relationships between amyloid PET signal and episodic memory or a composite measure that includes episodic memory [7, 42, 49, 64-66]. Others focused on global cognition, relating amyloid signal to well-known global cognition measures [40, 43, 67]. A few did examine how amyloid signal relates to episodic memory, but only detected significant relationships between amyloid signal and other cognitive measures [44, 68]. Others did not detect a significant relationship between amyloid signal and cognition [38, 69, 70]. These differing findings may be influenced by differences in methods, sample sizes, and cohort choices. In particular, studies that did not detect a direct relationship between amyloid signal and cognition largely focused on normal healthy older controls [38, 69, 70], while nearly all studies in which amyloid signal related to cognition also included cognitively impaired subjects. In one notable exception in controls [65], rather than relating amyloid signal to cognitive measures selected *a priori*, the authors used a discriminant function that weighted cognitive scores to best distinguish older adults with high versus low levels of PIB PET signal [65].

Even when higher levels of amyloid signal did not relate directly cognitive performance [40, 71], some found that they still correlated with future cognitive decline, including in controls [9, 38, 40, 71]. The relationship between amyloid and cognition may also vary by diagnosis. Landau and colleagues found that PIB signal was related to current global cognition in MCI, but only to future memory decline in controls [40]. Similarly, others found that amyloid signal related to episodic memory in MCI, but not in AD patients or controls [66]. Mormino and colleagues likewise found that PIB signal related to episodic

memory in MCI, but only in one cohort (out of two) of controls [49]. We examine why higher brain amyloid may relate inconsistently to cognitive performance - a key question for clinical trials where higher PIB signal is sometimes used as an enrollment criterion.

Neurodegeneration may influence how brain amyloid and cognition relate

Mormino and colleagues found that in MCI and controls, global PIB signal was related to hippocampal volume. When both the PIB index and hippocampal volume were included in the same model to predict episodic memory, hippocampal volume remained a significant predictor, but the PIB index did not. This suggests that rather than having a direct relationship with cognition, the effect of brain amyloid on cognition may be mediated by hippocampal volume [49]. High amyloid signal is among the earliest AD indications, while brain atrophy and detectable cognitive changes are more dynamic later [62]. This would explain why amyloid signal is more commonly related to cognition in people with MCI [40, 49, 66]. In MCI, greater AD-related neurodegeneration is expected than in controls. By the time AD processes have progressed enough to cause cognitive decline, amyloid may have promoted other mechanisms that influence cognition, such as toxicity caused by neurofibrillary tangles, inflammation, or Aβ oligomers [46]. The concept of neurodegeneration mediating the amyloid-cognition relationship also explains why some studies do not find a significant relationship between amyloid signal and cognition in AD patients [40, 66]. Brain amyloid rises rapidly early in AD, but may plateau as cognitive decline progresses [62]. Cognitive decline and other AD biomarkers such as hippocampal atrophy may continue to progress while the deposition of brain amyloid may not, resulting in a disconnection between amyloid and cognitive performance later in AD.

Several other studies also support the idea that brain amyloid in non-demented older adults exerts its effect on cognition via neurodegeneration [38, 69, 70, 72]. Dore and colleagues did not find that amyloid signal correlated directly with cognition, but greater amyloid signal was associated with thinner cortex in the posterior parietal and temporal lobes, and hippocampal region only in older controls who were PIB+ (had suprathreshold levels of global PIB signal). Thinner cortex in the precuneus and hippocampus was in turn associated with poorer episodic memory performance, even after controlling for amyloid signal [69]. Others likewise found significant associations in cognitively intact older adults between higher global PIB signal and lower cortical volume, in regions that included the hippocampus, temporal cortex, and anterior and posterior cingulate. Regional brain volume in those regions was also associated with memory performance [38]. In two other studies of older controls, high global PIB indices were not directly associated with cognition, or with measures of neurodegeneration such as structural MRI or FDG PET. However, brain amyloid still modulated the relationships between neurodegeneration and cognition. PIB+ controls had stronger relationships between greater neurodegeneration and cognition (specifically worse memory and executive function [70] and faster memory decline [71]) than PIB- controls.

Neurocognitive reserve may influence how AD pathology and cognition relate

Neurocognitive reserve is defined as the variability in clinical symptoms across people for a given a level of brain pathology. The term includes both brain structural health and the ability to compensate actively for pathological insult [73]. Reserve may be influenced by baseline intelligence, education, and lifetime cognitive engagement.

One large study related amyloid signal, brain structure, and cognitive performance in controls with and without memory complaints. PIB+ subjects without memory complaints had *larger* temporal lobes and better verbal learning performance [74] than PIB-controls. The

larger temporal lobes may have been necessary for PIB+ adults to maintain their cognitive ability. In contrast, PIB+ controls with subjective memory complaints had smaller regional brain volumes and worse global cognition and visual memory than PIB-controls with memory complaints. There was a trend toward complaint-free PIB+ adults having greater brain gray matter volume than PIB+ adults with memory complaint [74]. Possibly, PIB+ controls with memory complaints originally had less gray matter than those without memory complaints, and therefore had less neurocognitive reserve. Alternatively, perhaps PIB+ controls with memory complaints had more atrophy than PIB+ controls without memory complaints because of larger amounts or a longer duration of brain amyloid.

The notion of neurocognitive reserve suggests that improving brain structure and connectivity through cognitive or physical activity may help compensate for pathological insult to the brain. Intriguingly, cognitive activity may even modify amyloid deposition, rather than just compensating for it. In older controls, those who were the most cognitively active in their lifetimes had brain amyloid levels similar to young controls, but those who were least active cognitively had amyloid signal profiles that resembled AD patients [75]. Similarly, the longitudinal decline in FDG PET metabolism was slower in AD patients with higher premorbid intelligence, and therefore cognitive reserve [76].

Vascular health may influence cognition in older adults

At autopsy more than 60% of AD patients have deep white matter lesions thought to relate to cardiovascular risk [77]. These lesions are visible as white matter hyperintensities (WMH) on T2-weighted brain MRI scans. They contribute to the presentation of AD-like symptoms in older adults with higher brain amyloid levels [78]. Baseline WMH volume [79, 80] and extension of existing WMH, although not the appearance of new WMHs [45], were both associated with future cognitive decline, including global cognition [79], episodic memory [45], and executive function [45, 80]. WMHs in the temporal lobe are associated with memory impairment and those in the frontal lobe relate to slower mental speed [81]. WMH are related to FDG PET hypometabolism and executive function decline, but they are not correlated with CSF Aβ levels [82], an amyloid measure that correlates well with amyloid PET signal [83]. This suggests that WMHs do not affect amyloid; instead, their effect is additive to that of AD-specific pathology [82].

Multimodal imaging and cognitive deficits

Multi-modal brain imaging allows researchers to evaluate the effects on cognition of one specific biomarker (such as glucose metabolism) while controlling for the effects of others (such as hippocampal volume), to estimate the relative contribution of each. Several papers have evaluated the relative contributions of structural connectivity, assessed using diffusion tensor imaging (DTI), and regional brain volume or cortical thickness.

In two large studies, even after controlling for hippocampal volume, DTI mean diffusivity (MD) in the hippocampus was lower (more intact) in those with better episodic memory [84, 85]. Others found that in non-demented older adults, DTI measures in the fornix [86] and parahippocampal cingulum [87] correlated with memory performance better than hippocampal volume did. Lee and colleagues also found that in AD patients and non-demented adults, better performance specific to episodic memory and executive function tasks was related to higher fractional anisotropy (FA; more intact white matter) in the fornix body [88], whose fibers originate in the hippocampus. However, in contrast with the other studies [84, 85], when both DTI measures and hippocampal volumes were included in the same model, only hippocampal volume continued to be significantly associated with memory performance [88]. Unlike the other studies [84, 85], the study by Lee and colleagues included AD patients [88]. These differing results could be explained by a model in which myelin

degenerates early as has been proposed previously [89]. Hippocampal degeneration may be apparent on MRI later than deficits in fornix microstructure on DTI [87]. However, once hippocampal degeneration becomes more extensive, it begins to limit memory ability more than white matter integrity does. This notion is supported by another study in which the relationship between MD and memory was strongest in those with normal hippocampal volumes [84].

Correlating biomarkers with cognition

AD results in massive brain degeneration and eventually includes deficits in most cognitive functions. Therefore, in AD case-control studies, differences in any given cognitive domain may appear to relate to a wide range of biomarker differences, simply because the various markers all change with disease. Here, we selected papers that related imaging biomarkers to cognition in prodromal AD as well as patients. We focused on papers that either correlated longitudinal changes in imaging measures with longitudinal changes in cognitive measures, or those that included correlations with CSF biomarkers for AD.

The hippocampus is important for episodic memory and degenerates early in AD. Some studies have related hippocampal health to cognition. One found that global cognition and delayed episodic memory were both associated with hippocampal radial distance - the distance from each point on the hippocampal surface to the medial core of the hippocampus - in AD and MCI, but not in controls [90]. This again emphasizes that AD-related changes in hippocampal structure are likely to become detectable once cognitive decline is evident. After controlling for baseline hippocampal volume, memory performance at follow-up was correlated with hippocampal radial distance predominantly in CA1 of the hippocampus [90], a region with early deposition of neurofibrillary tangles in incipient AD [91]. Additionally, in MCI, greater longitudinal declines in resting state functional MRI (rs-fMRI) synchronicity - between the hippocampus and the left posterior cingulate - were associated with larger declines in episodic memory performance [92].

When analyses included the neocortex, higher medial temporal lobe atrophy rates in controls have been associated with a greater decline in verbal episodic memory performance and a baseline AD-related CSF biomarker [93]. In MCI, higher temporal lobe atrophy rates also correlated with greater declines in global cognition and episodic memory [94]. Also in MCI, memory decline has been specifically linked to longitudinal atrophy in the entorhinal cortex, while frontal lobe atrophy was associated with declines in executive function. Declines in semantic (category) fluency were related to atrophy rates in a broader network that included bilateral temporal lobe, left frontal lobe, and left anterior cingulate [95].

Lateral ventricle structure offers one of the highest effect sizes of all neuroimaging measures for distinguishing AD patients from contro[96]. In AD patients and non-demented older adults, differences in the ventricular surface were related to global cognition, longitudinal cognitive decline, and CSF levels of Aβ42 protein levels [39], which are reduced in AD patients [97]. Declines in executive function have been associated with right frontal and left temporal horn enlargement of the lateral ventricles [98].

Concluding remarks

In AD patients and those at increased risk, brain amyloid may influence cognition indirectly, through neurodegenerative processes. Other measures of brain health including vascular health, and individual differences in brain structure and connectivity throughout a lifetime, may influence the extent to which insult from AD pathology results in detectable cognitive changes. Longitudinal studies and studies with imaging biomarkers from multiple modalities provide valuable insights into cognitive deficits in AD.

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Glossary

Amyloid signal	We use the term “amyloid signal” throughout this review to mean the positron emission tomography (PET) signal that arises in the brain using a radiotracer designed to bind primarily (or selectively) to amyloid. See Box 1.
Controls	Unless otherwise stated, “controls” in this review refers to older adults whose cognitive test scores indicate that they are not cognitively impaired relative to their age- and education-matched peers. Most papers do not indicate whether or not these subjects have subjective memory complaints.
Episodic memory	Memories that can be explicitly stated, such as the recall of specific events and experiences. Episodic memory is impaired in the AD spectrum. It relies heavily on the intact function of the hippocampal formation, which degenerates in AD.
Executive function	Cognitive processes that regulate and control other processes. These include cognitive abilities such as planning, impulse control, mental flexibility, attention, problem solving. In some cognitive studies, working memory and language tasks such as phonemic and category fluency are included under this umbrella term as well.
Fluorodeoxyglucose positron emission	A brain imaging method used to measure glucose metabolism in living humans (or experimental animal models). The tracer molecule is retained more in tissues with high metabolic rates.

tomography (FDG PET)	Signal is associated primarily with synaptic activity. At rest AD patients and those at greater risk for AD show decreased FDG PET signal (hypometabolism) in characteristic brain regions [1].
Fractional anisotropy (FA)	A diffusion tensor imaging measure. FA measures the extent to which water is directionally constrained. Higher values are generally associated with greater white matter integrity.
Mean diffusivity (MD)	A diffusion tensor imaging measure. It is an average measure of water diffusivity along the axon and in two directions perpendicular to the axon. Higher values tend to be associated with less intact white matter.
Mild cognitive impairment (MCI)	a condition marked by cognitive changes beyond those expected for age and education, but not yet large enough to impair activities of daily living or be classified as dementia [2]. Having MCI increases the risk of developing Alzheimer's disease (AD) and, in many people with MCI, there already may be AD pathology.
Resting state functional magnetic resonance imaging (rs-fMRI)	also called “task-free” fMRIrs-fMRI measures regional changes in oxygenated blood in the brain while the subject lies quietly at rest, usually with their eyes open. The “default mode network” (DMN) is a group of brain regions - among them medial temporal lobe, posterior parietal and medial prefrontal frontal cortex - that are more active at rest than during a task. Activity in these network regions is typically correlated, but may become less synchronized in characteristic ways in those who have or are at increased risk for AD and certain other neurological disorders. Lower DMN synchronicity is associated with higher amyloid PET signal, even in cognitively intact older adults [3, 4].
Semantic memory	memory of meanings and other concept-based knowledge that make up general knowledge about the world.

Box 1

Amyloid imaging

Previously, a definitive AD diagnosis was possible only at autopsy by assessing AD neuropathological hallmarks - amyloid plaques and neurofibrillary tangles [5]. The unpredictable interval between the patients' last clinical assessments and their deaths made it difficult to relate pre-mortem cognition to the pattern of plaques and tangles found at autopsy. Recently, new methods have allowed us to evaluate brain amyloid levels in the living brain using positron emission tomography (PET). This has greatly advanced our ability to understand cognitive deficits in AD and disease progression [6]. Indeed, time-lapse movies that track the disease trajectory based on the expected amyloid signal at different disease stages have been created using regression models that relate PET measures to cognitive impairment or disease severity [7] (Figure 1). Additionally, non-demented adults with higher brain amyloid PET signal are more likely to decline cognitively over time, while those with low levels are less likely to decline cognitively in the short term [8,9].

Brain amyloid levels can be measured *in vivo* using various radiotracers sensitive to brain amyloid. Proof of concept for amyloid PET in live humans was established in 2002, using 2-(1-(6-[(2-[^{18}F]fluoroethyl)(methyl)amino]-2-naphthyl)ethylidene)malononitrile (also known as FDDNP) [10]. FDDNP PET is the only commonly used amyloid probe that also highlights neurofibrillary tangles in living humans. The PET probe, *N*-methyl-[11C]2-(4-methylaminophenyl)-6-hydroxybenzothiazole (known more commonly as “Pittsburgh Compound B” or PIB) was introduced in 2004 [11]. PIB binds with high specificity to senile amyloid plaques, but does not highlight neurofibrillary tangles. It has a higher signal to noise ratio than FDDNP, but the [^{11}C] radiotracer used to label PIB has a shorter radioactive half-life than the [^{18}F] tracer associated with FDDNP, so scans must be performed more rapidly after probe creation. Newer amyloid PET probes include [(18)F]3′-F-PiB (flutemetamol) [12], (18)F-AV-45 (florbetapir) [13], and (18)F-AV-1 (florbetaben) [14]. Like PIB, these tracers are specific to amyloid, but like FDDNP, they offer a longer half-life, improving practicality of use. All of these PET tracers are in relatively wide use, as are fluorodeoxyglucose (FDG) and perfusion PET. Along with Magnetic Resonance Imaging (MRI) and Computerized Tomography (CT) scans, these have been used to evaluate AD for two decades.

Neuropathological amyloid deposition should be distinguished from the PET measure of amyloid, which may highlight only a fraction of actual brain pathology [15]. Here, “amyloid signal” refers to the PET signal designed primarily to measure brain amyloid.

Box 2

Predicting cognitive decline

One of the most valuable tasks for Alzheimer's disease (AD) researchers is to identify baseline biomarkers typically associated with AD that will predict cognitive decline over time. Neuroimaging research has contributed considerably to this end. Some of these studies have been performed in cognitively intact older adults, often using longitudinal MRI to evaluate brain regions previously implicated in AD [16-18]. Across several studies, the integrity of various regions in the temporal lobe were among the best predictors of cognitive decline in controls e.g. [16, 17, 19, 20]. A few found that hippocampal volume specifically [19, 20], but not entorhinal cortex structure [19, 20] predicted cognitive decline.

In MCI too, cognitive decline is heralded by low integrity of medial temporal cortex, especially the entorhinal cortex, hippocampus, and amygdala across many studies e.g. [21-25]. In a smaller number of studies, integrity of (or atrophy in) the posterior cingulate cortex and precuneus was also an indicator of future decline [21, 23, 25-27]. Some studies found that FDG PET rather than MRI measures best predicted conversion from MCI to AD within a few years [28, 29]. However, typically models that combined information from multiple modalities, such as MRI, FDG PET, CSF biomarkers, and cognitive measures, predicted cognitive decline better than any one biomarker alone [28, 30-32]

The quest to identify new predictors of cognitive decline now includes high-field structural MRI scanning, diffusion imaging, arterial spin labeling (a form of MRI that measures perfusion), and resting state functional MRI, which measures coherence in brain activity. Other efforts to predict future cognitive or brain decline, or both, are adding information on common and rare genetic variants [33, 34] as well as data on gene expression, proteomics, and epigenetic markers of aging such as methylation. Another key area is how to predict decline most accurately when some patient data is missing; in clinical settings, not all patients will have the same sets of neuroimaging or genetic data collected, and specialized methods are being developed to best predict decline based on the available data [35]. Finally, as most people with AD also harbor some vascular pathology, a very active line of work in neuroimaging has related brain integrity and cognitive decline to cardiovascular health and other lifestyle factors, including diet and obesity [36], and physical activity [37].

Box 3

Future directions

- Many large AD studies correlate cross-sectional biomarker measures with longitudinal cognitive decline (e.g.,[38-40]). This is important for predicting cognitive decline - something vital to personal health and clinical studies [32]. ***However, more studies that correlate longitudinal brain biomarker changes with longitudinal cognitive changes (e.g.*, [41]*) would better clarify how these biomarkers relate to specific cognitive deficits***.
- Many correlations between amyloid PET and cognition use a global index (numeric summary) derived from the PET amyloid probe signal; only a few examine amyloid PET signal using voxelwise analyses [7, 42] or in individual regions of interest analyses [9, 43]. Numeric summaries limit the number of statistical comparisons and are simple and practical for clinical studies. ***However, more voxelwise amyloid PET studies may help relate specific cognitive functions to regional brain amyloid patterns***.
- ***To better identify pathological processes that promote specific cognitive symptoms*, *more researchers should examine the relationship between cognition and an imaging measure while controlling for levels of biomarkers from other modalities***. Relationships between biomarkers and cognition are disease stage-dependent, so focusing these studies on specific disease stages is particularly vital for understanding cognitive changes.
- Currently, measures of “memory” or “executive function” are often based on composite scores composed of test scores that vary widely from study to study (e.g, composite scores for “executive”, “frontal lobe”, or “non-memory” function might include working memory [44-47], and verbal fluency [45-47], or only mental flexibility and response inhibition [9, 48, 49]. ***Standardizing cognitive measures would help to interpret results in the context of earlier findings***.
- Large imaging studies in cognitively intact adults have explored how AD risk gene variants relate to brain measures (e.g., [50-52]). ***Future MRI genetics studies in healthy adults should also evaluate amyloid and tau pathology and their correlations to cognition, so that gene effects related and unrelated to AD pathology can be distinguished***.
- ***Technological imaging advances may advance our understanding of brain changes related to cognition in AD***. Ultra-high field 7 Tesla MRI provides sharper resolution of hippocampal microstructure - revealing hippocampal subregions and molecular layers whose properties can be linked to cognition [53]. Connectomics, which measures the organization, efficiency, and speed of brain networks, is beginning to be applied in AD research [51, 54-56]. Evaluating connectivity measures over time and in conjunction with specific cognitive tests -particularly in prodromal AD - would provide new insights into the circuitry underlying cognitive deficits in AD.

Highlights

- Amyloid PET signal inconsistently relates to cognition in Alzheimer's disease (AD).
- Neurodegeneration may mediate how neuropathology relates to cognition in AD.
- Vascular health and neurocognitive reserve may also modify this relationship.
- Biomarkers from multiple modalities help us investigate these relationships.

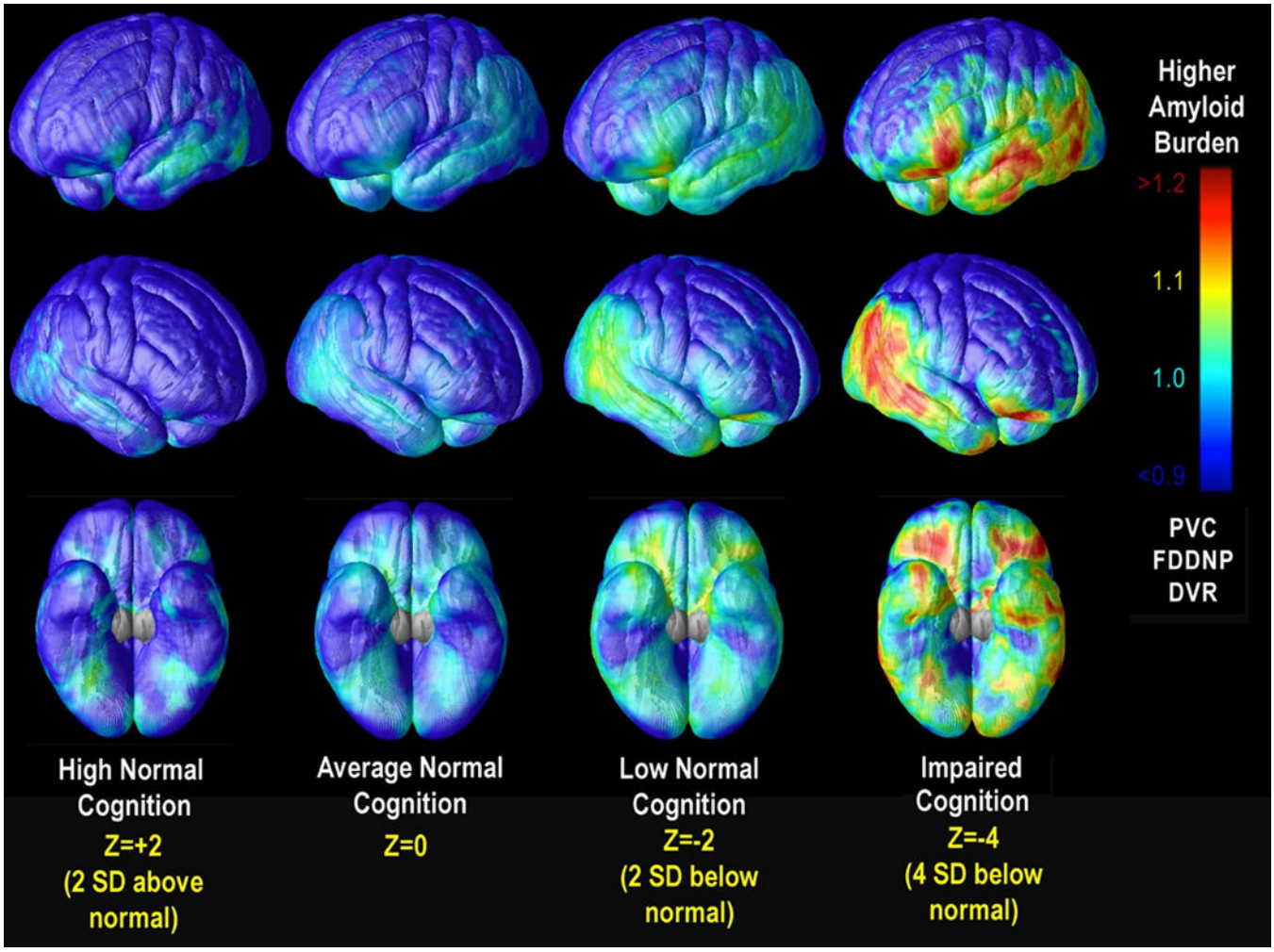

Figure 1.

Brain Pathology at Different Stages of Cognitive Decline. Here we show the projected mean [^{18}F]FDDNP signal, based on cross-sectional data from people with a broad range of impairment, and calculated for various levels of cognitive performance in AD and MCI patients and cognitively intact older adults. Red regions are those in which greater predicted [^{18}F]FDDNP signal was associated with lower cognitive *Z* scores at each cortical voxel. Adapted from [7] and reprinted with the permission of the journal and authors.