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Realizing the potential of positron emission tomography with ^{18}F-fluorodeoxyglucose to improve the treatment of Alzheimer's disease

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Abstract Positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose (FDG-PET) thus far rarely has been used to advance the development of new treatments for Alzheimer's disease (AD). Now that FDG-PET with standard acquisition protocols for dementia is widely available, change in cerebral glucose metabolism is a feasible outcome variable for clinical drug trials. Individual analysis of FDG-PET results also might prove valuable. FDG-PET can detect metabolic changes very early in the course of AD and identify subjects for earlier treatment. FDG-PET reliably distinguishes AD from frontotemporal dementia so that only those most likely to benefit are enrolled in trials. Finally, objectively identifying phenotypic variations of AD with FDG-PET might have pathogenic and prognostic implications that can be used for personalized treatment approaches. The judicious use of FDG-PET is needed to accelerate the evaluation of promising new drugs and more rationally target treatments for dementing diseases.

Keywords: Clinical trial design; Alzheimer's disease; Brain imaging; Positron emission tomography; Image analysis

1. Introduction

Leon Thal had a dramatic and lasting influence on the way we think about Alzheimer's disease (AD) and conduct clinical trials for dementing disorders. A review of his remarkably consistent and highly productive record of carefully designed clinical studies during more than 25 years shows that he dealt with all of the major issues of new drug development. He encouraged the evolving role of neuroimaging in drug trials, and under his leadership the Alzheimer's Disease Cooperative Study (ADCS) began to incorporate magnetic resonance imaging (MRI) as an outcome measure of treatment response [1]. Leon also played a central role in the Alzheimer's Disease Neuroimaging Initiative (ADNI), which is designed to validate imaging biomarkers as a surrogate measure of disease progression to speed the development of new therapies [2]. Thus, it is appropriate to review in his honor how we can better realize the potential of molecular imaging to enhance the development of treatments for AD.

The past 30 years have seen enormous advances in brain imaging technology. The development of computed tomography (CT) permitted the precise visualization of the brain and thus changed the practice of neurology. Soon thereafter, MRI brought our ability to see brain structure to new levels of detail and precision. With MRI, it became possible to precisely delineate gray matter and identify white matter hyperintensities in the aging brain that we still are challenged to fully understand. These structural brain imaging methods made it easy to diagnose tumors, stroke, and other focal destructive and mass lesions. Their use in diagnosing neurodegenerative diseases has been more challenging. Initial attempts with CT found that brain atrophy was greater on average in AD patients than in normal subjects, but there also was significant overlap, limiting its diagnostic value

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[3]. As a result, structural imaging was quickly adopted in dementia evaluations but only as part of a "rule-out" approach. MRI brought greater resolution and the ability to use coronal and sagittal views to better visualize the hippocampus. MRI now can be used to positively support a diagnosis of AD [4]. Nevertheless, most AD drug trials obtain MRI only to avoid enrollment of patients with extensive vascular or other focal lesions, rather than as a measure of treatment outcome.

Molecular brain imaging, including positron emission tomography (PET) and single photon emission tomography, developed in parallel to structural imaging and also has benefited from dramatic technical improvements. Following the early developmental work of Kuhl et al [5], Ter-Pogossian [6], and others, molecular imaging was rapidly applied to dementia. By the early 1980s, the essential features of the metabolic signature of AD had been delineated [7–9]. Much of the original promise of using molecular imaging to visualize biologic processes in the brain now has been realized. There are many potential radioligands that might be of value in dementia studies. Dopaminergic markers can identify dementia with Lewy bodies [10]. Presynaptic and postsynaptic receptor ligands are available that can assess the integrity of cholinergic pathways and assess the effects of drug-altering cholinergic transmission [11,12]. Particularly promising are markers of amyloid pathology [13,14]. Studies to validate these amyloid imaging agents by using human neuropathologic examinations are underway [15].

The developments in image analysis have been just as profound and critical to the potential for neuroimaging in clinical trials. Images provide an overwhelming mass of quantitative data that must be interpreted accurately. As scanner resolution has improved, the need to reduce this information to a more manageable form only has been compounded. Although clinical studies still primarily use simple planar image displays, image analysis programs are widely used in research to translate and warp images into stereotactic space, permitting individual and group comparisons [16,17]. Derived summary images of 3-dimensional data simplify scan displays, making interpretation easier, and permit the recognition of metabolic patterns that otherwise easily could be overlooked [18].

Advanced image processing allows statistical comparisons that help identify when changes recognized by the eye are truly significant and differentiate disease from normal variation. New statistical methods were required to address the problem of comparing images composed of thousands of data points. The theoretical basis for approaches like nonparametric permutation testing and false discovery ratio have led to greater assurance that reports of statistical differences in image studies are dependable [19,20].

It is easy to imagine how molecular imaging could assist at many stages in new drug development. Drugs can be radiolabeled to study their distribution and pharmacokinetics. The effects of drugs on neurotransmitter systems could be assessed. Nevertheless, this potential has not been fully realized. Meanwhile, PET with ^{18}F-fluorodeoxyglucose (FDG-PET) is ready for use now. We have considerable experience with FDG-PET technology and understand the challenges of its use in clinical trials and some of the practical solutions. A recent review described the promise of FDG-PET for advancing oncologic drug development [21]. This promise also applies to dementia drug development. Thus, it is timely to consider how FDG-PET can aid the testing of new treatments for AD.

2. Current status of clinical FDG-PET in dementia

In the past, the use of FDG-PET in drug development was hindered because of its limited availability and cost. FDG-PET, once restricted to a few academic centers and used solely in research, is now in wide clinical use. Although brain diseases occupied most of the initial focus of FDG-PET, studies in patients with systemic cancer found that it could help in disease staging and treatment selection [21]. This has led to reimbursement for clinical FDG-PET studies and rapid adoption of this technology in most medical centers.

The consideration of FDG-PET as a component of dementia evaluations has benefited from this broader acceptance of molecular imaging. Evidence continues to accumulate that FDG-PET can increase the accuracy of diagnosing dementia diseases. Many dementing diseases have distinctive metabolic signatures that can aid diagnosis [22]. FDG-PET is particularly valuable when there is diagnostic uncertainty. Clinical diagnosis is based on family reports of the timing and prominence of specific clinical features. When the medical history is ambiguous or informants are unavailable or unreliable, FDG-PET can provide objective evidence of a neurodegenerative disease and often identify its cause. FDG-PET also is particularly valuable for identifying diseases that can mimic AD. Dementia with Lewy bodies can be challenging to diagnose clinically, yet FDG-PET shows a recognizable pattern similar to AD with the added characteristic of occipital hypometabolism, whether or not there also is AD pathology [23]. Frontotemporal dementia (FTD) is another disorder easily confused with AD because it lacks distinctive neurologic signs and has a similar progressive course. Indeed FTD often meets criteria for AD [24]. Because FTD and AD have obverse patterns of glucose hypometabolism, FDG-PET is helpful in distinguishing AD and FTD [25]. This is now generally acknowledged, and most insurance providers now reimburse clinical FDG-PET for this indication. The evolving clinical role of FDG-PET in dementia evaluations supports and encourages its use in clinical trials.

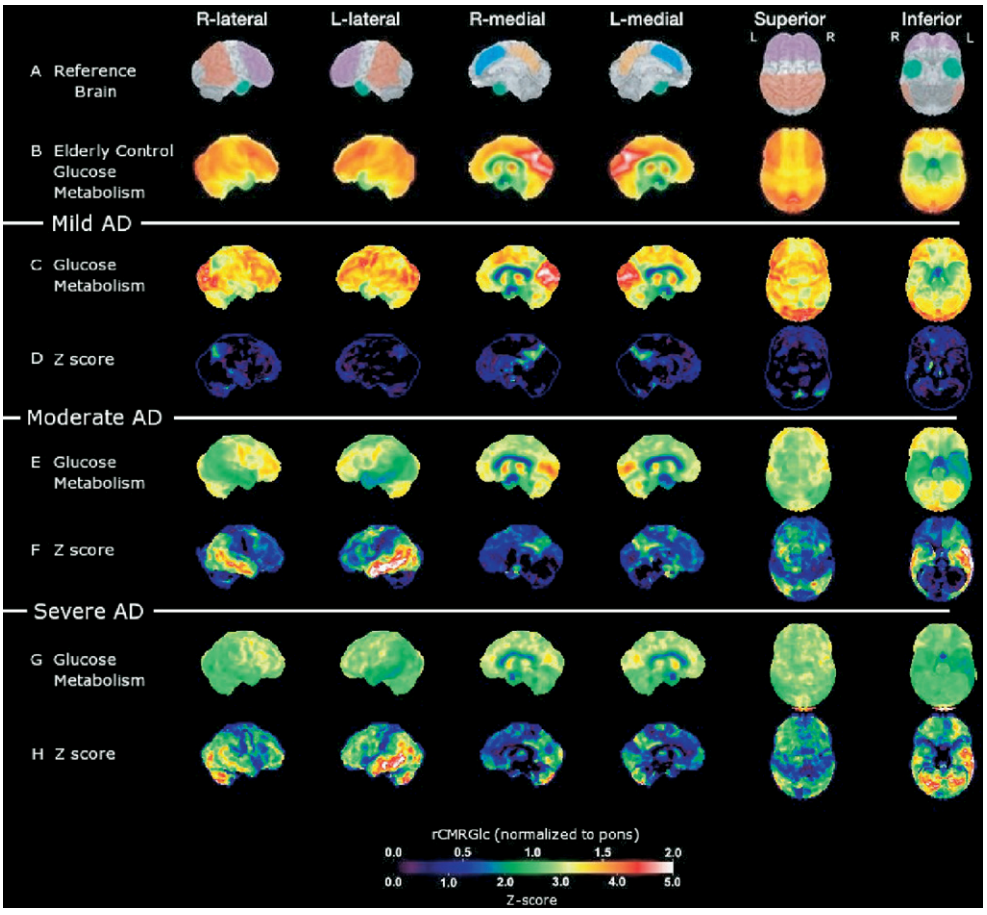

Fig. 1. Typical patterns of cerebral metabolism in mild, moderate, and severe AD. FDG-PET scans are displayed as 3-dimensional stereotactic surface projection (SSP) maps normalized to pons generated with the software program Neurostat. Maps are shown with relative cerebral metabolism or statistical significance increasing on the color scale from the lowest values shown in blue to the highest values in red and white. For orientation, a reference brain is shown in row A with regions of interest in dementia evaluations in color; orange areas usually hypometabolic in AD, blue and purple areas typically hypometabolic in FTD. Row B shows the pattern of metabolism in 27 normal elderly subjects. This is used for statistical comparisons with metabolism in individual patients (rows D, F, and H). There are increasing severity and extent of cerebral glucose hypometabolism as AD progresses from mild (rows C and D) and moderate (rows E and F) to severe (rows G and H).

3. Potential role of FDG-PET in development of promising drugs for AD

3.1. Objective measure of disease severity

Cerebral glucose metabolism declines as patients become more demented. This decline is global and involves progressively more of the brain (Figure 1). The first changes usually occur in the posterior cingulate gyrus [26]. It then becomes apparent in the posterior temporoparietal association cortex and finally affects the frontal cortex. Both the topographic extent and degree of hypometabolism correlate with dementia severity. This suggests that FDG-PET could serve as a surrogate marker of AD progression.

Four major factors prevent its use for this purpose. First, there are few longitudinal studies of FDG-PET in AD [27], and thus correlations with dementia severity primarily have been made in cross-sectional studies. It remains uncertain whether correlations remain close as dementia progresses in an individual. Second, the correlations with dementia have included patients with a wide range of dementia severity and duration. It will be important to determine whether changes in glucose metabolism can be detected during the period of time typical for clinical trials; if longer times are needed to detect change, then imaging would not speed drug evaluation. Furthermore, the degree of metabolic change needs to be assessed in patients with characteristics seen in current clinical trials, in which enrollment typically is limited to those with only mild dementia. Third, measures of glucose metabolism need to be shown to be closely linked to cognitive and functional measures currently agreed to be relevant to showing significant clinical benefit. Accepted AD clinical trial outcomes use neuropsychological measures such as the Alzheimer's Disease Assessment Scale (ADAS-cog) and the global clinician's assessment of change. FDG-PET has not been correlated with these measures of severity. To be validated as a surrogate marker for

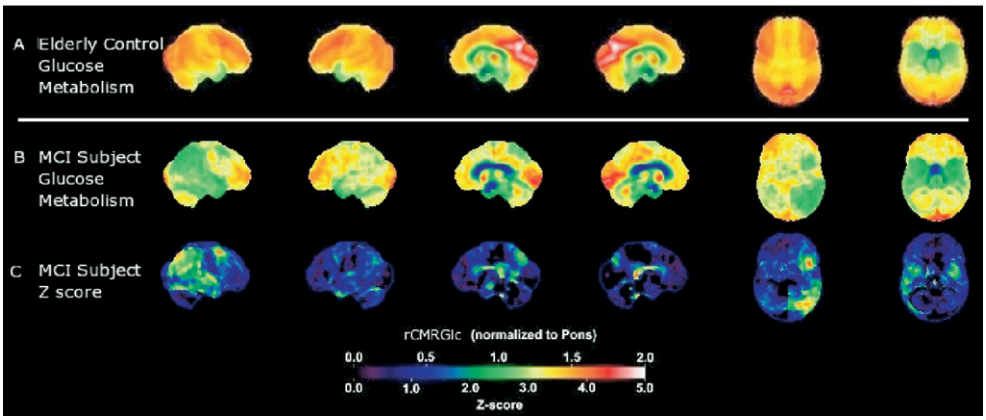

Fig. 2. FDG-PET scan in a subject with MCI who shows an AD pattern of glucose hypometabolism. Results are displayed as Neurostat SSP images as described in Fig. 1. This scan (rows B and C) is from a subject with MCI enrolled in the ADNI study. The statistical map (row C) is derived from calculating a pixel-by-pixel Z score when compared with 27 normal elderly control subjects (row A). There is hypometabolism predominantly involving the right posterior temporoparietal association cortex, with lesser changes in the posterior cingulate and frontal cortex in that hemisphere. It is interesting to note that relative sparing of the dominant left hemisphere might account for better performance on the heavily verbally weighted MMSE used to distinguish subjects with MCI from those with AD.

disease progression, FDG-PET will need to correlate closely with these measures or others that can be shown to have clinical relevance. It will have a significant role only if its variability is less than these standard measures. Finally, the FDG-PET measure most sensitive to change is uncertain. Possibilities include average rates in a predetermined region of interest, the global average of cerebral metabolic rate, and the topographic extent of significant hypometabolism. These are daunting challenges, but ADNI is intended to investigate them all [2]. There is now reason for great optimism that the solutions to these concerns will soon be resolved. Imaging measures are likely to be less susceptible to patient cooperation and environmental influences.

3.2. Early identification of AD

The current thrust for developing new AD treatments focuses on early interventions, before damage is already extensive and treatment therefore is likely to be more effective. Early treatment requires earlier diagnosis that retains at least the accuracy of current clinical methods and hopefully might even improve accuracy. One recent proposal is to base diagnosis on a combination of documented, objective deficit in episodic memory and biologic evidence of AD [28]. Although many questions still must be resolved before this approach is adopted [29], this approach would permit earlier and more consistent diagnoses than the current practice of requiring the presence of dementia. The international consensus group that proposed this new framework for AD diagnosis appropriately identified FDG-PET as one method of documenting biologic evidence of AD.

FDG-PET primarily is a measure of synaptic activity. Thus it is a reasonable early biomarker of AD. How early changes in metabolism occur is unknown, but groups of individuals presumed to be at high risk for AD on the basis of apolipoprotein E4 genotype show metabolic changes at an age long before symptoms are expected [30,31]. Furthermore, several studies have shown that FDG-PET helps distinguish individuals with symptoms that are a prodrome of AD. Nondemented individuals with mild cognitive impairment (MCI) can show cerebral glucose metabolism identical to patients with AD (Figure 2). Moreover, patients with MCI are much more likely to develop AD during the subsequent few years if they exhibit AD patterns of glucose hypometabolism than if they do not [32–34].

3.3. More accurate diagnosis of AD

Researchers long have been concerned that inappropriate subjects could inadvertently contaminate studies of AD. Without a validated, highly reliable diagnostic marker, individuals with pseudodementia and other clinically similar dementing diseases could easily dilute the effect of treatment and lead to erroneous conclusions. This was a significant concern of Leon Thal in his early studies of cholinesterase inhibitors. He developed an "enrichment design" that included patients in a randomized trial only if they "responded" during a brief exposure to drug. This design was based on the idea that nonresponders would not benefit from treatment if they did not have AD or a cholinergic deficit [35]. Subsequently, it became evident that brief exposure to cholinesterase inhibitors did not predict long-term response. The enrichment design was discarded, but concerns about inclusion of non-AD subjects have remained. Extraordinary and expensive efforts are taken in AD clinical trials to try to ensure the accuracy of diagnosis. Potential research subjects undergo extensive cognitive and neurologic testing. They have a battery of blood tests, structural imaging studies, and frequently an extensive neuropsychological battery. Entry

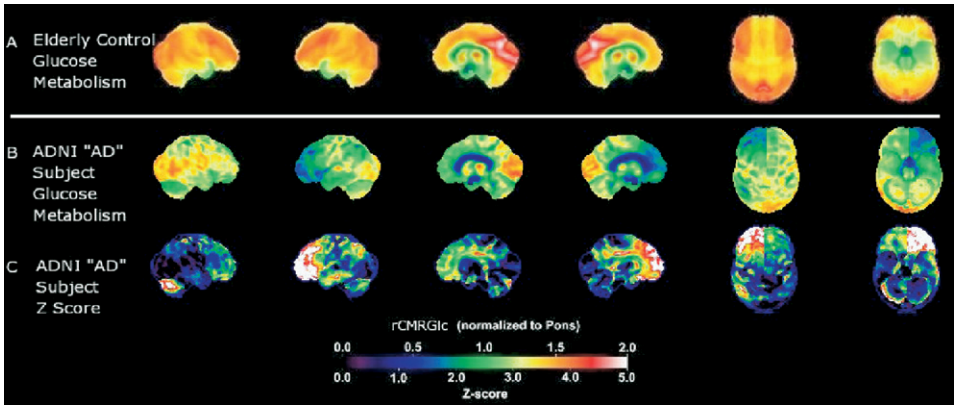

Fig. 3. FDG-PET scan in a subject diagnosed with AD who shows an FTD pattern of glucose hypometabolism. Results are displayed as Neurostat SSP images as described in Fig. 1. This scan (rows B and C) is from an AD subject enrolled in the ADNI study who meets NINCDS-ADRDA criteria. The statistical map (row C) is derived from calculating a pixel-by-pixel Z score when compared with 27 normal elderly control subjects (row A). There is hypometabolism predominantly involving the frontal cortex and anterior cingulate gyrus, a pattern typical for FTD. The left hemisphere is more affected than the right, and there is crossed, left cerebellar hypometabolism, frequently observed with severe frontal hypometabolism.

criteria are complicated and so restrictive that a relatively small proportion of those interested qualify.

Despite these efforts, evidence continues to accumulate that clinical diagnosis of AD is fallible. Patients meeting criteria for probable AD might instead have FTD [24]. Patients with a clinical diagnosis of AD might have dementia with Lewy bodies. Clinical criteria for these AD mimics have relatively poor sensitivity and cause misdiagnoses in community practice and at leading academic centers [36–38]. Diagnosis based on FDG-PET alone seems to have better sensitivity and specificity when compared with neuropathologic findings [39–41].

Is the extra expense of FDG-PET justified in a clinical trial to improve diagnostic accuracy? That depends on the frequency of misdiagnosis in AD clinical trials. Unfortunately, neuropathologic examinations are not often performed on patients participating in clinical drug trials. If autopsies are done, they occur many years after the clinical trial is completed, making it difficult to link trial and pathologic information. Data from ADNI provide an opportunity to consider this problem. Subjects in ADNI are enrolled at research sites and use enrollment procedures typical for a clinical drug trial. Individuals with AD meet National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria and are screened with high resolution, research quality MRI scans and then receive an FDG-PET scan. Subjects with MRI scans suggesting an alternative cause of dementia are excluded. We have performed 3-dimensional stereotactic surface projection (SSP) analysis of baseline scans performed in 93 patients with clinically diagnosed AD enrolled in the ADNI study. Our visual interpretation of these scans on the basis of predominant frontotemporal and anterior cingulate hypometabolism of individual SSP analyses finds approximately 10% of the AD subjects have a pattern of glucose hypometabolism suggesting that they have FTD (Figure 3). This is a higher proportion of patients than might be expected from epidemiologic studies [42]. On the other hand, this should not be surprising. FTD represents a higher proportion of dementia in younger patients, and younger patients are more likely to participate and qualify for AD drug trials. Furthermore, FTD patients might maintain a relatively high Mini Mental State Examination (MMSE) result for a longer period of time than AD patients because they have relative preservation of memory and orientation. Thus, even FTD patients with severe dementia might qualify for AD trials and be over-represented. It is difficult to know for sure whether this frequency of misdiagnosis is sufficient to significantly dilute the outcomes observed in a clinical trial. However, it is clear that the recent decrease in the rate of decline observed in placebo-treated AD subjects in trials makes accurate diagnosis even more important than in the past and might contribute to speculated effects of adverse subject selection [43].

3.4. Metabolic and phenotypic variation in AD

Clinical trials primarily focus on treatment of groups, but the individual variations are important and are the basis for the emerging field of personalized medicine. Personalized medicine recognizes that individual characteristics provide an opportunity to better focus treatment rather than simply being an irritating cause of seemingly random variation. It has long been recognized that AD can cause focal and asymmetric clinical syndromes [44]. Likewise, individuals with AD can have FDG-PET scans that appear remarkably different but still are recognizable variations of a distinctive pattern of hypometabolism. AD patients with prominent language deficits have predominant hypometabolism in the dominant hemisphere, whereas those with predominant visual-spatial deficits

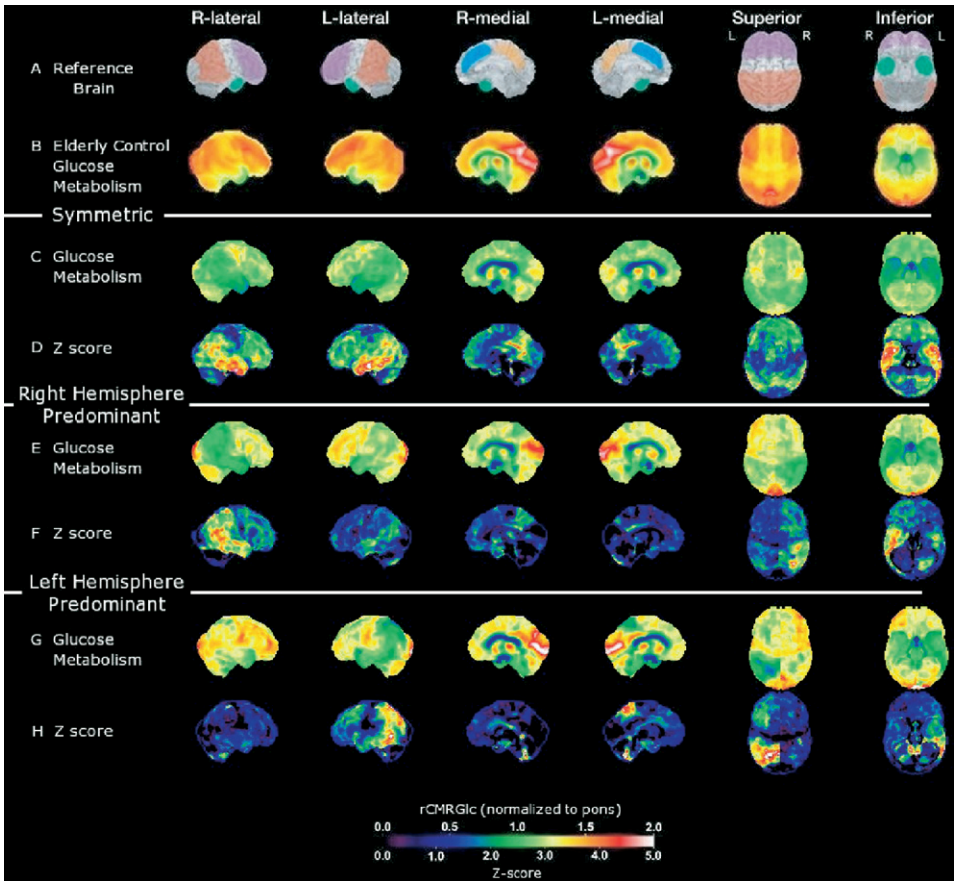

Fig. 4. Individual variations in the symmetry of glucose hypometabolism in AD. FDG-PET scans from three patients with AD enrolled in the ADNI study and meeting NINCDS-ADRDA criteria for probable AD. Scans are displayed as Neurostat SSP images as described in Fig 1. When FDG-PET results are averaged across groups of AD patients, metabolic abnormalities affect both hemispheres and appear symmetric. However, individual patients show significant variability, with one hemisphere often affected more than the other. In one patient (rows C and D), hypometabolism affects the posterior temporoparietal association cortex and posterior cingulate gyrus in both hemispheres symmetrically. In other patients these same areas are affected but asymmetrically, either with predominant hypometabolism in the right hemisphere (rows E and F) or left hemisphere (rows G and H).

have predominant hypometabolism in the nondominant hemisphere [45]. Patients with such metabolic asymmetry are routinely enrolled in AD drug trials, although these individual features remain unrecognized unless FDG-PET is performed. Whether this individual variation significantly affects the outcome of trials or leads to erroneous conclusions about drug effectiveness is unknown. Nevertheless, ADNI again serves as a useful reminder that metabolic asymmetry is often present in subjects enrolled in clinical trials. Figure 4 shows some examples.

The cause of this metabolic asymmetry is unknown. Genetic, environmental, and neurochemical factors are likely but have not yet been identified. Individuals with these metabolic patterns might differ in their rate of dementia progression or response to treatment. Further research clearly is needed. A significant barrier to understanding these phenomena has been the difficulty in recognizing when metabolic asymmetry is significant. Fortunately, new image analysis methods to tackle this problem are being developed and could mark a significant advance [46]. As we learn more about AD, it is clear that stereotypes are misleading. The full potential of therapeutics will not be realized until they can be tailored to address the variation of AD expression in individual patients.

4. Conclusions

FDG-PET is playing an increasing role in the clinical evaluation and management of dementing diseases. It provides unique, objective, and quantifiable information about the distribution and severity of brain pathology in AD. Accumulating experience with FDG-PET and new methods of image analysis have improved its reliability. It is time to use the advanced imaging technology of molecular imaging to hasten the development of new treatments and usher in an era of personalized medicine. The judicious use of FDG-PET could accelerate the evaluation of promising new drugs and lead to more rational targeting of treatments for dementing diseases.

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