Atypical forms of Alzheimer's disease: patients not to forget

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Purpose of review
The aim of this paper is to summarize the latest work on neuroimaging in atypical Alzheimer's disease (AD) patients and to emphasize innovative aspects in the clinic and research. The paper will mostly cover language (logopenic variant of primary progressive aphasia; lvPPA), visual (posterior cortical atrophy; PCA), behavioral (bvAD) and dysexecutive (dAD) variants of AD.

Recent findings
MRI and PET can detect and differentiate typical and atypical AD variants, and novel imaging markers like brain iron deposition, white matter hyperintensities (WMH), cortical mean diffusivity, and brain total creatine can also contribute. Together, these approaches have helped to characterize variant-specific distinct imaging profiles. Even within each variant, various subtypes that capture the heterogeneity of cases have been revealed. Finally, in-vivo pathology markers have led to significant advances in the atypical AD neuroimaging field.

Summary
Overall, the recent neuroimaging literature on atypical AD variants contribute to increase knowledge of these lesser-known AD variants and are key to generate atypical variant-specific clinical trial endpoints, which are required for inclusion of these patients in clinical trials assessing treatments. In return, studying these patients can inform the neurobiology of various cognitive functions, such as language, executive, memory, and visuospatial abilities.

Keywords
behavioral variant of Alzheimer's disease, dysexecutive variant of Alzheimer's disease, logopenic variant of primary progressive aphasia, neuroimaging, posterior cortical atrophy

INTRODUCTION

Early-onset Alzheimer's disease (AD) is a heterogenous group of syndromes in terms of pathology distribution, cognitive profile, and age of onset, usually appearing before the age of 65. Many of these patients present with an amnestic profile that is associated with other clinical manifestations such as greater impairment in attention, executive, language, behavior/personality, and visuospatial functions at the time of presentation (amnestic or typical AD (tAD); [1]).

In a small number of cases, these early-onset patients may present with nonamnestic symptoms in the first instance with relatively preserved memory; those patients are defined as atypical. First, the language variant corresponds to the logopenic variant of Primary Progressive Aphasia, lvPPA [2], characterized by impaired single-word retrieval, sentence repetition, and phonologic errors, and relative sparing of motor speech, grammar, and single-word comprehension. Significant brain damage is located in the left posterior temporoparietal region. The visual variant, named Posterior Cortical Atrophy (PCA), is characterized by initially isolated, progressive impairment of higher order visual and visuospatial skills, which usually manifest as visual agnosia, prosopagnosia, environmental disorientation, and elements of Balint's and/or Gerstmann's syndrome [3]. Patients with PCA show brain damage in the parietal occipital and posterior temporal

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KEY POINTS

- In recent years, distinct variant-specific imaging profiles have been characterized for atypical AD, namely the lvPPA, PCA, bvAD, and dAD.
- MRI and PET can detect and differentiate typical and atypical AD variants, and novel imaging markers like brain iron deposition, WMH, cortical mean diffusivity, and brain total creatine can also contribute.
- Within each atypical AD variant, subtypes that capture the heterogeneity of cases have been revealed.
- In-vivo pathology markers of amyloid and tau have led to significant advances in the atypical AD neuroimaging field.

cortices, which is often more prominent in the right hemisphere. The behavioral variant of AD (bvAD) must present two out of the five following symptoms, which are behavioral disinhibition, apathy or inertia, loss of empathy or sympathy, hyperorality and dietary changes, as well as documented impairments in executive functions and/or episodic memory with relatively preserved language and visuospatial abilities [4▪▪]. Brain damage in bvAD usually follows a frontotemporal or temporoparietal pattern. Finally, patients with the dysexecutive variant (dAD) have executive dysfunctions as core symptom with alterations of working memory, cognitive flexibility, and cognitive inhibitory control, in the absence of predominant behavioral features [5]. In the dAD, the alteration seems to depend on the interaction of the more anterior regions with the parietal regions, with a very important implication of the latter. Possible diagnoses of bvAD and dAD are given in the presence of AD biomarkers such as cerebrospinal fluid or positron emission tomography amyloid or tau. Other forms of atypical AD exist, such as the motor variant, which manifests as corticobasal syndrome. Given the emphasis on recent papers, the motor variant of AD will not be covered in this review as no article on this variant fulfilled the inclusion criteria.

The aim of this paper is to present the latest work on neuroimaging in atypical AD patients and to emphasize innovative aspects in the clinic as well as in research.

LOGOPENIC VARIANT OF PRIMARY PROGRESSIVE APHASIA

Compared to the other atypical variants of AD, the neuroimaging pattern of lvPPA is relatively homogeneous across patients and localized in the left temporoparietal, inferior parietal and posterior temporal regions [2,6]. This pattern was confirmed in a systematic review by Conca and colleagues, including 207 papers and reviewing grey matter atrophy, white matter fibre tracts, glucose metabolism and perfusion data in addition to clinical features [7▪▪]. This variant can be distinguished from other AD variants based on a higher degree of atrophy in left temporal regions (vs. tAD and PCA), a lower degree of hippocampal and entorhinal cortex atrophy (vs. tAD) and of right hippocampal and temporal regions (vs. PCA) [8]. lvPPA is also distinguishable from other PPA variants, namely the semantic variant of PPA (svPPA) and the nonfluent/agrammatic variants, using various neuroimaging markers, including the integrity of the dorsal and ventral streams of language [9].

Nonetheless, the differential diagnosis of lvPPA can remain challenging and for this reason, new pathology markers in imaging have been investigated. Quantitative susceptibility mapping able to detect iron has shown a specific pattern of iron deposition in lvPPA in expected regions such as the lateral temporal and parietal regions, predominantly in the left hemisphere, but also less expected regions like the occipital and medial temporal regions [10▪▪]. White matter hyperintensities (WMH) are markers of cerebral small vessel disease and are associated with higher risk of tAD. Nonetheless, the pattern of WMHs in lvPPA is mostly consistent with neurodegeneration, and this marker might be useful to differentiate lvPPA with PCA (greater subcortical WMHs in left parietal lobe and deep white matter WMHs) and tAD (greater frontooccipital subcortical and occipital periventricular WM) [11▪]. Other novel imaging markers include cortical mean diffusivity, which reflects microstructural disorganization [12▪]. It has been shown that this marker might be more sensitive than macroscopic cortical changes such as cortical thickness in lvPPA, since changes in cortical mean diffusivity were observed beyond the regions showing cortical thickness, as well as in very mild cases with minimal cortical thinning. Finally, new magnetic resonance spectroscopy markers, such as brain total creatine, are also emerging, and show a good ability to detect PPA variants [13▪].

Beyond the structural markers, it appears that the distribution of tau pathology (as measured using tau-PET) shows a highly network-specific distribution in each AD variant, and that it is predominantly correlated within the language network in lvPPA patients [14▪▪] (Fig. 1). Interestingly, regions with greater connectivity to the the disease-specific network hub (in the case of lvPPA, the left superior temporal gyrus), as defined in healthy controls, display similar longitudinal rates of tau accumulation,

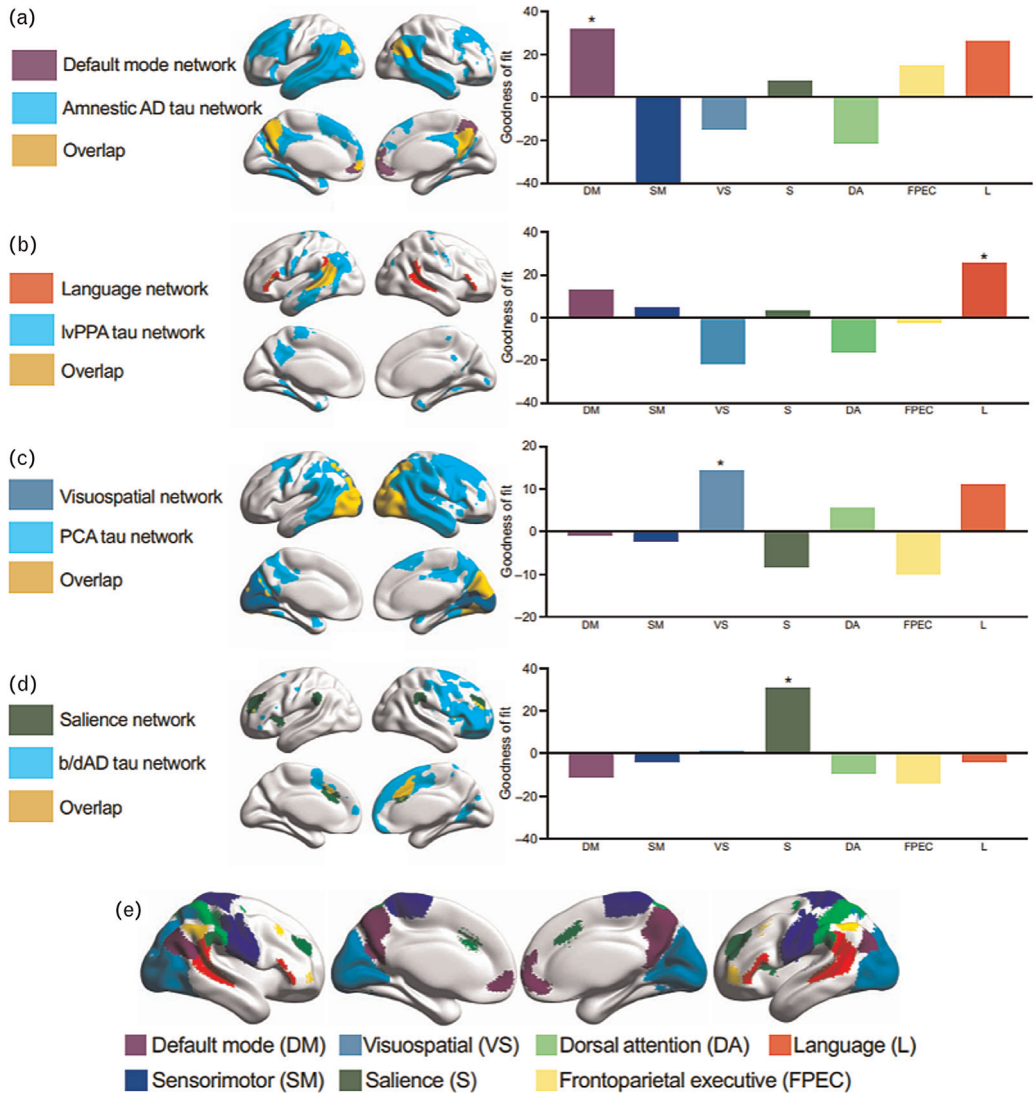

FIGURE 1. Tau covariance networks (on the left) and brain network template showing the best goodness of fit (on the right) in each AD variant: (A) typical AD (tAD); (B) logopenic variant of primary progressive aphasia (lvPPA); (C) posterior cortical atrophy (PCA); (D) behavioral variant AD (bvAD). Reproduction from (14). AD, Alzheimer's disease.

providing support to selective vulnerability and transneuronal spreading models of neurodegeneration [14▪▪].

POSTERIOR CORTICAL ATROPHY

Two main clinical variants of PCA have been described, depending on the main location of the brain damage: the biparietal variant, anatomically corresponding to an impairment of the dorsal visual pathway; the occipitotemporal variant corresponding to an impairment of the ventral visual pathway [15–17] (Fig. 2). One of the most frequent and invalidating symptoms in PCA patients is simultanagnosia which depends on both dorsal and ventral pathway. Simultanagnosia has been associated with gray matter reductions and decreased functional connectivity in the left middle occipital gyrus and the left inferior occipital gyrus [18]. In addition to the two mentioned variants, a rarer third phenotype is reported, called occipital variant, clinically characterized by basic-visual disorders and involvement of primary occipital cortices (Fig. 1). This third phenotype is also characterized by a less important hypometabolism in temporal-parietal regions compared with the other two variants [20▪▪]. Clinically, these patients have less ideomotor apraxia, absence of parkinsonism, and a milder degree overall symptom severity, including fewer neuropsychiatric features compared to the more documented phenotypes. Finally, a recent study also suggest that disease presentation might vary according to age of onset in PCA, with more involvement of temporal regions in late-onset cases and more involvement of

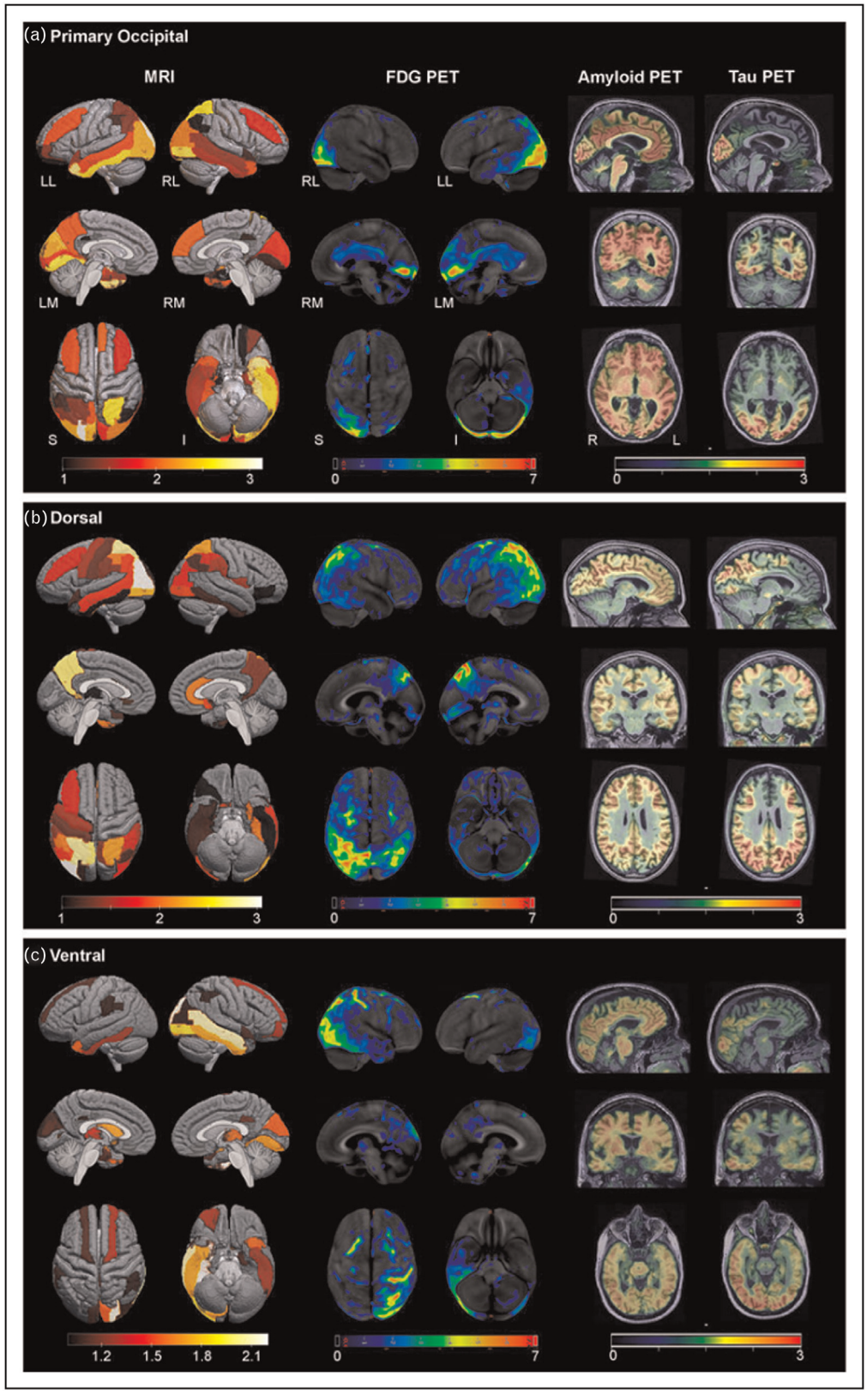

FIGURE 2. Neuroimaging features (Structural MRI on the left, fluorodeoxyglucose (FDG)-PET in the center, and amyloid- and tau-PET on the right) observed in the subvariants of posterior cortical atrophy: (A) primary occipital variant; (B) Dorsal variant; (C) Ventral variant. Reproduction from [20▪▪].

parietal regions in early-onset cases, as observed on FDG-PET [21].

PCA patients have greater thinning of lateral temporal structures in comparison to tAD [8]. Conversely, while some degree of episodic memory impairments and atrophy in the medial temporal lobe can be observed in PCA [19], these observations are significantly less severe than what is observed in tAD [8].

Structural and functional network changes occur early in AD but have not yet provided diagnostic specificity for atypical patients [22]. For these reasons, in recent times, new imaging markers have been used to study PCA. First, a specific pattern of iron deposition, mainly including middle occipital gyrus, amygdala, right inferior parietal, inferior temporal, and angular gyri, has been observed in PCA. Compared with tAD, PCA showed moderate and strong evidence for greater susceptibility particularly in medial and lateral parietal regions [10▪▪]. Furthermore, PCA patients have greater subcortical WMHs in right occipital, parietal, and temporal. Greater WMH is associated with visuoperceptual performance in PCA, but also in another atypical AD population, lvPPA [11▪].

While the distribution of tau pathology (as measured using tau-PET) shows a language network-specific distribution in lvPPA, it is predominantly correlated within the visuospatial network in PCA patients [14▪▪] (Fig. 1). Another study of functional connectivity and tau pathology in lvPPA and PCA has demonstrated high levels of tau pathology in the posteromedial cortex and hypoconnectivity between temporal and parietal nodes of the default mode network (DMN) [23]. However, several nodes remain strongly functionally connected to each other comparable to healthy controls, including parietal to frontal regions comprising the 'core' DMN. This suggests that regions with low tau (ex. anterior regions) are likely to retain functional connections with other regions with the DMN which carry a high tau burden (ex. posterior regions) until later stages of the disease [23].

BEHAVIORAL VARIANT OF ALZHEIMER'S DISEASE

In comparison to PCA and lvPPA, bvAD has been described very recently [4▪▪,24], but imaging patterns are starting to emerge, with atrophy observed in the frontal, parietal and temporal lobes. In view of the considerable heterogeneity in the neuroimaging profiles observed in bvAD patients, two different bvAD phenotypes that might exist on a continuum have recently been proposed [4▪▪] (Fig. 3). The first, and most prevalent, is an AD-like phenotype characterized by spared frontal regions, while the second is a bvFTD-like phenotype characterized by both posterior and anterior involvement.

Recent neuroimaging work on bvAD has continued to establish its differentiation with tAD (different phenotype associated with the same neuropathology) or with behavioral variant frontotemporal dementia (bvFTD; similar phenotype but with different neuropathology). In comparison to tAD, bvAD patients show more atrophy in frontal regions [4▪▪], and potentially higher gray matter volume in the posterior hippocampus [25]. In comparison to bvFTD, bvAD patients show more cortical thinning in left temporal-occipital regions, but less frontal and anterior temporal lobe atrophy [25].

While the distribution of tau pathology (as measured using tau-PET) shows a language network-specific distribution in lvPPA, it is predominantly

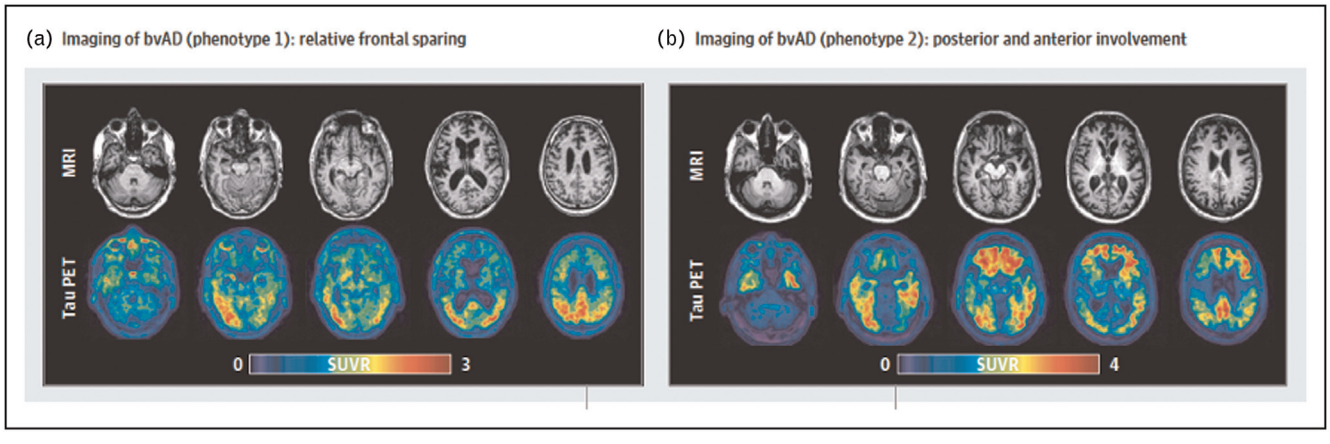

FIGURE 3. Neuroimaging features (Structural MRI on the top, tau-PET on the bottom) observed in the subvariants of behavioral variant of Alzheimer's disease (bvAD): (A) relative frontal sparing subvariant; (B) Posterior and anterior involvement subvariant. Reproduction from [4▪▪].

correlated within the salience network in bvAD patients [14▪▪] (Fig. 1). This network, which includes the anterior cingulate cortex, the ventral anterior insula, the amygdala, the hypothalamus, the ventral striatum, the thalamus, and specific brainstem nuclei, plays a large role in socioemotional function and shows selective vulnerability in bvFTD [26]. Nonetheless, tau aggregation is also observed in most bvAD patients in posterior parietal regions [14▪▪], which provides support to the two phenotypes proposed by Ossenkoppele and colleagues [4▪▪].

DYSEXECUTIVE VARIANT OF ALZHEIMER'S DISEASE

Similarly, to bvAD, dAD has been very recently described [5] and is characterized by fronto-parietal atrophy and hypometabolism. The pattern of neurodegeneration in dAD is different than in tAD, with lower cortical thickness observed in parieto-frontal areas in dAD and in hippocampal and temporal regions in tAD [27]. However, just like in PCA and bvAD, neuroimaging patterns in dAD is characterized by a large clinico-radiological heterogeneity [28,29▪▪], which has led to the preliminary extraction of different phenotypes [28] (Fig. 4). First, the ''bi-parietal-dominant'' subtype appears as the most frequent and is defined by a mild hypometabolism in bilateral parietal regions and younger age at onset. Second, the ''heteromodal-diffuse'' subtype, which appears almost as frequent as the ''bi-parietal-dominant'' subtype, is characterized by hypometabolism in bilateral heteromodal cortices, younger age at onset and more severe cognitive impairments. Third, patients with the ''left-dominant'' subtype present predominant hypometabolism in the left

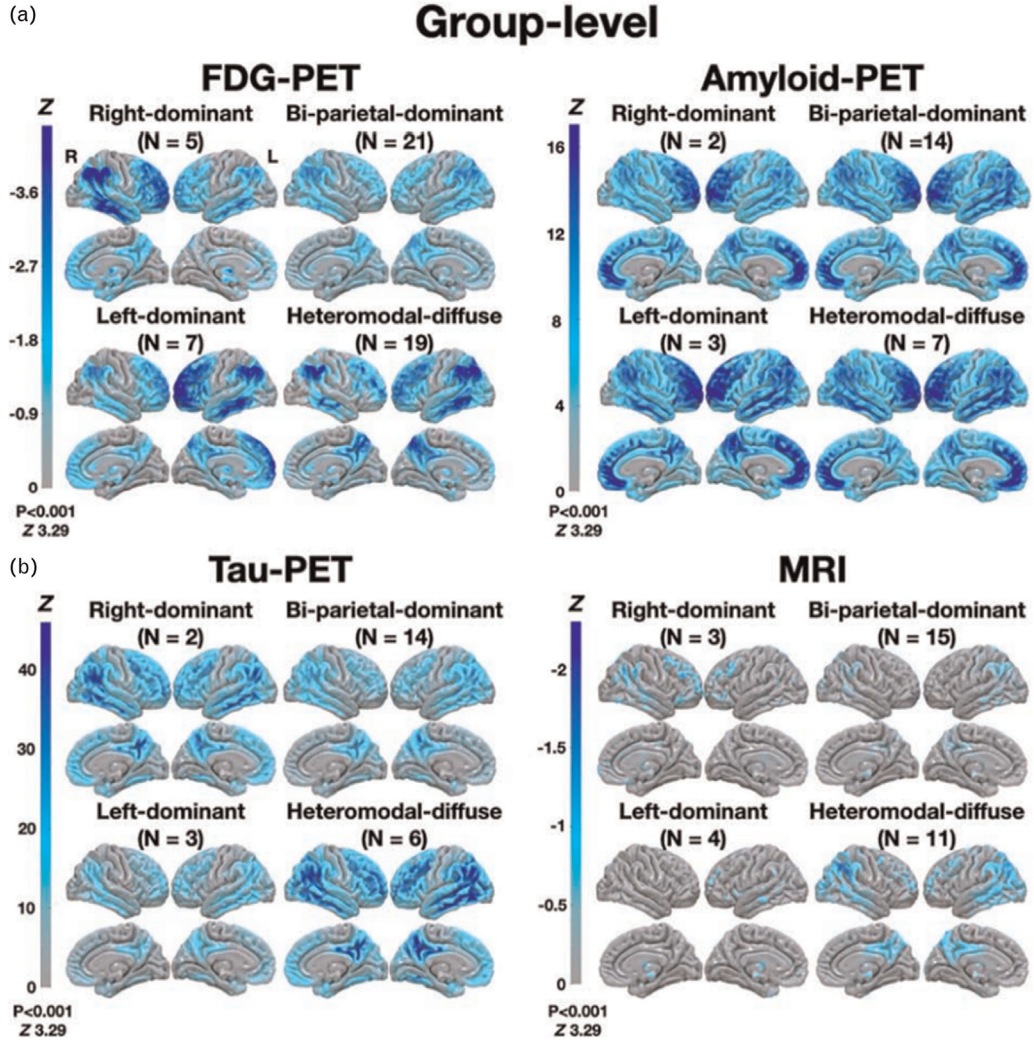

FIGURE 4. Neuroimaging features (FDG-PET in the top left, amyloid-PET on the top right, tau-PET on the bottom left, structural MRI on the bottom right) observed in the subvariants of dysexecutive variant of Alzheimer's disease (dAD): right-dominant, bi-parietal dominant, left-dominant and heteromodal diffuse subvariants. Reproduction from [29▪▪].

heteromodal cortices. Fourth, the ''right-dominant'' subtype shows predominant hypometabolism in the right heteromodal cortices. Interestingly, each subtype of dAD showed similar specific spatial patterns of tau-PET uptake and neurodegeneration to those seen in FDG-PET hypometabolism, but comparable patterns of amyloid deposition.

CONCLUSION

The field of atypical AD has seen tremendous growth in recent years, particularly in the study of imaging-based markers. These studies have highlighted the potential of tools such as structural/functional MRI and FDG/amyloid/tau PET to detect AD and distinguish typical and atypical variants from one another. One interesting development in the field is the investigation of new imaging markers such as brain iron deposition, WMH, cortical mean diffusivity, and brain total creatine.

Another important theme emerging from recent research is the recognition of the complexity of atypical AD variants. Studies have suggested that even within atypical AD variants (PCA, bvAD, dAD), various subtypes can be observed, which can better capture the heterogeneity of cases. While further validation is needed, this is an exciting perspective that could help clinicians and neuroscientists better understand and diagnose these patients, even if they present with rarer features. While clinical heterogeneity has also been reported in lvPPA, no study has proposed subtypes yet. Contrary to other dementias such as frontotemporal dementia, in-vivo pathology markers exist in tAD and atypical AD variants, which has led to significant advances in the neuroimaging field over the past year. Given that these markers are sensitive early in the disease process, we hope that this will facilitate the early diagnosis of atypical AD patients, as it is the case in tAD with concepts such as subjective cognitive decline and mild cognitive impairment, and more recently mild behavioral impairment [30].

While significant strides have been made in understanding atypical AD, there are also many aspects to be explored in the future. bvAD and dAD have been more recently described, and there is still much to be learned about them compared to better-characterized subtypes such as lvPPA and PCA. It is also important to further investigate the similarities and differences between bvAD and dAD, which were initially considered a single subtype. Additionally, AD pathology can cause other phenotypes not described in this review, such as motor variant of AD or even svPPA, which have been previously described as clinically indistinguishable from patients with non-AD svPPA but have a parietal involvement that is absent in the others [31]. While progress has been made in diagnosing atypical AD, more longitudinal studies are needed to understand the disease progression. Similarly, to what has been observed in tAD, tau-PET uptake plateaus or declines in older and more severe atypical AD cases [32▪▪], which has significant clinical implications. Furthermore, it is important to investigate the interaction between genetic factors and imaging marker. For example, in atypical AD patients (PCA & lvPPA), the influence of APOE ε4 on both the patterns of neurodegeneration and tau deposition has been established, with individuals carrying this genetic variant displaying more medial temporal involvement at baseline, although there is evidence that noncarriers may catch up in their rate of progression over time [33▪]. While there have been many group-based studies, it is also important to investigate single-subject markers that can be used in clinical settings, where borderline profiles can be observed [34,35].

In conclusion, while the focus on typical AD is understandable, it is important to understand the rarer subtypes of AD and their characteristics as they may open up new targets for therapy and enable better adaptation of existing treatments towards personalized medicine. Clinical trials have mostly focused on typical AD, but better characterization of atypical AD may facilitate their inclusion in disease-modifying treatment studies. Additionally, knowledge of the heterogeneity of AD may clarify the role of different parts of the brain in cognitive processes and behaviors, as well as in the pathogenesis of neurodegenerative diseases.

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Conflicts of interest

There are no conflicts of interest.

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- ▪ of special interest
- ▪▪ of outstanding interest

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