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Review

Frontal variant Alzheimer's disease: A systematic narrative synthesis

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ABSTRACT

Background: Frontal variant Alzheimer's disease (fvAD) is considered a rare form of Alzheimer's disease (AD) which may be misdiagnosed as behavioural variant frontotemporal dementia (bvFTD). The literature has tended to conflate behavioural and executive dysfunction in fvAD cohorts and uses both AD diagnostic criteria and bvFTD diagnostic criteria to classify fvAD cohorts. The primary aim of this narrative synthesis was to summarise neuropsychological findings in fvAD cohorts in the context of established AD pathology.

Methods: EMBASE, PsycINFO, PROQUEST and MEDLINE databases were searched for studies eligible for inclusion. Studies with both neuropsychological and biomarker evidence were included in the final narrative synthesis.

Results: Ten studies were reviewed, including samples totalling 342 fvAD participants, 178 typical AD participants and 250 bvFTD participants. The review revealed areas worthy of further investigation that may aid differential diagnosis, including the degree of executive dysfunction in fvAD cohorts relative to bvFTD cohorts, the onset of behavioural and cognitive symptomatology, and similarities between fvAD and typical AD cognitive profiles.

Conclusion: There was insufficient neuropsychological evidence to clearly differentiate fvAD and bvFTD cognitive phenotypes, however, the review has highlighted distinctive features of the two disorders that may guide differential diagnosis in future research. Moreover, the review has highlighted issues involving disparate diagnostic criteria used to classify fvAD cohorts, contributing to variation in findings.

Alzheimer's disease (AD) is the most common cause of dementia, accounting for approximately 60–70% of dementia diagnoses worldwide (World Health Organisation, 2019), and is characterised by an insidious onset and a progressive cognitive decline that markedly interferes with an individual's everyday functioning. One of the most commonly used clinical diagnostic criteria for AD was established by the National Institute on Aging and Alzheimer's Association (NIA-AA; McKhann et al., 2011) for presentations that classify as probable AD, possible AD, or probable or possible AD with

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biomarker evidence. Under these criteria, cognitive impairments are classified by amnestic and non-amnestic presentations. Generally speaking, the amnestic presentation refers to the typical AD profile with prominent episodic and semantic memory impairments relative to other cognitive domains, whilst non-amnestic presentations classify the less common phenotypic variants of AD which present with prominent impairment in language, executive, visuoperceptual and motor functions. These include logopenic aphasia, posterior cortical atrophy, corticobasal syndrome, and the focus of the present review, frontal variant AD (fvAD), which to date has conflated syndromes with a prominent behavioural presentation and prominent executive dysfunction (Dubois et al., 2014; Mathew, Bak, & Hodges, 2011; McKhann et al., 2011).

Frontal variant AD is not as well characterised as typical AD and consequently the prevalence of the disease is unknown, but it is cited as either a frequently misdiagnosed or rare AD variant (Sawyer, Rodriguez-Porcel, Hagen, Shatz, & Espay, 2017; Taylor, Probst, Miserez, Monsch, & Tolnay, 2008). This picture is further complicated by the highly similar presentation of fvAD and behavioural variant frontotemporal dementia (bvFTD), namely with frontally-focussed, behavioural undertones (Woodward, Rowe, Jones, Villemagne, & Varos, 2015), making for a complex differential diagnosis. To date, the lack of clinical consensus criteria for fvAD and the variation in nomenclature and descriptions of fvAD has resulted in disparities across research cohorts. These include investigations of fvAD network neurodegeneration such as the origin of fvAD pathology, the degree to which the medial temporal lobe (MTL) and hippocampus are spared, and the investigations of "frontal" features in the context of prominent executive impairments, behavioural dysfunction, or both. Recently, however, Townley et al. (2020) proposed a set of diagnostic criteria to classify a "progressive dysexecutive syndrome" for possible dysexecutive AD ("progressive dysexecutive syndrome with Alzheimer's pathologic change") and definite dysexecutive AD ("progressive dysexecutive syndrome due to Alzheimer's disease"). These newly established criteria assert a clear distinction from the behavioural variant AD as defined by Ossenkoppele et al. (2015), a condition with a predominant behavioural presentation with AD biomarkers, which would more closely meet the clinical criteria for bvFTD. Although some research has proposed executive dysfunction (e.g., difficulty with abstract reasoning, problem solving, judgement, mental flexibility, planning and organisation) as an early feature of AD (Chen et al., 2001; Perry & Hodges, 1999), this systematic narrative review will follow the suggestion from Townley et al. (2020) and refer to AD profiles with prominent executive dysfunction (early in the disease course) relative to other cognitive domains as fvAD classifications, and distinct from typical AD with predominant and early episodic and semantic memory impairments. It proceeds by summarising the cognitive and/or behavioural classifications of fvAD in the literature, and corresponding biomarker evidence.

Behavioural variant frontotemporal dementia (bvFTD) is a subtype of frontotemporal dementia (FTD) characterised by the progressive bilateral degeneration of prefrontal cortical regions and anterior temporal lobes. Disruption of emotional control and personality follow the deterioration of social cognition, emotional regulation and decision-making neural networks (Piguet & Hodges, 2013). Subtle distinctions in patterns of atrophy, proposed by Ranasinghe et al. (2016), suggest the existence of distinct bvFTD subtypes with specific cognitive, socioemotional, and motor symptoms, in addition to specific genetic abnormalities and rates of disease progression.

The diagnostic criteria proposed by Rascovsky et al. (2011) characterise bvFTD in terms of persistent and early symptoms of either behavioural disinhibition, apathy, loss of sympathy, compulsive/ritualistic behaviour, hyperorality and dietary changes (associated with weight gain), or dysexecutive features, in the context of relatively intact episodic memory and visuospatial functions. Although the Rascovsky group's diagnostic criteria support the relative sparing of episodic memory—and previous literature reports this as a "gold standard" indicator for differentiating typical AD from bvFTD—the evidence for episodic memory impairment in bvFTD has increased substantially in recent years, and a general consensus is slowly being reached that both typical AD and bvFTD may present with episodic memory impairments, potentially complicating differential diagnosis (Hodges & Piguet, 2018; Hornberger, Piguet, Graham, Nestor, & Hodges, 2010; Hornberger & Piguet; 2012; Piguet & Hodges, 2013; Wong et al., 2016).

The characteristic AD biomarkers of amyloid-β deposition, tau protein deposition and neurodegeneration preferentially impacting the anterior lobes have implicated the frontal cortex as the site of origin of fvAD (Habek, Hajnšek, Žarković, Chudy, & Mubrin, 2010; Johnson, Head, Kim, Starr, & Cotman, 1999; Phillips et al., 2019). Similarly, Taylor et al. (2008) described a fvAD patient with severe tau pathology in the frontal lobes, but the entorhinal cortex, hippocampus, and temporal lobes presented a comparatively low tau count. With reference to neuroimaging, hypometabolism in the prefrontal cortices of fvAD patients has been described as a distinct pattern of activation useful for differentiating fvAD from typical AD (Dronse et al., 2017; Phillips et al., 2019; Woodward et al., 2015), however, a differential diagnosis from bvFTD may prove more challenging, as Wong et al. (2016) argued that patterns of atrophy observed in fvAD populations are comparable with those seen in bvFTD populations, involving specifically the MTL and prefrontal cortex.

The regional distribution of fvAD pathology is unclear, however, in recent years there has been a growing body of research implicating parietal lobe regions. Townley et al. (2020) described a pattern of fronto-parietal pathology for a dysexecutive and/or behavioural AD cohort, and Ossenkoppele et al. (2015) evaluated three patient groups with predominant temporoparietal atrophy and relative sparing of the frontal lobes: behavioural-variant AD, dysexecutive-variant AD, and a combined behavioural/dysexecutive subtype.

Past research has suggested that hippocampal sparing/non-amnestic presentations are typically correlated with earlier disease onset and faster disease progression relative to typical AD (Mendez, 2019; Murray et al., 2012; Phillips et al., 2019; Whitwell et al., 2012). The presenilin 1 (PSEN1) mutation, commonly associated with early onset AD pathology, has also been linked to fvAD (Mendez & McMurtray, 2006; Monacelli et al., 2019; Nygaard, Lippa, Mehdi, & Baehring, 2014) and the behavioural changes seen in bvFTD patients

(Mendez & McMurtray, 2006). Calvo, Ramos, and de Lucena (2013) found fvAD patients were more likely to have a family history of AD and lower frequency of the APOE e4 allele compared with typical AD cohorts.

At present, consensus has not been reached regarding a cognitive profile for fvAD. Previous research has stressed the overlapping behavioural and dysexecutive features characteristic of fvAD and bvFTD patients, noting that this overlap has subsequently led to the frequent misdiagnosis of fvAD as bvFTD (Balasa et al., 2011; Blennerhassett, Lillo, Halliday, Hodges, & Kril, 2014; Ossenkoppele et al., 2015; Sawyer et al., 2017). Indeed, approximately 10–40% of individuals diagnosed with bvFTD are found to have AD biomarkers on amyloid PET imaging or on post mortem pathological analysis (Ossenkoppele et al., 2015). Sawyer et al. (2017) have described subtle distinctions between the two cohorts: in conversation, the fvAD patient may present with word-finding difficulties, naming difficulties, and semantic and phonemic paraphasias, whereas bvFTD patients may be lacking in social-emotional aspects of conversation and may miss subtle cues. The fvAD presentation is also suggested to encompass different behavioural features compared with bvFTD: for example, the presence of compulsive and perseverative behaviours frequently seen in bvFTD are reported as infrequent in fvAD. Notwithstanding these differences, a frequently used diagnostic criterion for fvAD is the fulfilment of a probable bvFTD diagnosis in conjunction with AD biomarker evidence (de Souza, Mariano, de Moraes, & Caramelli, 2019).

The complex nature of fvAD differential diagnosis and the variation found across previous reports has prompted this systematic narrative review which aims to summarise current classifications of fvAD in the literature and provide a background to appropriately position new research. As Perry et al. (2019) and Langheinrich et al. (2021) discuss, the detrimental effect of misdiagnosis includes inappropriate treatment or erroneous understanding of prognosis. It was concluded by Perry et al. that within a longitudinal review of patients with varying clinical diagnoses ($N = 313$), patients diagnosed with AD ($N = 49$) showed changes throughout their visits, with implications for clinical prognostication and responses, and reflecting the need for greater specificity; indeed, it was later determined that a large proportion of the cohort had their diagnosis revised to fvAD. Furthermore, it was highlighted that although the need is great, facilities with experience to evaluate bvFTD and any symptomatically-overlapping atypical AD are not common. Therefore, the primary outcome of this review will be to summarise cognitive and behavioural findings, and evaluate how these findings may differentiate fvAD from bvFTD in light of commonalities and newly recognised symptomatology.

1. Method

1.1. Protocol and registration

This review used the Preferred Reporting Items for Systematic reviews (PRISMA; 2009) checklist as a guideline for the dissemination of materials collected (Liberati, Altman, Tetzlaff, Mulrow, & Gøtzsche, 2009; Moher, Liberati, Tezlaff, & Altman, 2009) and was registered in PROSPERO (registration number CRD42020172733: 2020).

1.2. Eligibility criteria

Eligibility criteria were based on participants, methodology and outcome measures as described by the PICOS tool (Population, Intervention, Comparison, Outcome, Study Design; Methley, Campbell, Chew-Graham, McNally, & Cheraghi-Sohi, 2014).

Participants (1): Inclusion criteria included studies of human participants, examining populations with AD biomarkers (e.g., CSF, structural or functional neuroimaging, post mortem pathology) in conjunction with prominent behavioural and/or executive dysfunction. Exclusion criteria included published material describing mild cognitive impairment and subjective cognitive impairment, and comorbidities (e.g., intellectual disability, Parkinson's disease, Huntington's disease).

Intervention (2): Inclusion criteria were based on studies that explicitly stated/defined diagnostic criteria used to classify fvAD (or variant nomenclature; and therefore did not include consensus meetings amongst specialists), provided sufficient neuropsychological data on measures of the single domain of executive functioning or across multiple cognitive domains (e.g., attention, working memory, learning and memory, visuospatial), used a minimum sample size of 12 for the fvAD cohort (or variant nomenclature), and corresponding biomarker evidence. Biomarker evidence may include, although was not limited to, functional and structural neuroimaging, CSF, and genetic testing, or sufficient post-mortem evidence.

Comparisons (3): Comparisons made between fvAD cohorts and healthy controls, bvFTD, typical AD or other non-amnestic AD variants were eligible for inclusion.

Outcomes (4): Outcomes included cognitive outcomes characterising fvAD patients and corresponding biomarker evidence.

Study Design (5): Any research studies and randomised control trials, published in peer-reviewed journals in English were eligible for inclusion in the narrative synthesis component of this systematic review. Conference proceedings, case studies and case series were not included.

1.3. Information sources and search strategy

For published studies, the electronic databases EMBASE, PsycINFO, PROQUEST and MEDLINE were searched up to the 30th December 2021. The following search terms were used (“*frontal variant Alzheimer's*" OR "*dysexecutive Alzheimer's*" OR "*behavio?ral variant Alzheimer's*" OR "*dysexecutive AND Alzheimer's*"). Search terms “atypical Alzheimer's” and “non-amnestic” and “hippocampal sparing” were explored through database thesauruses and excluded from the search criteria. The rationale here was that (1) studies that classify cohorts with Alzheimer's pathology with prominent executive and/or behavioural features would be obtained via the current search criteria, and (2) using the current search criteria followed by Medical Subject Headings (MeSH)—the controlled thesaurus

for indexing articles—search did not reveal the latter three search terms. No date restrictions were applied. Published studies obtained through other sources such as reference lists of included reports and web searches were reviewed for additional data. PROQUEST searches were applied with the limit "peer reviewed only", for efficient extraction of literature.

1.4. Data extraction and analysis

Two investigators extracted the data and were involved in the study selection process. Stage 1 involved screening titles (and abstracts where titles alone did not give enough information about article content), Stage 2 included screening abstracts and full text, and in Stage 3 the remaining papers were assessed for review eligibility. Data extraction included specific details about the population (e.g., demographic data such as age) and participant characteristics, cognitive profiles, biomarkers, study methods and outcomes of significance for the review question. Authors were contacted if insufficient information was available. Disagreements between reviewers were resolved by careful assessment of the paper's eligibility with respect to the inclusion criteria (see Appendix A; Tables A1, A2, A3). At this stage, additional exclusions were made based on insufficient neuropsychological data and/or insufficient biomarker findings. A meta-analysis was deemed not appropriate due to the heterogeneity in study designs.

2. Results

2.1. Overview of search results

A total of 35091 citations were extracted. Following the removal of 20574 duplicates, 14517 citations were included in the initial title (or title and abstract in cases where titles were ambiguous) screening process. There were 193 records remaining to be screened following exclusion of 14324 articles based on titles/abstracts. Finally, abstract and full texts were screened against inclusion and exclusion criteria (see PRISMA flow diagram; Fig. 1), leaving ten experimental studies for qualitative synthesis (Appendix C). Seventeen case study designs and case series identified were not included in the narrative synthesis component of this review and instead were included as an additional resource for future research (Appendix D).

2.2. Study and participant characteristics

All participants included in the narrative synthesis had a dementia diagnosis of either typical AD (also referred to as amnestic AD in the literature), fvAD (also referred to as behavioural AD, dysexecutive AD, behavioural/dysexecutive AD, impaired executive AD), or bvFTD (in some cases classified into tau-positive and tau-negative cohorts). The synthesised experimental designs presented biomarker and neuropsychological outcomes of 342 fvAD participants, 178 typical AD participants and 250 bvFTD participants across longitudinal and cross-sectional designs (Appendix D). Participant mean age ranged from 57.1 to 72.8 years for fvAD cohorts, 59.4–75.9 years for typical AD cohorts, and 60.3–64.8 years for bvFTD cohorts.

2.3. Narrative synthesis

The narrative synthesis outlined below describes the findings of ten research studies in the literature (see Appendix C for details). Variation in classifications of fvAD either from presentation and neuropsychological test results, specific anatomical features (e.g., structural MRI or autopsy) or other biomarker driven findings (e.g., CSF) made direct comparisons between studies difficult and is further addressed in the discussion of this paper. Likewise, classifications of fvAD cohorts using variable diagnostic criterions including the McKhann et al. (2011) AD criteria, Dubois et al. (2014) AD criteria, Rascovsky et al. (2011) bvFTD criteria and the Lund and Manchester Group (1994) and/or the Neary et al. (1998) FTD clinical criteria, made across-study comparisons difficult and contributed largely to the variability in cohort findings. Table C (Appendix C) should be consulted for descriptive significant differences reported in the synthesis. As such, the findings of each study are discussed with constraint, with the discussion comprising comparative remarks.

2.4. Classification

Throughout the ten studies described and compared in this narrative synthesis, the predominant theme is the lack of consistency, importantly in which classification system each study chose to use, as well as diagnostic criteria and analysis measures. Firstly, Wong et al. (2016) compared bvFTD ($n = 22$) and AD cohorts ($n = 35$) across measures of episodic memory performance and cortical atrophy, dividing the AD cohort into an impaired executive function subgroup (IEF-AD, $n = 23$) and relatively spared executive function subgroup (SEF-AD, $n = 12$). The AD cohort was classified using the McKhann et al. (2011) diagnostic criteria and the bvFTD cohort was classified using the Rascovsky et al. (2011) diagnostic criteria. Similarly, Ossenkoppele et al. (2015) evaluated three cohorts with predominant temporoparietal atrophy and relative sparing of the frontal lobes: behavioural-variant AD ($n = 55$), dysexecutive-variant AD ($n = 29$), and a combined behavioural/dysexecutive AD subtype ($n = 75$). The diagnostic guidelines for probable AD also followed the McKhann et al. (2011) criteria and the bvFTD characterisations utilised the Rascovsky et al. (2011) standards. The behavioural AD cohorts' initial presentation was characterised by cognitive difficulties followed by behavioural features where 80% met the criteria for 'possible bvFTD', however only 52% met the formal criteria for a bvFTD diagnosis (Rascovsky et al., 2011). Notably, this finding is consistent with the difficulties highlighted in previous literature when differentiating fvAD and bvFTD cohorts. None of the dysexecutive-AD cohort met the criteria for possible bvFTD following Rascovsky et al. (2011) and only seven participants with the combined behavioural/dysexecutive subtype met the criteria for bvFTD; these cohorts were compared with a typical AD cohort ($n = 58$) and a bvFTD cohort ($n = 59$). Interestingly, however, Phillips and colleagues' (2018) study of amnestic and non-amnestic AD subjects demonstrated that AD pathology originated from different areas of the neocortex and followed distinct patterns of progression depending on the phenotype using four MRI-defined phases (with Phase 1 indicating disease origin). Non-amnestic subjects included

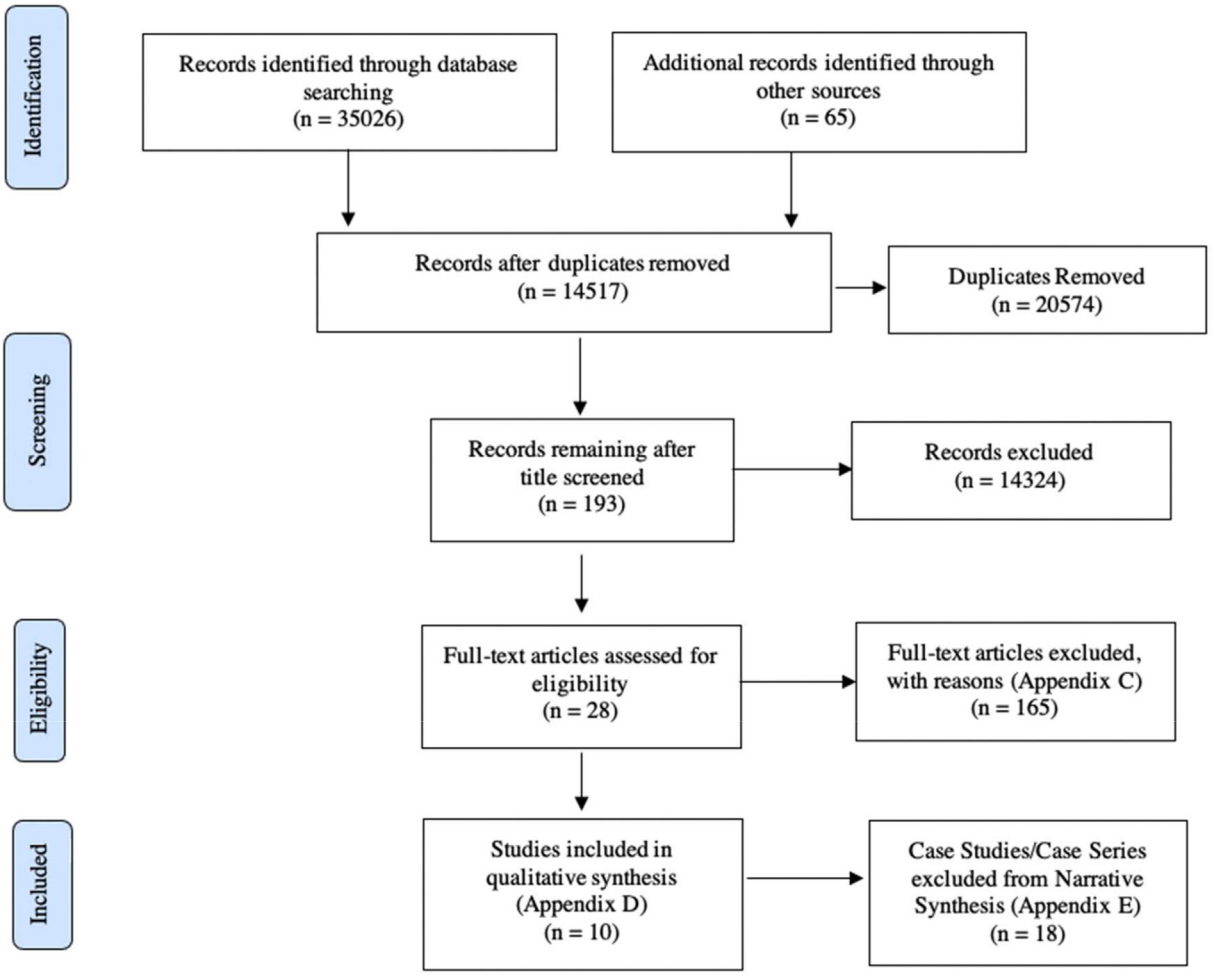

Fig. 1 – PRISMA flow diagram representing experimental and case study articles screened through database search and records identified through other sources.

behavioural variant AD (nb. the bvAD label in this instance is synonymous with fvAD and not the Ossenkoppele et al., 2015, behavioural AD terminology), logopenic variant primary progressive aphasia, posterior cortical atrophy and corticobasal syndrome. The amnestic AD cohort (n = 22) was classified using the McKhann et al. (2011) criteria, with patients presenting with primary memory impairments in addition to one or more other impacted domains.

Following the procedure of the previous studies, Phillips et al. (2019) investigated differences in disease progression in amnestic and non-amnestic (i.e., logopenic variant primary progressive aphasia, posterior cortical atrophy, fvAD) AD cohorts. The authors classified amnestic AD (n = 17) using the McKhann et al. (2011) criteria. fvAD cohorts (n = 12) were classified based on evidence of a behavioural/dysexecutive syndrome using the Rascovsky et al. (2011) bvFTD criteria. Similarly, Calvo, Ramos, and de Lucena (2013) investigated the clinical features of early onset typical AD (n = 47) and early onset ADfv (n = 13; nb. their ADfv label is synonymous with fvAD terminology). A diagnosis of AD was made using the McKhann et al. (1984) clinical diagnostic criteria of the National Institute of Neurologic, Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) and met the criteria for mild AD following the Clinical Dementia Rating method (CDR-1; Hughes, Berg, Danziger, Cohen, & Martin, 1982). However, in contrast with the previous studies that utilised the McKhann et al. (2011) criteria for fvAD diagnosis, in the case of bvAD (n = 22), patients were diagnosed using the Rascovsky et al. (2011) bvFTD criteria, based on deficits in social functioning or executive functioning with the co-occurrence of AD pathology.

Despite several studies following the same criteria for differentiating their patient populations, Forman et al. (2006) investigated neuropathological features of individuals presenting with social, behavioural, and/or language impairments characteristic of frontotemporal lobar degeneration (FTLD). The FTLD cohort conflated the bvFTD, fluent and

nonfluent aphasic patients using the Lund and Manchester (1994)clinical criteria and/or the Neary et al. (1998) clinical criteria. Of the patients who underwent neuropsychological evaluations, the presence of tau-positive inclusions classified the FTLD tauopathy subgroup ($n = 38$), the presence of ubiquitin-positive and tau-negative inclusions classified the FTLD TDP-43 subgroup, and dementia lacking distinctive histology (DLDH) cohorts were classified by the relative absence of inclusion pathology ($n = 26$). The AD cohort ($n = 17$) met the clinical criteria for FTLD (either Lund and Manchester Group, 1994 and/or Neary et al., 1998), however, had a primary post mortem neuropathological diagnosis of AD.

Furthermore, using an autopsy registry of more than 500 patients with neurodegenerative diseases at the Center for Neurodegenerative Disease Research of the University of Pennsylvania, Grossman et al. (2007) compared imaging features of tau-positive FTD ($n = 22$) and tau-negative FTD ($n = 25$) with fvAD ($n = 14$) cohorts. The classifications of the FTD and AD cohorts were based on an initial clinical diagnosis FTD spectrum disorder and autopsy (histopathologic and immunohistochemical analysis) findings, whilst neuropsychological findings and MRI profiles contributed to antemortem diagnostic accuracy. Using the same registry, Grossman et al. (2008) investigated the longitudinal progression of decline in cognitive functioning in autopsy proven cohorts of FTLD and fvAD. The FTLD cohorts were classified using criteria that specified tau-positive ($n = 17$) as well as tau-negative ($n = 11$) subgroups, and the fvAD cohort ($n = 12$) had a clinical misdiagnosis of FTLD spectrum disorder and histopathological evidence of AD.

Sala et al. (2020) investigated patterns of hypometabolism across typical AD ($n = 22$) and atypical AD variants (fvAD, $n = 15$), diagnosed according to the IWG-2 criteria (Dubois et al., 2014), and in contrast with the aforementioned studies, Townley et al. (2020) proposed their own set of diagnostic criteria for a dysexecutive AD cohort, in an attempt to distinguish between clinical presentations of behavioural variant AD and dysexecutive AD phenotypes. Townley and colleagues investigated 55 individuals who were positive for AD pathology and who met the criteria of prominent executive dysfunction (i.e., working memory, cognitive flexibility, and inhibition) in the absence of predominant behavioural features. Overall, it appears there is a lack of consensus, and therefore a lack of generalisability between studies. Without consistent diagnostic criteria and measures, one cannot accurately compare results between studies.

2.5. *Neuropsychological assessment*

The extent and specific nature of neuropsychological assessment varied significantly across the reviewed studies. Across several domains, there was general consistency in the coverage of executive function features, however consideration of other domains of cognition was variable across studies in terms of analysis and discussion.

2.6. *Executive function*

Wong et al. (2016) compared bvFTD and AD (subdivided into cohorts of IEF-AD and SEF-AD). On measures of executive functioning used to classify the IEF- AD and SEF-AD cohorts, the authors found the SEF-AD cohort performed better than the bvFTD cohort on measures of verbal fluency and the Hayling Sentence Completion Test. No significant differences were discernible between the IEF-AD and bvFTD cohort across measures of executive function, indicative of the potential for misdiagnosis. The authors noted that the bvFTD cohort demonstrated greater behavioural disturbances, however, and suggested that further research is required to determine if this would successfully distinguish between the IEF-AD cohort and bvFTD cohort. Additionally, Ossenkoppele et al. (2015), in their evaluation of three cohorts with predominant temporoparietal atrophy and relative sparing of the frontal lobes (i.e., behavioural-variant AD, dysexecutive-variant AD, and combined behavioural/dysexecutive AD subtype) also found the dysexecutive AD cohort and behavioural AD cohort had impaired executive functioning which did not differ significantly between groups, supporting the cautions of Wong et al. (2016). However, both groups were significantly impaired when compared with the typical AD and bvFTD patients. Foreman et al. (2006), when comparing fvAD with tau-negative FTLD participants discovered that the fvAD cohort demonstrated greater impairments on a measure of attention (Digit Span Forward) relative to the tau-negative cohort. Grossman et al. (2007) noted the tau-negative FTLD cohort presented with greater behavioural changes and problems with verbally-mediated executive functions. The authors concluded these findings were in favour of greater executive dysfunction in the FTLD cohorts relative to fvAD cohorts, supported by the results of Foreman et al. (2006). Calvo, Ramos, and de Lucena (2013) investigated the clinical features of early onset typical AD and early onset ADfv. Their neuropsychological assessment found severe executive dysfunction (Trail Making Test B, Stroop interference, and letter fluency) with scores greater than two standard deviations below the mean, pronounced disinhibition and apathy, and reduced insight in fvAD cohorts compared with typical AD. When comparing the results of behavioural-AD and bvFTD participants, Ossenkoppele et al. (2015) found that behavioural-AD cases presented with milder behavioural features (i.e., prominent apathy, disinhibition, and loss of empathy) than bvFTD cases (with greater hyperorality and perseverative behaviours). Moreover, cognitive dysfunction preceded behavioural impairments in the behavioural AD cohort, and the dysexecutive-AD presentation was characterised by greater executive dysfunction relative to memory dysfunction. In agreement with Ossenkoppele et al. (2015), Phillips et al. (2018) found on formal cognitive testing that the bvAD cohort also had significantly lower scores than the amnestic AD cohort on the behavioural subscale of the Philadelphia Brief Assessment of Cognition. In an extension of their own work, Phillips et al. (2019) further discovered that deficits in executive functioning (Oral Trail Making Test, Digit Span Backward) and social behaviour (an 18-point scale assessing apathy, disinhibition, empathy, ritualistic behaviours, and social comportment), expected to be exclusive to the fvAD cohort, were found in both fvAD and amnestic AD groups. Sala et al. (2020) also found that the fvAD cohort presented with early predominant behavioural changes (e.g., apathy, anxiety, social withdrawal) or a predominant

dysexecutive syndrome (e.g., disinhibition, inattention, problem solving deficits), in comparison with their typical AD population. Townley et al. (2020) investigated individuals who were positive for AD pathology and who met the criteria of prominent executive dysfunction (i.e., working memory, cognitive flexibility, and inhibition) in the absence of predominant behavioural features, indicated on measures such as the Trail Making Test A and B, verbal fluency, Stroop, Digit Span, and Letter Number Sequencing. Sixteen of the 55 individuals presented with behavioural symptoms, however, these were not considered to be a prominent feature of their profile. While common themes emerge from the literature of behavioural and executive features present in fvAD cohorts, there is a lack of consistency in both the described symptoms across similar comparisons as well as what aspects of executive functioning are shown to discern fvAD from bvFTD and typical AD. Furthermore, some findings (i.e., Wong et al., 2016) even found contradictory evidence in group comparisons, highlighting the lack of evidence and support thus far.

2.7. *Memory*

Wong et al. (2016) describe indistinguishable memory performance across their three cohorts (bvFTD, IEF-AD, SEF-AD) but did propose differences in the underlying neuronal processes underpinning impaired memory performance. Specifically, whilst memory performance in all cohorts implicated prefrontal cortex and MTL structures, IEF-AD and bvFTD cohorts implicated greater atrophy in prefrontal cortical regions, with bilateral involvement from the orbitofrontal and lateral prefrontal cortices, and frontal pole. This was in contrast to SEF-AD cohorts, with implications of greater emphasis in MTL regions, whereby relatively circumscribed regions of PFC and MTL atrophy were observed, involving the right hippocampus and left inferior and middle frontal gyri. Conversely, Foreman et al. (2006) did find that their fvAD cohort demonstrated greater impairments on measures of episodic and short term memory (word list recall) compared with their FTLD tauopathy and tau-negative cohorts. Grossman et al. (2007) compared findings in their fvAD cohort with tau-positive and -negative FTD groups, demonstrating greater impairments with episodic memory. However, the authors commented that episodic memory dysfunction was the most valuable discriminating feature of the fvAD cohort from the FTD cohorts. Grossman et al. (2008) investigated the longitudinal progression of decline in cognitive functioning in autopsy-proven cohorts of FTLD and fvAD, showing that fvAD cohorts performed better than FTLD cohorts (both tau-positive and tau-negative) on measures of letter fluency and had impaired episodic memory relative to FTLD cohorts. To support Grossman et al.'s (2007) conclusions, Grossman et al. (2008) suggest that in the fvAD cohort, episodic memory findings correlated with cortical volume and amyloid burden in temporal regions. In sum, these findings were in favour of greater memory dysfunction in fvAD cohorts relative to FTLD cohorts.

On formal testing, Ossenkoppele et al. (2015) found the behavioural-AD profile was characterised by significantly worse composite memory scores relative to the dysexecutive cohort and the bvFTD cohort. Memory scores did not significantly differ from the typical AD cohort. Phillips et al. (2018) discovered that the bvAD cohort presented with relatively preserved episodic memory performance at initial diagnosis, however, this was noted to decline with MRI phase and was attributed to the atrophy of brain regions responsible for lexical retrieval and working memory, and not hippocampal atrophy. The amnestic AD cohort had the lowest mean recognition memory score relative to the non-amnestic AD cohorts. Phillips et al. (2019) found no clear difference in recognition memory performance in the fvAD cohort relative to the amnestic AD cohort.

2.8. *Verbal abilities*

Wong et al. (2016) identified significant differences between their IEF-AD and SEF-AD cohort on measures of verbal fluency, Digit Span Backward and the Hayling Sentence Completion Test, with the IEF-AD cohort demonstrating worse performance across all measures. Similarly, Forman et al. (2006) investigated neuropathological features of individuals presenting with social, behavioural, and/or language impairments characteristic of FTLD. On formal testing, the tauopathy subgroup overall demonstrated greater impairments on a category fluency measure (animals) relative to the fvAD cohort, and the tau-negative subgroup demonstrated greater impairments on a naming measure (Boston Naming Test) relative to the tauopathy subgroup. Grossman et al. (2007) compared findings in the fvAD cohort with tau-positive and negative FTD, demonstrating fewer words recalled after a delay relative to the tau-negative group. The fvAD cohort also performed better than the tau-positive group on measures of category fluency (animals), however, these findings did not reach significance, similar to the work of Foreman et al. (2006). Grossman et al. (2007) noted that the tau-negative cohort was reported to have greater problems with language as well as worse letter fluency than both the fvAD and tau-positive subgroups. Interestingly, Phillips and colleagues' (2018) disease phase duration was significant across all measures except for letter fluency and semantic knowledge, demonstrated through the Pyramids and Palm Trees test. Conversely, Phillips et al. (2019) found letter fluency exclusively was lower for the fvAD cohort relative to the amnestic AD cohort. Sala et al. (2020) also found that the fvAD group performed poorly relative to typical AD cases across all measures from the MMSE, Token Test and verbal fluency (letter and category).

2.9. *Visual abilities*

Grossman et al. (2007) noted difficulties in their tau-positive cohort with visuoperceptual spatial functions, extrapyramidal features, and worse performance on figure copying compared with tau-negative and fvAD subgroups. Between two cohorts of typical AD and early onset ADfv, Calvo et al. (2013) found greater impairments in processing speed and visuoconstruction, thereby distinguishing this fvAD cohort from probable FTD due to a clear visuospatial deficit that is absent in the bvFTD presentation.

2.10. *Biomarker data*

The last important criterion for determining diagnostic features included biomarker data, whereby the selection of

studies discussed administered different investigations. Several studies utilised MRI as the primary indicator for biomarker data, including Grossman et al. (2007), who compared imaging features of tau-positive FTD and tau-negative FTD with fvAD cohorts. Utilising autopsy (histopathologic and immunohistochemical analysis) findings together with MRI profiles contributed to antemortem diagnostic accuracy. T_1-weighted MRI revealed that the fvAD cohort showed significant bilateral temporal (including the hippocampus) and parietal atrophy with some extension to the frontal lobes. The tau-positive FTD group had greater bilateral frontal and parietal region atrophy with a right hemisphere predilection, and the tau-negative cohort showed significant bilateral frontal and temporal lobe atrophy. Wong et al. (2016) found that when comparing bvFTD, IEF-AD and SEF-AD cohorts, voxel-based morphometry analyses revealed that the SEF-AD cohort, most closely resembling typical AD, demonstrated right hippocampal and left and middle frontal gyri atrophy. The IEF-AD cohort, most closely resembling fvAD, showed similar atrophic changes to the bvFTD cohort, including bilateral hippocampal, temporal (MTL) and frontal lobe (orbitofrontal, lateral prefrontal, and frontal pole regions) atrophy. Phillips et al. (2018) created a series of inclusion criteria to analyse biomarker data: at least one MRI scan was required, with either autopsy confirmation of Alzheimer's disease pathology or no autopsy data (and thus excluding additional primary neuropathological diagnoses), and AD-indicative CSF. With respect to atrophic changes, AD pathology in the bvAD cohort originated in the middle frontal gyrus, anterior insula, and medial temporal gyrus, progressing to prefrontal and parietal cortices in later stages. At initial diagnosis, the hippocampus and MTL regions were relatively preserved. The amnestic AD cohort demonstrated greater atrophy of the medial and lateral temporal lobes originating from the right hippocampus and superior and middle temporal gyrus with progression into prefrontal and parietal regions. Phillips et al. (2019) then extended their research again incorporating CSF or autopsy biomarker evidence, which indicated subtle differences between bvFTD cohorts and fvAD cohorts, however, this did not rule out the potential for dual bvFTD and AD diagnoses. The authors found pathology originating from specific areas of the cortex to differ between patient cohorts: in fvAD there was prominent frontal lobe pathology, with specific atrophic changes found in the anterior insula, middle frontal gyrus, right angular gyrus, and bilateral middle temporal gyri, whilst the amnestic AD cohort demonstrated the prototypical atrophic changes in the hippocampal, temporal lobe, and the entorhinal cortex, in addition to the left middle frontal gyrus and right angular gyrus.

Utilising PET imaging, Sala et al. (2020) found that when testing the accuracy of [18F]FDG-PET brain hypometabolism as a biomarker of neurodegeneration, the prototypical pattern involved bilateral parietal and lateral temporal lobes and the precuneus and posterior cingulate cortex in the typical AD cohort, whilst the fvAD cohort presented with hypometabolism in parietal and temporal regions (akin to typical AD) with widespread hypometabolism in the dorsolateral and orbitofrontal cortex. This pattern was considered extremely distinct from that observed in bvFTD cohorts. Similarly, Ossenkoppele et al. (2015) evaluated three cohorts with predominant temporoparietal atrophy and relative sparing of the frontal lobes: behavioural-variant AD, dysexecutive-variant AD and a combined behavioural/dysexecutive AD subtype. AD pathology was confirmed via biomarker analysis, either autopsy confirmation and/or in vivo evidence of amyloid pathology on PET or in CSF. Here the behavioural-AD subgroup demonstrated temporoparietal atrophy with the involvement of the orbitofrontal cortex and frontal poles to a lesser extent, and a high APOE e4 prevalence (60%). The dysexecutive-AD presentation was characterised by atrophic changes in temporoparietal, cingulate gyrus and parahippocampal gyrus regions, and an intermediate APOE e4 prevalence (40%). The combined behavioural/dysexecutive AD subtype had evidence of prefrontal and temporal lobe atrophy. Townley et al. (2020) followed a similarly procedure in their attempt to propose a set of diagnostic criteria for a dysexecutive AD cohort. Through analyses including CSF and FDG-PET, biomarker findings of the dysexecutive AD cohort revealed frontoparietal hypometabolism. Despite the conclusion that the MTL was relatively spared in the dysexecutive AD cohort, which was distinct from typical AD, the authors suggest that a dysexecutive AD syndrome should not be associated with an anatomical structure given the variation in findings. Alternatively, Calvo et al. (2013) classified the AD groups using SPECT imaging whereby the fvAD cohort indicated frontal hypoperfusion whilst the typical AD demonstrated patterns of unilateral temporal or bilateral temporoparietal hypoperfusion. Additionally, fvAD patients were more likely to have a family history of AD, greater functional impairment, grasp reflex impairment, and caregiver load compared with typical AD cohorts. The authors found a higher prevalence of APOE e4 alleles in the typical AD cohort (53%) relative to the fvAD cohort (15%), and no neuropathological confirmation of clinical diagnoses. With regard to differential diagnosis of fvAD from FTD, the authors noted that the age of onset in their fvAD population was higher than that generally observed in FTD populations.

3. Discussion

This systematic narrative review and synthesis aimed to explore neuropsychological features of fvAD cohorts across a variety of study designs. The strict inclusion of studies with both neuropsychological findings and biomarker evidence was intended to increase the certainty of AD pathology in defined fvAD cohorts. Due to the difficulty in differentiating fvAD and bvFTD at diagnosis, findings from the latter cohort were provided as a point of comparison.

3.1. *Current difficulties with fvAD classification*

A primary concern raised in this synthesis involves the variation in classification of fvAD cohorts in the literature, including the McKhann et al. (2011) non-amnestic AD criteria (highlighting prominent executive dysfunction in fvAD cohorts), the Dubois et al. (2014) atypical AD criteria (emphasising a bvFTD-like presentation for fvAD cohorts), the Rascovsky et al. (2011) bvFTD criteria, and the Lund and Manchester Group (1994) and/or the Neary et al. (1998) FTD

clinical criteria. Sala et al. (2020), for example, used the Dubois et al. (2014) clinical criteria for atypical AD, Grossman et al. (2007, 2008) classified fvAD cohorts using patients with a clinical diagnosis of FTD (in conjunction with AD pathology on autopsy), and Calvo, Ramos and de Lucena (2013) used the McKhann et al. (2011) criteria for an atypical executive AD presentation.

Ossenkoppele et al. (2015) found patients meeting the criteria for bvFTD of prominent early behavioural changes relative to cognitive impairment, but with AD biomarkers, defined a behavioural variant AD cohort. Patients who presented with selective impairment of executive functions relative to memory functions, in conjunction with AD biomarker evidence, defined a dysexecutive-variant AD cohort. Studies which sought to distinguish between dysexecutive AD and behavioural AD subtypes of fvAD (e.g., Ossenkoppele et al., 2015; Townley et al., 2020), established that clinical presentations of behavioural AD present similarly to bvFTD more so than dysexecutive AD presentations. These findings within fvAD subtypes (i.e., behavioural and dysexecutive AD) are lost in studies where authors have initially classified fvAD cohorts using bvFTD criteria (e.g., Phillips et al., 2018, 2019; Rascovsky et al., 2011) or conflated both dysexecutive features and behavioural features into a single diagnosis of fvAD.

3.2. *Current difficulties with neuropsychological data in the literature*

Importantly, impaired performance on formal neuropsychological testing may be underpinned by dysfunction in several cortical systems. For example, some findings have indicated that impaired memory performance on formal testing may be due to either frontal lobe dysfunction in bvFTD cohorts, or hippocampal and MTL dysfunction seen in typical AD cohorts. However, in the absence of recognition trials in episodic memory tests or prompting cues in naming tests, or studies which fail to elaborate on such test findings despite their inclusion, research may overlook the nature and anatomical underpinnings of these cognitive impairments in fvAD cohorts.

Executive functioning findings from the current narrative synthesis are mixed. Some research has suggested greater executive dysfunction in bvFTD cohorts relative to fvAD cohorts (Forman et al., 2006; Grossman et al., 2007, 2008). On the other hand, Ossenkoppele et al. (2015) found greater executive dysfunction for both behavioural AD and dysexecutive AD cohorts relative to bvFTD, and Wong et al. (2016) found no significant difference in executive dysfunction between their IEF-AD cohort (equivalent to fvAD nomenclature) and bvFTD cohorts.

Previous research posits that fvAD typically presents with cognitive impairment prior to behavioural changes, in contrast with the typical bvFTD presentation (e.g., in the behavioural AD cohorts of Sawyer et al., 2017, and Ossenkoppele et al., 2015). The findings of this synthesis suggest specific behavioural features including prominent apathy and anxiety are more likely to be found in fvAD cohorts, whilst hyperorality and social disinhibition are more likely to be found in bvFTD cohorts (Ossenkoppele et al., 2015; Wong et al., 2016). However, further research is required to tease out the subtle distinctions in behavioural changes seen in fvAD and bvFTD cohorts.

Furthermore, the clinical criteria for "non-amnestic" ("hippocampal sparing") fvAD proposed by Dubois et al. (2014) describe a behavioural presentation with comparatively preserved memory function in keeping with relative sparing of the hippocampus and MTL. However, Phillips et al. (2019) have proposed that the term non-amnestic or hippocampal sparing may be misleading as the absence of MTL atrophy may reflect delayed neurodegeneration rather than a sparing of the region. The literature is consistent with this view, describing fvAD patients with frontal lobe AD pathology and a dysexecutive/behavioural presentation accompanied by memory dysfunction characteristic of AD (Habek et al., 2010; Li, Zhou, Lu, Wang, & Zhang, 2016; Sawyer et al., 2017; Wong et al., 2016).

In general terms, distinct profiles tend to emerge when executive dysfunction and/or behaviour are considered in the context of memory impairments. That is, there is a general consensus that greater episodic memory dysfunction (not aided by cueing) would favour an fvAD diagnosis (Forman et al., 2006; Grossman et al., 2007, 2008) and a marked behavioural presentation and/or executive deficits relative to episodic memory impairment (aided by cueing) would favour a bvFTD diagnosis.

3.3. *Conclusions and future directions*

A key outcome of this synthesis was to identify neuropsychological markers that would help distinguish between fvAD and bvFTD cohorts. Notwithstanding variation in fvAD clinical classifications highlighted in this synthesis, the evidence suggests that fvAD cohorts can be discriminated from bvFTD by greater episodic memory impairment relative to executive dysfunction, episodic memory impairments aided by cueing in bvFTD cohorts and not aided by cueing in fvAD cohorts, cognitive deficits preceding behavioural dysfunction, or the nature of behavioural features. The variability in studies, however, suggests that further research is still required to establish a cognitive profile of fvAD. In addition, in light of the lack of consistent research implicating fvAD subtypes (i.e., behavioural AD and dysexecutive AD), results should be interpreted with caution. Difficulty in differentiating between fvAD and bvFTD still suggests that a diagnosis of fvAD requires AD biomarker evidence (Woodward et al., 2010).

Unlike bvFTD and typical AD, a network degeneration model associated with fvAD has not yet been established, and while Ossenkoppele et al. (2015) propose a posterior origin of the disease, Phillips et al. (2018, 2019) propose an anterior origin. Townley et al. (2020) avoid these issues by making no anatomical reference, however, this may prove problematic when attempting to aid diagnosis using neuroimaging techniques (e.g., hypometabolism with PET, hypoperfusion with SPECT, atrophy with MRI) and thus a biomarker-focused synthesis of the current literature is still required.

Interestingly, the clinical diagnostic criteria proposed by McKhann et al. (2011), Dubois et al. (2014) and Townley et al. (2020) advise that a comprehensive neuropsychological evaluation should only be performed when history-taking (patient/informant) and cognitive impairments (identified

through unspecified formal evaluation, e.g., bedside evaluation or mental status examination; McKhann et al., 2011) fail to provide sufficient evidence for a diagnosis. The NIA-AA research framework proposed by Jack et al. (2018) similarly advised that the diagnosis of AD in research studies should be achieved using biomarker evidence solely, either post mortem or in vivo, and exclude the use of cognitive or syndrome descriptions as they fail to encapsulate neuropathologic changes or identify individuals who are positive for AD pathology but are not yet manifesting symptoms. Furthermore, Talbot et al. (2000) suggested two criteria to diagnose fvAD, whereby they found that prefrontal tissue samples displayed a density of neurofibrillary tangles unusually high when compared to typical AD populations, and the observed density of the entorhinal cortex was the same or higher than those with typical AD. Thus, in clinical settings where biomarker evidence is not always available, the overlapping features between bvFTD and fvAD would indicate that this approach should warrant some caution. Bedside evaluations and screening examinations (e.g., using the Mini-Mental State Examination; MMSE; Folstein, Folstein, & McHugh, 1975) tend be perfunctory in nature. Our review suggests that differentiating fvAD from bvFTD is a complex task which requires extensive continued research in search of clear definitions and markers to aid in diagnosis, and that comprehensive neuropsychological assessment can contribute valuable data.

Author statement

Andrea Brown: Conceptualization, Methodology, Investigation, Writing- Original draft preparation; Sarah Salo: Validation, Writing- Reviewing and Editing; Greg Savage: Writing-Reviewing and Editing, Supervision.

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Appendix A

Table A1 – Database Title Screen

	Search Strategy	EMBASE	MEDLINE	PsycINFO	PROQUEST			Total
1	frontal variant Alzheimer's.mp.	12	9	4	14346	Peer Reviewed Only	7308	
2	dysexecutive Alzheimer's.	5	3	3	1374	Peer Reviewed Only	732	
3	behavio?ral variant Alzheimer's.mp.	0	0	0	22711	Peer Reviewed Only	10616	
4	(dysexecutive AND Alzheimer's).mp.	205	121	165	1388	All Screened.	1388	
5	OR	219	132	182	27752	Peer Reviewed Only	13922	
	Gross [search 1 to 5] (A)	441	265	354			33966	35026
	Duplicates Removed (B)	222	136	172			20044	20574
	Title Screen Excluded (C)	167	120	169			13868	14324
	Net [A-B-C = net)	55	9	13			54	131

Note: Titles that were ambiguous had abstracts screened as well.

Table A2 – Records Collected through Other Sources

Gross	65
Duplicates Removed	0
Title Screen Excluded	0
Net	65

Table A3 – Abstract and Full Text Screen (Database search and other sources)

	EMBASE	MEDLINE	PsycINFO	PROQUEST	Other	TOTAL
Eligible (Case study + Experimental Designs)	6	2	9	10	0	27
Full text excluded w/reasons	46	7	4	44	65	166
no fvAD participants/fvAD not defined	19	1	1	24	38	83
Methodological limitations [insufficient neuropsychological data/biomarker evidence]	9	1	1	12	7	30
Not original quantitative research				7	15	22
English text not available	1		1		1	3
Full text not available	7					7
Additional duplicates					2	2
Conference abstracts/Poster Sessions	10	5	1	1	2	19
TOTAL SCREENED	52	9	13	54	65	193

Appendix B

Table B – Excluded articles with reasons

Citation	Reason for exclusion
EMBASE	
Akers, C., Acosta, L. M. Y., Considine, C., Claassen, D., Kirshner, H., & Schrag, M. (2019). Atypical clinical manifestations of cerebral amyloid angiopathy.Current Neurology and Neuroscience Reports, 19(9), 64.	fvAD not defined/included
Alexander, J., Kalev, O., Mehrabian, S., Traykov, L., Raycheva, M., Kanakis, D., … & Schuster, M. (2016). Familial early-onset dementia with complex neuropathologic phenotype and genomic background.Neurobiology of Aging, 42, 199–204.	fvAD not defined/confirmed
Andriuta, D., Roussel, M., Barbay, M., Despretz-Wannepain, S., Godefroy, O., & Godefroy and GRECogVASC study group. (2018). Differentiating between Alzheimer's disease and vascular cognitive impairment: Is the "memory versus executive function" contrast still relevant?Journal of Alzheimer's Disease, 63(2), 625–633.	Full text not available
Andriuta, D., Roussel, M., Dufouil, C., Chene, G., Fischer, C., Azouani, C., … & Tison, F. (2018). The cortical lesion pattern of dysexecutive syndrome in MEMENTO cohort (P5. 186).	Full text not available
Apostolova, L. G., Iaccarino, L., Collins, J. A., Aisen, P. S., Borowski, B. J., Eloyan, A., … & Kramer, J. H. (2019). P1-349: Advancing clinical and biomarker research in AD: The lead Study. Alzheimer's & Dementia, 15, P383–P384.	Poster presentation/conference abstract
Belin, C., Maillet, D., Nizzi, M. C., Sacko, A., & Carpentier, A. (2012). P1-041: Contribution of Alzheimer's biomarkers in the diagnosis of Alzheimer's disease in nonamnestic presentations. Alzheimer's & Dementia, 8(4S_Part_3), P121–P121.	Poster presentation/conference abstract
Bischof, G., Johannis, W., Faber, J., Neumaier, B., Onur, O., Kukolja, J., … & VanEimeren, T. (2017). Differential sensitivity of CSF markers of p-tau and t-tau to in vivo tau deposition assessed with [18F]-AV-1451 in typical and atypical Alzheimer's disease.Journal of Nuclear Medicine, 58(supplement 1), 628–628.	Full text not available
Borrello, L., Cupidi, C., Lagana, V., Anfossi, M., Conidi, M. E., Smirne, N., … & Bruni, A. C. (2016). Angela R.: A familial Alzheimer's disease case in the days of Auguste D.Journal of Neurology, 263(12), 2494–2498.	fvAD not defined/included
Boutoleau-Bretonnière, C. (2016). Les formes frontales de maladie d'Alzheimer. Pratique Neurologique-FMC, 7(2), 145–148.	English text not available
Clark. L.R., Koscik. R., Berman, S.E., Racine. A.M., Mueller. K.D., ….& Johnson S.C.. (2016). Distinct cognitive trajectories in late middle-age and their associations with brain structure and Alzheimer's disease biomarkers: Findings from the Wisconsin registry for Alzheimer's prevention. Neuropsychology, 3, 09.	Poster presentation/conference abstract
D'Onofrio, G., Panza, F., Sancarlo, D., Addante, F., Solfrizzi, V., Cantarini, C., … & Lozupone, M. (2018). Executive dysfunction detected with the Frontal Assessment Battery in Alzheimer's disease versus vascular dementia.Journal of Alzheimer's Disease, 62(2), 699–711.	fvAD not defined/included
Da Re, F., Phillips, J. S., Dratch, L., Ferrarese, C., Irwin, D. J., McMillan, C. T., Lee, E., Shaw, L. M., Trojanowski, J. Q., Wolk, D. A., & Grossman, M. (2017). Amnestic and non-amnestic phenotypes of Alzheimer's Disease: An MRI-based phasing analysis. Alzheimer's & Dementia, 13(7), 1365–6.	Poster presentation/conference abstract
Daoud, S., Farhat, N., Sakka, S., Hdiji, O., Moalla, K., Kacem, H. H., … & Mhiri, C. (2019). Frontal presentation of Alzheimer's Disease.Journal of the Neurological Sciences, 405, 110.	Poster presentation/conference abstract
Dickerson, B. C., Wolk, D. A., & Alzheimer's Disease Neuroimaging Initiative. (2011). Dysexecutive versus amnesic phenotypes of very mild Alzheimer's disease are associated with distinct clinical, genetic and cortical thinning characteristics.Journal of Neurology, Neurosurgery & Psychiatry, 82(1), 45–51.	Methodological limitations [Inclusion of MCI]

(*continued on next page*)

Table B – (*continued*)

Citation	Reason for exclusion
Dodich, A., Cerami, C., Cappa, S. F., Marcone, A., Golzi, V., Zamboni, M., … & Iannaccone, S. (2018). Combined socio-behavioral evaluation improves the differential diagnosis between the behavioral variant of frontotemporal dementia and Alzheimer's disease: In search of neuropsychological markers.Journal of Alzheimer's Disease, 61(2), 761–772.	fvAD not defined/included
Gallo, M., Frangipane, F., Cupidi, C., De Bartolo, M., Turone, S., Ferrari, C., … & Bernardi, L. (2017). The novel PSEN1 M84V mutation associated to frontal dysexecutive syndrome, spastic paraparesis, and cerebellar atrophy in a dominant Alzheimer's disease family.Neurobiology of Aging, 56, 213-e7.	Methodological limitations [Insufficient NPsyc data/Npsyc data N/A]
Gleichgerrcht, E., Chade, A., Roca, M., Torralva, T., & Manes, F. Stereotypies and repetitive motor behavior in patients with Alzheimer's disease who present spared vs. impaired executive functioning: 1035.Movement Disorders, 25.	Poster presentation/conference abstract
Godefroy, O., Roussel, M., & Martinaud, O. (2012). The profile of dysexecutive disorders in Alzheimer's disease and MCI. Implications for diagnosis: P2008.European Journal of Neurology, 19.	Poster presentation/conference abstract
Godefroy, O., Martinaud, O., Verny, M., Mosca, C., Lenoir, H., Bretault, E., … & GREFEX Study Group. (2014). The dysexecutive syndrome of Alzheimer's disease: The GREFEX study.Journal of Alzheimer's Disease, 42(4), 1203–1208.	fvAD not defined/included
Göthlin, M., Eckerström, M., Lindwall, M., Rolstad, S., Eckerström, C., Jonsson, M., … & Wallin, A. (2020). Latent cognitive profiles differ between incipient Alzheimer's disease and dementia with subcortical vascular lesions in a memory clinic population.Journal of Alzheimer's Disease, (Preprint), 1–12.	Methodological limitations [Inclusion of MCI]
Kuzmickienė, J., & Kaubrys, G. (2016). Specific features of executive dysfunction in Alzheimer-type mild dementia based on Computerized Cambridge Neuropsychological Test Automated Battery (CANTAB) Test results.Medical Science Monitor: International Medical Journal of Experimental and Clinical Research, 22, 3605.	fvAD not defined/included
Laforce Jr, R., Tosun, D., Ghosh, P., Lehmann, M., Madison, C. M., Weiner, M. W., … & Rabinovici, G. D. (2014). Parallel ICA of FDG-PET and PiB-PET in three conditions with underlying Alzheimer's pathology.NeuroImage: Clinical, 4, 508–516.	fvAD not defined/included
Lam, B., Masellis, M., Freedman, M., Stuss, D. T., & Black, S. E. (2013). Clinical, imaging, and pathological heterogeneity of the Alzheimer's disease syndrome.Alzheimer's Research & Therapy, 5(1), 1–14.	fvAD not defined/included
Lehmann, M., Madison, C., Ghosh, P. M., Miller, Z. A., Greicius, M. D., Kramer, J. H., … & Seeley, W. W. (2015). Loss of functional connectivity is greater outside the default mode network in nonfamilial early-onset Alzheimer's disease variants.Neurobiology of Aging, 36(10), 2678–2686.	fvAD not defined/included
Lim, A. W. L., See, C. J. C., Lim, L., Chander, R. J., Yong, T. T., Ting, S., Hameed, S., Kandiah, N., & Ng, A. S. L. (2017). [P2-304]: Differentiating frontal variant Alzheimer's disease from behavioural variant frontotemporal dementia. Alzheimer's & Dementia, 13(7), 734.	Poster presentation/conference abstract
Lowe, V. J., Wiste, H. J., Senjem, M. L., Weigand, S. D., Therneau, T. M., Boeve, B. F., … & Kantarci, K. (2018). Widespread brain tau and its association with ageing, Braak stage and Alzheimer's dementia.Brain, 141(1), 271–287.	fvAD not defined/included
Mez, J., Cosentino, S., Brickman, A. M., Huey, E. D., Manly, J. J., & Mayeux, R. (2013). Dysexecutive versus amnestic Alzheimer's disease subgroups: analysis of demographic, genetic, and vascular factors.Alzheimer Disease and Associated Disorders, 27(3), 218.	Methodological limitations [Inclusion of MCI]
Mez, J., Cosentino, S., Brickman, A. M., Huey, E. D., Manly, J. J., & Mayeux, R. (2013). Faster cognitive and functional decline in dysexecutive versus amnestic Alzheimer's subgroups: a longitudinal analysis of the National Alzheimer's Coordinating Center (NACC) database.PLoS One, 8(6), e65246.	Methodological limitations [Insufficient NPsyc data/Npsyc data N/A]
Moreira, H. S., Lima, C. F., & Vicente, S. G. (2014). Examining executive dysfunction with the Institute of Cognitive Neurology (INECO) Frontal Screening (IFS): Normative values from a healthy sample and clinical utility in Alzheimer's disease.Journal of Alzheimer's Disease, 42(1), 261–273.	fvAD not defined/included
Mukherjee, S., Trittschuh, E., Gibbons, L. E., Mackin, R. S., Saykin, A., Crane, P. K., & Alzheimer's Disease Neuroimaging Initiative. (2012). Dysexecutive and amnesic AD subtypes defined by single indicator and modern psychometric approaches: relationships with SNPs in ADNI.Brain imaging and Behavior, 6(4), 649–660.	Methodological limitations [Insufficient NPsyc data/Npsyc data N/A]

Table B – (*continued*)

Citation	Reason for exclusion
Ossenkoppele R., Rabinovici G., Grinberg L., Jagust W., Kramer J., Miller B., et al (2014). Frontal variant Alzheimer's disease: Clinical and neuroimaging features of 55 autopsy/biomarker-confirmed patients.American Journal of Neurodegenerative Diseases, 3(SUPPL. 1), 252	Poster presentation/conference abstract
Pai, M. C., & Hsiao, S. (2002). Incipient symptoms of Alzheimer's disease and effect of education on the onset age: A study of 155 Taiwanese patients.Acta Neurologica Taiwanica, 11(2), 66–69.	Full text not available
Pasquini, L., Benson, G., Scherr, M., Yakushev, I., Grimmer, T., Myers, N., … & Sorg, C. (2016). O3-08–05 Global and local interactions between amyloid-b pathology and intrinsic connectivity along the spectrum of Alzheimer's disease. Neuropsychology, 3, 09.	Poster presentation/conference abstract
Phillips, J., Irwin, D., Rascovsky, K., Van Deerlin, V., Lee, V., Trojanowski, J., … & Grossman, M. (2016). Cognitive and behavioral trajectory of behavioral-variant frontotemporal dementia differs according to underlying pathology: P147.Journal of Neurochemistry, 138, 297–298.	Full text not available
Phillips, J. S., Xie, L., Wisse, L., Gee, J. C., Yushkevich, P. A., Grossman, M., & Irwin, D. (2019). IC-P-143: Relative sparing of medial temporal subregion volumes in non-amnestic Alzheimer's disease. Alzheimer's & Dementia, 15, P116–P117.	Full text not available
Phillips, J., Wisse, L., Yushkevich, P., Gee, J., Grossman, M., & Irwin, D. (2019). Medial temporal lobe subfield volumes are spared in non-amnestic Alzheimer's disease. (15 Supplement) P5. 7–001.	Full text not available
Price, C. C., Tanner, J. J., Schmalfuss, I. M., Brumback, B., Heilman, K. M., & Libon, D. J. (2015). Dissociating statistically-determined Alzheimer's disease/vascular dementia neuropsychological syndromes using white and gray neuroradiological parameters.Journal of Alzheimer's Disease, 48(3), 833–847.	Methodological limitations [comorbidities]
Ranasinghe, K. G., Hinkley, L. B., Beagle, A. J., Mizuiri, D., Dowling, A. F., Honma, S. M., … & Vossel, K. A. (2014). Regional functional connectivity predicts distinct cognitive impairments in Alzheimer's disease spectrum.NeuroImage: Clinical, 5, 385–395.	fvAD not defined/included
Risacher, S. L., Anderson, W. H., Charil, A., Castelluccio, P. F., Shcherbinin, S., Saykin, A. J., … & Alzheimer's Disease Neuroimaging Initiative. (2017). Alzheimer disease brain atrophy subtypes are associated with cognition and rate of decline.Neurology, 89(21), 2176–2186.	fvAD not defined/included
Sahoo, A., Bejanin, A., Murray, M. E., Tosakulwong, N., Weigand, S. D., Senjem, M. L., … & Petersen, R. C. (2018). TDP-43 and Alzheimer's disease pathologic subtype in non-amnestic Alzheimer's disease dementia.Journal of Alzheimer's Disease, 64(4), 1227–1233.	fvAD not defined/included
Shinagawa, Y., Nakaaki, S., Hongo, J., Murata, Y., Sato, J., Matsui, T., … & Furukawa, T. A. (2007). Reliability and validity of the Japanese version of the Dysexecutive Questionnaire (DEX) in Alzheimer's disease: validation of a behavioral rating scale to assess dysexecutive symptoms in Japanese patients with Alzheimer's disease.International Journal of Geriatric Psychiatry: A Journal of the Psychiatry of Late Life and Allied Sciences, 22(10), 951–956.	fvAD not defined/included
Sutovsky, S., Blaho, A., Kollar, B., Siarnik, P., Csefalvay, Z., Dragasek, J., & Turcani, P. (2014). Clinical accuracy of the distinction between Alzheimer's disease and frontotemporal lobar degeneration.Bratislavske Lekarske Listy, 115(3), 161–167	fvAD not defined/included
Vasconcelos, L. D. G., Jackowski, A. P., Oliveira, M. O. D., Flor, Y. M. R., Souza, A. A. L., Bueno, O. F. A., & Brucki, S. M. D. (2014). The thickness of posterior cortical areas is related to executive dysfunction in Alzheimer's disease.Clinics, 69(1), 28–37	fvAD not defined/included
Woodward, M., Brodaty, H., Boundy, K., Ames, D., Blanch, G., & Balshaw, R. (2010). Does executive impairment define a frontal variant of Alzheimer's disease?International Psychogeriatrics, 22(8), 1280–1290.	Methodological limitations [no biomarker evidence]
Woodward, M. C., Rowe, C. C., Jones, G., Villemagne, V. L., & Varos, T. A. (2015). Differentiating the frontal presentation of Alzheimer's disease with FDG-PET.Journal of Alzheimer's Disease, 44(1), 233–242.	Methodological limitations [Insufficient NPsyc data/Npsyc data N/A]
Yokoyama, J. S., Bonham, L. W., Sears, R. L., Klein, E., Karydas, A., Kramer, J. H., … & Coppola, G. (2015). Decision tree analysis of genetic risk for clinically heterogeneous Alzheimer's disease.BMC Neurology, 15(1), 47.	fvAD not defined/included

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Table B – (*continued*)

Citation	Reason for exclusion
MEDLINE	
Belin, C., Maillet, D., Nizzi, M-C., Sacko, A., & Carpentier, A. (2012). P1-041: Contribution of Alzheimer's biomarkers in the diagnosis of Alzheimer's disease in nonamnestic presentations. Alzheimer's & Dementia, 8(4), 121.	Poster presentation/conference abstract
Blennerhassett, R., Lillo, P., Halliday, G. M., Hodges, J. R., & Kril, J. J. (2014). Distribution of pathology in frontal variant Alzheimer's disease.Journal of Alzheimer's Disease, 39(1), 63–70.	Methodological limitations [Insufficient NPsyc data/Npsyc data N/A]
Lapalus, P., Paquet, C., Hugon, J., Dumurgier, J., Guichard, J. P., Peoch, K., & Habert, M. O. (2011). P1-105: Behavioral variant of Alzheimer's disease in an old woman mimicking frontotemporal dementia: Diagnosis contribution of CSF biomarkers. Alzheimer's & Dementia, 7(4), 143–4.	Poster presentation/conference abstract
Lehmann, M., Ghosh, P. M., Madison, C., Karydas, A., Coppola, G.' O'Neil, J. P., … & Rabinovici, G. D. (2014). Greater medial temporal hypometabolism and lower cortical amyloid burden in APOE ε4-positive AD patients. Journal of Neurology, Neurosurgery & Psychiatry, 85(3), 266–273.	fvAD not defined/included
Mez, J., Cosentino, S., Brickman, A., Huey, E., Manly, J., & Mayeux, R. (2012). O4-10–06: An Alzheimer's disease dysexecutive subgroup demonstrates slower cognitive decline than an amnestic subgroup in the National Alzheimer's Coordinating Center database. Alzheimer's & Dementia, 8(4), 635–6.	Poster presentation/conference abstract
Mez, J., Cosentino, S., Brickman, A., Huey, E., Manly, J., & Mayeux, R. (2016). Characterization of Dysexecutive Versus Amnestic Alzheimer's Disease Phenotypes in the National Alzheimer's Coordinating Center (NACC) Database (P04.209). Neurology, 78(1), 209.	Poster presentation/conference abstract
Ossenkoppele, R., Pijnenburg, Y. A. L., Perry, D., Cohn-Sheehy, B., Scheltens, N. M. E., Vogel, J. W., … Rabinovici, G. D. (2015). F2-03–03: Characterization of the behavioral and dysexecutive variants of Alzheimer's disease. Alzheimer's & Dementia, 11(7), 168.	Poster presentation/conference abstract
PSYCINFO	
Herrero-San, A. M., Villarejo-Galende, A., Rabano-Gutierrez, A., Guerrero-Marquez, C., Porta-Etessam, J., & Bermejo-Pareja, F. (2013). Frontal variant of Alzheimer's disease. Two pathologically confirmed cases and a literature review.Revista de Neurologia, 57(12), 542–548.	English text not available
Ossenkoppele, R. (2017). PET and MRI studies in atypical variants of Alzheimer's Disease. Alzheimer's & Dementia, 13(7), 1210.	Poster presentation/conference abstract
Therriault, J., Pascoal, T. A., Savard, M., Benedet, A. L., Chamoun, M., Tissot, C., … & Rosa-Neto, P. (2021). Topographic Distribution of Amyloid-β, Tau, and Atrophy in Patients With Behavioral/Dysexecutive Alzheimer Disease.Neurology, 96(1), e81-e92.	fvAD not defined (consensus meeting)
Cai, H., Ning, S., Li, W., Li, X., Xiao, S., & Sun, L. (2020). Patient with frontal-variant syndrome in early-onset Alzheimer's disease.General psychiatry, 33(2). doi: 10.1136/gpsych-2019–100173	Methodological limitations [Insufficient Npsyc data/Npsyc data N/A]
PROQUEST	
Alexiou, A., Kamal, M. A., & Ashraf, G. M. (2019). Alzheimer's disease as a current challenge.Frontiers in Neuroscience, 13, 768.	Not original quantitative research
Alladi, S., Xuereb, J., Bak, T., Nestor, P., Knibb, J., Patterson, K., & Hodges, J. R. (2007). Focal cortical presentations of Alzheimer's disease.Brain, 130(10), 2636–2645.	fvAD not defined/included
Back-Madruga, C., Boone, K. B., Briere, J., Cummings, J., McPherson, S., Fairbanks, L., & Thompson, E. (2002). Functional ability in executive variant Alzheimer's disease and typical Alzheimer's disease.The Clinical Neuropsychologist, 16(3), 331–340.	Methodological limitations [no biomarker evidence]
Banks, S., & Leger, G. (2014). A-88 The confusing case of the stuttering sommelier.Archives of Clinical Neuropsychology, 29(6), 536–536.	Poster presentation/conference abstract
Bergmans, B. A., & De Strooper, B. (2010). Gamma-secretases: From cell biology to therapeutic strategies. The Lancet Neurology, 9(2) 215–26.	Not original quantitative research
Bondi, M. W., Edmonds, E. C., & Salmon, D. P. (2017). Alzheimer's disease: past, present, and future.Journal of the International Neuropsychological Society: JINS, 23(9–10), 818	Not original quantitative research
Caminiti, S. P., Ballarini, T., Sala, A., Cerami, C., Presotto, L., Santangelo, R., … & Magnani, G. (2018). FDG-PET and CSF biomarker accuracy in prediction of conversion to different dementias in a large multicentre MCI cohort.NeuroImage: Clinical, 18, 167–177.	Methodological limitations [Inclusion of MCI]
Caroli, A., & Frisoni, G. B. (2009). Quantitative evaluation of Alzheimer's disease.Expert review of medical devices, 6(5), 569–588.	fvAD not defined/included

Table B – (*continued*)

Citation	Reason for exclusion
Di Patre, P. L., Read, S. L., Cummings, J. L., Tomiyasu, U., Vartavarian, L. M., Secor, D. L., & Vinters, H. V. (1999). Progression of clinical deterioration and pathological changes in patients with Alzheimer disease evaluated at biopsy and autopsy.Archives of Neurology, 56(10), 1254–1261.	fvAD not defined/included
Dubois, B., Feldman, H. H., Jacova, C., Cummings, J. L., DeKosky, S. T., Barberger-Gateau, P., … & Gauthier, S. (2010). Revising the definition of Alzheimer's disease: a new lexicon.The Lancet Neurology, 9(11), 1118–1127.	Not original quantitative research
Duyckaerts, C. (2011). Disentangling Alzheimer's disease. The Lancet Neurology, 10(9), 774–5.	Not original quantitative research
Galante, E., Muggia, S., Spinnler, H., & Zuffi, M. (1999). Degenerative dementia of the frontal type: Clinical evidence from 9 cases. Dementia and Geriatric Cognitive Disorders, 10(1), 28–39.	fvAD not defined/included
Giau, V. V., Senanarong, V., Bagyinszky, E., An, S. S. A., & Kim, S. (2019). Analysis of 50 neurodegenerative genes in clinically diagnosed early-onset Alzheimer's disease.International Journal of Molecular Sciences, 20(6), 1514.	fvAD not defined/included
Guarino, A., Favieri, F., Boncompagni, I., Agostini, F., Cantone, M., & Casagrande, M. (2019). Executive functions in Alzheimer disease: a systematic review.Frontiers in Aging Neuroscience, 10, 437.	fvAD not defined/included
Habek, M., Hajnšek, S., Žarković, K., Chudy, D., & Mubrin, Z. (2010). Frontal variant of Alzheimer's disease: Clinico-CSF-pathological correlation.Canadian Journal of Neurological Sciences, 37(1), 118–120.	Methodological limitations [Insufficient NPsyc data/Npsyc data N/A]
Janocko, N. J., Brodersen, K. A., Soto-Ortolaza, A. I., Ross, O. A., Liesinger, A. M., Duara, R., Graff-Radford, N. R., Dickson, D. W., & Murray, M. E. (2012). Neuropathologically defined subtypes of Alzheimer's disease differ significantly from neurofibrillary tangle-predominant dementia.Acta Neuropathologica, 124, 681–92.	fvAD not defined/included
Johnson, J. K., Vogt, B. A., Kim, R., Cotman, C. W., Head, E. (2004). Isolated executive impairment and associated frontal neuropathology. Dementia and Geriatric Cognitive Disorders, 17(4), 360–7.	Methodological limitations [inclusion of MCI/Insufficient biomarker data]
Keshavan, A., Heslegrave, A., Zetterberg, H., & Schott, J. M. (2017). Blood biomarkers for Alzheimer's disease: Much promise, cautious progress.Molecular Diagnosis & Therapy, 21(1), 13–22.	fvAD not defined/included
Léger, G. C., & Banks, S. J. (2014). Neuropsychiatric symptom profile differs based on pathology in patients with clinically diagnosed behavioral variant frontotemporal dementia.Dementia and Geriatric Cognitive Disorders, 37(1–2), 104–112.	fvAD not defined/included
Martyr, A., & Clare, L. (2012). Executive function and activities of daily living in Alzheimer's disease: a correlational meta-analysis.Dementia and Geriatric Cognitive Disorders, 33(2–3), 189–203.	fvAD not defined/included
Monacelli, F., Martella, L., Parodi, M. N., Odetti, P., Fanelli, F., & Tabaton, M. (2019). Frontal variant of Alzheimer's disease: A Report of a novel PSEN1 mutation.Journal of Alzheimer's Disease, 70(1), 11–15.	Methodological limitations [Insufficient NPsyc data/Npsyc data N/A]
Nolan, A., Resende, E. dP. F., Petersen, C., Neylan, K., Spina, S., Huang, E., Seeley, W., Miller, Z., & Grinberg, L. T. (2019) Astrocytic tau deposition is frequent in typical and atypical Alzheimer disease presentations. Journal of Neuropathology and Experimental Neurology, 78(12), 1112–23.	fvAD not defined/included
O'Callaghan, C., Bertoux, M., & Hornberger, M. (2014). Beyond and below the cortex: the contribution of striatal dysfunction to cognition and behaviour in neurodegeneration. Journal of Neurology, Neurosurgery and Psychiatry, 85(4), 371–8.	Not original quantitative research
Paterson, R. W., Toombs, J., Slattery, C. F., Nicholas, J. M., Andreasson, U., Magdalinou, N. K., … & Lunn, M. P. (2015). Dissecting IWG-2 typical and atypical Alzheimer's disease: insights from cerebrospinal fluid analysis.Journal of Neurology, 262(12), 2722–2730.	Methodological limitations [Insufficient NPsyc data/Npsyc data N/A]
Perry, R. J., & Hodges, J. R. (1999). Attention and executive deficits in Alzheimer's disease: A critical review.Brain, 122(3), 383–404.	fvAD not defined/included
Petersen, R. C. (1998). Clinical subtypes of Alzheimer's disease. Dementia and Geriatric Cognitive Disorders, 9, 16–24.	Methodological limitations [Insufficient Npsyc data/biomarker evidence]

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Table B – (*continued*)

Citation	Reason for exclusion
Petersen, C., Nolan, A. L., Resende, E. dP. F., Miller, Z., Ehrenberg, A. J., Gorno-Tempini, M. L., Rosen, H. J., Kramer, J. H., Spina, S., Rabinovici, G. D., Miller, B. L., Seeley, W. W., Heinsen, H., & Grinberg, L. T. (2019). Alzheimer's disease clinical variants show distinct regional patterns of neurofibrillary tangle accumulation. Acta Neuropathologica, 138(4), 597–612.	fvAD not defined/included
Pijnenburg, Y. A. L., Schoonenboom, S. N. M., Mehta, P. D., Mehta, S. P., Mulder, C., Veerhuis, R., … & Scheltens, P. (2007). Decreased cerebrospinal fluid amyloid beta (1–40) levels in frontotemporal lobar degeneration.Journal of Neurology, Neurosurgery & Psychiatry, 78(7), 735–737.	fvAD not defined/included
Rawtaer, I. & Krishnamoorthy, A. (2017). Co-occurring frontal variant Alzheimer's dementia and carrier of Huntington's disease allele with reduced penetrance. Psychogeriatrics, 17(6), 488–90.	Methodological limitations [Insufficient Npsyc data/biomarker evidence/ comorbidities]
Scheltens, N. M. E, Galindo-Garre, F., Pijnenburg, Y. A. L., van der Vlies, A. E., Smits, L. L., Koene, T., Teunissen, C. E., Barkhof, F., Wattjes, M. P., Scheltens, P., & van der Flier, W. M. (2016). The identification of cognitive subtypes in Alzheimer's disease dementia using latent class analysis. Journal of Neurology, Neurosurgery and Psychiatry, 87(3), 235–43.	fvAD not defined/included
Seifan, A., Assuras, S., Huey, E. D., Mez, J., Tsapanou, A., & Caccappolo, E. (2015). Childhood learning disabilities and atypical dementia: a retrospective chart review.PLoS One, 10(6), e0129919.	Methodological limitations [comorbidities]
Senanarong, V., An, S. S. A., Van Giau, V., Limwongse, C., Bagyinszky, E., & Kim, S. (2020). Pathogenic PSEN1 Glu184Gly Mutation in a family from Thailand with probable autosomal dominant early onset Alzheimer's disease.Diagnostics, 10(3), 135.	fvAD not defined/included
Serino, S., Morganti, F., Colombo, D., Pedroli, E., Cipresso, P., & Riva, G. (2018). Disentangling the contribution of spatial reference frames to executive functioning in healthy and pathological aging: An experimental study with virtual reality.Sensors, 18(6), 1783.	fvAD not defined/included
Swanberg, M. M., Tractenberg, R. E., Mohs, R., Thal, L. J., & Cummings, J. L. (2004). Executive dysfunction in Alzheimer disease.Archives of Neurology, 61(4), 556–560.	fvAD not defined/included
Talbot, K., Young, R. A., Jolly-Tornetta, C., Lee, V. M. Y., Trojanowski, J. Q., & Wolf, B. A. (2000). A frontal variant of Alzheimer's disease exhibits decreased calcium-independent phospholipase A2 activity in the prefrontal cortex.Neurochemistry International, 37(1), 17–31.	Methodological limitations [Insufficient NPsyc data/Npsyc data N/A]
van der Flier, W. M., Pijnenburg, Y. A., Fox, N. C., & Scheltens, P. (2011). Early-onset versus late-onset Alzheimer's disease: the case of the missing APOE ϵ4 allele. The Lancet Neurology, 10(3), 280–288	fvAD not defined/included
van Gool, W. A., & Eikelenboom, P. (2000). The two faces of Alzheimer's disease. Journal of Neurology, 247(7), 500–5	Not original quantitative research
Vanhoutte, M., Semah, F., Leclerc, X. Sillaire, A. R., Jaillard, A., Kuchcinski, G., Delbeuck, X., Fahmi, R., Pasquier, F., & Lopes, R. (2020). Three-year changes of cortical ^{18}F-FDG in amnestic vs. non-amnestic sporadic early-onset Alzheimer's disease. European Journal of Nuclear Medicine and Molecular Imaging, 47, 304–18.	fvAD not defined/included
von Gunten, A., Miklossy, J., Suvà, M. L., Hof, P., & Giannakopoulos, P. (2004). Environmental reduplicative paramnesia in a case of atypical Alzheimer's disease.Journal of neurology,251(6), 750–752	fvAD not defined/included
Wang, Y., Shi, Z., Zhang, N., Cai, L., Li, Y., Yang, H., … & Gao, S. (2019). Spatial patterns of hypometabolism and amyloid deposition in variants of Alzheimer's disease corresponding to brain networks: A prospective cohort study.Molecular Imaging and Biology, 21(1), 140–148.	Methodological limitations [Insufficient NPsyc data/Npsyc data N/A]
Woodward, M., Jacova, C., Black, S. E., Kertesz, A., Mackenzie, I. R., Feldman, H., & ACCORD investigator group. (2010). Differentiating the frontal variant of Alzheimer's disease. International Journal of Geriatric Psychiatry, 25(7), 732–738.	Methodological limitations [Insufficient Biomarker evidence]
Xie, S. X., Libon, D. J., Wang, X., Massimo, L., Moore, P., Vesely, L., … & Liang, T. W. (2010). Longitudinal patterns of semantic and episodic memory in frontotemporal lobar degeneration and Alzheimer's disease.Journal of the International Neuropsychological Society, 16(2), 278–286.	fvAD not defined/included
Yoshida, H., Terada, S., Sato, S., Kishimoto, Y., Ata, T., Ohshima, E., … & Kuroda, S. (2009). Frontal assessment battery and brain perfusion imaging in early dementia.Dementia and Geriatric Cognitive Disorders, 27(2), 133–138.	fvAD not defined/included

Table B – (*continued*)

Citation	Reason for exclusion
Zhang, S., Li, X., Zhang, L., Meng, X., Ma, L., Zhang, G., Wu, H., Liang, L., Cao, M., & Mei, F. (2020). Identification of a rare PSEN1 mutation (Thr119Ile) in late-onset Alzheimer's disease with early presentation of behavioral disturbance. Frontiers in Psychiatry, 11, 347.	fvAD not defined/included
Other Sources	
Apostolova, L. G., Risacher, S. L., Duran, T., Stage, E. C., Goukasian, N., West, J. D., … & Phillips, M. (2018). Associations of the top 20 Alzheimer disease risk variants with brain amyloidosis.JAMA Neurology, 75(3), 328–341.	Methodological limitations [Insufficient NPsyc data/Npsyc data N/A/Inclusion of MCI]
Balasa, M., Gelpi, E., Antonell, A., Rey, M. J., Sanchez-Valle, R., Molinuevo, J. L., & Llado, A. (2011). Clinical features and APOE genotype of pathologically proven early-onset Alzheimer disease.Neurology, 76(20), 1720–1725.	fvAD not defined/included
Bergeron, D., Bensaïdane, R., & Laforce, R. (2016). Untangling Alzheimer's disease clinicoanatomical heterogeneity through selective network vulnerability–an effort to understand a complex disease.Current Alzheimer Research, 13(5), 589–596.	Not original quantitative research
Bertoux, M., O'Callaghan, C., Flanagan, E., Hodges, J. R., & Hornberger, M. (2015). Fronto-striatal atrophy in behavioral variant frontotemporal dementia and Alzheimer's disease.Frontiers in Neurology, 6, 147.	fvAD not defined/included
Bhutani, G. E., Montaldi, D., Brooks, D. N., & McCulloch, J. (1992). A neuropsychological investigation into frontal lobe involvement in dementia of the Alzheimer type.Neuropsychology, 6(3), 211.	fvAD not defined/included
Binetti, G., Magni, E., Padovani, A., Cappa, S. F., Bianchetti, A., & Trabucchi, M. (1996). Executive dysfunction in early Alzheimer's disease.Journal of Neurology, Neurosurgery & Psychiatry, 60(1), 91–93.	fvAD not defined/included
Blanken, A. E., Dutt, S., Li, Y., Nation, D. A., & Alzheimer's Disease Neuroimaging Initiative. (2019). Disentangling heterogeneity in Alzheimer's disease: Two empirically-derived subtypes.Journal of Alzheimer's Disease, 70(1), 227–239.	fvAD not defined/included
Bouts, M. J., Möller, C., Hafkemeijer, A., van Swieten, J. C., Dopper, E., van der Flier, W. M., … & Barkhof, F. (2018). Single subject classification of Alzheimer's disease and behavioral variant frontotemporal dementia using anatomical, diffusion tensor, and resting-state functional magnetic resonance imaging.Journal of Alzheimer's Disease, 62(4), 1827–1839.	fvAD not defined/included
Boyle, P. A., Malloy, P. F., Salloway, S., Cahn-Weiner, D. A., Cohen, R., & Cummings, J. L. (2003). Executive dysfunction and apathy predict functional impairment in Alzheimer disease.The American Journal of Geriatric Psychiatry, 11(2), 214–221.	fvAD not defined/included
Cai, H., Ning, S., Li, W., Li, X., Xiao, S., & Sun, L. (2020). Patient with frontal-variant syndrome in early-onset Alzheimer's disease.General Psychiatry, 33(2): e100173.	Duplicate
Calvo, B. F., Ramos-Campos, F., & de Lucena, V. M. (2013). Frontal variant of Alzheimer's disease and typical Alzheimer's disease: A comparative study.Anales de Psicología/Annals of Psychology, 29(1), 293–300.	Duplicate
Caselli, R. J., Beach, T. G., Knopman, D. S., & Graff-Radford, N. R. (2017, June). Alzheimer disease: scientific breakthroughs and translational challenges. InMayo Clinic Proceedings(Vol. 92, No. 6, pp. 978–994). Elsevier.	Not original quantitative research
Chen, S. T., Sultzer, D. L., Hinkin, C. H., Mahler, M. E., & Cummings, J. L. (1998). Executive dysfunction in Alzheimer's disease: association with neuropsychiatric symptoms and functional impairment.The Journal of Neuropsychiatry and Clinical Neurosciences, 10(4), 426–432.	fvAD not defined/included
Chételat, G., Ossenkoppele, R., Villemagne, V. L., Perrotin, A., Landeau, B., Mézenge, F., … & Seeley, W. W. (2016). Atrophy, hypometabolism and clinical trajectories in patients with amyloid-negative Alzheimer's disease.Brain, 139(9), 2528–2539.	fvAD not defined/included
Clarke, M. T., Brinkmalm, A., Foiani, M. S., Woollacott, I. O., Heller, C., Heslegrave, A., … & Blennow, K. (2019). CSF synaptic protein concentrations are raised in those with atypical Alzheimer's disease but not frontotemporal dementia.Alzheimer's Research & Therapy, 11(1), 105.	fvAD not defined/included
Cousins, K. A., Irwin, D. J., Wolk, D. A., Lee, E. B., Shaw, L. M., Trojanowski, J. Q., … & Phillips, J. S. (2020). ATN status in amnestic and non-amnestic Alzheimer's disease and frontotemporal lobar degeneration.Brain, 143(7), 2295–2311.	fvAD not defined/included

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Table B – (*continued*)

Citation	Reason for exclusion
Dickerson, B. C., McGinnis, S. M., Xia, C., Price, B. H., Atri, A., Murray, M. E., … & Wolk, D. A. (2017). Approach to atypical Alzheimer's disease and case studies of the major subtypes.CNS Spectrums, 22(6), 439–449.	Methodological limitations [Inclusion of MCI]
Dubois, B., Feldman, H. H., Jacova, C., Hampel, H., Molinuevo, J. L., Blennow, K., … & Cappa, S. (2014). Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria.The Lancet Neurology, 13(6), 614–629.	Not original quantitative research
Ferreira, D., Nordberg, A., & Westman, E. (2020). Biological subtypes of Alzheimer disease: A systematic review and meta-analysis.Neurology, 94(10), 436–448.	fvAD not defined/included
Finger, E., Zhang, J., Dickerson, B., Bureau, Y., & Masellis, M. (2017). Disinhibition in Alzheimer's disease is associated with reduced right frontal pole cortical thickness.Journal of Alzheimer's Disease, 60(3), 1161–1170.	fvAD not defined/included
Galton, C. J., Patterson, K., Xuereb, J. H., & Hodges, J. R. (2000). Atypical and typical presentations of Alzheimer's disease: A clinical, neuropsychological, neuroimaging and pathological study of 13 cases.Brain, 123(3), 484–498.	fvAD not defined/included
Gleichgerrcht, E., Chade, A., Torralva, T., Roca, M., & Manes, F. (2011). Comparing the neuropsychiatric profile of patients with Alzheimer disease who present spared versus impaired executive functioning.Current Gerontology and Geriatrics Research.	Methodological limitations [no biomarker evidence]
Greicius, M. D., Geschwind, M. D., & Miller, B. L. (2002). Presenile dementia syndromes: An update on taxonomy and diagnosis.Journal of Neurology, Neurosurgery & Psychiatry, 72(6), 691–700.	Not original quantitative research
Harwood, D. G., Sultzer, D. L., Feil, D., Monserratt, L., Freedman, E., & Mandelkern, M. A. (2005). Frontal lobe hypometabolism and impaired insight in Alzheimer disease.The American Journal of Geriatric Psychiatry, 13(11), 934–941.	fvAD not defined/included
Hoffmann, M. (2013). The human frontal lobes and frontal network systems: an evolutionary, clinical, and treatment perspective.ISRN neurology.	Not original quantitative research
Jeong, Y., Han, D. H., Yi, H. A., Cho, S. S., Chin, J. H., Gang, S. J., … & Na, D. L. (2003). Neuropsychological and neuroimaging findings of frontal variant of Alzheimer's disease.Journal of the Korean Neurological Association, 21(1), 32–40.	English text not available
Jenner, C., Reali, G., Puopolo, M., & Silveri, M. C. (2006). Can cognitive and behavioural disorders differentiate frontal variant-frontotemporal dementia from Alzheimer's disease at early stages?Behavioural Neurology, 17(2), 89–95.	fvAD not defined/included
Joshi, A., Barsuglia, J. P., Mather, M. J., Jimenez, E. E., Shapira, J., & Mendez, M. F. (2014). Evaluation of emotional blunting in behavioral variant frontotemporal dementia compared to Alzheimer's disease.Dementia and Geriatric Cognitive Disorders, 38(1–2), 79–88.	fvAD not defined/included
Johnson, J. K., Lipton, A., Allison, S., Martin-Cook, K., Merrilees, J., Miller, B. L., & Rosen, H. J. (2004). O4-06–08 Behavioral disturbance in frontotemporal dementia and frontal variant Alzheimer disease.Neurobiology of Aging, (25), S87.	Poster presentation/conference abstract
Kiselica, A. M., & Benge, J. F. (2019). Quantitative and qualitative features of executive dysfunction in frontotemporal and Alzheimer's dementia.Applied Neuropsychology: Adult, 1–15.	fvAD not defined/included
Kuzmickienė, J., & Kaubrys, G. (2016). Specific features of executive dysfunction in Alzheimer-type mild dementia based on Computerized Cambridge Neuropsychological Test Automated Battery (CANTAB) Test results.Medical Science Monitor: International Medical Journal of Experimental and Clinical Research, 22, 3605.	fvAD not defined/included
Larner, A. J. (2004). Getting it wrong: the clinical misdiagnosis of Alzheimer's disease.International Journal of Clinical Practice, 58(11), 1092–1094.	fvAD not defined/included
Lehmann, M., Rohrer, J. D., Clarkson, M. J., Ridgway, G. R., Scahill, R. I., Modat, M., … & Fox, N. C. (2010). Reduced cortical thickness in the posterior cingulate gyrus is characteristic of both typical and atypical Alzheimer's disease.Journal of Alzheimer's Disease, 20(2), 587–598.	fvAD not defined/included
Lehmann, M., Ghosh, P. M., Madison, C., Laforce Jr, R., Corbetta-Rastelli, C., Weiner, M. W., … & Miller, B. L. (2013). Diverging patterns of amyloid deposition and hypometabolism in clinical variants of probable Alzheimer's disease.Brain, 136(3), 844–858.	fvAD not defined/included

Table B – (*continued*)

Citation	Reason for exclusion
Mattsson, N., Schott, J. M., Hardy, J., Turner, M. R., & Zetterberg, H. (2016). Selective vulnerability in neurodegeneration: Insights from clinical variants of Alzheimer's disease.Journal of Neurology, Neurosurgery & Psychiatry, 87(9), 1000–1004.	Not original quantitative research
Mendez, M. F. (2019). Early-onset Alzheimer disease and its variants.Continuum (Minneapolis, Minn.), 25(1), 34.	Not original quantitative research
Mendez, M. F. (2012). Early-onset Alzheimer's disease: nonamnestic subtypes and type 2 AD.Archives of Medical Research, 43(8), 677–685.	fvAD not defined/included
Mendez, M. F., Lee, A. S., Joshi, A., & Shapira, J. S. (2012). Nonamnestic presentations of early-onset Alzheimer's disease.American Journal of Alzheimer's Disease & Other Dementias®, 27(6), 413–420.	fvAD not defined/included
Mendez, M. F., Joshi, A., Tassniyom, K., Teng, E., & Shapira, J. S. (2013). Clinicopathologic differences among patients with behavioral variant frontotemporal dementia. Neurology, 80(6), 561–568.	Methodological limitations
Mez, J., Mukherjee, S., Thornton, T., Fardo, D. W., Trittschuh, E., Sutti, S., … & Gross, A. (2016). The executive prominent/memory prominent spectrum in Alzheimer's disease is highly heritable.Neurobiology of Aging, 41, 115–121.	fvAD not defined/included
Murray, M. E., Graff-Radford, N. R., Ross, O. A., Petersen, R. C., Duara, R., & Dickson, D. W. (2011). Neuropathologically defined subtypes of Alzheimer's disease with distinct clinical characteristics: a retrospective study.The Lancet Neurology, 10(9), 785–796.	fvAD not defined/included
Naeije, G., Vokaer, M., Fery, P., Vilain, C., Abramowicz, M., Van den Broeck, M., … & Bier, J. C. (2011). Focal cortical presentations genetically proven Alzheimer disease. InThe Clinical Spectrum of Alzheimer's Disease-The Charge Toward Comprehensive Diagnostic and Therapeutic Strategies. IntechOpen.	Not original quantitative research
Ossenkoppele, R., Iaccarino, L., Schonhaut, D. R., Brown, J. A., La Joie, R.' O'Neil, J. P., … & Miller, B. L. (2019). Tau covariance patterns in Alzheimer's disease patients match intrinsic connectivity networks in the healthy brain.NeuroImage: Clinical, 23, 101848.	fvAD not defined/included
Phillips, J. S., Da Re, F., Dratch, L., Xie, S. X., Irwin, D. J., McMillan, C. T., … & Trojanowski, J. Q. (2018). Neocortical origin and progression of gray matter atrophy in nonamnestic Alzheimer's disease. Neurobiology of Aging, 63, 75–87.	Duplicate
Phillips, J., Irwin, D., Roll, E., McMillan, C., Da Re, F., Lee, E., … & Grossman, M. (2019). A/T/N Criteria are Inconsistent in Autopsy-Confirmed Non-Amnestic Alzheimer's Disease (S34. 008).	fvAD not defined/included
Powell, A., Foxe, D., Halliday, G., Piguet, O., Hodges, J., & Burrell, J. (2019). 037 Frontotemporal dementia or frontal variant Alzheimer's disease? A case series.Journal of Neurology, Neurosurgery, and Psychiatry, 90(e7).	Poster presentation/conference abstract
Ramanan, S., Bertoux, M., Flanagan, E., Irish, M., Piguet, O., Hodges, J. R., & Hornberger, M. (2017). Longitudinal executive function and episodic memory profiles in behavioral-variant frontotemporal dementia and Alzheimer's disease.Journal of the International Neuropsychological Society, 23(1), 34–43	fvAD not defined/included
Razani, J., Casas, R., Wong, J. T., Lu, P., Alessi, C., & Josephson, K. (2007). Relationship between executive functioning and activities of daily living in patients with relatively mild dementia.Applied Neuropsychology, 14(3), 208–214.	fvAD not defined/included
Russo, C., Schettini, G., Saido, T. C., Hulette, C., Lippa, C., Lannfelt, L., … & Teller, J. K. (2000). Presenilin-1 mutations in Alzheimer's disease.Nature, 405(6786), 531–532.	fvAD not defined/included
Scheltens, N. M., Tijms, B. M., Koene, T., Barkhof, F., Teunissen, C. E., Wolfsgruber, S., … & Rabinovici, G. D. (2017). Cognitive subtypes of probable Alzheimer's disease robustly identified in four cohorts.Alzheimer's & Dementia, 13(11), 1226–1236	fvAD not defined/included
Smits, L. L., Pijnenburg, Y. A., Koedam, E. L., van der Vlies, A. E., Reuling, I. E., Koene, T., … & van der Flier, W. M. (2012). Early onset Alzheimer's disease is associated with a distinct neuropsychological profile.Journal of Alzheimer's Disease, 30(1), 101–108.	fvAD not defined/included
Silveri, M. C. (2007). Frontotemporal dementia to Alzheimer's disease.Dialogues in Clinical Neuroscience, 9(2), 153.	Not original quantitative research

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Table B – (*continued*)

Citation	Reason for exclusion
Singleton, E. H., Pijnenburg, Y. A., Sudre, C. H., Groot, C., Kochova, E., Barkhof, F., … & Cardoso, M. J. (2019). Investigating the clinico-anatomical dissociation in the behavioral variant of Alzheimer's disease. MedRxiv, 19006676.	Not peer reviewed
Schöll, M., Lockhart, S. N., Schonhaut, D. R., O'Neil, J. P., Janabi, M., Ossenkoppele, R., … & Rabinovici, G. D. (2016). PET imaging of tau deposition in the aging human brain.Neuron, 89(5), 971–982.	Methodological limitations [Insufficient NPsyc data/Npsyc data N/A]
Stopford, C. L., Snowden, J. S., Thompson, J. C., & Neary, D. (2007). Distinct memory profiles in Alzheimer's disease.Cortex, 43(7), 846–857.	fvAD not defined/included
Taipa, R., Pinho, J., & Melo-Pires, M. (2012). Clinico-pathological correlations of the most common neurodegenerative dementias.Frontiers in Neurology, 3, 68.	Not original quantitative research
Turcano, P., Stang, C. D., Mielke, M. M., Martin, P. R., Upadhyaya, S. G., Josephs, K. A., … & Savica, R. (2019). Incidence of frontotemporal disorders in Olmsted County: A population-based study.Alzheimer's & Dementia.	fvAD not defined/included
Vardy, E. R., Ford, A. H., Gallagher, P., Watson, R., McKeith, I. G., Blamire, A., & O'Brien, J. T. (2013). Distinct cognitive phenotypes in Alzheimer's disease in older people.International Psychogeriatrics, 25(10), 1659–1666.	fvAD not defined/included
Villain, N., & Dubois, B. (2019). Alzheimer's disease including focal presentations. InSeminars in Neurology(Vol. 39, No. 02, pp. 213–226).	Not original quantitative research
Wallin, A., & Blennow, K. (1996). Clinical subgroups of the Alzheimer syndrome.Acta Neurologica Scandinavica, 94(S165), 51–57.	fvAD not defined/included
Warren, J. D., Fletcher, P. D., & Golden, H. L. (2012). The paradox of syndromic diversity in Alzheimer disease.Nature Reviews Neurology, 8(8), 451–464.	Not original quantitative research
Weiner, M. W., Veitch, D. P., Aisen, P. S., Beckett, L. A., Cairns, N. J., Cedarbaum, J., … & Luthman, J. (2015). 2014 Update of the Alzheimer's Disease Neuroimaging Initiative: A review of papers published since its inception.Alzheimer's & Dementia, 11(6), e1-e120.	Not original quantitative research
Weiner, M. W., Veitch, D. P., Aisen, P. S., Beckett, L. A., Cairns, N. J., Green, R. C., … & Petersen, R. C. (2017). Recent publications from the Alzheimer's Disease Neuroimaging Initiative: Reviewing progress toward improved AD clinical trials.Alzheimer's & Dementia, 13(4), e1-e85.	Not original quantitative research
Wolk, D. A. (2013). Amyloid imaging in atypical presentations of Alzheimer's disease.Current Neurology and Neuroscience Reports, 13(12), 412.	Not original quantitative research
Wolk, D. A., Dickerson, B. C., & Alzheimer's Disease Neuroimaging Initiative. (2010). Apolipoprotein E (APOE) genotype has dissociable effects on memory and attentional–executive network function in Alzheimer's disease.Proceedings of the National Academy of Sciences, 107(22), 10256–10261.	fvAD not defined/included

Appendix C

Table C – Cross-sectional and cohort studies.

Citation	Population Characteristics *n*: sample size [M (range/SD)]	MMSE † M (range/SD)	Study Design	Study Objective	Biomarker	Cognitive	Findings (significance of cognitive/biomarker relationship for fvAD cohort)
Forman et al. 2006	fvAD: $n = 17$ [60.3 (34–82)] Tauopathy: $n = 38$ [60.3(46–79)] FTLD-U/DLDH: $n = 26$ [60.3 (46–79)] DLDH: $n = 4$ [54.8 (43–80)]	fvAD: 20.1 (2–29) Tauopathy: 22.6 (4–30) FTLD: 22.4 (8–30)	Cohort Study	Assessment of clinical features of Frontotemporal lobar degeneration predict the underlying pathology.	Post mortem	BNT Verbal Fluency- Category Word list recall Digit Span- Forwards	Biomarker Findings • all pathological subgroups of FTD: widespread distribution of pathology at autopsy; no specific predilection for the frontal lobes. Neuropsychological Findings • Neuropsychological profiles statistical association with underlying pathology. • Category fluency: Tauopathy subgroup greater impairment than fvAD group ($p < .05$) • Word list recall task: fvAD subgroup had greater impairment than tauopathy subgroup ($p < .05$) and the FTLD-U/DLDH subgroup ($p < .01$). • Digit Span Forwards: fvAD subgroup had greater impairment than FTLDU/DLDH subgroup ($p < .05$). • Boston Naming Test: FTLD-U/DLDH subgroup had greater impairments than the tauopathy subgroup ($p < .05$).

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Table C – (*continued*)

Citation	Population Characteristics *n*: sample size [M (range/SD)]	MMSE † M (range/SD)	Study Design	Study Objective	Biomarker	Cognitive	Findings (significance of cognitive/biomarker relationship for fvAD cohort)
Grossman et al. 2007	fvAD: $n = 14$ [69.79 (11.3)] Tau-Positive FTD: $n = 22$ [64.73 (11.9)] Tau-Negative FTD: $n = 25$ [64.64 (9.5)]	fvAD: 21.86 (4.8) Tau-Positive FTD: 19.18 (8.3) Tau-Negative FTD: 22.65 (6.9)	Retro-spective clinical-patholog-ical survey	Use of clinical, neuropsychological & neuroimaging evidence to aid the differential diagnosis of fvAD, Tau-Positive FTD: 1 & Tau-Negative FTD.	MRI Post mortem Antibodies	WAIS-R Digit Span-Forwards & Backwards Verbal Fluency TMT B Stroop -BNT-15 Semantic category membership task, Copying geometric designs Verbal Serial List Learning Test	Biomarker Findings MRI: • Tau-positive FTD subgroup significant atrophy bilateral frontal & parietal regions (prominent in the right hemisphere). • Tau-negative FTD subgroup significant atrophy bilateral frontal & temporal distributions. • fvAD subgroup significant atrophy bilateral temporal & parietal regions (including the hippocampus & extension into the frontal cortex). Post mortem: • tau-positive group - abundant tau inclusions no amyloid plaques, particularly in the frontal, parietal, lateral temporal, hippocampal, & basal ganglia regions • tau-negative subgroup, greater amounts of ubiquitin compared with tau & amyloid were noted in the frontal, parietal, temporal, & hippocampal regions. • fvAD group, all 3 types of pathology were equally severe in all areas of the brain that were sampled. Neuropsychological Findings • Behaviour: Tau-negative FTD subgroup greater changes than tau-positive FTD ($p = .03$) and fvAD ($p < .001$) subgroups. • Figure Copy: Tau-positive subgroup poorer than tau-negative ($p < .001$) & fvAD ($p < .001$) subgroup. • Letter Fluency: Tau-negative FTD poorer than tau-positive FTD ($p < .001$) fvAD ($p < .001$). • Confrontation naming: lower for tau-negative FTD compared with tau-positive FTD ($p = .04$). • Animal fluency: Tau-positive group produced lower scores than fvAD ($p = .08$). • Delayed recall condition of the verbal memory test: fvAD recalled fewer words than tau-negative FTD ($p = .03$).

Grossman et al. 2008	fvAD: $n = 12$ [63.67 (11.02)] Tau-positive FTD: $n = 17$ [64.82 (12.80)] Tau-negative FTD: $n = 11$ [63.91 (8.69)]	fvAD 21.75 (4.20) T-positive FTD: 19.88 (7.04) T-negative FTD: 22.55 (6.68)	Cohort Study	Examine longitudinal decline in cognitive functioning in an autopsy-proven cohort of patients with diagnosis of FTLD spectrum disorder or FTLD pathology. On autopsy patients are categorized according tau-positive FTLD, tau-negative FTLD, & frontal variant-Alzheimer disease (fvAD) subgroups.	Post mortem Immunohisto-chemistry Antibody	WAIS-R Digit Span-Forwards & Backwards Verbal Fluency- Letter & Category Confrontation Naming Verbal Serial List Learning Figure Copy(4 geometric designs) Semantic Memory - Judge the membership of color photos and words in a familiar semantic category (vegetables, tool)	Biomarker Findings. • Immunohistochemistry was performed on sections of neocortex, hippocampus, putamen, globus pallidus, cerebellum, & midbrain, with antibodies. Neuropsychological Findings • FAS letter fluency: fvAD subgroups performed better than tau-positive patients ($p < .001$) & tau-negative subgroups ($p < .01$). • Visual constructions: tau-positive subgroups impaired relative to tau-negative subgroups ($p < .05$). • fvAD: significant difficulty longitudinally on verbal memory recall, recognition memory, semantic memory, confrontation naming, & animal naming fluency compared to other measures.
Calvo, Ramos-Campos, & de Lucena, 2013	fvAD: $n = 13$ [72.8 (7.6)] Typical AD: $n = 47$ [75.9 (5.5)] Control: $n = 24$ [72.8 (4.6)]	fvAD: 22.5 (2.1) Typical AD: 22.8 (1.2) Controls: 28.3 (1.3)	Cross Sectional Study	Use of clinical features investigate the clinical heterogeneity of early onset AD, specifically fvAD compared to Typical AD.	CT or MRI SPECT APOE Genotype	TMT A & B A-Test HVLT-RA BVRT RCFT + recall Verbal Fluency CDT-Copy; Stroop test (part C) WAIS-R Similarities + Comprehension + DSST + Digit Span- Forwards & Backwards NPI	Biomarker Findings • AD cohort was classified according to the result of the brain SPECT. fvAD (frontal hypoperfusion); typical AD (without frontal hypoperfusion) with a general pattern of unilateral temporal, or bilateral temporoparietal hypoperfusion. • APOE genotype analysis: fvAD group, APOE $\varepsilon 4 = 15\%$; Typical AD, APOE $\varepsilon 4 = 53\%$. Neuropsychological Findings • The fvAD cohort performed poorer on all neuropsychological tests relative to the typical AD cohort. • Significant group differences ($p < .001$) for processing speed (TMT A; DSST) & visuoconstruction tasks (CDT Copy, RCFT copy). • Logistic regression analysis revealed that the processing speed & mental flexibility (TMT − B) scores significantly predicted a diagnosis of fvAD.

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Table C – (*continued*)

Citation	Population Characteristics *n*: sample size [M (range/SD)]	MMSE † M (range/SD)	Study Design	Study Objective	Biomarker	Cognitive	Findings (significance of cognitive/biomarker relationship for fvAD cohort)
Ossenkoppele et al. 2015	Behav/Dysexec AD: $n = 75$ [65.8 (8.5)] bvAD: $n = 55$ [64.7 (8.8)] Dysexecutive AD: $n = 29$ [69.2 (8.5)] Typical AD $n = 58$ [64.4 (8.6)] bvFTD $n = 59$ [63.8(6.8)] Controls $n = 61$ [63.7 (8.1)]	Behav/Dysexec AD: 22.7 (5.6) Behavioural AD: 22.5 (5.4) Dysexecutive AD: 24.6 (3.3) Typical AD: 22.5 (4.1) bvFTD: 23.7 (5.4) Controls: 29.4 (.7)	Cross Sectional Study	Investigate "frontal variant" of Alzheimer's disease in patients with predominant behavioural or dysexecutive deficits caused by Alzheimer's disease pathology.	MRI PET CSF	CVLT Benson Figure Test RAVLT Visual Association Test Digit Span- Backwards TMT B Stroop Color-Word Verbal Fluency – Letter & Category BNT VOSP – Number Location RCFT(modified)	Biomarker Findings • Combined behavioural/dysexecutive AD cohort: minimal frontal lobe atrophy; greater involvement of prefrontal & temporal regions; atrophy pattern similar to typical AD, though typical AD had greater occipital involvement; in comparison to bvFTD the b/dAD cohort had greater posterior involvement & bvFTD had greater anterior involvement. • bvAD: predominant temporoparietal & small regions of the left orbitofrontal cortex, frontal poles & middle & superior frontal gyri atrophy • Dysexecutive AD: distributed grey matter reductions in superior, middle & inferior temporal gyrus, anterior & posterior cingulate, inferior parietal lobule & parahippocampal gyrus. Neuropsychological Findings • Composite memory scores: bvAD poorer than dysexecutive Alzheimer's disease ($p < .001$) & behavioural variant FTD ($p < .01$) patients, • BvAD memory scores did not significantly differ from typical Alzheimer's disease patients ($p = .06$). • Composite executive function scores: dysexecutive AD & bvAD cohorts lower than typical AD ($p < .05$) & bvFTD patients ($p < .05$), & did not differ from each other. • Individual cohorts did not differ in composite scores for language & visuospatial functions.

Wong et al. 2016	AD impaired executive function (IEF-AD): $n = 23$ [63.91 ± 7.87] AD with relatively spared executive functioning (SEF-AD): $n = 12$ [65.17 (7.87)] bvFTD: $n = 22$ [60.95 (6.24)] Controls: $n = 38$ [65.58 (5.53)]	IEF-AD: 72.78 (7.62) SEF-AD: 80.92 (7.25) bvFTD: 76.32 (11.75) Control: 95.21 (3.48) ACE-R †	Cross Sectional Study	Investigate the differences in prefrontal atrophy & episodic memory performance in dysexecutive AD & bvFTD patient cohorts.	Voxel-based morpho-metry analyses	Digit Span- Backwards COWAT TMT HSCT RAVLT RCFT FRS CDR CBI-R	Biomarker Findings • SEF-AD cohort demonstrated atrophy in the right hippocampus & left inferior & middle frontal gyri. • IEF-AD cohort showed bilateral hippocampus atrophy; bilateral temporal & frontal poles, left inferior, middle & superior frontal gyri, left orbitofrontal cortex, & left fusiform cortex atrophy. • bvFTD patients showed widespread bilateral atrophy including the hippocampus, frontal pole, orbitofrontal cortex, paracingulate cortex, subcallosal cortex, anterior cingulate cortex, medial prefrontal cortex, inferior, middle & superior frontal gyri, precentral gyrus, & temporal pole. • No PFC or MTL regions were found to be significantly more atrophic in IEF-AD or SEF-AD compared to bvFTD. • Greater atrophy in the right superior frontal gyrus & frontal pole in the IEF-AD cohort relative to the SEF-AD cohort. The reverse contrast did not reveal any regions of significantly greater atrophy in SEF-AD compared to IEF-AD patients. Neuropsychological Findings • SEF-AD > bvFTD: COWAT total correct $p < .01$; Digit Span- Backwards total correct n.s.; TMT B-A time [seconds] n.s.; Hayling AB error score $p < .001$ • IEF-AD vs. bvFTD: COWAT total correct n.s.; Digit Span- Backwards total correct n.s.; TMT B-A time [seconds] n.s.; Hayling AB error score n.s. • IEF-AD < SEF-AD: COWAT total correct $p < .05$; Digit Span- Backwards total correct $p < .05$; TMT B-A time [seconds] n.s. ; Hayling AB error score $p < .01$ • No differences between groups for episodic memory recall (RAVLT, RCFT-3 minute recall) CBI-R Post hoc comparisons between patient groups: • BvFTD showed greater disturbance in eating habits relative to SEF-AD ($p = .031$) and IEF-AD ($p < .001$) • bvFTD showed more symptoms of abnormal behaviour ($p = .003$), stereotypic and motor behaviours ($p < .001$), and reduced motivation ($p = .015$) relative to IEF-AD. • SEF-AD and IEF-AD patients did not differ on any of the CBI-R subscores (all p values > .05).

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Table C – (*continued*)

Citation	Population Characteristics *n*: sample size [M (range/SD)]	MMSE † M (range/SD)	Study Design	Study Objective	Biomarker	Cognitive	Findings (significance of cognitive/biomarker relationship for fvAD cohort)
Phillips et al. 2018	bvAD: $n = 22$ [64.3 (8.2)] aAD: $n = 22$ [64.9 (9.7)] lvPPA: $n = 41$ [62.5 (7.2)] PCA: $n = 27$ [59.4 (7.3)] CBS: $n = 17$ [59.9 (7.0)] Control: $n = 115$ [62.7 (8.2)]	bvAD: 19.6(8.4) aAD: 18.3 (6.4) lvPPA: 22.4 (5.8) PCA: 22.2(4.3) CBS: 18.6(6.7)	Cohort Study	Investigate the differences in anatomical origin & progression of atrophy in of typical amnestic AD cohorts & non-amnestic cohorts.	MRI Post-mortem CSF	PBAC PVLT Verbal Fluency - Category WAIS-R -Digit Span-Forward & Backwards RCFT Pyramids & Palm Trees PBAC	Biomarker Findings • BvAD model included the left MFG, left anterior insula, & right MTG. This model indicated a subsequent spread of atrophy to bilateral prefrontal, temporal, & inferior parietal cortices. • aAD - only group with early involvement of hippocampus & MTL • CBS & PCA groups - hippocampal atrophy. Neuropsychological Findings • PCA patients significantly better executive functioning than both CBS & bvAD patients $p < .05$. • Visuospatial subscale also significantly differed by group ($p < .001$). Posthoc tests indicated that lvPPA patients had significantly better visuospatial function than both PCA ($p < .001$) & CBS patients ($p < .005$). Additionally, at a threshold of $p < .05$ (uncorrected), aAD & bvAD patients' scores exceeded those of PCA patients • A main effect of group was additionally observed on the behavioral subscale (PBAC) ($p < .001$), reflecting lower scores for the bvAD group than for aAD ($p < .001$), lvPPA ($t = -6.4$, $p < .001$), PCA ($p < .001$), & CBS patients ($p < .001$). • No effect of group was observed on the language subscale ($p > .50$) or the verbal memory subscale ($p > .1$).
Phillips et al. 2019	fvAD: $n = 12$ [63.9 IQR 59.7, 69.5] aAD: $n = 17$ [59.4 IQR 53.5, 70.3]; lvPPA: $n = 25$ [58.5 IQR 56.9, 64.5] PCA: $n = 20$ [58.0 IQR 55.1, 61.4]] Control: $n = 37$ [61.9 IQR 57.9, 65.6]	fvAD 23.0 [17.0, 26.0] aAD 23.0 [20.0, 25.0] lvPPA 25.0 [23.0, 28.0] PCA 24.5 [18.8, 25.2] Control 29.0 [28.0, 30.0]	Cohort Study	Investigate the anatomical progression of disease in three non-amnestic patients using longitudinal imaging to differentiate earlier atrophy & later disease spread.	MRI, Post-mortem	PBAC Digit Span Verbal Fluency - Letter RCFT JLO Oral TMT PVLT or PBAC verbal memory test	Biomarker Findings • fvAD cohort greater atrophy rates in left anterior insula than lvPPA ($p < .04$) & PCA patients ($p < .02$). • amnestic AD cohort rapid atrophy in right middle temporal gyrus than lvPPA ($p < .01$) & PCA patients ($p < .01$); in left middle temporal gyrus relative to lvPPA ($p < .03$); in right precuneus relative to lvPPA ($p < .04$) & frontal-variant Alzheimer's disease ($p < .02$); & in right supramarginal gyrus relative to all three non-amnestic Alzheimer's disease groups (all $p < .01$). • All patient groups demonstrated significant atrophy relative to controls in one or more MTL structures & we found no significant differences between patient groups in atrophy rates for bilateral hippocampi, entorhinal cortex, or parahippocampal gyri. Neuropsychological Findings • Between group significance (Kruskal-Wallis $\leqq .05$) across all test measures with the exception of oral trail making test.

Townley et al. 2020	fvAD: $n = 55$ [57.1 (48–71)]	STMS 19.9/38 (8.9) averaged across all participants	Cross Sectional Study	Investigate a patient cohort with a progressive dementia syndrome characterized by predominant executive dysfunction, relatively young age of onset & positive biomarkers for Alzheimer's pathophysiology.	EEG CSF Amyloid PET Tau PET FDG PET MRI Genotyping	DRS-2 Letter Number Sequence, Digit Span- Forward & Backwards WMS Logical Memory I & II WMS Visual Reproduction I, & II, RAVLT TMT A+ B Stroop (Word, Colour) COWAT Verbal Fluency- Category BNT RCFT	Biomarker Findings • PET Hypometabolism: frontal & parietal regions with relative sparing of MTL • At least one APOE E4 allele found in 14/26 participants • EEG- abnormal/diffuse slowing. • CSF/neuroimaging biomarkers: consistent with AD pathophysiology; CSF p-tau was normal in 24% of cases. Neuropsychological Findings (p values not reported) • See paper - Not all participants underwent neuropsychological evaluation • fvAD: Multidomain cognitive impairment w/primary impairment in executive functioning. • Behavioural symptoms in 16/55 participants - not predominant symptom in this fvAD cohort
Sala et al. 2020	typical AD: $n = 22$ [67.32 (6.83)] Posterior Variant AD: $n = 16$ [60.88 (6.78)] lvPPA AD: $n = 14$ [73.00 (5.60)] fvAD: $n = 15$ [62.47(5.70)] bvFTD: $n = 30$ [71.02 (7.07)]	typical AD: 21.19 (4.14) Posterior Variant AD: 19.93(4.17) lvPPA AD: 17.36(4.67) fv AD: 16.47(5.18) bvFTD: 22.83 (6.06)	Cross Sectional Study	FDG-PET biomarker to assess spectrum of AD variants	FDG - PET	Token Test Verbal Fluency Short Story Digit Span- Forward CDT Attentive Matrices RCFT + recall	Biomarker findings • W-score group maps demonstrated group-specific patterns of hypometabolism for typical AD & for each AD variant • Typical AD: hypometabolism- bilateral lateral temporal & parietal regions, & the precuneus & posterior cingulate cortex • fvAD: hypometabolism - parietal regions, temporal regions, dorsolateral & orbitofrontal cortex • Hypometabolism patterns discriminate fvAD from bvFTD with AUC = .942 (sensitivity = 1, specificity = .833). Neuropsychological Findings • MMSE: fvAD worse than typical AD ($p = .011$) • Token Test: fvAD < typical AD ($p = .014$) • Verbal Fluency: Letter - fvAD < PCA ($p = .006$); Semantic - fvAD < typical AD ($p = .001$) • Attentive Matrices fvAD < typical AD ($p = .001$) • bvFTD significantly differed from the fvAD group both on age ($p < .001$) & MMSE ($p < .005$)

† Alternate screening examination; n.s. nonsignificant; behavioural variant Alzheimer's Disease (bvAD); amnestic Alzheimer's disease (aAD); logopenic variant primary progressive aphasia (lvPPA); posterior cortical atrophy (PCA); corticobasal syndrome (CBS); frontal variant Alzheimer's disease (fvAD); behavioural variant frontotemporal dementia (bvFTD); Dementia lacking distinctive histology (*DLDH*); frontotemporal dementia (FTD); frontotemporal lobar degeneration-ubiquitin (FTLD-U); Short Test of Mental Status (STMS); Mini-Mental State Examination (MMSE); Montreal Cognitive Assessment (MoCA); Montreal Cognitive Assessment- Chinese Version (MoCA-C); Addenbrooke's Cognitive Examination – Revised Version (ACE-R); Alzheimer Disease Assessment Scale cognitive (ADAS-COG); Dementia Rating Scale-2 (DRS-2); Neuropsychiatric Inventory (NPI-Q); Frontal Assessment Battery (FAB); Frontal Behavioural Inventory (FBI); Hachinski Ischemia Scale (HIS); the Alzheimer's Disease Cooperative Study/Activities of Daily Living (ADCS-ADL); 21-items Hamilton Depression Rating Scale (HADM-21); Wechsler Adult Intelligence Scale - Fourth Edition (WAIS-IV); Wechsler Adult Intelligence Scale - Revised Edition (WAIS-R); Digit Span (DS); Boston Naming Test (BNT); Benton Visual Retention Test (BVRT); California Verbal Learning Test (CVLT); California Verbal Learning Test - Second Edition (CVLT-II); Clock Drawing Test (CDT); Cognitive Estimation Test (CET); Controlled Oral Word Association Test (COWAT; Benton, Hamsher, & Sivan, 1994); Digit Symbol Substitution Test (DSST); Free & Cued Selective Reminding Test (FCSRT); Hayling Sentence Completion Test (HSCT); Kendrick Digit Copy Task (KDCT); Reading the Mind in the Eyes (RME) Rey Auditory Verbal Learning Test (RAVLT) (Schmidt, 1996).; Rey Complex Figure Test (RCFT); Symbol Digit Modalities Test (SDMT); The Awareness of Social Inference Test (TASIT) Theory of Mind – 15 (TOM-15); Trail Making Test- Form A & B (TMT A&B); Verbal Fluency - Letter and Semantic/Category Fluency; Wisconsin Card Sorting Test (WCST); Weschler Memory Scale (WMS); Tests for Attentional Performance Battery [Digit Span, Corsi block-tapping, TMT (A & B), letter/category/design fluency, Stroop test]; Consortium to Establish a registry for AD neuropsychological battery (CERAD): Philadelphia Brief Assessment of Cognition (PBAC); Philadelphia Verbal Learning Test (PVLT); F-fluorodeoxyglucose positron emission tomography (FDG-PET); magnetic resonance imaging (MRI); computerised tomography (CT); Cerebrospinal Fluid (CSF); Electroencephalogram (EEG); single-photon emission computerized tomography (SPECT); Apolipoprotein E (APOE).

Appendix D

Table D1 – Case study designs.

Citation	fvAD Case (non-fvAD comparison)	MMSE (/screening measure)	Biomarker Evidence	Cognitive Measures
Larner (2006)	A. 52 yo Male B. 56 yo Male	A. 23/30 B. 16/30 & 20/30	CT, EEG, MRI (Pt. A only)	WTAR, NART, ACE, Graded Naming Test, RCFT Stroop, Verbal Fluency
Taylor, et al. 2008	66 yo Male	Time 1. 28/30 Time 2. 27/30 Time 3. 25/30 1 year interval	Brain MRI, SPECT, Genetic analyses, Post-mortem	Tests for Attentional Performance Battery, CVLT, CERAD, Object & famous face identification, Praxis
Duker et al. 2012	58 yo Male (CBS: $n = 2$) (PCA: $n = 1$) (lvPPA: $n = 1$)	N/A	MRI, PET, FDG-PET imaging	TMT, Learning a list of 5 words, Verbal fluency RCFT
Nygaard et al. 2014	52 yo Male	30/30	Genetic analyses, MRI, PET	Verbal fluency, CDT, Verbal Abstract Reasoning, Go-no sequence
Li et al. 2016	71 yo Female (bvFTD $n = 1$)	15/30 MOCA-C 11/30 †	MRI, FDG-PET, CT, PIB PET	CDT, ADAS-COG, BNT, NPI-Q, FAB, FBI, HIS, ADCS-ADL, HADM-21
Scialò et al. 2016	68 yo Female	Time 1. 27/30 Time 2. 24/30 1 year interval	FDG-Pet, CSF, F-florbetapir PET, Genetic analyses	RAVLT. WCST, Stroop (Colour & Colour-Word), Digit Symbol, Corsi Span, Digit Span, TMT (A & B), Verbal Fluency, BNT, CDT, Figure Copying
Kawakatsu, Kobayashi, & Hayashi, 2017	56 yo Male (Typical AD: $n = 2$) (PCA: $n = 6$) (lvPPA: $n = 1$)	8/30	MRI, CT, SPECT, Genetics, Post-mortem	FAB, Figure copy. HDS-R
Duclos et al. 2017	61 yo Female	N/A	CSF, MRI - voxel-based morphometry analyses	TOM-15, RME test, SNK, FBI
Sawyer et al. 2017	A. 72 yo Male B. 79 yo Male C. 78 yo Female	A. MoCA 21/30 B. MMSE 28/30 MoCA 23/30 C. MoCA 8/30	MRI, CSF, Post-mortem	
Gallucci et al. 2019	61 yo Female	Time 1. 24/30 Time 2. 25/30 1 year interval	F-FDG, PET, MRI, Genetic analyses	Digit Span, Visuospatial Span, Short-Story Memory Test, Attentive Matrices, Verbal Fluency, Token Test, Design Copy Test, Apraxia Test, CDT, CET, RAVLT, TMT A, NPI, Interference Memory Test, FCSRT, Stroop Test, Visual Words Comprehension, Auditory/Visual Sentence Comprehension, Calculation Processing
de Souza et al. 2019	68 yo Female	Time 1. 29/30 Time 2. 26/30 2 year interval	CSF, PET, MRI	RAVLT, RCFT, Tower of London Test, Figure Memory Test, Verbal fluency, Reading, writing & comprehension of written language, Theory of mind, the faux pas test & the TOM-15 (Time only), ACE-R (Time 2 only), HSCT

Wong et al. 2019	57 yo Male (EOAD: $n = 1$) (bvFTD: $n = 1$) (Controls: $n = 20$)		PiB-PET, MRI	RAVLT, Doors & People Test, Digit Span Backwards, COWAT, TMT A & B, HSCT, The Emotion-Selection Task, The Emotion Evaluation subtest from the TASIT
Li et al. 2020	66 yo Male	10/30	FDG-PET F-labelled T807 Tau PET PiBPET Plasma biomarker measures using immunomagnetic reduction (IMR) assay	FAB, TMT A & B, Stroop, FBI, JLO, 3D block construction model, FCSRT, Praxis, Visual Naming, Token Test, Aural Comprehension
Paquin, Therriault, Pascoal, Rosa-Neto, & Gauthier, 2020	60 yo Female	Time 1. 28/30 Time 2. 25/30	Amyloid-beta and tau PET imaging	FAB, Praxis tasks

Table D2 – Case Series.

Citation	fvAD Case (non-fvAD comparison [Mean age (SD/range)])	MMSE†	Biomarker Evidence	Cognitive Measures
Johnson (1999)	fvAD: $n = 3$ [71.7(8.1)] (Typical AD: $n = 3$ [64.7(9.6)])	A. 18 B. 21 C. 22 Mean 20.33	NFT pathology confirmed on autopsy	TMT A, COWAT, BNT- 30 item, CERAD - Animal, Naming, Word List, Constructional Praxis, WAIS-R - Vocabulary, Digit Span, Block Design, SDMT, KDCT
de Souza et al. 2013	fvAD: $n = 8$ [63.5 (8.9)] (Typical AD: $n = 18$ [64.8 (9.6)]) (bvFTD: $n = 18$, [65.7 (7.9)]) (Controls: $n = 18$, [68.6 (7)])	A. 16 B. 22 C. 10 D. 19 E. 26 F. 10 G.17 H. 21 Mean 17.6 (5.6)	CSF	MATTIS (/144), Memory: Encoding (FCSRT) (/16), Verbal Span, Verbal Fluency, FAB, WCST, mini-SEA
Bergeron et al. 2020	fvAD $n = 8$ [59.5 (7.9)] (bvFTD: $n = 8$ [64 (5.0)]) (Typical AD: $n = 37$ [74.2 (6.9)])	A. 11 B. 20 C. 28 D. 21 E. 25 F. 27 G. 21 H. 26 Mean 22.3 (5.9)	MRI, EEG, FDG-PET	Digit Span (Forward & Backwards), List learning recall & recognition task, Visual recognition of overlapping figures and spatial rotation, geometric figure drawing test, backward Digit Span, Months Backward test, Alternating graphic sequence test Verbal Abstraction task, Verbal Fluency (letter & category), Modified Stroop test, Scene Description task, Naming task, Single-word writing task, a Multi-sentence writing test, Sentence – Picture Matching test, repetition of long and short sentences.

See legend from Table C (Appendix C).
Additional abbreviations: C-labelled Pittsburgh compound B (PiB) PET; neurofibrillary tangles (NFT); Early Onset Alzheimer's Disease (EOAD); Social norm knowledge (SNK).

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[**] Included in case studies/ case series, Appendix D

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