Neuropsychologia 140 (2020) 107391

Contents lists available at ScienceDirect

Neuropsychologia

journal homepage: http://www.elsevier.com/locate/neuropsychologia

Word retrieval across the biomarker-confirmed Alzheimer's disease syndromic spectrum

Deepti Putcha, PhD [a,c,d,*], Bradford C. Dickerson, MD [a,d,e], Michael Brickhouse, BS [a], Keith A. Johnson, MD [b,c,d,e], Reisa A. Sperling, MD [b,c,d,e], Kathryn V. Papp, PhD [b,c,d,e]

[a] Frontotemporal Disorders Unit & Alzheimer's Disease Research Center, Departments of Psychiatry and Neurology, Massachusetts General Hospital, Boston, MA, 02129, USA
[b] Center for Alzheimer Research and Treatment, Department of Neurology, Brigham and Women's Hospital, Boston, MA, 02115, USA
[c] Center for Brain/Mind Medicine, Brigham and Women's Hospital, Boston, MA, 02115, USA
[d] Harvard Medical School, Boston, MA, 02115, USA
[e] Department of Neurology, Massachusetts General Hospital, Boston, MA, 02129, USA

ARTICLE INFO

Keywords:
Posterior cortical atrophy
Logopenic variant primary progressive aphasia
Amnestic
Cortical atrophy
Verbal fluency
Naming

ABSTRACT

Alzheimer's disease (AD) is now conceptualized as a biological entity defined by amyloid and tau deposition and neurodegeneration, with heterogeneous clinical presentations. With the aid of *in vivo* biomarkers, clinicians are better poised to examine clinical syndromic variability arising from a common pathology. Word retrieval deficits, measured using verbal fluency and confrontation naming tests, are hallmark features of the early clinical stages of the amnestic presentations of AD, specifically in category fluency and naming with relatively spared letter fluency. As yet, there is no consensus regarding performance on these tests in atypical clinical phenotypes of AD, including posterior cortical atrophy (PCA) and logopenic primary progressive aphasia (lvPPA), in individuals who are amyloid-positive (Aβ+) but present with different clinical profiles and patterns of neurodegeneration compared to amnestic AD. The goal of the current study is to determine how Aβ+ individuals across the syndromic spectrum of AD perform on three different word retrieval tasks. A secondary goal is to determine the neuroanatomical substrates underlying word retrieval performance in these Aβ+ individuals. Thirty-two Aβ+ participants with the amnestic presentation, 16 with Aβ+ PCA, 22 with Aβ+ lvPPA, and 99 amyloid-negative (Aβ-) control participants were evaluated with verbal fluency and visual confrontation naming tests as well as high-resolution MRI. The Aβ+ patient groups were rated at very mild or mild levels of severity (CDR 0.5 or 1) and had comparable levels of global cognitive impairment (average MMSE = 23.7 ± 3.9). Behaviorally, we found that the word retrieval profile of PCA patients is comparable to that of amnestic patients, characterized by intact letter fluency but impaired category fluency and visual confrontation naming, while lvPPA patients demonstrated impairment across all tests of word retrieval. Across all AD variants, we observed that letter fluency was associated with cortical thickness in prefrontal, central precuneus, lateral parietal and temporal cortex, while category fluency and naming were associated with cortical thickness in left middle frontal gyrus, posterior middle temporal gyrus, and lateral parietal cortex. Visual confrontation naming was uniquely associated with atrophy in inferior temporal and visual association cortex. We conclude that a better understanding of the word retrieval profiles and underlying neurodegeneration across the AD syndromic spectrum will help improve interpretation of neuropsychological profiles with regard to the localization of neurodegeneration, particularly in the atypical AD variants.

1. Introduction

Alzheimer's disease (AD), historically defined as a clinico-pathological entity requiring autopsy verification for definitive diagnosis, has more recently been understood as a biological entity reliant on validated, widely-used *in vivo* biomarkers that serve as proxies for AD neuropathic change (Jack et al., 2018; McKhann et al., 2011). These tools allow researchers to investigate the entire AD syndromic

* Corresponding author. Frontotemporal Disorders Unit Massachusetts General Hospital Boston, MA, 02129, USA.
E-mail address: dputcha@partners.org (D. Putcha).

https://doi.org/10.1016/j.neuropsychologia.2020.107391
Received 20 May 2019; Received in revised form 30 January 2020; Accepted 9 February 2020
Available online 10 February 2020

spectrum, rather than select individuals based on initial symptoms or signs. Apart from the typical amnestic presentation of AD, which is characterized most prominently by episodic memory impairment (Petersen, 2004) as well as semantic processing and fluency deficits (Henry et al., 2004; Monsch et al., 1992; Papp et al., 2016; Salmon et al., 1999), other clinical variants arising from AD pathology are posterior cortical atrophy (PCA) and logopenic primary progressive aphasia (lvPPA) (Koedam et al., 2010; Snowden et al., 2007). PCA, commonly thought of as a "visual variant" of AD (Benson et al., 1988), is a clinical syndrome characterized by a progressive decline in higher-order visual processing and other posterior cortical functions (Lehmann et al., 2011; Tang-Wai et al., 2004). In addition to visual cognitive deficits, word retrieval deficits have also been identified in PCA though there is no consensus on the precise nature of this impairment, with some investigations identifying phonemic fluency deficits (Crutch et al., 2013) and others identifying impairment in confrontation naming and semantic fluency (Putcha et al., 2018). LvPPA is characterized by variably non-fluent speech, difficulties with word retrieval, naming, sentence repetition, and phonological speech errors (Gorno-Tempini et al., 2011). It is as yet unknown how word retrieval impairment in lvPPA and PCA compares to that observed in the amnestic syndrome of AD on the most commonly used neuropsychological tests measuring word retrieval abilities: verbal fluency and confrontation naming tests. Additionally, the specific patterns of cortical atrophy across these three variants, while largely dissociable, share the overlapping involvement of posterior temporal and parietal cortex (Migliaccio et al., 2009; Ossenkoppele et al., 2015; Warren et al., 2012), regions posited to subserve word retrieval (Leyton et al., 2017; Vonk et al., 2018). Here we aimed to bring these converging lines of observation together in a study of word retrieval deficits across the AD syndromic spectrum (amnestic, PCA, and lvPPA), and associated patterns of cortical atrophy.

Word retrieval deficits are most commonly evaluated using verbal fluency tests, measuring speeded word retrieval to letter (phonemic fluency) and category (semantic fluency) cues. Word retrieval to a cue is also commonly measured with visual confrontation naming tests, requiring an individual to retrieve the name of a pictured item. Letter and category fluency tasks both call upon executive functions (initiation, goal-directed retrieval, updating, inhibition), which generally rely upon the coordinated effort of mid-dorsolateral prefrontal and lateral inferior parietal cortical regions that have historically been considered to be hubs within the frontoparietal network (FPN; Vincent et al., 2008), as well as regions of the superior frontal cortex and regions in and around the inferior parietal sulcus (IPS), considered to be hubs within the dorsal attention network (DAN) supporting top-down attention and working memory (Corbetta and Shulman, 2002). These types of verbal fluency tasks also rely on verbal processing and lexical retrieval skills (i.e., vocabulary size, retrieval of orthographic or semantic memory; Shao et al., 2014) which rely upon regions in lateral temporal cortex, temporoparietal junction and angular gyrus, and medial parietal cortex, nodes of the default mode (DMN) language subsystem and semantic networks (Andrews-Hanna et al., 2010; Binder et al., 2009; Hickok and Poeppel, 2007; Patterson et al., 2007). However, there are some important differences between the two fluency tasks: letter fluency is considered to be particularly reliant on executive functions, specifically selecting and retrieving words based on spelling/orthography (Birn et al., 2010; Shao et al., 2014), while category fluency is considered to rely on a combination of executive retrieval as well as on lexical and semantic processing (Papp et al., 2016; Shao et al., 2014; Vonk et al., 2018). The posterior middle temporal gyrus (MTG) in particular, which has functional connections with prefrontal hubs of both the DMN and FPN, has been posited as playing a critical role as a "functional nexus" implicated in the executive control of semantic processing (Davey et al., 2016; Noonan et al., 2013), facilitating so-called "controlled semantic cognition."

Structural MRI and functional magnetic resonance imaging (fMRI) investigations have reported varied and distributed regions as supporting word retrieval, generally representing hubs of the large-scale FPN, DAN, DMN and semantic networks. The variability in reported anatomical associations likely stem from paradigm-specific task characteristics and differences across study populations, which have most often been healthy individuals or patient groups with specific and circumscribed lesion sites (e.g., stroke patients). Letter fluency has been primarily associated with the integrity of the left hemisphere predominant inferior frontal cortex and bilateral middle frontal gyrus (Birn et al., 2010; Gourovitch et al., 2000; Meinzer et al., 2009; Vonk et al., 2018). Additionally, one report dissociated a posterior-dorsal peak of activity within inferior frontal cortex in response to letter fluency from an anterior-ventral peak within the inferior frontal cortex in response to category fluency (Costafreda et al., 2006). In contrast, category fluency has historically been associated with the integrity of medial temporolimbic structures (Hirni et al., 2013; Pihlajamaki et al., 2000), in part due to observations that category fluency is particularly impaired in early amnestic MCI, a population in which disease progression is prominent in the medial temporal regions (Henry et al., 2004). However, more recent fMRI investigations suggest that these findings may be a feature of the autobiographical relevance of category being tested (Sheldon and Moscovitch, 2012). Indeed, category fluency has also been associated with left-hemisphere inferior and middle frontal cortex (Meinzer et al., 2009), medial parietal cortex and superior parietal lobule (Pihlajamaki et al., 2000) as well as inferior parietal regions including the angular gyrus (Vonk et al., 2018) and left inferior temporal lobe (Grogan et al., 2009) in healthy individuals. This pattern has been reported with less specificity in prodromal amnestic AD (Eastman et al., 2013) in that category fluency was associated with bilateral atrophy of largely the same regions. Visual confrontation naming impairment (e.g., performance on Boston Naming Test) is also commonly reported across the AD spectrum (Crutch et al., 2013; Leyton et al., 2017) and has similarly been associated with cognitive processes that include both executive goal-directed retrieval demands supported by the frontoparietal regions described above, in addition to regions consistent with processing of visual information, including left middle and inferior occipital gyri and inferior temporal gyrus, in healthy individuals (Abrahams et al., 2003) and in prodromal AD (Leyton et al., 2017; Pravata et al., 2016) and other neurodegenerative diseases such as FTD and CBD (Grossman et al., 2004). Considering the diffuse cortical substrates of these related and distinct word retrieval tasks, we expect word retrieval impairment profiles to vary between the different AD syndromes.

The focus of the present study was to determine how individuals with each AD syndrome—PCA, lvPPA, and amnestic—differ from each other with regard to word retrieval performance, measured by common neuropsychological tests of verbal fluency and visual confrontation naming. A secondary goal was to determine the neuroanatomical substrates of each type of word retrieval deficit, using measures of cortical atrophy across the AD syndromic spectrum. Given the predominant posterior temporal and parietal abnormalities in these patients, we hypothesized that amnestic and PCA syndromes would demonstrate comparable verbal fluency profiles, with relatively intact letter fluency but impaired category fluency and visual confrontation naming performance, while lvPPA would demonstrate comparable impairment across all word retrieval tasks consistent with the broader lexical-phonological processing deficit pathognomonic to this group. We further hypothesized that letter fluency would be primarily associated with regions comprising the FPN (middle prefrontal cortex, posterior parietal cortex) thought to support goal-directed retrieval as well as lateral temporal cortical regions involved in lexical processing, and that category fluency and naming would be associated with regions of the semantic memory/language network implicated in controlled semantic cognition (lateral MTG and inferior parietal cortex) in addition to the frontoparietal regions underlying goal-directed retrieval. Finally, we hypothesized that naming performance would be additionally be associated with cortical atrophy in occipitotemporal visual association areas supporting visual object processing.

2. Methods

2.1. Participant characteristics

Data for this study were obtained from one hundred sixty-nine participants (32 amnestic, 16 PCA, and 22 lvPPA, and 99 healthy control participants; Table 1) in studies affiliated with the Massachusetts Alzheimer's Disease Center Frontotemporal Disorders Unit, or the Harvard Aging Brain Study. All participants received a standard clinical evaluation comprising a comprehensive neurological and psychiatric history and exam and structured informant interviews following the Clinical Dementia Rating (CDR) protocol, and a separate neuropsychological battery including the National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS) version 2.0 or 3.0 battery. For each patient, clinical diagnostic formulation was performed through consensus conference, with each patient being classified based on all clinical information as having mild cognitive impairment or dementia (global clinical status), and then each patient's cognitive-behavioral syndrome being diagnosed according to standard diagnostic criteria (Dickerson et al., 2017; Wong et al., in press). Initially, 25 patients met diagnostic criteria for PCA (Crutch et al., 2017; Renner et al., 2004; Tang-Wai et al., 2004), 23 patients met criteria for lvPPA (Gorno-Tempini et al., 2011), and 43 patients met criteria for amnestic MCI or dementia (McKhann et al., 2011). The patient sample was further restricted to those participants who had a positive amyloid status (Aβ+), as assessed by either visual read according to previously published procedures (Rabinovici et al., 2010) and biomarker criteria for probable Alzheimer's disease (distribution volume ratio $>$ 1.2; Villeneuve et al., 2015) or CSF amyloid-β levels ($\leq$192 pg/mL) supportive of likely presence of amyloid plaques and neurofibrillary tangles (Shaw et al., 2009). This resulted in a final patient sample size of 32 Aβ+ amnestic, 16 Aβ+ PCA, and 22 Aβ+ lvPPA participants. We also included a group of cognitively normal (CN; CDR = 0) individuals who all performed within normal limits on neuropsychological testing, had normal brain structure based on MRI, and low cerebral amyloid based on quantitative analysis of amyloid PET (DVR $<$ 1.2; Mormino et al., 2014), resulting in a CN sample of 99 individuals who were amyloid negative (Aβ- CN). This Aβ- CN group was used primarily for behavioral and cortical thickness comparisons. Individuals were excluded from this cohort if they had a primary psychiatric or other neurologic disorder including major cerebrovascular infarct or stroke, seizure, brain tumor, hydrocephalus, multiple sclerosis, HIV-associated cognitive impairment, or acute encephalopathy. This work was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. All participants and their informants/caregivers provided informed consent in accordance with the protocol approved by the Partners HealthCare Human Research Committee Institutional Review Board in Boston, Massachusetts.

Table 1
Demographic characteristics. Mean (SD) presented for each continuous demographic factor. * indicates statistical significance at the level of $p < 0.05$ compared to the CN- group. M = Male; F= Female, R = Right Handed; L = Left Handed; MMSE = Mini-Mental State Examination; CDR= Clinical Dementia Rating.

Demographic	Aβ- CN (N = 99)	Aβ+ Amnestic (N = 32)	Aβ+ PCA (N = 16)	Aβ+ lvPPA (N = 22)
Age (years)	68.7 (7.5)	70.4 (7.2)	63.9 (8.2)*	69.4 (7.1)
Sex Ratio (Male: Female)	33M: 66F	22M: 12F*	5M: 11F	15M: 7F*
Education (years)	16.1 (2.6)	16.4 (2.7)	16.9 (1.3)	16.4 (2.5)
Handedness (R:L)	86R: 13L	32R: 2L	15R: 1L	20R: 2L
MMSE (out of 30)	29.4 (0.9)	24.4 (3.4)*	23.7 (4.7)*	22.7 (3.9)*
CDR Global	0	0.5 (N = 24); 1 (N = 10)	0.5 (N = 9); 1 (N = 7)	0.5 (N = 20); 1 (N = 2)

2.2. Word retrieval tasks and neuropsychological battery

Letter and category fluency were assessed using the Controlled Oral Word Association Test (Spreen and Strauss, 1991), with the measure of interest being the total number of correct words produced in 1 min trials to three different letter cues—F, A, and S—and two different category cues—Animals and Vegetables. Performance was totaled and normed based on age-education-, and sex-based normative data (Spreen and Strauss, 1991), and averaged across the two category fluency trials to produce composite letter fluency and category fluency variables. Visual confrontation naming was measured using performance on the 30-item Boston Naming Test (BNT; Kaplan et al., 1983) from the NACC UDS Version 2 battery. Performance was normed based on age-education-, and sex-based normative data (Shirk et al., 2011). Performance differences between Aβ+ AD syndromic groups were investigated using one-way analysis of variance, with post-hoc independent sample *t*-tests to verify between group differences. Effect sizes were calculated with Cohen's D for unequal sample sizes (Cohen, 1988). Performance differences across tasks within groups were computed using paired t-tests and Cohen's D accounting for the correlation strength between the tasks within group, using G*Power. Statistical significance was set to a threshold of $p < 0.05$. Primary hypothesis-driven analyses were conducted on just 3 measures of word retrieval with no corrections for multiple comparisons applied. Statistical analyses were conducted in IBM SPSS Version 24.0 (Armonk, NY).

Tests of attention, working memory, processing speed, executive functioning, episodic memory, and visuospatial cognition from NACC UDS2 or UDS3 are also presented to describe the remainder of the cognitive profile. This battery included Digit Span Forward and Backward (longest spans), Trail Making Test Part A and Part B (seconds to completion), a story memory encoding and delayed recall task (either Logical Memory in UDS2 or Craft Story in UDS3), and Benson Figure copy and delayed recall in UDS3, which only the PCA and lvPPA groups received. A subset of the PCA (n = 8) and lvPPA (n = 8) patients also received tests of visual matching from NACC UDS3 that did not have verbal retrieval demands: Word-picture matching and Semantic Associates. Performance on these tests are included in the Supplemental Materials, to demonstrate intact low-level visual perception in both patient groups. Additionally, we report performance on the Benton Visual Form Discrimination, a multiple choice match-to-sample test of figure recognition, for the CN and amnestic groups in order to represent visuospatial functioning. Z-scores were demographically-adjusted (age-, sex-, and education-corrected) based on published norms for each test (Spreen and Strauss, 1991; Shirk et al., 2011) and reported for all tests in order to better compare performance across groups and across tests within groups.

2.3. Neuroimaging acquisition and analysis

All participants in the final sample received a structural T1-weighted scan at MGH. All scans were acquired using a Siemens Trio 3T scanner (Siemens Medical Systems). T1 image volumes were examined qualitatively by a cortical surface-based reconstruction and analysis of cortical thickness using FreeSurfer version 6.0 (http://surfer.nmr.mgh.harvard.edu). The general procedures for this processing method have been described in detail and applied and validated in a number of publications and presentations; the technical details can be found in select manuscripts (Dale et al., 1999; Fischl and Dale, 2000; Fischl et al., 2002; Fischl et al., 2004). A subset of participants (26 amnestic, 10 PCA and 6 lvPPA, 99 CN) underwent ^{11}C- Pittsburgh Compound B (amyloid) PET scans, which were spherically registered to align each individual's cortical surface between PET and MR scans. The ^{11}C-PiB PET radiotracer was acquired with an 8.5–15 mCi bolus injection followed immediately by a 60-min dynamic acquisition in 69 frames (12 × 15 s, 57 × 60 s). All PET data were acquired using a Siemens/CTI (Knoxville, TN) ECAT HR + scanner (3D mode; 63 image planes; 15.2 cm axial field of view; 5.6

mm transaxial resolution and 2.4 mm slice interval). Data were reconstructed and attenuation corrected; each frame was evaluated to verify adequate count statistics; interframe head motion was corrected prior to further processing. Visual inspection confirmed accurate registration between anatomical and PET volumes. To evaluate the anatomy of PET binding, each individual's PET data set was rigidly co-registered to the subject's MPRAGE data using SPM8 (Wellcome Department of Cognitive Neurology, Function Imaging Laboratory, London). Similar to a previous report, ^{11}C-PiB PET data were expressed as the distribution volume ratio (DVR) with the cerebellar grey matter as a reference (Becker et al., 2011), where regional time-activity curves (TAC) were used to compute regional DVRs for each ROI using the Logan graphical method applied to data from 40 to 60 min after injection. PET data were not partial volume corrected and were performed using geometric transform matrix as implemented in FreeSurfer stable release version 6.0.

Using methods we have previously published (Dickerson et al., 2008; Makaretz et al., 2018; Xia et al., 2017), whole cortex general linear models (GLM) were created to determine where cortical atrophy was present in amnestic, PCA, and lvPPA Aβ+ patient groups separately, compared to the Aβ- CN group using FreeSurfer version 6.0 (Fig. 1). In order to visualize regions of cortical atrophy, a whole brain cortical thickness map was contrasted (vertex-based *t*-test) between each of our AD syndromic groups (amnestic, PCA, and lvPPA) and the age-matched Aβ- CN group. Effect size (gamma) showing areas that are at least 0.2 mm thinner in each AD syndromic group compared to Aβ- CN is projected onto the cortical mantle in each hemisphere. Then, to determine if performance on word retrieval tasks was related to cortical atrophy in hypothesized regions, we conducted whole cortical surface general linear models (GLM) for the effects of the task performance on cortical thickness at each vertex point on the cortical surface. We used age-, education-, and sex-adjusted performance scores and thus did not control for these demographic factors again in our cortical thickness GLM analysis. Follow-up analysis ensured that cortical thickness was not related in any significant way to any of these demographic factors. GLM analyses was implemented using the *mri_glmfit* utility within FreeSurfer version 6. Given our specific *a priori* hypotheses, an uncorrected statistical threshold of $p < 0.01$ was set.

3. Results

3.1. Demographic characteristics and cognitive profiles

A total of 70 Aβ+ patients (32 amnestic, 16 PCA, and 22 lvPPA) and 99 Aβ- CN healthy control participants were included in this study (Table 1). The mean Mini Mental State Examination (MMSE) score was 24.4 for the amnestic group, 23.7 for PCA, and 22.7 for lvPPA (ANOVA: $F = 0.95$, $p = 0.40$). MMSE scores in each AD group were statistically comparable: amnestic vs. PCA, $t = 0.21$, $p = 0.83$; amnestic vs. lvPPA, $t = 1.33$, $p = 0.19$; PCA vs. lvPPA, $t = 0.73$, $p = 0.48$. The Aβ- CN group also performed better on total MMSE score compared to the three Aβ+ AD groups, as expected ($p < 0.05$). The majority of Aβ+ AD patients were given a global CDR of 0.5, consistent with mild cognitive impairment, though more individuals within the amnestic group were given a CDR of 1 ($\chi^2 = 22.6$, $p = 0.02$). All Aβ- CN participants were given a global CDR of 0, and earned an average MMSE of 29.4, consistent with no cognitive impairment. The Aβ- CN group differed from only the PCA patient group on age ($t = 2.3$, $p = 0.02$); there were no other between-group differences on age or education ($p > 0.05$).

In addition to word retrieval deficits, we observed varying degrees of impairment in other cognitive domains across the Aβ+ syndromic groups (Table 2). While only Aβ+ PCA and Aβ+ lvPPA groups demonstrated impairment ($z < -1.0$) on a test of auditory-verbal simple attention (Digit Span Forward) and working memory (Digit Span Backward), all three Aβ+ groups were impaired on visuomotor sequencing (Trail Making Test Part A) and set-shifting (Trail Making Test Part B), as well as story memory encoding and delayed recall. In the visuospatial domain, the Aβ+ amnestic group demonstrated mild deficits on visual form discrimination, and just the Aβ+ PCA group (but not the Aβ+ lvPPA group) demonstrated impairment on a measure of visuoconstruction (Benson Figure Copy). Both Aβ+ PCA and lvPPA groups were impaired on Benson Figure Recall.

3.2. Word retrieval profiles across the Aβ+ syndromic spectrum

Performance on category fluency and visual confrontation naming (BNT) was impaired across all three Aβ+ syndromic groups, while letter fluency was intact in Aβ+ amnestic and Aβ+ PCA groups (Fig. 1). Table 3 summarizes the differences both between and within groups across these word retrieval tests. Between-group analysis revealed that the Aβ+ amnestic group performed better than the Aβ+ lvPPA group on letter

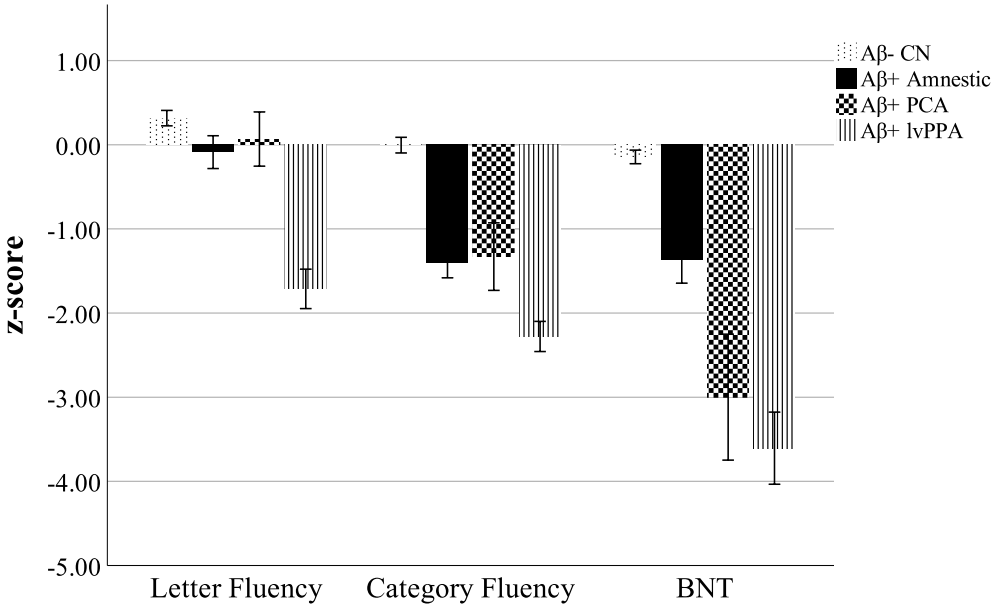

Fig. 1. Category fluency and naming (BNT) performance is impaired across all AD syndromic groups, while letter fluency is spared only in Aβ+ amnestic and Aβ+ PCA. Group means of demographically-adjusted z-scores indicate that Aβ+ amnestic and Aβ+ PCA groups are intact on letter fluency but comparably impaired on category fluency, and impaired on naming, with the Aβ+ PCA group performing worse than the Aβ+ amnestic group. The Aβ+ lvPPA group is normatively impaired across all three word retrieval tasks, though letter fluency is relatively less impaired compared to category fluency and naming. Cognitively normal (Aβ- CN) data are also presented for reference. Error bars indicate ±1 standard error of the mean. Statistical differences are presented in Table 3.

Table 2
Cognitive profile. Mean (SD) of demographically-adjusted z-scores are presented for each test on the remainder of the NACC UDS neuropsychological battery. [1]Story memory composite z-scores were aggregated across UDS2 Logical Memory and UDS3 Craft Story.

Test	Aβ- CN (N = 99)	Aβ+ Amnestic (N = 32)	Aβ+ PCA (N = 16)	Aβ+ lvPPA (N = 22)
Digit Span Forward	0.05 (0.89)	−0.07 (1.42)	−1.00 (1.39)	−2.44 (1.72)
Digit Span Backward	0.17 (0.98)	−0.44 (1.24)	−1.41 (1.18)	−2.09 (1.21)
Trail Making Test A	−0.03 (0.79)	−1.47 (2.09)	−7.45 (1.31)	−2.17 (2.9)
Trail Making Test B	0.09 (0.79)	−1.6 (2.10)	−4.56 (1.00)	−3.05 (2.05)
Story Memory Encoding	0.88 (0.88)	−2.07 (0.90)	−2.12 (0.86)	−2.54 (0.69)
Story Memory Delayed Recall	0.96 (0.86)	−2.35 (0.83)	−1.95 (0.76)	−2.17 (0.65)
Benton Visual Form Discrimination	0.52 (0.82)	−1.10 (1.95)	–	–
Benson Figure Copy	–	–	−8.89 (0.83)	−0.84 (2.29)
Benson Figure Delayed Recall	–	–	−3.57 (0.35)	−1.52 (1.40)

Table 3
Word retrieval performance across the Aβ+ AD syndromic spectrum. Between-group and within-group task differences shown in Fig. 1 are listed, with t-values and Cohen's d effect sizes. *Statistical significance is set at a threshold of $p < 0.05$.

Significant between-group differences*	t	Cohen's d
Letter Fluency		
Amnestic > lvPPA	5.34	0.76
PCA > lvPPA	4.89	1.63
Category Fluency		
Amnestic > lvPPA	3.36	0.95
PCA > lvPPA	2.43	0.77
Boston Naming Test (BNT)		
Amnestic > PCA	2.45	0.72
Amnestic > lvPPA	4.60	1.27
*Significant within-group differences**	*t*	*Cohen's D*
Amnestic		
Letter Fluency > Category Fluency	7.60	1.34
Letter Fluency > BNT	4.52	0.80
PCA		
Letter Fluency > Category Fluency	5.83	1.51
Letter Fluency > BNT	4.41	1.27
Category Fluency > BNT	4.56	0.68
lvPPA		
Letter Fluency > Category Fluency	2.56	0.54
Letter Fluency > BNT	4.19	0.89
Category Fluency > BNT	3.54	0.76

and category fluency, and better than both Aβ+ lvPPA and Aβ+ PCA groups on the BNT. Further, the Aβ+ PCA group also performed better than the Aβ+ lvPPA group on letter and category fluency; the Aβ+ PCA and Aβ+ lvPPA groups performed comparably on the BNT. The Aβ+ amnestic and Aβ+ PCA groups were comparable on letter and category fluency tasks. Within-group analysis revealed that performance on letter fluency was stronger than category fluency and BNT performance in all three Aβ+ syndromic groups. Within the Aβ+ PCA and Aβ+ lvPPA groups, category fluency was also stronger than BNT performance. The Aβ- CN performed better than all Aβ+ syndromic groups on all word retrieval tasks ($p < 0.05$), with the exception of letter fluency on which performance was comparable to the Aβ+ PCA group ($p = 0.3$). Performance on category fluency trials to animal and vegetable cues were also analyzed separately (Supplementary Materials Fig. 1); though between-group differences remained similar as the composite category fluency performance reported above, we did observe poorer vegetable fluency compared to animal fluency in Aβ+ PCA ($t = 2.6$, $p = 0.02$, Cohen's d = 0.62) and Aβ+ lvPPA ($t = 3.1$, $p = 0.005$, Cohen's d = 0.66), as well as the Aβ- CN group (t = 4.03, p = 0.0001, Cohen's d = 0.41) but comparable performance between animal and vegetable fluency in the Aβ+ amnestic group ($p > 0.05$).

As expected, performance on these three word retrieval tasks were correlated with each other. Across the Aβ+ groups combined, Supplementary Materials Fig. 2 plots the correlations between Letter and Category Fluency ($r = 0.64$, $p = 4.3 \times 10^{-9}$), Letter Fluency and Naming ($r = 0.41$, $p = 0.001$) and Category Fluency and Naming ($r = 0.54$, $p = 0.00005$). To control for the effects of each fluency trial on the other (i.e., effects of generative word retrieval on category fluency, and effects of semantic processing on letter fluency), performance on each fluency condition with the other regressed out is also shown, and a similar pattern of results to our main findings was found such that Aβ+ amnestic and Aβ+ PCA groups were stronger on "pure" letter fluency compared to "pure" category fluency, while the reverse was true of the Aβ+ lvPPA group (Supplementary Materials Fig. 3). A subset of PCA and lvPPA patients also received tests of visual matching from NACC UDS3 that did not have verbal retrieval demands: Word-picture matching and Semantic Associates. These PCA and lvPPA individuals performed near ceiling levels (Supplementary Materials Fig. 4) on both tasks, indicating that low-level visual perception and semantic memory was not impaired in these patient groups, and thus unlikely to be affecting performance on the word retrieval tasks that were the focus of our study.

3.3. Cortical atrophy signatures are distinct but overlapping across the AD spectrum

Compared to Aβ- CN, whole-cortex analyses revealed that Aβ+ individuals demonstrate syndrome-specific as well as overlapping patterns of neurodegeneration (Fig. 2). Compared to Aβ- CN, individuals with Aβ+ amnestic syndrome (Fig. 2A) demonstrated cortical atrophy in medial and lateral temporal cortices, precuneus/posterior cingulate cortex, and dorsolateral prefrontal cortex. Compared to Aβ- CN, individuals with Aβ+ PCA (Fig. 2B) demonstrated atrophy in occipital, ventral and posterolateral temporal, lateral parietal, precuneus, and posterior cingulate cortex with a slight right hemisphere predominance. Compared to Aβ- CN, individuals with Aβ+ lvPPA (Fig. 2C) demonstrated atrophy in lateral temporal, lateral parietal, precuneus, and posterior cingulate cortices, with a left hemisphere predominance. Cortical atrophy common to all three AD syndromic groups can be observed in bilateral temporal and parietal cortical regions.

3.4. Word retrieval impairment is associated with atrophy in prefrontal, lateral and medial parietal, and lateral temporal cortex across the Aβ+ syndromic spectrum

Next, we tested our *a priori* hypotheses regarding the neuroanatomical correlates of word retrieval by conducting three separate whole-cortex GLMs predicting performance on letter fluency, category fluency, and confrontation naming (BNT) respectively. We combined all Aβ+ individuals (amnestic, PCA, lvPPA) together for these analyses in an effort to capitalize on the heterogeneity in cognitive profile and neurodegeneration across groups. We found associations in several regions known to atrophy in the course of AD, including regions of the prefrontal, parietal, and temporal lobes; these relationships were overlapping and dissociable depending on the word retrieval task examined (Fig. 3). Specifically, we observed circumscribed associations between letter fluency performance and cortical thickness in the right middle frontal gyrus, right precuneus, left lateral parietal cortex, and left posterior MTG (Fig. 3A). Category fluency performance was associated with cortical thickness in predominantly left middle frontal gyrus, lateral parietal cortex, posterior cingulate cortex, and posterior MTG (Fig. 3B). While visual confrontation naming performance was also associated

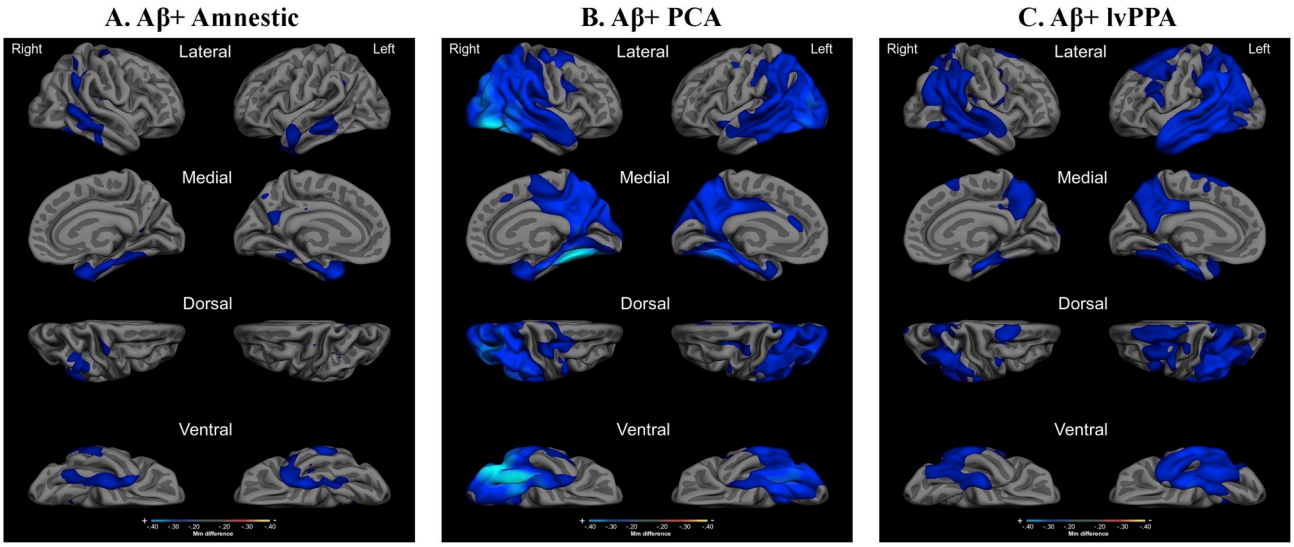

Fig. 2. Syndromic variability across the AD spectrum. Compared to Aβ- CN participants, whole-brain cortical thickness analyses reveal that Aβ+ individuals across AD clinical syndromes of amnestic, PCA, and lvPPA demonstrate syndrome-specific and some overlapping patterns of cortical atrophy. All Aβ+ individuals are characterized as CDR 0.5 or 1. Effect size (gamma) is shown for cortical areas that are at least 0.2 mm thinner in each Aβ+ syndromic group compared to Aβ- CN. Color scale shows magnitude of atrophy difference from 0.2 mm to 0.4 mm. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

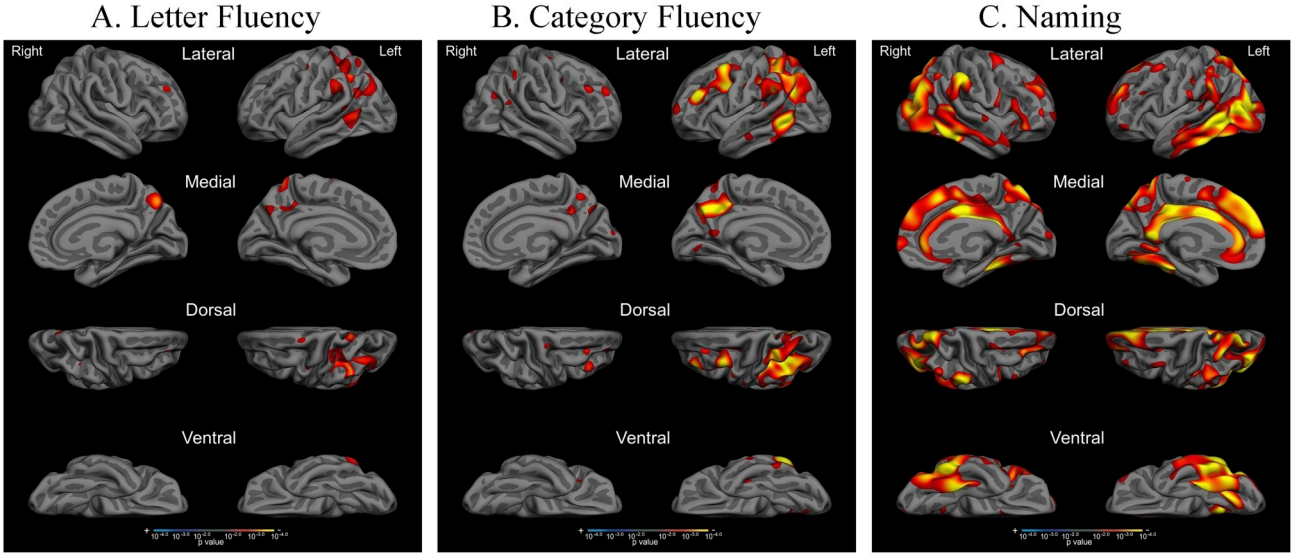

Fig. 3. Word retrieval impairment is associated with atrophy in prefrontal, lateral and medial parietal, and lateral temporal cortex across the Aβ+ syndromic spectrum. Whole cortex general linear models demonstrate that cortical thickness was associated with performance on (A) Letter Fluency, (B) Category Fluency, and (C) Naming. Results show maps of p values, thresholded at $p < 0.01$.

with many of these same regions as observed in the correlation with category fluency, including lateral parietal cortex and MTG, we observed additional unique associations between naming performance and cortical thickness in bilateral superior prefrontal cortex and cingulate gyri, as well as bilateral inferior temporal cortex extending posteriorly into the visual association cortices and anteriorly into the left anterior temporal lobe (Fig. 3C). Of note, neither category fluency nor naming performance was associated with cortical thickness in entorhinal cortex (Supplementary Materials Fig. 5), arguing against theories that semantic fluency and naming are supported by medial temporolimbic regions.

We illustrate areas of overlap and dissociation in the correlations between performance on these three word retrieval task and regional cortical thickness in Fig. 4. We selected the left MTG as an area common to supporting performance on all three word retrieval tasks; cortical thickness in the left MTG was strongly correlated with letter fluency ($r = 0.36$, $p = 0.004$; Fig. 4A), category fluency ($r = -0.53$, $p = 0.000007$; Fig. 4B) and naming performance on the BNT ($r = 0.52$, $p = 0.00002$; Fig. 4C). As for dissociations, we show that letter fluency was strongly associated with cortical thickness in the right central precuneus ($r = 0.44$, $p = 0.0004$; Fig. 4D), category fluency was related to cortical thickness in the left angular gyrus ($r = 0.50$, $p = 0.00003$; Fig. 4E), and naming performance on the BNT was associated with cortical thickness in the left inferior temporal gyrus ($r = 0.58$, $p = 0.0001$; Fig. 4F).

4. Discussion

Word retrieval deficits are commonly reported symptom across

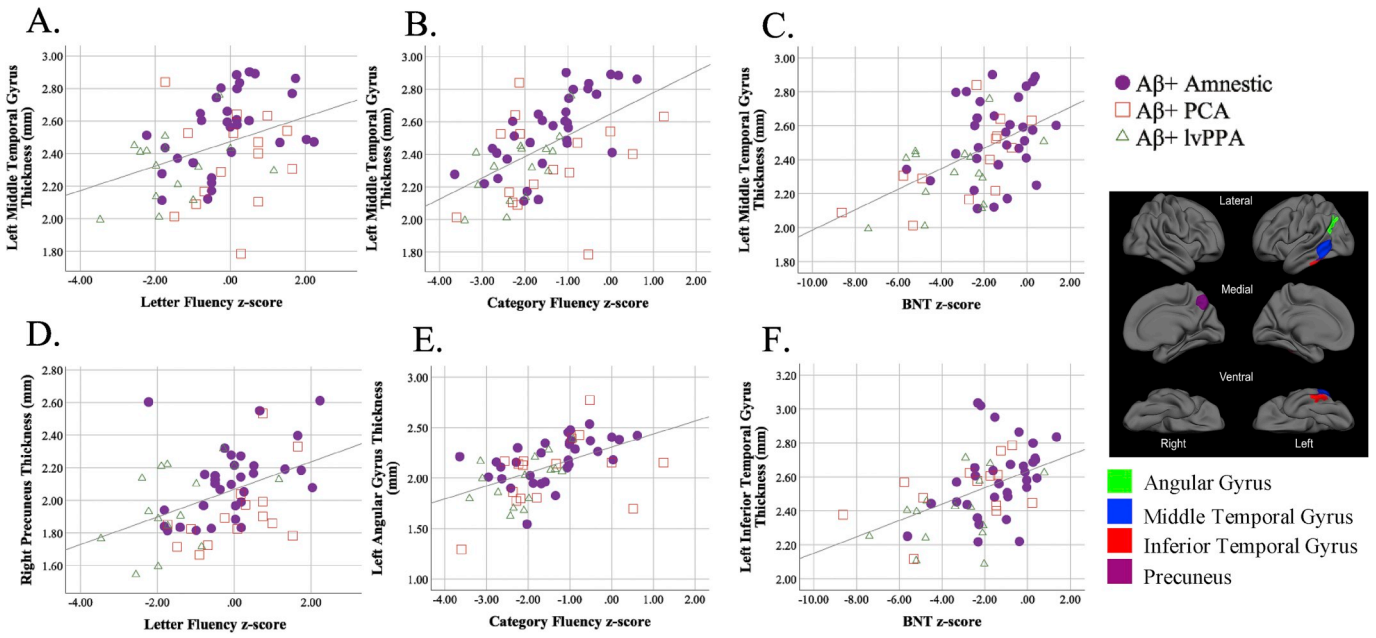

Fig. 4. Scatterplots of overlapping and dissociable associations between word retrieval performance with cortical thickness. We observed areas of overlap in correlations between cortical thickness in the Left Middle Temporal Gyrus and (A) Letter Fluency, (B) Category Fluency and (C) Naming. We also observed more specific associations with each type of word retrieval task; (D) Letter fluency performance was associated with cortical thickness in the right central precuneus, (E) Category fluency performance was associated with cortical thickness in the left angular gyrus, and (F) Naming (BNT) performance was associated with cortical atrophy in the left inferior temporal gyrus. All regions of interest shown here were drawn from peak areas of correlation in the whole-cortex GLMs presented in Fig. 4, and chosen for purely illustrative purposes.

multiple clinical syndromes of AD. However, the localization of neurodegeneration underlying these deficits may vary, leading to different types of word retrieval difficulty. While individuals with an amnestic syndrome have well-documented impairment in category fluency and confrontation naming, with relatively spared letter fluency, the word retrieval profiles of the atypical presentations of AD (PCA, lvPPA) and their anatomical underpinnings have been less clearly understood. We found in this investigation that performance on both category fluency and visual confrontation naming was impaired across all Aβ+ syndromic groups, while letter fluency was intact in Aβ+ amnestic and Aβ+ PCA groups but impaired in the Aβ+ lvPPA group. Consistent with our hypotheses, no performance differences were observed between Aβ+ amnestic and Aβ+ PCA groups on letter or category fluency. Though both of these groups were impaired on visual confrontation naming, the Aβ+ PCA group performed relatively worse than the Aβ+ amnestic group. Of note, naming scores from the BNT analyzed in this study included correct responses to semantic cues, minimizing any effect of visual misperceptions and primarily reflecting word retrieval ability. Furthermore, a subset of Aβ+ PCA participants performed near ceiling levels on tests of visual semantic matching, demonstrating intact basic visual function necessary to perform a visual confrontation naming test. However, we cannot discount the combined cognitive demands of visual integration and semantic controlled retrieval needed to perform this visual confrontation naming task, which may explain our observations of worse performance in Aβ+ PCA group compared to Aβ+ amnestic group on the BNT.

Together, these behavioral results suggest that despite different patterns of cortical atrophy, the Aβ+ amnestic and Aβ+ PCA syndromic groups have similar word retrieval profiles on these common neuropsychological tests, while Aβ+ lvPPA participants demonstrate a primary disorder of the phonological loop, impacting all types of word retrieval studied here. Our results in the Aβ+ lvPPA group is consistent with prior reports of difficulty with lexical retrieval in conversational speech (Gorno-Tempini et al., 2011), as well as on the formal neuropsychological tests of word retrieval evaluated in the current study (Gorno-Tempini et al., 2008; Leyton et al., 2017). Our attribution of these findings to a primary phonological loop dysfunction is further supported by our additional analysis of "process pure" measures of letter and category fluency (Supplementary Materials Fig. 3), where we observed that "pure" letter fluency was more impaired than "pure" category fluency only in the lvPPA group. This impairment has been attributed to a disorder of the phonological loop, a component of working memory responsible for short-term representation of auditory-verbal information (Ash et al., 2013; Gorno-Tempini et al., 2008; Leyton, Savage, et al., 2014), as well as speech-sound errors related to language processing in the context of a limited phonological buffer (Ash et al., 2013; Leyton, Ballard, Piguet and Hodges, 2014). Our results are also consistent with previously published accounts of category fluency and naming impairment in amnestic syndrome (Henry et al., 2004; Papp et al., 2016), as well as prior descriptions of language deficits in PCA, which comprise a "logopenic syndrome" including anomia, reduced verbal fluency, and slowed speech rate (Crutch et al., 2013; Magnin et al., 2013; Putcha et al., 2018). We add support to one previous report that PCA show equivalent performance on letter and category fluency tasks compared to amnestic AD, and that both syndromic groups demonstrate greater impairment on category compared to letter fluency (Rogers et al., 2006). However, some contradictory findings have also been reported in PCA: one study identified impairments in letter as well as category fluency (Crutch et al., 2013), while another reported that verbal fluency is stronger in PCA compared to amnestic AD (Mendez et al., 2002), though this latter study only examined one category ("Animals") and did not evaluate letter fluency at all. The varied reports from published literature may stem from the fact that investigations differ in sample sizes and task demands, and that many include individuals who may or may not be Aβ+, thus including individuals with atypical AD syndromes primarily due to another underlying neuropathology (e.g., Lewy body disease or corticobasal degeneration). Our results add some clarity to these discrepant reports by focusing solely on Aβ+ individuals, though of course this does not entirely eliminate the possibility of superimposed or secondary Lewy

body disease (Tang-Wai et al., 2004). Thus, we may have identified here a specific language profile in the atypical syndromes compared to amnestic individuals, in patients where pathological dysfunction is most likely due to underlying AD.

A secondary goal of this study was to investigate the anatomical underpinnings of these different word retrieval tasks, capitalizing on the heterogeneity of clinical syndromes and neurodegenerative profiles across the AD syndromic variants. Compared to Aβ- CN, whole-cortex analyses revealed syndrome-specific as well as overlapping patterns of neurodegeneration. Specifically, we observed cortical atrophy in medial and lateral temporal cortices and precuneus/posterior cingulate cortex in the Aβ+ amnestic group, in occipital, inferior and posterolateral temporal, lateral parietal, precuneus/posterior cingulate cortex with a slight right hemisphere predominance in Aβ+ PCA, and in lateral temporal, lateral parietal, precuneus/posterior cingulate cortex, with a left hemisphere predominance in Aβ+ lvPPA. In examining the relationships between word retrieval performance and cortical thickness, we found some overlapping associations across tasks in temporoparietal and posterior MTG, with greater left hemisphere predominance in category fluency and bilateral correlations observed with naming performance. Category fluency was also associated with cortical thickness in left hemisphere predominant middle prefrontal cortex, angular gyrus, and posterior cingulate cortex—regions comprising the FPN and semantic language networks— while naming was uniquely associated with cortical thickness in bilateral inferior temporal cortices. Neither category fluency nor naming was associated with thickness in medial temporal cortices, arguing against attributions of semantic processing to medial temporal dysfunction in AD (Henry et al., 2004; Pihlajamaki et al., 2000). In contrast, performance on letter fluency was associated with more circumscribed atrophy in right hemisphere middle frontal gyrus and central precuneus, as well as left-hemisphere lateral parietal cortex (hubs of the FPN; Margulies et al., 2009; Vincent et al., 2008) and posterior MTG.

While all three word retrieval tasks included in this study call upon many of the same cognitive processes, including sustained attention, devising a search strategy, selecting appropriate words, inhibiting competitors, engaging working memory, and articulating output, there are important differences. Letter fluency requires selecting and retrieving information based on spelling (orthography) as well as, in many instances, speech-sounds (phonology), while category fluency and object naming place a greater demand on conceptual knowledge stores in addition to executive organizational search and retrieval efforts (Schmidt et al., 2017; Shao et al., 2014). Letter fluency has been associated most consistently with the left inferior frontal cortex and left temporoparietal cortex (Gourovitch et al., 2000; Rogalski et al., 2011), and regions of occipitotemporal cortex, where the visual word form area is found, supporting orthographic word recognition critical to performing the letter fluency task (McCandliss et al., 2003). In contrast, category fluency and naming have been associated with a more widespread and left-lateralized controlled semantic language network (Binder et al., 2009; Ralph et al., 2017), which includes posterior regions of the lateral temporal cortex (Gourovitch et al., 2000; Leyton et al., 2017; Perani et al., 2003) and left lateralized inferior parietal lobule (Chouiter et al., 2016; Eastman et al., 2013; Putcha et al., 2018; Schonknecht et al., 2011) as well as medial parietal cortex linked with semantic processing and retrieval (McGraw et al., 2001). Picture naming in particular has been shown to depend, in addition to the anterior temporal lobe, on left posterior inferior temporal cortex (Ahn et al., 2011; Birn et al., 2010).

Our findings are largely consistent with the literature on anatomical underpinnings of word retrieval, though we did not observe the expected inferior frontal cortical associations with word retrieval performance. There are a number of possible explanations for this in Aβ+ patients, as much of the prior work influencing our understanding that verbal fluency performance is supported by inferior frontal dysfunction was conducted in healthy adults (Moscovitch, 1994; Vonk et al., 2018) or stroke patients or other focal lesion models (Baldo and Shimamura, 1998; Chouiter et al., 2016; Miller, 1984). First, the strong correlations with cortical thickness in the left hemisphere posterior MTG across word retrieval tasks observed in this study may be representing the posterior node of a controlled lexical retrieval network, which is functionally connected to the inferior frontal sulcus (Davey et al., 2016), and likely more vulnerable to AD pathology in prodromal stages of the disease than the inferior frontal cortical regions. Indeed, together with the correlations observed between performance across retrieval tasks and thickness in the left hemisphere temporoparietal cortex and intraparietal sulcus broadly, our observations may reflect that in our Aβ+ patient population, much of the tau pathology and cortical atrophy that occurs at this stage of AD progression occurs in posterior parietal and temporal cortices, rather than in the inferior frontal cortex (Warren et al., 2012). We may be observing a reflection of more prominent dysfunction of the posterior nodes of these networks before the anterior nodes, thus emphasizing the importance of lateral parietal dysfunction in explaining lexical retrieval deficits in early stages across the AD syndromic spectrum (Vasconcelos et al., 2014). Second, the inferior frontal gyrus has been posited to be critical for response inhibition, or a "braking" function within the larger domain of cognitive control (Aron et al., 2004, 2014; Novick et al., 2005). We propose that in order to accomplish these word retrieval tasks, our patient population relies less on inhibitory control and more on generativity and goal-directed retrieval, thus explaining our observed correlations with regions of the FPN, but not inferior frontal gyrus. Recent work has shown that individuals with MCI and AD who had attention deficits were more influenced by word frequency impacting retrieval access, and less influenced by semantic similarity (Pakhomov et al., 2016); thus, the Aβ+ patients studied here may not be recruiting response inhibition skills to complete these fluency tasks as much as healthy controls. Lastly, these word retrieval tasks require integration of controlled retrieval and specific lexical or semantic/conceptual demands, highlighting the left hemisphere posterior MTG, angular gyrus, and intraparietal sulcus which have functional connections with the inferior frontal gyrus (Davey et al., 2016; Noonan et al., 2013), more broadly supporting controlled semantic cognition (Ralph et al., 2017), rather than focal associations with the inferior frontal gyrus.

Our study has some important limitations. First, our study samples of AD syndromes were uneven (32 amnestic compared to 16 PCA and 22 lvPPA), and as such, certain groups (i.e., PCA) may have been underrepresented in the correlations between retrieval performance and cortical thickness. Reassuringly, we observed a robust association with full range in all patient groups between task performance and atrophy when data were plotted, and our *a priori* hypotheses were largely confirmed. Nevertheless, these correlation results require replication in a larger sample of the atypical syndromic groups. Second, the associations between cortical atrophy and task performance reported in this study were cross-sectional and correlational in nature. Causal relationships between biomarkers of AD-related neurodegeneration and pathology (including amyloid and tau pathology not evaluated in this study due to inadequate sample sizes) and decline in word retrieval across the AD syndromic spectrum requires follow-up longitudinal investigation. Lastly, as our study focused specifically on cortical thickness markers of AD-driven neurodegeneration, we did not investigate the subcortical circuitry that may be related to word retrieval performance which represents an important avenue of further investigation.

In summary, we reported on the word retrieval profiles in amnestic and atypical syndromes of PCA and lvPPA in Aβ+ individuals who were rated as being at the stage of MCI (CDR 0.5) or mild dementia (CDR 1). We found that Aβ+ amnestic and Aβ+ PCA variants of AD demonstrated impaired category fluency and naming deficits, with spared letter fluency, while Aβ+ lvPPA are impaired across all word retrieval types. We further linked category fluency and naming performance to cortical thickness of frontoparietal regions comprising the FPN as well as

distributed controlled semantic cognitive network, while letter fluency was primarily associated with thickness in the right hemisphere precuneus and middle frontal gyrus as well as left hemisphere lateral parietal and temporal cortex, important nodes of FPN and lexical control networks supporting goal-directed retrieval. Though AD is now understood as a biological entity comprised of variant syndromic subtypes which informs confidence about underlying pathology without waiting for autopsy confirmation, clinical diagnosis is still difficult to make and often delayed, particularly in the atypical variants (e.g., PCA, lvPPA), due in part to a still-emerging understanding of cognitive profiles and underlying anatomical substrates. We hope our observations in this study will improve understanding of how neurodegeneration is associated with observed clinical symptomatology within the spectrum of AD and improve tracking of symptomatology in clinical trials aiming to include the broad spectrum of patients with AD.

Funding

This research was supported by NIH grants R21 AG051987, R01 DC014296, P01AG005134, and P50 AG005134 and by the David Mooney Family Fund for PCA Research. Additional support was received from R01AG027435, P01AG036694 and R01 AG046396. KVP is supported by 1K23AG053422-01 and the Alzheimer's Association. This research was carried out in part at the Athinoula A. Martinos Center for Biomedical Imaging at the MGH, using resources provided by the Center for Functional Neuroimaging Technologies, P41EB015896, a P41 Biotechnology Resource Grant supported by the National Institute of Biomedical Imaging and Bioengineering (NIBIB), National Institutes of Health. This work also involved the use of instrumentation supported by the NIH Shared Instrumentation Grant Program and/or High-End Instrumentation Grant Program; specifically, grant number(s) S10RR021110, S10RR023043, S10RR023401.

Declaration of competing interest

Dr. Dickerson has been a consultant for Lilly, Inc.

CRediT authorship contribution statement

Deepti Putcha: Conceptualization, Methodology, Writing - original draft, Formal analysis, Visualization, Investigation. **Bradford C. Dickerson:** Writing - review & editing, Supervision, Funding acquisition. **Michael Brickhouse:** Visualization, Software. **Keith A. Johnson:** Resources. **Reisa A. Sperling:** Resources, Funding acquisition. **Kathryn V. Papp:** Conceptualization, Writing - review & editing, Supervision.

Acknowledgements:

The authors thank the patients and families who participated in this research, without whose partnership this research would not have been possible.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuropsychologia.2020.107391.

References

Abrahams, S., Goldstein, L.H., Simmons, A., Brammer, M.J., Williams, S.C., Giampietro, V.P., Andrew, C.M., Leigh, P.N., 2003. Functional magnetic resonance imaging of verbal fluency and confrontation naming using compressed image acquisition to permit overt responses. Hum. Brain Mapp. 20, 29–40.

Ahn, H.J., Seo, S.W., Chin, J., Suh, M.K., Lee, B.H., Kim, S.T., Im, K., Lee, J.M., Lee, J.H., Heilman, K.M., Na, D.L., 2011. The cortical neuroanatomy of neuropsychological deficits in mild cognitive impairment and Alzheimer's disease: a surface-based morphometric analysis. Neuropsychologia 49, 3931–3945.

Andrews-Hanna, J.R., Reidler, J.S., Sepulcre, J., Poulin, R., Buckner, R.L., 2010. Functional-anatomic fractionation of the brain's default network. Neuron 65, 550–562.

Aron, A.R., Robbins, T.W., Poldrack, R.A., 2004. Inhibition and the right inferior frontal cortex. Trends Cognit. Sci. 8, 170–177.

Aron, A.R., Robbins, T.W., Poldrack, R.A., 2014. Inhibition and the right inferior frontal cortex: one decade on. Trends Cognit. Sci. 18, 177–185.

Ash, S., Evans, E., O'Shea, J., Powers, J., Boller, A., Weinberg, D., Haley, J., McMillan, C., Irwin, D.J., Rascovsky, K., Grossman, M., 2013. Differentiating primary progressive aphasias in a brief sample of connected speech. Neurology 81, 329–336.

Baldo, J.V., Shimamura, A.P., 1998. Letter and category fluency in patients with frontal lobe lesions. Neuropsychology 12, 259–267.

Becker, J.A., Hedden, T., Carmasin, J., Maye, J., Rentz, D.M., Putcha, D., Fischl, B., Greve, D.N., Marshall, G.A., Salloway, S., Marks, D., Buckner, R.L., Sperling, R.A., Johnson, K.A., 2011. Amyloid-beta associated cortical thinning in clinically normal elderly. Ann. Neurol. 69, 1032–1042.

Benson, D.F., Davis, R.J., Snyder, B.D., 1988. Posterior cortical atrophy. Arch. Neurol. 45, 789–793.

Binder, J.R., Desai, R.H., Graves, W.W., Conant, L.L., 2009. Where is the semantic system? A critical review and meta-analysis of 120 functional neuroimaging studies. Cerebr. Cortex 19, 2767–2796.

Birn, R.M., Kenworthy, L., Case, L., Caravella, R., Jones, T.B., Bandettini, P.A., Martin, A., 2010. Neural systems supporting lexical search guided by letter and semantic category cues: a self-paced overt response fMRI study of verbal fluency. Neuroimage 49, 1099–1107.

Chouiter, L., Holmberg, J., Manuel, A.L., Colombo, F., Clarke, S., Annoni, J.M., Spierer, L., 2016. Partly segregated cortico-subcortical pathways support phonologic and semantic verbal fluency: a lesion study. Neuroscience 329, 275–283.

Cohen, J., 1988. Statistical Power Analysis for the Behavioral Sciences, second ed. Lawrence Erlbaum Associates, New Jersey.

Corbetta, M., Shulman, G.L., 2002. Control of goal-directed and stimulus-driven attention in the brain. Nat. Rev. Neurosci. 3, 201–215.

Costafreda, S.G., Fu, C.H., Lee, L., Everitt, B., Brammer, M.J., David, A.S., 2006. A systematic review and quantitative appraisal of fMRI studies of verbal fluency: role of the left inferior frontal gyrus. Hum. Brain Mapp. 27, 799–810.

Crutch, S.J., Lehmann, M., Warren, J.D., Rohrer, J.D., 2013. The language profile of posterior cortical atrophy. J. Neurol. Neurosurg. Psychiatry 84, 460–466.

I. A. A. s. D. a. A. S. P. I. A. Crutch, S.J., Schott, J.M., Rabinovici, G.D., Murray, M., Snowden, J.S., van der Flier, W.M., Dickerson, B.C., Vandenberghe, R., Ahmed, S., Bak, T.H., Boeve, B.F., Butler, C., Cappa, S.F., Ceccaldi, M., de Souza, L.C., Dubois, B., Felician, O., Galasko, D., Graff-Radford, J., Graff-Radford, N.R., Hof, P.R., Krolak-Salmon, P., Lehmann, M., Magnin, E., Mendez, M.F., Nestor, P.J., Onyike, C. U., Pelak, V.S., Pijnenburg, Y., Primativo, S., Rossor, M.N., Ryan, N.S., Scheltens, P., Shakespeare, T.J., Suarez Gonzalez, A., Tang-Wai, D.F., Yong, K.X.X., Carrillo, M., Fox, N.C., on behalf of the Alzheimer's Association, 2017. Consensus classification of posterior cortical atrophy Alzheimer's Dementia 13, 870–884.

Dale, A.M., Fischl, B., Sereno, M.I., 1999. Cortical surface-based analysis. I. Segmentation and surface reconstruction. Neuroimage 9, 179–194.

Davey, J., Thompson, H.E., Hallam, G., Karapanagiotidis, T., Murphy, C., De Caso, I., Krieger-Redwood, K., Bernhardt, B.C., Smallwood, J., Jefferies, E., 2016. Exploring the role of the posterior middle temporal gyrus in semantic cognition: integration of anterior temporal lobe with executive processes. Neuroimage 137, 165–177.

Dickerson, B.C., Fenstermacher, E., Salat, D.H., Wolk, D.A., Maguire, R.P., Desikan, R., Pacheco, J., Quinn, B.T., Van der Kouwe, A., Greve, D.N., Blacker, D., Albert, M.S., Killiany, R.J., Fischl, B., 2008. Detection of cortical thickness correlates of cognitive performance: reliability across MRI scan sessions, scanners, and field strengths. Neuroimage 39, 10–18.

Dickerson, B.C., McGinnis, S.M., Xia, C., Price, B.H., Atri, A., Murray, M.E., Mendez, M. F., Wolk, D.A., 2017. Approach to atypical Alzheimer's disease and case studies of the major subtypes. CNS Spectr. 22, 439–449.

Eastman, J.A., Hwang, K.S., Lazaris, A., Chow, N., Ramirez, L., Babakchanian, S., Woo, E., Thompson, P.M., Apostolova, L.G., 2013. Cortical thickness and semantic fluency in Alzheimer's disease and mild cognitive impairment. Am J Alzheimers Dis (Columbia) 1, 81–92.

Fischl, B., Dale, A.M., 2000. Measuring the thickness of the human cerebral cortex from magnetic resonance images. Proc. Natl. Acad. Sci. U. S. A. 97, 11050–11055.

Fischl, B., Salat, D.H., Busa, E., Albert, M., Dieterich, M., Haselgrove, C., van der Kouwe, A., Killiany, R., Kennedy, D., Klaveness, S., Montillo, A., Makris, N., Rosen, B., Dale, A.M., 2002. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. Neuron 33, 341–355.

Fischl, B., van der Kouwe, A., Destrieux, C., Halgren, E., Segonne, F., Salat, D.H., Busa, E., Seidman, L.J., Goldstein, J., Kennedy, D., Caviness, V., Makris, N., Rosen, B., Dale, A. M., 2004. Automatically parcellating the human cerebral cortex. Cerebr. Cortex 14, 11–22.

Gorno-Tempini, M.L., Brambati, S.M., Ginex, V., Ogar, J., Dronkers, N.F., Marcone, A., Perani, D., Garibotto, V., Cappa, S.F., Miller, B.L., 2008. The logopenic/phonological variant of primary progressive aphasia. Neurology 71, 1227–1234.

Gorno-Tempini, M.L., Hillis, A.E., Weintraub, S., Kertesz, A., Mendez, M., Cappa, S.F., Ogar, J.M., Rohrer, J.D., Black, S., Boeve, B.F., Manes, F., Dronkers, N.F., Vandenberghe, R., Rascovsky, K., Patterson, K., Miller, B.L., Knopman, D.S., Hodges, J.R., Mesulam, M.M., Grossman, M., 2011. Classification of primary progressive aphasia and its variants. Neurology 76, 1006–1014.

Gourovitch, M.L., Kirkby, B.S., Goldberg, T.E., Weinberger, D.R., Gold, J.M., Esposito, G., Van Horn, J.D., Berman, K.F., 2000. A comparison of rCBF patterns during letter and semantic fluency. Neuropsychology 14, 353–360.

Grogan, A., Green, D.W., Ali, N., Crinion, J.T., Price, C.J., 2009. Structural correlates of semantic and phonemic fluency ability in first and second languages. Cerebr. Cortex 19, 2690–2698.
Grossman, M., McMillan, C., Moore, P., Ding, L., Glosser, G., Work, M., Gee, J., 2004. What's in a name: voxel-based morphometric analyses of MRI and naming difficulty in Alzheimer's disease, frontotemporal dementia and corticobasal degeneration. Brain 127, 628–649.
Henry, J.D., Crawford, J.R., Phillips, L.H., 2004. Verbal fluency performance in dementia of the Alzheimer's type: a meta-analysis. Neuropsychologia 42, 1212–1222.
Hickok, G., Poeppel, D., 2007. The cortical organization of speech processing. Nat. Rev. Neurosci. 8, 393–402.
Hirni, D.I., Kivisaari, S.L., Monsch, A.U., Taylor, K.I., 2013. Distinct neuroanatomical bases of episodic and semantic memory performance in Alzheimer's disease. Neuropsychologia 51, 930–937.
Jack Jr., C.R., Bennett, D.A., Blennow, K., Carrillo, M.C., Dunn, B., Haeberlein, S.B., Holtzman, D.M., Jagust, W., Jessen, F., Karlawish, J., Liu, E., Molinuevo, J.L., Montine, T., Phelps, C., Rankin, K.P., Rowe, C.C., Scheltens, P., Siemers, E., Snyder, H.M., Sperling, R., Contributors, 2018. NIA-AA Research Framework: toward a biological definition of Alzheimer's disease. Alzheimers Dement 14, 535–562.
Kaplan, E., Goodglass, H., Weintraub, S., 1983. The Boston Naming Test. Lea and Febiger, Philadelphia.
Koedam, E.L., Lauffer, V., van der Vlies, A.E., van der Flier, W.M., Scheltens, P., Pijnenburg, Y.A., 2010. Early-versus late-onset Alzheimer's disease: more than age alone. J Alzheimers Dis 19, 1401–1408.
Lehmann, M., Barnes, J., Ridgway, G.R., Wattam-Bell, J., Warrington, E.K., Fox, N.C., Crutch, S.J., 2011. Basic visual function and cortical thickness patterns in posterior cortical atrophy. Cerebr. Cortex 21, 2122–2132.
Leyton, C.E., Ballard, K.J., Piguet, O., Hodges, J.R., 2014a. Phonologic errors as a clinical marker of the logopenic variant of PPA. Neurology 82, 1620–1627.
Leyton, C.E., Hodges, J.R., Piguet, O., Ballard, K.J., 2017. Common and divergent neural correlates of anomia in amnestic and logopenic presentations of Alzheimer's disease. Cortex 86, 45–54.
Leyton, C.E., Savage, S., Irish, M., Schubert, S., Piguet, O., Ballard, K.J., Hodges, J.R., 2014b. Verbal repetition in primary progressive aphasia and Alzheimer's disease. J Alzheimers Dis 41, 575–585.
Magnin, E., Sylvestre, G., Lenoir, F., Dariel, E., Bonnet, L., Chopard, G., Tio, G., Hidalgo, J., Ferreira, S., Mertz, C., Binetruy, M., Chamard, L., Haffen, S., Ryff, I., Laurent, E., Moulin, T., Vandel, P., Rumbach, L., 2013. Logopenic syndrome in posterior cortical atrophy. J. Neurol. 260, 528–533.
Makaretz, S.J., Quimby, M., Collins, J., Makris, N., McGinnis, S., Schultz, A., Vasdev, N., Johnson, K.A., Dickerson, B.C., 2018. Flortaucipir tau PET imaging in semantic variant primary progressive aphasia. J. Neurol. Neurosurg. Psychiatry 89, 1024–1031.
Margulies, D.S., Vincent, J.L., Kelly, C., Lohmann, G., Uddin, L.Q., Biswal, B.B., Villringer, A., Castellanos, F.X., Milham, M.P., Petrides, M., 2009. Precuneus shares intrinsic functional architecture in humans and monkeys. Proc. Natl. Acad. Sci. U. S. A. 106, 20069–20074.
McCandliss, B.D., Cohen, L., Dehaene, S., 2003. The visual word form area: expertise for reading in the fusiform gyrus. Trends Cognit. Sci. 7, 293–299.
McGraw, P., Mathews, V.P., Wang, Y., Phillips, M.D., 2001. Approach to functional magnetic resonance imaging of language based on models of language organization. Neuroimaging Clin. 11, 343–353 (x).
McKhann, G.M., Knopman, D.S., Chertkow, H., Hyman, B.T., Jack Jr., C.R., Kawas, C.H., Klunk, W.E., Koroshetz, W.J., Manly, J.J., Mayeux, R., Mohs, R.C., Morris, J.C., Rossor, M.N., Scheltens, P., Carrillo, M.C., Thies, B., Weintraub, S., Phelps, C.H., 2011. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 7, 263–269.
Meinzer, M., Flaisch, T., Wilser, L., Eulitz, C., Rockstroh, B., Conway, T., Gonzalez-Rothi, L., Crosson, B., 2009. Neural signatures of semantic and phonemic fluency in young and old adults. J. Cognit. Neurosci. 21, 2007–2018.
Mendez, M.F., Ghajarania, M., Perryman, K.M., 2002. Posterior cortical atrophy: clinical characteristics and differences compared to Alzheimer's disease. Dement. Geriatr. Cognit. Disord. 14, 33–40.
Migliaccio, R., Agosta, F., Rascovsky, K., Karydas, A., Bonasera, S., Rabinovici, G., Miller, B., Gorno-Tempini, M.L., 2009. Clinical syndromes associated with posterior atrophy: early age at onset AD spectrum. Neurology 73, 1571–1578.
Miller, E., 1984. Verbal fluency as a function of a measure of verbal intelligence and in relation to different types of cerebral pathology. Br. J. Clin. Psychol. 23 (Pt 1), 53–57.
Monsch, A.U., Bondi, M.W., Butters, N., Salmon, D.P., Katzman, R., Thal, L.J., 1992. Comparisons of verbal fluency tasks in the detection of dementia of the alzheimer type. Arch. Neurol. 49, 1253–1258.
Alzheimer's Disease Neuroimaging, I., Australian Imaging, B., Lifestyle Flagship Study of, A., & Harvard Aging Brain, S. Mormino, E.C., Betensky, R.A., Hedden, T., Schultz, A. P., Ward, A., Huijbers, W., Rentz, D.M., Johnson, K.A., Sperling, R.A., 2014. Amyloid and APOE epsilon4 interact to influence short-term decline in preclinical Alzheimer disease Neurology 82, 1760–1767.
Moscovitch, M., 1994. Cognitive resources and dual-task interference effects at retrieval in normal people: the role of the frontal lobes and medial temporal cortex. Neuropsychology 8, 524–534.
Noonan, K.A., Jefferies, E., Garrard, P., Eshan, S., Lambon Ralph, M.A., 2013. Demonstrating the qualitative differences between semantic aphasia and semantic dementia: a novel exploration of nonverbal semantic processing. Behav. Neurol. 26, 7–20.
Novick, J.M., Trueswell, J.C., Thompson-Schill, S.L., 2005. Cognitive control and parsing: reexamining the role of Broca's area in sentence comprehension. Cognit. Affect Behav. Neurosci. 5, 263–281.
Ossenkoppele, R., Cohn-Sheehy, B.I., La Joie, R., Vogel, A.C., Moller, C., Lehmann, M., van Berckel, B.N., Seeley, W.W., Pijnenburg, Y., Gorno-Tempini, M.L., Kramer, J.H., Barkhof, F., Rosen, H., van der Flier, W.M., Jagust, W., Miller, B., Scheltens, P., Rabinovici, G., 2015. Atrophy patterns in early clinical stages across distinct phenotypes of Alzheimer's disease. Hum. Brain Mapp. 36, 4421–4437.
Pakhomov, S.V.S., Eberly, L., Knopman, D., 2016. Characterizing cognitive performance in a large longitudinal study of aging with computerized semantic indices of verbal fluency. Neuropsychologia 89, 42–56.
Papp, K.V., Mormino, E.C., Amariglio, R.E., Munro, C., Dagley, A., Schultz, A.P., Johnson, K.A., Sperling, R.A., Rentz, D.M., 2016. Biomarker validation of a decline in semantic processing in preclinical Alzheimer's disease. Neuropsychology 30, 624–630.
Patterson, K., Nestor, P.J., Rogers, T.T., 2007. Where do you know what you know? The representation of semantic knowledge in the human brain. Nat. Rev. Neurosci. 8, 976–987.
Perani, D., Cappa, S.F., Tettamanti, M., Rosa, M., Scifo, P., Miozzo, A., Basso, A., Fazio, F., 2003. A fMRI study of word retrieval in aphasia. Brain Lang. 85, 357–368.
Petersen, R.C., 2004. Mild cognitive impairment as a diagnostic entity. J. Intern. Med. 256, 183–194.
Pihlajamaki, M., Tanila, H., Hanninen, T., Kononen, M., Laakso, M., Partanen, K., Soininen, H., Aronen, H.J., 2000. Verbal fluency activates the left medial temporal lobe: a functional magnetic resonance imaging study. Ann. Neurol. 47, 470–476.
Pravata, E., Tavernier, J., Parker, R., Vavro, H., Mintzer, J.E., Spampinato, M.V., 2016. The neural correlates of anomia in the conversion from mild cognitive impairment to Alzheimer's disease. Neuroradiology 58, 59–67.
Putcha, D., McGinnis, S.M., Brickhouse, M., Wong, B., Sherman, J.C., Dickerson, B.C., 2018. Executive dysfunction contributes to verbal encoding and retrieval deficits in posterior cortical atrophy. Cortex 106, 36–46.
Rabinovici, G.D., Furst, A.J., Alkalay, A., Racine, C.A., O'Neil, J.P., Janabi, M., Baker, S. L., Agarwal, N., Bonasera, S.J., Mormino, E.C., Weiner, M.W., Gorno-Tempini, M.L., Rosen, H.J., Miller, B.L., Jagust, W.J., 2010. Increased metabolic vulnerability in early-onset Alzheimer's disease is not related to amyloid burden. Brain 133, 512–528.
Ralph, M.A., Jefferies, E., Patterson, K., Rogers, T.T., 2017. The neural and computational bases of semantic cognition. Nat. Rev. Neurosci. 18, 42–55.
Renner, J.A., Burns, J.M., Hou, C.E., McKeel Jr., D.W., Storandt, M., Morris, J.C., 2004. Progressive posterior cortical dysfunction: a clinicopathologic series. Neurology 63, 1175–1180.
Rogalski, E., Cobia, D., Harrison, T.M., Wieneke, C., Thompson, C.K., Weintraub, S., Mesulam, M.M., 2011. Anatomy of language impairments in primary progressive aphasia. J. Neurosci. 31, 3344–3350.
Rogers, T.T., Ivanoiu, A., Patterson, K., Hodges, J.R., 2006. Semantic memory in Alzheimer's disease and the frontotemporal dementias: a longitudinal study of 236 patients. Neuropsychology 20, 319–335.
Salmon, D.P., Butters, N., Chan, A.S., 1999. The deterioration of semantic memory in Alzheimer's disease. Can. J. Exp. Psychol. 53, 108–117.
Schmidt, C.S.M., Schumacher, L.V., Romer, P., Leonhart, R., Beume, L., Martin, M., Dressing, A., Weiller, C., Kaller, C.P., 2017. Are semantic and phonological fluency based on the same or distinct sets of cognitive processes? Insights from factor analyses in healthy adults and stroke patients. Neuropsychologia 99, 148–155.
Schonknecht, O.D., Hunt, A., Toro, P., Guenther, T., Henze, M., Haberkorn, U., Schroder, J., 2011. Bihemispheric cerebral FDG PET correlates of cognitive dysfunction as assessed by the CERAD in Alzheimer's disease. Clin. EEG Neurosci. 42, 71–76.
Shao, Z., Janse, E., Visser, K., Meyer, A.S., 2014. What do verbal fluency tasks measure? Predictors of verbal fluency performance in older adults. Front. Psychol. 5, 772.
Shaw, L.M., Vanderstichele, H., Knapik-Czajka, M., Clark, C.M., Aisen, P.S., Petersen, R. C., Blennow, K., Soares, H., Simon, A., Lewczuk, P., Dean, R., Siemers, E., Potter, W., Lee, V.M., Trojanowski, J.Q., Alzheimer's Disease Neuroimaging, I., 2009. Cerebrospinal fluid biomarker signature in Alzheimer's disease neuroimaging initiative subjects. Ann. Neurol. 65, 403–413.
Sheldon, S., Moscovitch, M., 2012. The nature and time-course of medial temporal lobe contributions to semantic retrieval: an fMRI study on verbal fluency. Hippocampus 22, 1451–1466.
Shirk, S.D., Mitchell, M.B., Shaughnessy, L.W., Sherman, J.C., Locascio, J.J., Weintraub, S., Atri, A., 2011. A web-based normative calculator for the uniform data set (UDS) neuropsychological test battery. Alzheimer's Res. Ther. 3, 32.
Snowden, J.S., Stopford, C.L., Julien, C.L., Thompson, J.C., Davidson, Y., Gibbons, L., Pritchard, A., Lendon, C.L., Richardson, A.M., Varma, A., Neary, D., Mann, D.M.A., 2007. Cognitive phenotypes in alzheimer's disease and genetic risk. Cortex 43, 835–845.
Spreen, O., Strauss, E., 1991. A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary. Oxford University Press, New York.
Tang-Wai, D.F., Graff-Radford, N.R., Boeve, B.F., Dickson, D.W., Parisi, J.E., Crook, R., Caselli, R.J., Knopman, D.S., Petersen, R.C., 2004. Clinical, genetic, and neuropathologic characteristics of posterior cortical atrophy. Neurology 63, 1168–1174.
Vasconcelos, L.G., Jackowski, A.P., Oliveira, M.O., Ribeiro Flor, Y.M., Souza, A.A., Bueno, O.F., Brucki, S.M., 2014. The thickness of posterior cortical areas is related to executive dysfunction in Alzheimer's disease. Clinics 69, 28–37.
Villeneuve, S., Rabinovici, G.D., Cohn-Sheehy, B.I., Madison, C., Ayakta, N., Ghosh, P.M., La Joie, R., Arthur-Bentil, S.K., Vogel, J.W., Marks, S.M., Lehmann, M., Rosen, H.J., Reed, B., Olichney, J., Boxer, A.L., Miller, B.L., Borys, E., Jin, L.W., Huang, E.J.,

Grinberg, L.T., DeCarli, C., Seeley, W.W., Jagust, W., 2015. Existing Pittsburgh Compound-B positron emission tomography thresholds are too high: statistical and pathological evaluation. Brain 138, 2020–2033.
Vincent, J.L., Kahn, I., Snyder, A.Z., Raichle, M.E., Buckner, R.L., 2008. Evidence for a frontoparietal control system revealed by intrinsic functional connectivity. J. Neurophysiol. 100, 3328–3342.
Vonk, J.M.J., Rizvi, B., Lao, P.J., Budge, M., Manly, J.J., Mayeux, R., Brickman, A.M., 2018. Letter and category fluency performance correlates with distinct patterns of cortical thickness in older adults. Cerebr. Cortex 29 (6), 2694–2700.
Warren, J.D., Fletcher, P.D., Golden, H.L., 2012. The paradox of syndromic diversity in Alzheimer disease. Nat. Rev. Neurol. 8, 451–464.
Wong, B., Lucente, D., MacLean, J., Padmanabhan, J., Quimby, M., Brandt, K. D., Putcha, D., Sherman, J. C., Frosch, M. P., McGinnis, S., & Dickerson, B. C. (in press). Diagnostic evaluation and monitoring of patients with posterior cortical atrophy. Neurodegener. Dis. Manag..
Xia, C., Makaretz, S.J., Caso, C., McGinnis, S., Gomperts, S.N., Sepulcre, J., Gomez-Isla, T., Hyman, B.T., Schultz, A., Vasdev, N., Johnson, K.A., Dickerson, B.C., 2017. Association of in vivo [18F]AV-1451 tau PET imaging results with cortical atrophy and symptoms in typical and atypical alzheimer disease. JAMA Neurol 74, 427–436.