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Full title

Reduced cortical thickness in the posterior cingulate gyrus is characteristic of both typical and atypical Alzheimer's disease

Running title

Cortical thickness in typical and atypical AD

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Keywords

Alzheimer's disease, cortical thickness, pathology, magnetic resonance imaging, FreeSurfer

Abstract

Alzheimer's disease (AD) and frontotemporal lobar degeneration (FTLD) can be difficult to differentiate clinically due to overlapping symptoms. Subject classification in research studies is often based on clinical rather than pathological criteria which may mean some subjects are misdiagnosed and misclassified. Recently, methods measuring cortical thickness using magnetic resonance imaging (MRI) have been suggested to be effective in differentiating between clinically-defined AD and frontotemporal dementia (FTD) in addition to showing disease-related patterns of atrophy. In this study we used FreeSurfer, a freely-available and automated software tool, to measure cortical thickness in 28 pathologically-confirmed AD patients, of which 11 had a typical amnestic presentation and 17 an atypical presentation during life, 23 pathologically-confirmed FTLD subjects, and 25 healthy controls. Patients with AD pathology, irrespective of clinical diagnosis, showed reduced cortical thickness bilaterally in the medial temporal lobe, posterior cingulate gyrus, precuneus, posterior parietal lobe, and frontal pole compared with controls. We further showed that lower cortical thickness in the posterior cingulate gyrus, parietal lobe and frontal pole is suggestive of AD pathology in patients with behavioural or language deficits. In contrast, lower cortical thickness in the anterior temporal lobe and frontal lobe is indicative of the presence of FTLD pathology in patients with a clinical presentation of FTD. Reduced cortical thickness in the posterior cingulate gyrus is characteristic of AD pathology in patients with typical and atypical clinical presentations of AD, and may assist a clinical distinction of AD pathology from FTLD pathology.

1. Introduction

Alzheimer's disease (AD) and frontotemporal lobar degeneration (FTLD) are histopathologically distinct, with AD being characterized by the presence of extracellular amyloid plaques, intraneuronal neurofibrillary tangles and neuronal loss [1], and FTLD by neuronal loss and the presence of non-AD histological pathology, most commonly either tau-positive inclusions or ubiquitin-positive, TDP-43-positive inclusions [2].

Clinically, patients with underlying AD and FTLD pathology may present with overlapping symptoms. Typically, patients with AD pathology present with amnestic symptoms which gradually progress to involve multiple cognitive domains [3]. However, an increasing number of studies stress the importance of 'atypical' forms of AD, i.e. dementia in which the underlying pathology is AD, but in which memory is not the primary deficit [4;5]. Some patients with AD pathology may present with visuospatial and visuoperceptual problems and are diagnosed with posterior cortical atrophy (PCA) [6]; whilst others present with marked behavioural features (so called 'frontal-variant AD') [7;8]; yet others have a predominantly language presentation which often has features of logopenic/phonological aphasia (LPA) [9]. These atypical behavioural and language presentations of AD can be difficult to distinguish from patient with FTLD pathology.

Patients with underlying FTLD pathology may also present with a range of different clinical symptoms. The clinical heterogeneity of FTLD is enshrined in diagnostic criteria which explicitly describe different clinical subtypes or variants. Three main clinical syndromes are distinguished: behavioural variant frontotemporal dementia (bvFTD), semantic dementia (SD), and progressive non-fluent aphasia (PNFA); the latter two are often referred to as primary progressive aphasia (PPA) [10].

In this study, the term frontotemporal dementia (FTD) refers to the clinical (frontotemporal) syndrome which includes both behavioural and language variants, whereas FTLD refers to the confirmation of tau- or ubiquitin-positive pathology. Furthermore, the term 'typical AD'

refers to patients with a typical amnestic presentation of AD and underlying AD pathology, whereas ‘atypical’ AD in this study refers to patients with AD pathology but who had a clinical diagnosis of either FTD or PCA. Within this group, the term AD-FTD refers to those patients who presented with FTD symptoms (behavioural or language deficits) and yet had underlying AD pathology at autopsy.

A number of studies have used magnetic resonance imaging (MRI) to assess brain atrophy in these disorders [11;12]. These patterns of atrophy may aid diagnosis - *in vivo* an atrophy ‘signature’ in life may predict the underlying pathology [13]. In many research studies, however, autopsy confirmation is lacking and ‘clinically diagnosed’ patients are included. Clinical prediction of histopathology is inevitably imperfect; more importantly there is a risk of circularity. Clinically diagnosed subjects reflect ‘typical’ presentations of these diseases as the purpose of clinical criteria is to describe the most typical presentations to reduce misdiagnosis.

We investigated atrophy patterns in patients with pathology confirmation including atypical and typical clinical presentations of AD and FTLD. We wished to incorporate non-amnestic presentations of AD including language and behavioural presentations which are more likely to overlap with FTLD in terms of atrophy. The aim of this study was to assess the commonality of cortical thickness patterns between patients with AD pathology who presented with either typical amnestic deficits or atypical non-amnestic deficits during life. We further investigated patients clinically diagnosed as FTD to assess whether there were differences in cortical atrophy patterns between those who were subsequently found to have AD pathology and those with FTLD pathology.

2. Materials and Methods

2.1. Subjects

We initially selected 62 patients from a database of pathologically-confirmed cases: 32 individuals with a pathological diagnosis of AD and 30 subjects with pathologically-confirmed FTLD who had undergone volumetric MR imaging as part of their diagnostic work-up. Twenty-five healthy controls that had undergone MRI assessment were also included. All clinically affected subjects had attended the Specialist Cognitive Disorders Clinic at the National Hospital for Neurology and Neurosurgery, London, UK. Informed consent was obtained from all subjects and the study had local ethics committee approval. Some of these patients have been included in previous imaging studies [14-16]. All patients underwent comprehensive clinical assessment which included the mini-mental state examination (MMSE) [17]. We excluded subjects with mixed AD and dementia with Lewy body pathology.

Pathologically-confirmed AD subjects were divided into typical and atypical AD patients based on their clinical ante-mortem presentation. Typical AD patients were defined as those who presented with amnestic deficits during life, whereas atypical patients presented predominantly with language, behavioural or visuoperceptual and visuospatial deficits, accompanied by some degree of memory impairment at the time of scan (Figure 1). After image processing, 11 subjects were excluded (see below). The study therefore included 28 AD patients, 23 with FTLD, and 25 controls: the demographics of the 76 subjects included are summarized in Table 1. Of the 11 typical AD subjects, 10 had post-mortem and 1 had brain biopsy confirmation. All of these AD patients had been diagnosed ante-mortem with AD according to NINCDS-ADRDA criteria [3]. Of the 17 atypical AD subjects, 12 had post-mortem confirmation and 5 had biopsy confirmation. This group consisted of 9 patients who had a clinical diagnosis of PPA, 6 patients with PCA, and 2 patients with bvFTD (Figure 1). Of the 23 pathologically-confirmed FTLD subjects, 20 had post-mortem confirmation and 3 had brain biopsy. The FTLD group comprised 10 tau-positive patients (5 bvFTD, 4 PNFA, 1 atypical SD) and 13 tau-negative, ubiquitin-positive patients (10 SD and 3 bvFTD). All FTLD subjects were clinically-diagnosed with FTD [10].

2.2. MRI Acquisition

T1-weighted volumetric MR scans were performed on 1.5 Tesla Signa units (General Electric, Milwaukee) using a volumetric spoiled gradient recalled (SPGR) sequence with 1.5mm thick slices covering the head (except one FTLD subject with 1.7mm thick slices).

2.3 Image processing

Cortical thickness measurements were made using the freely-available software FreeSurfer, version 4.0.3. (http://surfer.nmr.mgh.harvard.edu/). The detailed procedure for the surface construction has been described and validated in previous publications [18]. Cortical thickness was smoothed with a 20mm full-width at half height Gaussian kernel to reduce local variations in the measurements for further analysis. Two modifications to the standard FreeSurfer processing stream were undertaken: a locally-generated brain mask was used for skull stripping and FreeSurfer ventricular segmentations were added to the white matter mask to improve cortical segmentation [19].

All images were visually inspected and on average edited and re-run three times as suggested (http://surfer.nmr.mgh.harvard.edu/fswiki/FsTutorial/TroubleshootingData). At this stage, as mentioned above, four individuals with AD and seven with FTLD were excluded due to poor image quality causing poor segmentations.

2.4. Statistical analysis

Regional cortical thickness variations between the patient groups and the control group were assessed using a vertex-by-vertex general linear model (GLM), performed with the SurfStat software (http://www.stat.uchicago.edu/~worsley/surfstat/). Cortical thickness (C) was modelled as a function of group, controlling for age, gender and scanner by their inclusion as covariates. We used separate models for the two comparisons of interest.

Comparison 1 assessed cortical thickness in typical and atypical AD, and was modelled $C = \beta_1 (\text{controls}) + \beta_2 (\text{typical AD}) + \beta_3 (\text{atypical AD}) + \beta_4 \text{age} + \beta_5 \text{gender} + \beta_6 \text{scanner} + \varepsilon$ (where ε is error), contrasting β_1 vs. β_2 (controls vs. typical AD), β_1 vs. β_3 (controls vs. atypical AD), and

β_2 vs. β_3 (typical AD vs. atypical AD; see Figure 1). Contrasts were calculated using two-tailed t-tests.

Comparison 2 assessed cortical thickness in AD-FTD (including the clinically diagnosed PPA and bvFTD patients with AD pathology) vs. FTLD, and was modelled C = β_1 (controls) + β_2 (AD-FTD) + β_3 (FTLD) + β_4 age + β_5 gender + β_6 scanner + ε, contrasting β_1 vs. β_2 (controls vs. AD-FTD), β_1 vs. β_3 (controls vs. FTLD), and β_2 vs. β_3 (AD-FTD vs. FTLD, see Figure 1). Maps were produced showing percentage differences in average cortical thickness and statistically significant differences with false discovery rate (FDR) correction at $p<0.05$ [20]. Intersection maps highlight regions which two patient groups compared with controls had in common.

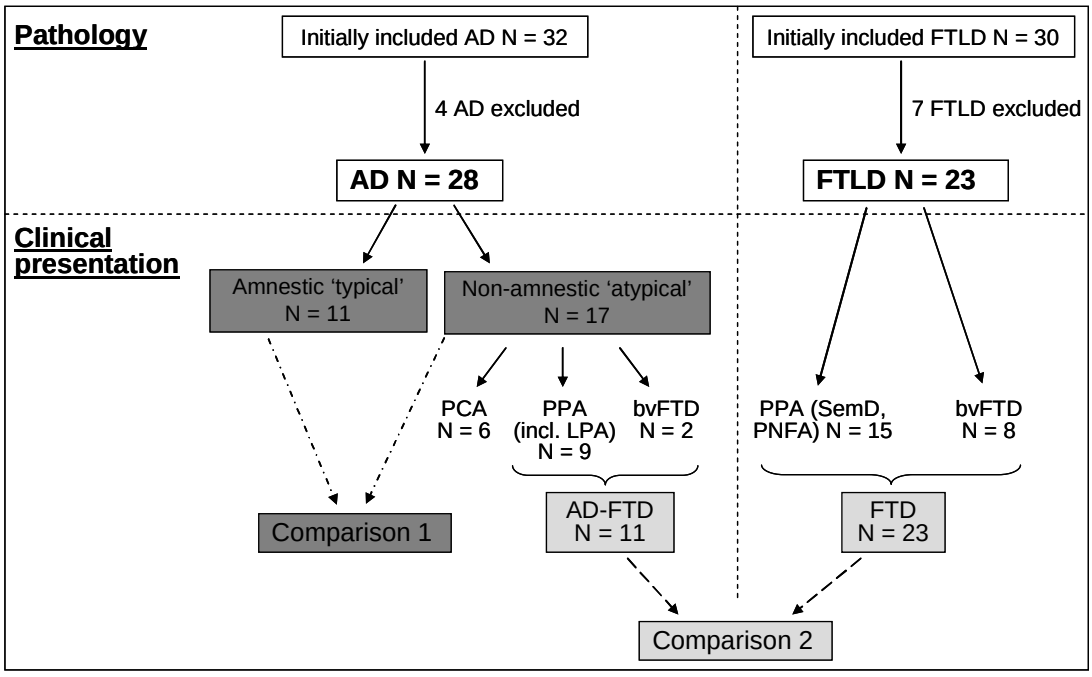

Figure 1: Overview groups and comparisons. Comparison 1 assessed differences in cortical thickness between patients with underlying AD pathology but different clinical presentations ('typical' amnestic vs. 'atypical' non-amnestic), whereas comparison 2 assessed differences in cortical thickness between patients with a clinic presentation of FTD but different underlying pathologies, i.e. AD pathology (AD-FTD) vs. FTLD pathology (FTD). PPA - primary progressive aphasia; LPA - logopenic/phonological aphasia; PCA - posterior cortical atrophy; SD - semantic dementia; PNFA - progressive non-fluent aphasia; bvFTD - behavioural variant frontotemporal dementia.

2.5 Support vector machine

A linear support vector machine (SVM) was used to classify subjects [21;22], implemented with LIBSVM version 2.89 [23] under MATLAB (version 7.2.0). The same scans as in the vertex-wise statistical comparisons described above were used for this analysis. The comparison of interest was the classification of the FTLD and AD-FTD groups (which relates to comparison 2 described above, see Figure 1), i.e. assessing how well patients with a clinical diagnosis of FTD who were subsequently found to have either AD or FTLD pathology can be classified into their respective group.

Subjects were represented as points in an n-dimensional space, where n=299881 is the total number of vertices in the cortical surface (including left and right hemispheres, but excluding the medial wall). SVMs identify an optimal separating hyperplane in this space such that subjects from each group lie as far as possible from the hyperplane, on opposite sides. Once the hyperplane has been defined scores can be generated by projecting the points onto the normal of the hyperplane; the direction of the normal can be visualised as an image, showing the relative weights and signs of vertices' contributions to the classifier scores. We use the C-SVM formulation, employing a two-level nested cross-validation to optimize the misclassification penalty parameter C using a leave-one-out procedure within the main leave-one-out loop [24]. This ensures an unbiased estimation of generalisation accuracy by leaving each scan in turn entirely out of the training procedure.

3. Results

3.1 Subjects

No significant differences across groups were found for gender, disease duration and time to death (Table 1). Age difference across all groups was not significant, however, the atypical AD group was significantly younger than controls ($p<0.05$). MMSE scores across patient groups differed significantly ($p<0.05$) which was mainly driven by the high MMSE scores in the FTLD group which differed from the typical and atypical AD groups ($p<0.001$ and $p<0.01$ respectively).

Table 1: Subject demographics.

	N	Gender male / female ‡	Age in years, mean (S.D.) ±	MMSE, mean (S.D.) **1	Disease duration, mean (S.D.) ±	Time to death, mean (S.D.) ±	Scanner a	b	c	d
Controls	**25**	**17 / 8**	**64.2 (9.4)**	**N/A**	**N/A**	**not available**	**6**	**15**	**0**	**4**
Typical AD	**11**	**8 / 3**	**68.0 (10.5) *2**	**14.4 (7.0) ***4**	**3.6 (2.3)**	**3.8 (2.7) ††**	**4**	**7**	**0**	**0**
Atypical AD	**17**	**9 / 8**	**59.2 (6.5) *3**	**17.7 (6.9) **4**	**3.7 (1.5)**	**4.7 (1.7) †††**	**0**	**14**	**3**	**0**
PPA	9	6 / 3	58.6 (6.9)	16.6 (7.1)	3.8 (1.2)	3.5 (1.3)	0	7	2	0
PCA	6	2 / 4	60.2 (7.5)	22.2 (4.3)	3.4 (2.2)	6.0 (0.9)	0	5	1	0
bvFTD	2	1 / 1	59.0 (1.4)	9.5 (0.7)	4.4 (1.0)	6.6	0	2	0	0
FTLD	**23**	**13 / 10**	**62.5 (10.1)**	**23.4 (5.6) †**	**4.3 (2.1)**	**6.0 (3.4) ††††**	**0**	**18**	**2**	**3**
SD	11	6 / 5	65.9 (6.0)	22.2 (5.6)	4.3 (2.4)	8.0 (3.0)	0	7	1	3
bvFTD	8	4 / 4	58.3 (14.2)	22.7 (5.1)	4.3 (2.3)	3.6 (2.3)	0	7	1	0
PNFA	4	3 / 1	62.8 (6.9)	27.7 (1.2)	4.4 (0.7)	4.0 (2.6)	0	4	0	0

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

‡ Fischer's exact test: p = NS; ± ANOVA: p = NS

1 ANOVA; 2 difference to atypical AD; 3 difference to controls; 4 difference to FTLD

† available for 20 FTLD (10 SD, 7 bvFTD, 3 PNFA); †† available for 10 Typical AD; ††† available for 13 Atypical AD (7PPA, 5 PCA, 1bvFTD); †††† available for 21 FTLD (11SD, 7bvFTD, 3bvFTD)

a, b, c, d - different 1.5T GE scanners.

n/a - not applicable

3.2. Comparison 1: typical vs. atypical AD

Compared with controls, typical AD showed lower thickness across the cortex, with the most prominent reduction bilaterally in the medial and posterior temporal regions, posterior cingulate gyrus, and frontal lobe regions (Figure 2A). The atypical AD group showed reduced cortical thickness bilaterally in the medial temporal lobe, posterior cingulate gyrus, precuneus, posterior parietal lobe, and frontal pole (Figure 2B). The intersection map shows areas of reduced cortical thickness common to both typical and atypical AD compared with controls (Figure 2C) bilaterally in the medial temporal lobe, posterior cingulate gyrus, precuneus, posterior parietal lobe, and frontal pole.

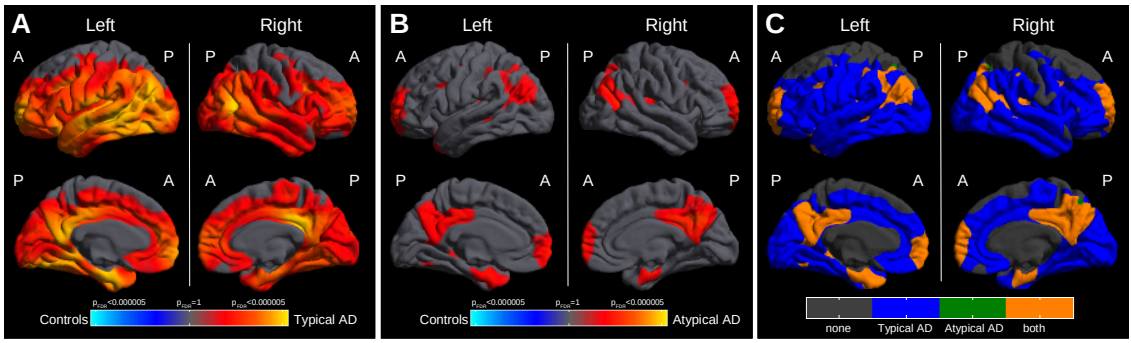

Figure 2: Reduced cortical thickness in typical and atypical AD compared with controls. The figure shows differences in cortical thickness between **A)** typical AD and controls, **B)** atypical AD and controls, for left and right hemispheres. The colour scale represents FDR-corrected p values thresholded at a 0.05 significance level. Red and yellow represent lower cortical thickness in the patient group, whereas blue represents lower cortical thickness in the control group. **C)** Intersection map showing regional differences in cortical thickness between typical AD and controls, and atypical AD and controls. Blue represents areas which are reduced in the typical AD group only, green represents regions which are reduced in atypical AD only, and orange shows areas which are reduced in both typical and atypical AD compared with controls.

The direct comparison of typical and atypical AD showed lower cortical thickness predominantly in the left posterior temporal lobe and left occipital lobe in the typical AD group compared with atypical AD (Figure 3A). However, this difference was reduced when including disease duration as covariate, and disappeared completely when correcting for MMSE. No regions were found to be significantly thinner in the atypical AD group compared with typical. However, the percent difference maps indicate trends towards lower cortical thickness bilaterally in the precuneus and superior parietal lobe in the atypical compared with typical AD group (Figure 3B).

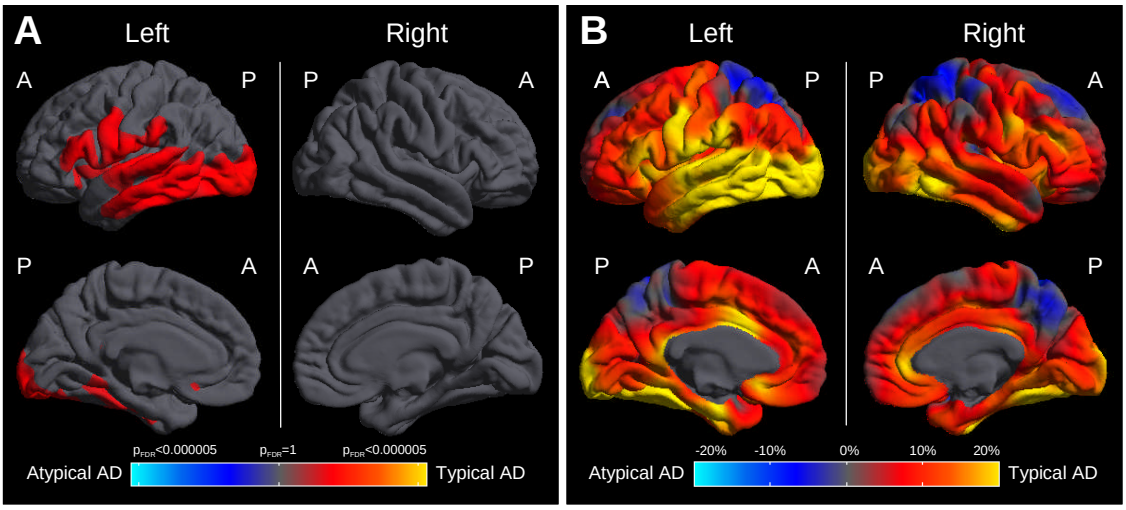

Figure 3: Differences in cortical thickness between typical and atypical AD. Differences in cortical thickness between typical and atypical AD are shown as **A)** statistical difference map, and **B)** percent difference map. The colour scale of the statistical difference map represents FDR-corrected p values thresholded at a 0.05 significance level whereas the colour bar for percent difference represents magnitude of cortical thickness group difference expressed as a percentage of mean thickness across both groups (adjusted for age, gender and scanner). Red and yellow represent lower cortical thickness in the typical AD group, whereas blue represents lower cortical thickness in the atypical AD group.

3.3. Comparison 2: AD-FTD vs. FTLD

Compared with controls, AD-FTD patients showed lower cortical thickness in the left superior temporal lobe, as well as bilaterally in the posterior cingulate gyrus, precuneus, left posterior parietal lobe and bilateral frontal pole (Figure 4A). The FTLD group showed widespread thinning with the most prominent reductions found bilaterally in the anterior temporal lobe (Figure 4B). The intersection map reveals regions in which both AD-FTD and FTLD show reduced cortical thickness compared with controls which include the bilateral posterior cingulate gyrus, left superior temporal lobe and left medial temporal lobe (Figure 4C).

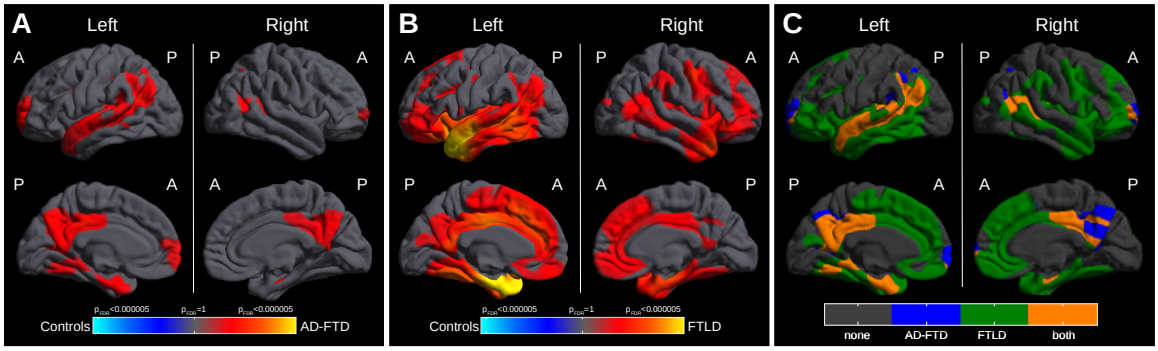

Figure 4: Reduced cortical thickness in AD-FTD and FTLD compared with controls. Differences in cortical thickness are shown between **A)** AD-FTD and controls, and **B)** FTLD and controls for left (L) and right (R) hemispheres. The colour scale represents FDR-corrected p values thresholded at a 0.05 significance level. Red and yellow represent lower cortical thickness in the patient group, whereas blue represents lower cortical thickness in the controls. **C)** Intersection map showing regional differences in cortical thickness between AD-FTD and controls, and FTLD and controls. Blue represents areas which are reduced in the AD-FTD group only, green represents regions which are reduced in FTLD only, and orange shows areas which are reduced in both AD-FTD and FTLD compared with controls.

Differences in cortical thickness between AD-FTD and FTLD in a direct comparison did not reach statistical significance after FDR correction. However, percent difference maps show tendencies of reduced thickness bilaterally in the anterior temporal lobe and frontal lobe regions in the FTLD group compared with AD-FTD, whereas the AD-FTD group showed lower cortical thickness in left posterior parietal regions, bilaterally in the precuneus, posterior cingulate gyrus and frontal pole compared with FTLD (Figure 5A).

The classification analysis produced a classification accuracy of 79.4% with 95% confidence intervals [62.1%, 91.3%]. Of the AD-FTD patients 54.5% [23.4%, 83.3%] were correctly classified (sensitivity), whereas 91.3% [72.0%, 98.9%] of the FTLD patients were correctly classified (specificity). The area under the receiver operating characteristic (ROC) curve is 0.87 (Supplementary Figure 1). Areas in which reduced cortical thickness contributed most to the classification of AD-FTD were shown bilaterally in the posterior cingulate gyrus, posterior parietal lobe, precuneus, medial temporal lobe, and frontal pole (Figure 5B). In contrast, regions which contributed most towards a classification of FTLD were shown bilaterally in frontal lobe regions and the lateral temporal lobe.

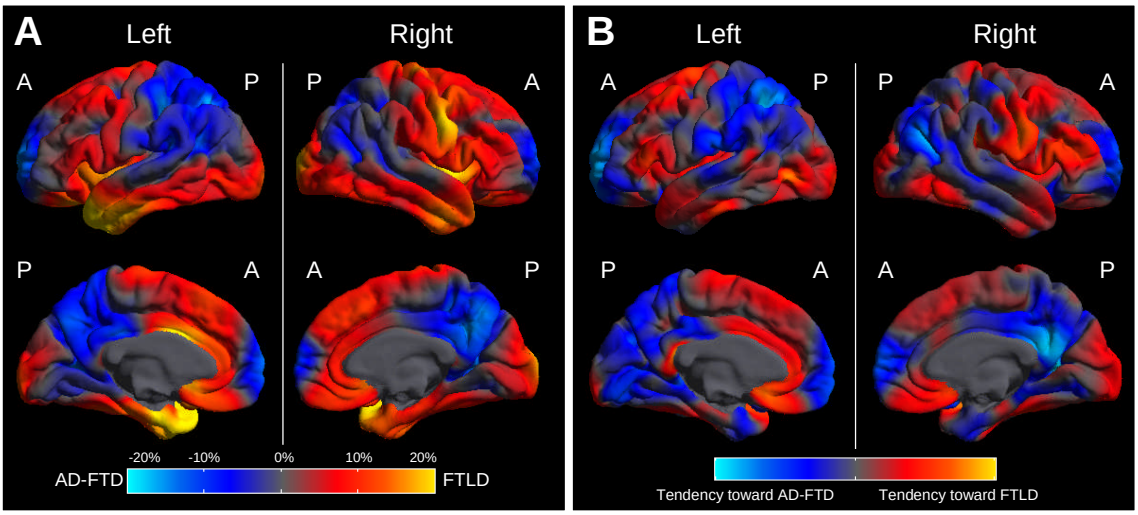

Figure 5: Differences in cortical thickness between AD-FTD and FTLD. **A)** Regional differences in cortical thickness between AD-FTD and FTLD shown as percent difference map. The colour bar represents magnitude of cortical thickness group difference expressed as a percentage of mean thickness of the two groups. Red and yellow represent lower cortical thickness in the FTLD group, whereas blue represents lower cortical thickness in the AD-FTD group. **B)** Classification map showing regions that were most influential in making a classification between AD-FTD and FTLD. Red represents areas where low cortical thickness indicates FTLD, whereas blue shows areas where lower cortical thickness indicates AD-FTD.

4. Discussion

We have described distinct patterns of cortical thinning in pathologically-confirmed AD and FTLD patients. Patients with AD pathology and a typical amnestic presentation during life showed reduced cortical thickness bilaterally in the medial temporal lobe, posterior cingulate gyrus, precuneus, posterior parietal regions, and frontal lobe. The association of an amnestic presentation of AD with medial temporal lobe atrophy was expected [11;25;26]. The finding of prominent thinning in the posterior cingulate cortex and precuneus concurs with increasing recognition that atrophy as well as hypometabolism in these regions is characteristic of AD [15;27]. However, frontal pole involvement was less expected.

A similar pattern of cortical thinning, compared with controls, was found in patients with AD pathology who had a different ante-mortem clinical diagnosis; however, thinning was less widespread. A direct comparison between these two patient groups revealed greater loss in

left posterior temporal lobe and left occipital lobe in the typical AD group compared with atypical AD. The fact that this difference is diminished after correcting for disease duration and MMSE may suggest that these differences simply reflect severity differences. However, mean disease duration was almost identical between groups. Disease progression in typical and atypical forms of AD may vary which means that disease duration is not a very accurate marker of disease severity. MMSE is also an imperfect indicator of disease severity in dementias in which memory is not the primary deficit, and the high mean MMSE in atypical AD subjects is largely driven by the PCA subjects included.

The intersection analysis illustrates the commonality of cortical thinning in typical and atypical AD. Cortical thickness was reduced in both the typical and atypical AD groups, compared with controls, bilaterally in the medial temporal lobe, posterior cingulate gyrus, precuneus, posterior parietal lobe and frontal pole. Cortical thinning in these regions may indicate the presence of AD pathology irrespective of clinical presentation. Cortical thinning in the medial temporal lobe in typical and atypical AD is consistent with the presence of memory deficits at the time of scan in both groups. Our general AD-specific findings are in accordance with previous imaging studies which investigated differences in cortical thickness [11;12] and grey matter volume using voxel-based morphometry [28;29] in typical forms of AD.

A strong involvement of the posterior cingulate gyrus in AD has been shown in a number of structural [15;28;30;31] and functional imaging studies [32]. Most functional imaging studies (PET, SPECT and fMRI) have reported reduced activity in this region in early stages of the disease [33-35]. The regions showing reduced cortical thickness in pathologically-confirmed AD patients in our study are consistent with those associated with the ‘default mode’ network [36]. Our finding adds to the growing number of studies suggesting that functional imaging findings are not as dissociated from atrophy as was once thought; temporal associations, however, remain unclear [37].

The involvement of the frontal lobe in AD, and more specifically of the prefrontal cortex and frontal pole, remains controversial. A number of studies have shown reduced cortical

thickness [11;12] and grey matter volumes [28;29;38] in this region. However, a number of studies have failed to show involvement of any frontal areas (for an overview see [39]). Our study with the advantage of pathology confirmation does support frontal pole atrophy in AD. There is always the theoretical possibility that this could be an artefact of the analysis technique, however, after careful visual inspection of this area in each subject we could not see any signal drop off or any kind of fault in the FreeSurfer surfaces which would explain reduced cortical thickness in this region.

The second subject group comparison revealed that patients with AD pathology and a clinical diagnosis of FTD during life (either behavioural or language variant) had a thinner cortex in the medial temporal lobe, posterior parietal regions, posterior cingulate gyrus and frontal pole than patients with FTLD pathology. In contrast, patients with FTLD pathology showed reduced cortical thickness predominantly in anterior temporal and frontal lobe regions. The highly significant reduction in the anterior temporal lobe in the FTLD group is possibly driven by the high proportion of semantic dementia patients in this group who are known to have marked atrophy in this region [31;40;41]. The patterns of cortical thinning observed in the FTLD group are consistent with previous histopathological and volumetric MRI studies [39;40;42;43].

Although differences in the direct comparison between AD-FTD and FTLD did not reach statistical significance, tendencies of cortical thinning as shown in the percent difference maps are consistent with the patterns observed in the control comparisons. Thinner cortex in the posterior cingulate gyrus, parietal lobe and frontal pole suggests the presence of AD pathology, whereas cortical thinning in the anterior temporal lobe and frontal lobe regions suggests the presence of FTLD pathology. Our classification algorithm showed that subjects could be correctly classified in 79% of cases. The ROC curve illustrates that although the original sensitivity is relatively low, this is probably driven by the imbalance in subject numbers between the two groups. The high area under the curve reveals that the classifier performs well, and a more favourable balance of sensitivity and specificity could be obtained by altering the threshold. The pattern of cortical thinning shown to separate the two patient

groups best was consistent with that observed in the direct comparison between AD-FTD and FTLD.

One strength of this study is that all AD and FTLD cases had pathological confirmation. This is particularly important considering that the clinical diagnosis of possible or probable AD (i.e. fulfilling NINCDS-ADRDA criteria) typically gives accuracies of approximately 90% [44], and the Neary criteria have been shown to have similar accuracies [45]. Consequently, a number of individuals included in studies of AD and FTLD will inevitably have a different type of pathology (i.e. only 10% of clinically-diagnosed AD cases were found to have non-AD pathology at post mortem [44]). A post-mortem study further revealed 30% of patients diagnosed with a language subtype of FTLD (i.e. PNFA, SD) had AD pathology [46]. It should be noted that in the current study clinical diagnoses were obtained retrospectively from a cohort of pathologically-confirmed AD cases. Since post mortem confirmation of disease is less likely to be requested for patients with a typical AD presentation, the proportion of atypical compared with typical AD patients in this study is larger than commonly seen in a clinic. Furthermore, the inclusion of only pathologically-confirmed cases inevitably limits subject numbers, reducing the power to detect differences between disease groups. Pathology confirmation was not obtained for the whole control group and it may be that some controls had a neurological condition but were asymptomatic. This is, however, unlikely and would only have reduced our ability to detect differences.

Another limitation is the variety in image acquisition which has been shown to affect thickness measures [47]. We therefore adjusted for scanner type in our statistical models. It should also be noted that there was an imbalance in scanner type between groups, with scanner A being present only in the control and typical AD group. However, excluding subjects imaged using scanner A from the analysis gave very similar results. Our groups were matched for disease duration, but not for disease severity as measured by MMSE. As expected, MMSE scores varied significantly between individual groups owing to the weighting of questions towards memory and orientation.

In summary, we have shown common areas of lower cortical thickness in two groups of patients with AD pathology but different clinical presentations which included the medial temporal lobe, posterior cingulate gyrus, precuneus, posterior parietal cortex and frontal pole. We further showed that lower cortical thickness in the posterior cingulate gyrus, medial temporal lobe, parietal lobe and frontal pole can be suggestive of AD pathology in patients with behavioural or language deficits. In contrast, lower cortical thickness in the anterior temporal lobe and frontal lobe regions is indicative of the presence of FTLD pathology in patients with a clinical presentation of FTLD.

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Reference List

[1] Braak H, Braak E (1991) Neuropathological staging of Alzheimer-related changes. *Acta Neuropathol* **82**, 239-259.

[2] Cairns NJ, Bigio EH, Mackenzie IR, Neumann M, Lee VM, Hatanpaa KJ, White CL, III, Schneider JA, Grinberg LT, Halliday G, Duyckaerts C, Lowe JS, Holm IE, Tolnay M, Okamoto K, Yokoo H, Murayama S, Woulfe J, Munoz DG, Dickson DW, Ince PG, Trojanowski JQ, Mann DM (2007) Neuropathologic diagnostic and nosologic criteria for frontotemporal lobar degeneration: consensus of the Consortium for Frontotemporal Lobar Degeneration. *Acta Neuropathol* **114**, 5-22.

[3] McKhann GM, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM (1984) Clinical diagnosis of Alzheimer's Disease - Report of the NINCDS-ADRDA work group under the

auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* **34,** 939-944.

[4] Chawluk JB, Mesulam MM, Hurtig H, Kushner M, Weintraub S, Saykin A, Rubin N, Alavi A, Reivich M (1986) Slowly progressive aphasia without generalized dementia: studies with positron emission tomography. *Ann Neurol* **19**, 68-74.

[5] Galton CJ, Patterson K, Xuereb JH, Hodges JR (2000) Atypical and typical presentations of Alzheimer's disease: a clinical, neuropsychological, neuroimaging and pathological study of 13 cases. *Brain* **123,** 484-498.

[6] Benson F, Davis J, Snyder BD (1988) Posterior Cortical atrophy. *Arch Neurol* **45**, 789-793.

[7] Johnson JK, Head E, Kim R, Starr A, Cotman CW (1999) Clinical and pathological evidence for a frontal variant of Alzheimer disease. *Arch Neurol* **56**, 1233-1239.

[8] Taylor KI, Probst A, Miserez AR, Monsch AU, Tolnay M (2008) Clinical course of neuropathologically confirmed frontal-variant Alzheimer's disease. *Nat Clin Pract Neurol* **4,** 226-232.

[9] Gorno-Tempini ML, Brambati SM, Ginex V, Ogar J, Dronkers NF, Marcone A, Perani D, Garibotto V, Cappa SF, Miller BL (2008) The logopenic/phonological variant of primary progressive aphasia. *Neurology* **71**, 1227-1234.

[10] Neary D, Snowden JS, Gustafson L, Passant U, Stuss D, Black S, Freedman M, Kertesz A, Robert PH, Albert M, Boone K, Miller BL, Cummings J, Benson DF (1998) Frontotemporal lobar degeneration - A consensus on clinical diagnostic criteria. *Neurology* **51**, 1546-1554.

[11] Du AT, Schuff N, Kramer JH, Rosen HJ, Gorno-Tempini ML, Rankin K, Miller BL, Weiner MW (2007) Different regional patterns of cortical thinning in Alzheimer's disease and frontotemporal dementia. *Brain* **130**, 1159-1166.

[12] Lerch JP, Pruessner JC, Zijdenbos A, Hampel H, Teipel SJ, Evans AC (2005) Focal decline of cortical thickness in Alzheimer's disease identified by computational neuroanatomy. *Cereb Cortex* **15**, 995-1001.

[13] Likeman M, Anderson VM, Stevens JM, Waldman AD, Godbolt AK, Frost C, Rossor MN, Fox NC (2005) Visual assessment of atrophy on magnetic resonance imaging in the diagnosis of pathologically confirmed young-onset dementias. *Arch Neurol* **62**, 1410-1415.

[14] Kloppel S, Stonnington CM, Chu C, Draganski B, Scahill RI, Rohrer JD, Fox NC, Jack CR, Jr., Ashburner J, Frackowiak RS (2008) Automatic classification of MR scans in Alzheimer's disease. *Brain* **131**, 681-689.

[15] Barnes J, Godbolt AK, Frost C, Boyes RG, Jones BF, Scahill RI, Rossor MN, Fox NC (2007) Atrophy rates of the cingulate gyrus and hippocampus in AD and FTLD. *Neurobiol Aging* **28**, 20-28.

[16] Rohrer JD, Warren JD, Modat M, Ridgway GR, Douiri A, Rossor MN, Ourselin S, Fox NC (2009) Patterns of cortical thinning in the language variants of frontotemporal lobar degeneration. *Neurology* **72**, 1562-1569.

[17] Folstein MF, Folstein SE, Mchugh PR (1975) Mini-Mental State - Practical Method for Grading Cognitive State of Patients for Clinician. *J Psychiatr Res* **12**, 189-198.

[18] Fischl B, Dale AM (2000) Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proc Natl Acad Sci USA* **97**, 11050-11055.

[19] Lehmann M, Crutch SJ, Ridgway GR, Ridha BH, Barnes J, Warrington EK, Rossor MN, Fox NC (2009) Cortical thickness and voxel-based morphometry in posterior cortical atrophy and typical Alzheimer's disease. *Neurobiol Aging,* doi:10.1016/j.neurobiolaging.2009.08.017.

[20] Genovese CR, Lazar NA, Nichols T (2002) Thresholding of statistical maps in functional neuroimaging using the false discovery rate. *Neuroimage* **15**: 870-878.

[21] Vapnik V (1995) *The nature of statistical learning theory*. Springer, New York.

[22] Vapnik V (1998) *Statistical learning theory.* John Wiley and Sons, New York.

[23] Chang CC, Lin CJ (2001) Training nu-support vector classifiers: Theory and algorithms. *Neural Comput* **13**, 2119-2147.

[24] Wilson SM, Ogar JM, Laluz V, Growdon M, Jang J, Glenn S, Miller BL, Weiner MW, Gorno-Tempini ML (2009) Automated MRI-based classification of primary progressive aphasia variants. *Neuroimage* **47**, 1558-1567.

[25] Teipel SJ, Pruessner JC, Faltraco F, Born C, Rocha-Unold M, Evans A, Moller HJ, Hampel H (2006) Comprehensive dissection of the medial temporal lobe in AD: measurement of hippocampus, amygdala, entorhinal, perirhinal and parahippocampal cortices using MRI. *J Neurol* **253**, 794-800.

[26] Ridha BH, Barnes J, Bartlett JW, Godbolt A, Pepple T, Rossor MN, Fox NC (2006) Tracking atrophy progression in familial Alzheimer's disease: a serial MRI study. *Lancet Neurol* **5**, 828-834.

[27] Nestor PJ, Fryer TD, Smielewski P, Hodges JR (2003) Limbic hypometabolism in Alzheimer's disease and mild cognitive impairment. *Ann Neurol* **54,** 343-351.

[28] Baron JC, Chetelat G, Desgranges B, Perchey G, Landeau B, de la Sayette V, Eustache F (2001) In vivo mapping of gray matter loss with voxel-based morphometry in mild Alzheimer's disease. *Neuroimage* **14**, 298-309.

[29] Busatto GE, Garrido GEJ, Almeida OP, Castro CC, Camargo CHP, Cid CG, Buchpiguel CA, Furuie S, Bottino CM (2003) A voxel-based morphometry study of temporal lobe gray matter reductions in Alzheimer's disease. *Neurobiol Aging* **24**, 221-231.

[30] Jones BF, Barnes J, Uylings HBM, Fox NC, Frost C, Witter MP, Scheftens P (2006) Differential regional atrophy of the cingulate gyrus in Alzheimer disease: A volumetric MRI study. *Cereb Cortex* **16**, 1701-1708.

[31] Boxer AL, Rankin KP, Miller BL, Schuff N, Weiner M, Gorno-Tempini ML, Rosen HJ (2003) Cinguloparietal atrophy distinguishes Alzheimer disease from semantic dementia. *Arch Neurol* **60**, 949-956.

[32] Lustig C, Snyder AZ, Bhakta M, O'Brien KC, McAvoy M, Raichle ME, Morris JC, Buckner RL (2003) Functional deactivations: change with age and dementia of the Alzheimer type. *Proc Natl Acad Sci USA* **100**, 14504-14509.

[33] Minoshima S, Giordani B, Berent S, Frey KA, Foster NL, Kuhl DE (1997) Metabolic reduction in the posterior cingulate cortex in very early Alzheimer's disease. *Ann Neurol* **42**, 85-94.

[34] Johnson KA, Jones K, Holman BL, Becker JA, Spiers PA, Satlin A, Albert MS (1998) Preclinical prediction of Alzheimer's disease using SPECT. *Neurology* **50**, 1563-1571.

[35] Matsuda H (2001) Cerebral blood flow and metabolic abnormalities in Alzheimer's disease. *Ann Nucl Med* **15**, 85-92.

[36] Greicius MD, Srivastava G, Reiss AL, Menon V (2004) Default-mode network activity distinguishes Alzheimer's disease from healthy aging: evidence from functional MRI. *Proc Natl Acad Sci USA* **101**, 4637-4642.

[37] Villain N, Desgranges B, Viader F, de la Sayette V, Mezenge F, Landeau B, Baron JC, Eustache F, Chetelat G (2008) Relationships between hippocampal atrophy, white matter disruption, and gray matter hypometabolism in Alzheimer's disease. *J Neurosci* **28**, 6174-6181.

[38] Davatzikos C, Resnick SM, Wu X, Parmpi P, Clark CM (2008) Individual patient diagnosis of AD and FTD via high-dimensional pattern classification of MRI. *Neuroimag*e **41**, 1220-1227.

[39] Whitwell JL, Josephs KA, Rossor MN, Stevens JM, Revesz T, Holton JL, Al Sarraj S, Godbolt AK, Fox NC, Warren JD (2005) Magnetic resonance imaging signatures of tissue pathology in frontotemporal dementia. *Arch Neurol* **62**, 1402-1408.

[40] Rosen HJ, Gorno-Tempini ML, Goldman WP, Perry RJ, Schuff N, Weiner M, Feiwell R, Kramer JH, Miller BL (2002) Patterns of brain atrophy in frontotemporal dementia and semantic dementia. *Neurology* **58**, 198-208.

[41] Chan D, Fox NC, Scahill RI, Crum WR, Whitwell JL, Leschziner G, Rossor AM, Stevens JM, Cipolotti L, Rossor MN (2001) Patterns of temporal lobe atrophy in semantic dementia and Alzheimer's disease. *Ann Neurol* **49**, 433-442.

[42] Grossman M, McMillan C, Moore P, Ding LJ, 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.

[43] Broe M, Hodges JR, Schofield E, Shepherd CE, Kril JJ, Halliday GM (2003) Staging disease severity in pathologically confirmed cases of frontotemporal dementia. *Neurology* **60**, 1005-1011.

[44] Jellinger KA (2006) Clinicopathological analysis of dementia disorders in the elderly--an update. *J Alzheimers Dis* **9**, 61-70.

[45] Knopman DS, Boeve BF, Parisi JE, Dickson DW, Smith GE, Ivnik RJ, Josephs KA, Petersen RC (2005) Antemortem diagnosis of frontotemporal lobar degeneration. *Ann Neurol* **57**, 480-488.

[46] Knibb JA, Xuereb JH, Patterson K, Hodges JR (2006) Clinical and pathological characterization of progressive aphasia. *Ann Neurol* **59**, 156-165

[47] Han X, Jovicich J, Salat D, van der Kouwe A, Quinn B, Czanner S, Busa E, Pacheco J, Albert M, Killiany R, Maguire P, Rosas D, Makris N, Dale A, Dickerson B, Fischl B (2006) Reliability of MRI-derived measurements of human cerebral cortical thickness: The effects of field strength, scanner upgrade and manufacturer. *Neuroimage* **32**, 180-194.

Supplementary material

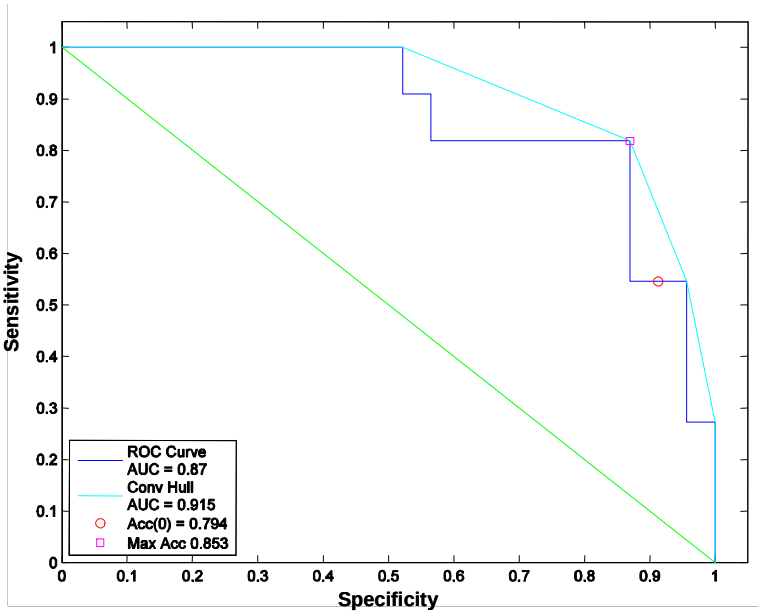

Figure 1: ROC curve for comparison of AD-FTD vs. FTLD classification. Shown is the tradeoff between sensitivity and specificity. The receiver operating characteristic (ROC) curve is plotted by varying the decision threshold. The low sensitivity reported in the main results arises from unbalanced group numbers, which allow high accuracy from high specificity. The ROC curve shows that relatively high sensitivity and specificity are simultaneously achievable if the threshold is altered. AUC - area under the curve, acc - accuracy.