



Combined imaging markers dissociate Alzheimer's disease and frontotemporal lobar degeneration – an ALE meta-analysis

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To compare and dissociate the neural correlates of Alzheimer's disease (AD) and frontotemporal lobar degeneration (FTLD), we combine and synthesize here recent comprehensive meta-analyses. Systematic and quantitative meta-analyses were conducted according to the QUOROM statement by calculating anatomical likelihood estimates (ALE). AD ($n = 578$) and the three subtypes of FTLD, frontotemporal dementia, semantic dementia (SD), and progressive non-fluent aphasia ($n = 229$), were compared in conjunction analyses, separately for atrophy and reductions in glucose metabolism. Atrophy coincided in the amygdala and hippocampal head in AD and the FTLD subtype SD. The other brain regions did not show any overlap between AD and FTLD subtypes for both atrophy and changes in glucose metabolism. For AD alone ($n = 826$), another conjunction analysis revealed a regional dissociation between atrophy and hypoperfusion/hypometabolism, whereby hypoperfusion and hypometabolism coincided in the angular/supramarginal gyrus and inferior precuneus/posterior cingulate gyrus. Our data together with other imaging studies suggest a specific dissociation of AD and FTLD if, beside atrophy, additional imaging markers in AD such as abnormally low parietal glucose utilization and perfusion are taken into account. Results support the incorporation of standardized imaging inclusion criteria into future diagnostic systems, which is crucial for early individual diagnosis and treatment in the future.

Keywords: Alzheimer's disease, differential diagnosis, FDG-PET, frontotemporal lobar degeneration, MRI, perfusion

INTRODUCTION

Neurodegenerative disorders are a major public health problem (Dubois et al., 2007; Kipps et al., 2009). The early detection, prediction, and dissociation of dementia syndromes are of paramount interest, in particular for treatment purposes. Based on the unprecedented rapid development of techniques for structural, functional, and molecular brain imaging, it has recently been suggested to incorporate standardized imaging inclusion criteria into future diagnostic systems such as the diagnostic and statistical manual of mental disorders (DSM-V) or the international classification of diseases system (ICD-11; Dubois et al., 2007; Hyman, 2007; Kipps et al., 2009).

Comprehensive meta-analyses are an excellent method of validating the impact of imaging markers on diagnosis and differential diagnosis of dementia syndromes. Recently, we have identified the prototypical neural correlates of two frequent dementia disorders, Alzheimer's disease (AD), and frontotemporal lobar degeneration (FTLD), in comprehensive systematic and quantitative meta-analyses conducted according to the QUOROM statement (Schroeter et al., 2007, 2009). These meta-analyses involved 1618 patients and 1448 healthy control subjects and applied the anatomical likelihood estimate (ALE) method, which is regarded as the most sophisticated and best-validated of coordinate-based voxelwise meta-analyses (Fox et al., 2005; Glahn et al., 2008; Laird

et al., 2009). This meta-analytic method uses peaks of atrophy, hypometabolism, or hypoperfusion in patients with dementia if compared with control subjects, and determines brain regions that exhibit a higher density of peak coordinates reported across single studies than would arise by chance. The ALE map represents the prototypical neural correlates of a specific dementia syndrome.

For AD and its prodromal stage, amnesic mild cognitive impairment (MCI), the meta-analysis revealed atrophy and reductions in metabolism and perfusion in a mainly temporoparietal network related to episodic memory processing (Thompson et al., 2003; Schroeter et al., 2009; McDonald et al., 2010; Walhovd et al., 2010). AD additionally involved frontomedian-thalamic structures. Atrophy in the (trans-) entorhinal area/hippocampus, and hypometabolism/-perfusion in the inferior parietal lobules most reliably predicted the progression from amnesic MCI to AD, whereas decreases in metabolism and perfusion in the posterior cingulate cortex and precuneus were unspecific (Schroeter et al., 2009).

For FTLD, the meta-analyses "triple dissociated" the prototypical neural substrates of its three subtypes (Neary et al., 1998; Schroeter et al., 2007, 2008). Frontotemporal dementia (FTD) – clinically characterized by changes in behavior and personality – affected a frontomedian network discussed in the context of social cognition. For the two other FTLD subtypes, the main clinical symptom is language impairment. Semantic dementia (SD) was related to the

inferior temporal poles and amygdalae – brain regions that have been discussed in the context of conceptual knowledge, semantic information processing, and social cognition. Progressive non-fluent aphasia (PNFA) involved the whole left frontotemporal network for phonological and syntactical processing. These meta-analytic results corresponded with other studies including also different imaging approaches and provided a basis for the understanding of clinical symptoms (Gorno-Tempini et al., 2004; Diehl-Schmid et al., 2007; Salmon et al., 2009; McDonald et al., 2010; Walhovd et al., 2010).

Besides the early detection of dementia syndromes, the dissociation of their neural correlates is crucial for their early differential diagnosis and treatment – an issue that is particularly relevant for the incorporation of standardized imaging inclusion criteria into future diagnostic systems (Dubois et al., 2007; Hyman, 2007; Kipps et al., 2009). While our previous meta-analyses identified the neural correlates of AD and FTLT (Schroeter et al., 2007, 2009), we now combine and synthesize these meta-analyses in a conjunction analysis in order to compare and dissociate the neural correlates of AD and FTLT, and to validate the specificity of imaging criteria for these disorders.

MATERIALS AND METHODS

MedLine and Current Contents search engines were used to systematically identify studies on morphometry, glucose utilization, and perfusion in AD, MCI, and FTLT (Schroeter et al., 2007, 2009). Studies were examined to fulfil the following inclusion criteria: peer-reviewed, original studies, patients diagnosed according to internationally recognized diagnostic criteria, patients compared to age-matched healthy controls, or age included as a covariate in the analysis, quantitative automated whole brain analysis method, results normalized to a stereotactic space such as the Talairach or the Montreal Neurological Institute (MNI) reference system, and respective coordinates are available. When maxima were reported in the MNI reference system, they were transformed to the Talairach space. We also applied the following exclusion criteria. Studies using solely region-of-interest analysis were excluded to prevent any *a priori* assumptions with regard to the involved neural networks and to enable a data-driven approach, as were case studies, and studies investigating substantially overlapping patient populations. Moreover, we generally excluded functional imaging studies investigating brain activation during cognitive stimulation, because they apply diverse psychological paradigms making a comparison of the individual studies in a meta-analysis impossible. The literature search, selection of studies according to the inclusion and exclusion criteria and compilation of coordinates for the several contrasts were performed independently by two investigators and any disagreements were resolved by consensus.

Contrasts between patients and healthy control subjects were included, reporting either atrophy [magnetic resonance imaging (MRI)], decreases in glucose utilization [^{18}F -fluorodeoxyglucose-positron emission tomography (FDG-PET)], or perfusion [H_2^{15}O -PET, $^{99\text{m}}\text{Tc}$ -hexamethylpropyleneamine oxime-(HMPAO)-single photon emission computed tomography (SPECT), $^{99\text{m}}\text{Tc}$ -ethylcysteinate dimmer-(ECD)-SPECT]. Finally, for AD and MCI, 40 studies were identified involving 1351 patients and 1097 healthy control subjects reporting either atrophy or decreases in glucose utilization and perfusion (see Schroeter et al., 2009). For FTLT, 19

relevant studies were extracted measuring atrophy or decreases in glucose utilization in 267 patients and 351 healthy control subjects (see Schroeter et al., 2007). Here, the analysis was performed for each of the three subtypes as proposed by Neary et al. (1998): FTD, SD, and PNFA. No perfusion study fulfilled the inclusion criteria for FTLT. The meta-analysis flow charts, further information as required according to the QUOROM statement and the studies included are listed in detail in our previous papers (Schroeter et al., 2007, 2009).

To extract the prototypical neural networks, we applied the ALE meta-analysis method (Turkeltaub et al., 2002; Fox et al., 2005; Schroeter et al., 2007, 2008, 2009; Glahn et al., 2008). The idea behind this method is to determine brain regions that exhibit a higher density of peak coordinates reported across studies than would arise by chance. Based on peaks of atrophy, hypometabolism or hypoperfusion as reported in the single studies, the algorithm calculates an ALE map that represents the likelihood for each voxel that at least one of the reported peaks is located there. ALE values were determined on a grid of isotropic $2\text{mm} \times 2\text{mm} \times 2\text{mm}$ voxels. In a second step, these empirical ALE maps were compared to ALE maps for randomly distributed maxima. The same number of maxima as included in the empirical ALE map was uniformly distributed 1000 times over a brain volume mask. Histograms of the thousand sets of randomly distributed maxima were averaged to obtain a histogram representing the noise distribution of ALE values. This histogram served as a null hypothesis against which the significance of the empirical ALE values was tested. A conservative ALE threshold corresponding to a level of 0.01% ($p < 0.0001$) was chosen to reduce the probability of type I errors and to identify only the most consistent regions of atrophy, hypometabolism, and hypoperfusion (Turkeltaub et al., 2002). The null hypothesis of random distribution was rejected for the voxels that exceeded this threshold. Results of the ALE analysis separately for AD and FTLT as well as a detailed description of the method applied are reported elsewhere (Schroeter et al., 2007, 2008, 2009).

Here, we compare and dissociate the neural correlates of AD and FTLT by combining and synthesizing these recent comprehensive meta-analyses. Accordingly, a conjunction analysis was conducted across results for AD and FTLT, separately for the different imaging approaches, namely MRI investigating atrophy and FDG-PET measuring changes in glucose utilization. Because the meta-analysis did not reveal any relevant study measuring changes in perfusion in FTLT, the conjunction analysis for AD and FTLT could not be performed for this imaging approach. A second conjunction analysis compared the results for the three imaging methods in AD alone. Here, a sufficient number of studies investigating atrophy (MRI), glucose utilization (FDG-PET), and perfusion (SPECT/PET) were available.

RESULTS

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

Table 1 illustrates the demographic and clinical characteristics of the different dementia cohorts involved in the meta-analysis. Note that we did not include subjects with amnesic MCI, because it is considered as a prodromal stage of AD and the FTLT subtypes may be associated with other non-amnesic prodromal stages such as dysexecutive MCI or mild behavioral (FTD) or language

impairment (PNFA and SD; Winblad et al., 2004). Further, we excluded studies focused on undifferentiated FTLD, where the specific subtype was not identified. Distribution of dementia subgroups in the meta-analyses corresponds with epidemiological reports, because AD is the most frequent dementia syndrome (Dubois et al., 2007; Schroeter et al., 2009), whereas FTLD represents the second most common diagnosis of dementia in individuals younger than 65 years (Schroeter et al., 2007). It is also well known that approximately half of all FTLD diagnoses are FTD cases; SD and PNFA account for one quarter each (Johnson et al., 2005).

An ANOVA including dementia subtype (AD vs. FTD vs. PNFA vs. SD) as a between subjects factor and method (MRI vs. FDG-PET vs. perfusion) as an additional factor revealed no influences of both factors on severity of dementia as measured by the mini-mental

state examination (MMSE) and no significant interaction between both factors (dementia subtype: $F = 1.4$, degrees of freedom, $df = 3$, $p = 0.40$; method: $F = 0.3$, $df = 2$, $p = 0.77$; interaction $F = 1.3$, $df = 3$, $p = 0.29$). One might conclude that the dementia subtypes did not show differences in dementia severity. The ANOVA for age showed a different result – namely the factor dementia subtype was significant ($F = 10.8$, $df = 3$, $p = 0.04$), whereas there was no significant impact of imaging methods or interaction between both factors ($F = 27.1$, $df = 2$, $p = 0.84$; $F = 0.62$, $df = 3$, $p = 0.61$). *Post hoc* analyses with unpaired Student's *t*-tests revealed that patients with AD were older than patients with FTD or SD ($T = -7.1$, $df = 22.2$, $T = -3.0$, $df = 39$). Furthermore, patients with PNFA were older than those with FTD ($T = -6.1$, $df = 9$; $p < 0.05$; other comparisons not significant; two tailed *p*, Bonferroni corrected and adjusted for inequality of variance if necessary). Age differences between groups are in accordance with the literature – in particular later age at onset in PNFA in comparison with other FTLD subtypes (Johnson et al., 2005) and increasing prevalence of AD with aging (Dubois et al., 2007; Schroeter et al., 2009). Because the original studies generally controlled for effects of age, no impact of age on the results of the meta-analysis was assumed.

Table 1 | Demographic and clinical characteristics.

Dementia subtype	Imaging methods	Number of studies	Number of subjects	Age (years)	MMSE
AD	MRI, PET, Perf.	26	826	70.4 ± 4.8	20.4 ± 2.8
FTD	MRI, PET	7	132	62.3 ± 2.1	20.1 ± 4.4
PNFA	MRI, PET	4	38	69.0 ± 0.8	23.0 ± 2.0
SD	MRI, PET	7	59	64.7 ± 3.1	23.2 ± 1.2

Mean ± SD. AD, Alzheimer's disease; Co, controls; FTD, frontotemporal dementia; MMSE, mini-mental state examination; MRI, magnetic resonance imaging; Perf., perfusion; PET, 18F-fluorodeoxyglucose-positron emission tomography; PNFA, progressive non-fluent aphasia; SD, semantic dementia.

NEURAL CORRELATES OF ALZHEIMER'S DISEASE AND FRONTOTEMPORAL LOBAR DEGENERATION

Figure 1 illustrates the neural correlates for the several dementia syndromes as revealed by the ALE meta-analysis. Results are shown for the three imaging methods separately. AD affected a temporoparietal and frontomedian-thalamic network. For FTLD, the meta-analyses specifically isolated the neural substrates for its three subtypes. FTD involved a frontomedian and thalamic

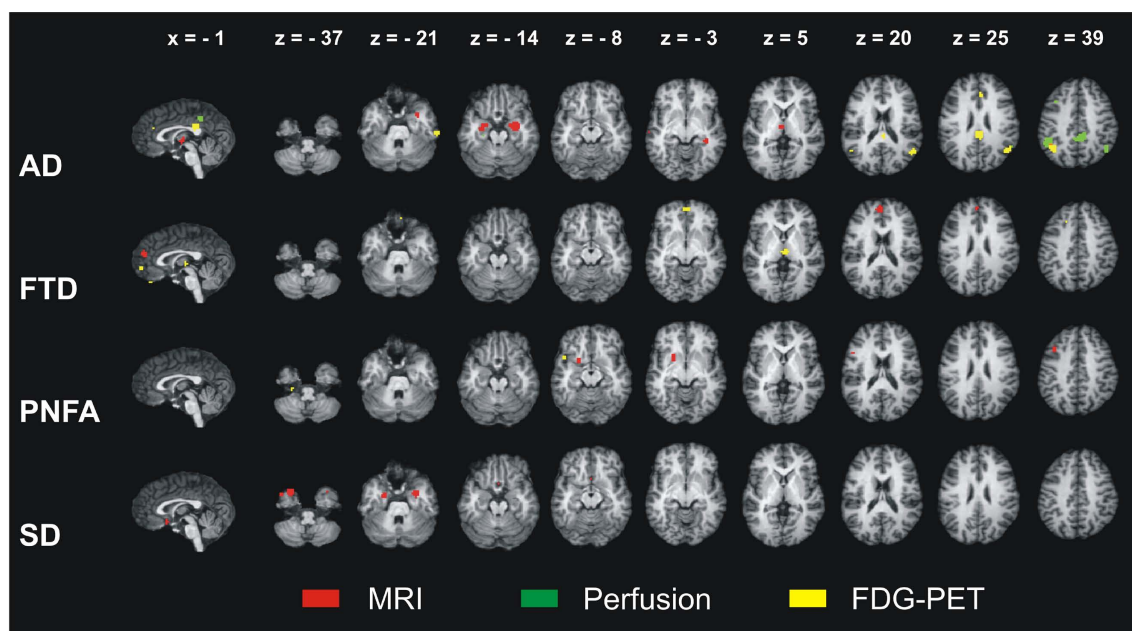


FIGURE 1 | Results of the ALE meta-analyses identifying the neural correlates of Alzheimer's disease (AD), frontotemporal dementia (FTD), progressive non-fluent aphasia (PNFA), and semantic dementia (SD). Atrophy as measured by magnetic resonance imaging (MRI) and decreases in glucose

utilization as measured by ^{18}F -fluorodeoxyglucose-positron emission tomography (FDG-PET) in patients compared with control subjects. For AD, reductions in perfusion are additionally shown (no studies available for FTD, PNFA, and SD). ALE – anatomical likelihood estimates. Coordinates in Talairach space. Left is left.

network. PNFA was related to a left frontotemporal network and the lentiform nucleus, whereas SD was associated with changes in the inferior temporal poles, amygdalae, and subcallosal area. Details of the involved anatomical structures and a discussion of their functional correlates may be found in Schroeter et al. (2007, 2009).

FIRST CONJUNCTION ANALYSIS – ALZHEIMER'S DISEASE VS. FRONTOTEMPORAL LOBAR DEGENERATION

Results of the conjunction analysis for the comparison between the neural correlates of AD and the three subtypes of FTLT are illustrated in **Figure 2**. Note that the conjunction analysis was conducted separately for the two relevant imaging approaches MRI and FDG-PET. Because the meta-analysis did not reveal any relevant study measuring perfusion changes in FTLT, this conjunction analysis could not be performed for this imaging approach.

In the final analysis, 578 patients with AD and 229 patients with FTLT were included. For detailed information with respect to the studies included see Schroeter et al. (2007, 2009). There were no significant differences of dementia severity as rated with the MMSE between AD and FTLT cohorts (see above). The conjunction analysis identified only one brain region bilaterally where atrophy as measured with MRI coincided in AD and the FTLT subtype SD (**Figure 2**, top). This region included the amygdala and hippocampal head. The other brain regions did not show any overlap in AD and the FTLT subtypes for atrophy (MRI) or glucose utilization (FDG-PET).

SECOND CONJUNCTION ANALYSIS – IMAGING IN ALZHEIMER'S DISEASE

The second conjunction analysis compared the neural correlates for AD alone as revealed by the respective three different imaging approaches, measuring either atrophy (MRI), glucose utilization (FDG-PET), or perfusion (SPECT/PET; **Figure 2**, bottom). Eight hundred twenty-six patients were included in this analysis. For detailed information with respect to the studies included see Schroeter et al. (2009). Regarding the AD cohorts of the studies applying the three different imaging approaches, there were no significant differences of dementia severity as rated with the MMSE. Again no impact of age on results of the conjunction analysis was assumed.

As illustrated in **Figure 2**, the analysis focusing on different imaging approaches in AD revealed a regional dissociation between atrophy as measured with MRI on the one side and hypoperfusion (SPECT/PET) and hypometabolism (FDG-PET) on the other side. Both hypoperfusion (SPECT/PET) and hypometabolism (FDG-PET) coincided in the angular and supramarginal gyrus (Brodmann area 39 and 40). Additionally, perfusion and metabolism were reduced in tightly adjoining areas in the inferior precuneus and posterior cingulate cortex (Brodmann area 7/31 and 23).

DISCUSSION

Together with our recent findings (Schroeter et al., 2007, 2008, 2009), the data suggest a specific dissociation of affected brain regions in AD and the three FTLT subtypes if different imaging

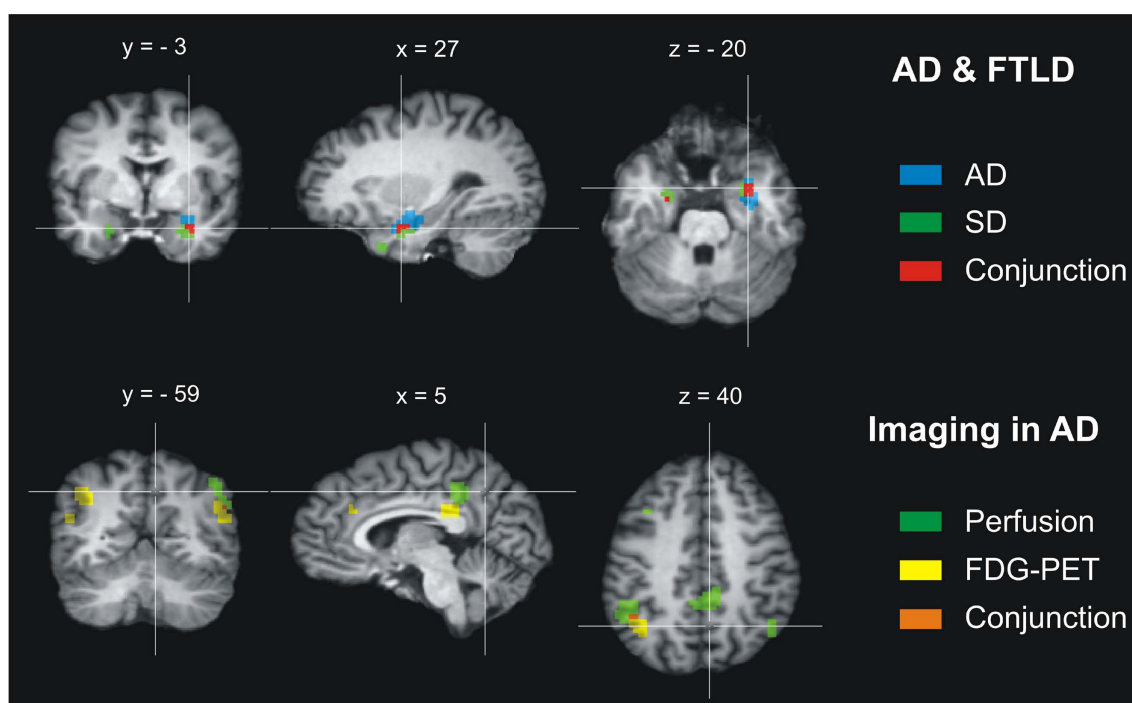


FIGURE 2 | Results of the conjunction analysis for Alzheimer's disease (AD) and frontotemporal lobar degeneration (FTLD). *Upper row:* Atrophic brain regions overlap in AD and the FTLT subtype semantic dementia (SD) in both amygdalae and hippocampal heads (maximum/cluster size: left -26 -9 $-18/27$ mm^3 , right 25 0 $-21/243$ mm^3). No further overlap of atrophy (MRI) or changes in glucose utilization (FDG-PET) was found for AD and the three FTLT

subtypes. *Lower row:* Abnormally low perfusion and glucose utilization overlap in AD in both angular and supramarginal gyri (left -47 -52 $40/135$ mm^3 , right 49 -58 $31/27$ mm^3) and affect tightly adjoining brain regions in the inferior precuneus and posterior cingulate cortex, whereas atrophy was regionally dissociated from these functional imaging measures. Coordinates in Talairach space. Left is left.

modalities are combined. MRI alone, if investigating atrophy, could not reliably dissociate AD and FTLN, because it revealed a common atrophic temporal brain region in AD and one subtype of FTLN, SD. However, this overlap might have no significant influence on reliable differential diagnosis in dementia syndromes if other imaging markers in AD such as abnormally low glucose utilization and perfusion in the parietal lobes (Figure 1, bottom) are carefully taken into account (Dubois et al., 2007; Drzezga et al., 2008). Moreover, high amyloid plaque load in AD in contrast, among others, to SD might contribute to differentiating dementia disorders, although to date no ALE meta-analysis can be performed across amyloid imaging studies due to their limited number (Dubois et al., 2007; Drzezga et al., 2008).

As MRI is more easily available than SPECT or PET in clinical settings, one might prefer a reliable imaging approach for the differential diagnosis of dementia syndromes based only on this method. In this context, the results of the second conjunction analysis are of particular interest – namely the regional coincidence of changes in glucose utilization and perfusion in AD (beside their dissociation from regional atrophy in agreement with former studies; see for instance Luckhaus et al., 2010). Accordingly, combining two MRI approaches, morphometric MRI, and arterial spin labeling (ASL) MRI measuring atrophy and changes in perfusion might yield sufficient information to dissociate AD and FTLN in the future (Alsop et al., 2010). Remarkably, a recent study underlines the importance of ASL in differentiating between AD and FTLN (Hu et al., 2010). In conclusion, due to its lack of specificity, structural MRI should be supported by other imaging modalities in the differential diagnosis of dementia.

Finally, one has to discuss the study's limitations and prospects. Beside the three subtypes of FTLN as suggested by the classification of Neary et al. (1998) future meta-analyses should also include other closely related dementia types, i.e., corticobasal degeneration, progressive supranuclear palsy, and logopenic aphasia, once enough studies are available (Gorno-Tempini et al., 2004; Rabinovici and Miller, 2010; Seelaar et al., 2011). Furthermore, the method applied has to be discussed critically. Because ALE meta-analyses generally include maxima and not cluster sizes of the various studies, they extract the prototypical, most characteristic neural networks representing the brain regions that are consistently involved in specific dementia syndromes. Accordingly, single studies might have shown that dementia disorders may affect other brain structures and may be regionally more unspecific than the present meta-analysis

suggests (see for instance Seeley et al., 2009; Dukart et al., 2010; Raczka et al., 2010). Consequently, in single imaging studies the regional overlap between AD and FTLN might be larger than suggested by our meta-analysis (particularly frontotemporal regions) – leading to generally less specific regional dissociations between both dementia syndromes. Moreover, the ALE meta-analysis might have missed parietal and posterior cingulate atrophy in AD as has been observed in single studies with MRI (Thompson et al., 2003).

However, for diagnostic purposes, the most consistent prototypical brain networks are of highest interest. Future classification systems for dementia require prediction, diagnosis, and differential diagnosis in individual subjects (Dubois et al., 2007; Hyman, 2007; Kipps et al., 2009). To address this issue we suggest focusing individual image analyses, for instance with support vector machine classification, on the regions-of-interest that have been identified in our studies based on independent large patient cohorts (Klöppel et al., 2008; Wilson et al., 2009). Indeed, we could show recently in our own patient cohort that the accuracy of the individual diagnosis of AD and FTLN can be improved by applying this method with multimodal imaging including MRI and FDG-PET (Dukart et al., 2011). These results supply first evidence that ALE meta-analytic based approaches may decisively improve the sensitivity and specificity in individual diagnosis of dementia syndromes – although results have to be confirmed by studies combining *in vivo* imaging with post mortem histopathological validation of dementia subtypes – to date the golden standard of dementia diagnosis.

In conclusion, our data together with other imaging studies suggest that combined brain imaging markers can reliably dissociate the most frequent neurodegenerative dementia disorders, AD, and FTLN. Results support the incorporation of standardized imaging inclusion criteria into future diagnostic systems, which will be crucial for early diagnosis and treatment in the future (Dubois et al., 2007; Hyman, 2007; Kipps et al., 2009).

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