Based on the network degeneration hypothesis: separating individual patients with different neurodegenerative syndromes in a preliminary hybrid PET/MR study

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Running title: Classification on neurodegenerative syndromes

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Abstract
The network degeneration hypothesis (NDH) of neurodegenerative syndromes suggests that pathological brain changes distribute primarily along distinct brain networks, which are characteristic for different syndromes. Brain changes of neurodegenerative syndromes can be characterized in-vivo by different imaging modalities. Our aim was to test the hypothesis whether multi-modal imaging based on the NDH separates individual patients with different neurodegenerative syndromes.

Methods: Twenty patients with Alzheimer’s disease (AD) and 20 patients with frontotemporal lobar degeneration (behavioral variant frontotemporal dementia (bvFTD, n=11), semantic dementia (SD, n=4), or progressive non-fluent aphasia (PNFA, n=5)) underwent simultaneous magnetic resonance imaging (MRI) and 18-fluorodeoxy-glucose positron emission tomography (FDG-PET) in a hybrid PET/MR scanner. The three outcome measures were voxel-wise values of degree centrality as a surrogate for regional functional connectivity, glucose metabolism as a surrogate for regional metabolism, and volumetric-based morphometry as a surrogate for regional grey matter volume. Outcome measures were derived from pre-defined core regions of four intrinsic networks based on the NDH, which have been demonstrated to be characteristic for AD, bvFTD, SD, PNFA, respectively. Subsequently, we applied support vector machine to classify individual patients via combined imaging measures, and results were evaluated by leave-one-out cross-validation.

Results: Based on multi-modal voxel-wise regional patterns, classification accuracies for separating patients with different neurodegenerative syndromes were 77.5% for AD vs. others, 82.5% for bvFTD vs. others, 97.5% for SD vs. others, and 87.5% for PNFA vs. others. Multi-modal classification results were significantly superior to uni-modal approaches.

Conclusion: Our finding provides initial evidence that the combination of regional metabolism, functional connectivity, and grey matter volume, which were derived from disease characteristic networks, separates individual patients with different neurodegenerative syndromes. Preliminary results suggest that multi-modal imaging
based on network degeneration hypothesis may generate promising biomarkers of neurodegenerative syndromes.

**Key words:** Neurodegenerative syndromes, Network degeneration hypothesis, Alzheimer’s disease, Frontotemporal lobar degeneration, Hybrid PET/MR
Introduction

Due to increasing loss of neuronal function and integrity, neurodegenerative syndromes result in dementia characterized by progressive cognitive and behavioral dysfunction (1). In line with clinical variation of distinct dementia syndromes (e.g. socio-behavioral and language symptoms stand out in frontotemporal lobar degeneration (FTLD), while memory and attention deficits dominate in Alzheimer’s disease (AD)), cumulative evidence suggests that neurodegenerative syndromes do not distribute randomly across the brain but primarily affect specific functional networks, corresponding roughly with cognitive-behavioral functions (2-5). The network degeneration hypothesis (NDH) of neurodegenerative syndromes suggests that both initiation and propagation of pathological changes are happening primarily along specific brain networks (4, 6, 7). Intrinsic brain networks are characterized by coherent ongoing activity at slow frequency (<0.1Hz) (8), and have been demonstrated to be candidates for such network-based pathology spread (4, 5, 7, 9, 10). Specifically, NDH suggests that each neurodegenerative disease may start in neuronal populations of preferentially targeted intrinsic network and progressively spread to connected regions within and then outside the network (4, 5, 9). Proteins, which are believed to be responsible for disease pathogenesis such as amyloid-ß and tau in AD, are known to disturb synaptic activity and axonal transport, which lead to a reduction in brain network integrity (11-14). In particular, it has been demonstrated that tau proteins may be able to travel across neurons, suggesting the expansion of pathology along connectivity pathways (12, 15).

Modern neuroimaging facilitates multi-modal in-vivo characterization of brain changes in neurodegenerative syndromes (16). For example FDG-PET and structural MRI, respectively, detect regional hypometabolism, which reflects lowered regional neural activity, and atrophy, which reflects neurodegeneration, and both procedures are used for individual diagnostics (17-19). Resting-state functional-MRI (rs-fMRI) facilitates the measurement of coherent ongoing brain activity, which reflects patterns of intrinsic functional connectivity including those of intrinsic brain networks (8, 20). Recently, based on these advances in neuroimaging, several biomarkers have been proposed to differentiate between various neurodegenerative syndromes in individual patients (18, 21).
However, neuroimaging-based distinction between neurodegenerative syndromes is a challenge, since valid large-scale models, which are both available for different syndromes and informative for macroscopic imaging, are rare (28).

At that point, we stated the question whether multi-modal neuroimaging based on NDH can separate individual patients with different neurodegenerative syndromes. To get initial evidence, we performed a preliminary study, which combines multi-modal imaging at a hybrid PET/MR scanner with ideas of NDH and canonical multi-variate pattern classification. Specifically, we focused on patients with AD and subtypes of FTLD, namely behavioral variant frontotemporal dementia (bvFTD), semantic dementia (SD), and progressive non-fluent aphasia (PNFA), and corresponding core regions of four intrinsic networks, which have been previously linked with these four syndromes based on NDH (4). Patients were assessed by resting-state functional magnetic resonance imaging (rs-fMRI), 18-Fluorodeoxyglucose positron emission tomography (FDG-PET), and structural MRI (sMRI) within one imaging session. We measured multi-modal properties of network cores including intrinsic functional connectivity, regional metabolism, and grey matter volume. Concretely, for each patient and for each network core, we calculated degree centrality (DC) as surrogate for intrinsic functional connectivity, regional FDG-glucose metabolism (MET) as surrogate for regional activity, and volumetric-based morphometry (VBM) as surrogate for regional grey matter volume. We hypothesized that such multi-modal properties separate individual patients with different neurodegenerative syndromes. To test this hypothesis, support vector machine (SVM) was applied to patterns of outcome measures in order to estimate classification accuracy of individual patients.
Material and Methods

Patients
Forty patients with dementia due to different neurodegenerative syndromes (20 AD, 11 bvFTD, 4 SD, 5 PNFA) were included in this hybrid PET/MR study. Summary of subjects' demographics and relevant clinical information is listed in Table 1 and the supplemental data.

Data acquisition and preprocessing
This study was registered and approved by the medical ethical board of Technische Universität München (TUM) in line with Human Research Committee guidelines of TUM. Scanning of patients at the hybrid PET/MR scanner and subsequent imaging data preprocessing followed standard protocols of our center, and have been described previously (details in the supplemental data) (29-31).

Definition of intrinsic network cores
Based on network degeneration hypothesis, AD, bvFTD, SD, PNFA and are associated with distinct intrinsic brain networks, which are preferentially affected in each disorder. It has been demonstrated that core regions of these networks overlap strikingly with peak atrophy in patients affected by the respective syndromes (4). We selected four core regions of each network, respectively, according to Seeley and colleagues: (i) for AD, right angular gyrus (RAng) of the default mode network with coordinates (52, -58, 36); (ii) for bvFTD, right fronto-insular cortex (RFI) of the salience network with (35, 24, 5); (iii) for SD, left temporal lobe (LT) of a temporal pole-anterior cingulate centered network with (-44, 14, -25); (iv) for PNFA, left inferior frontal gyrus (IFG) of left lateralized fronto-parietal "language" network with (-43, 15, 27). We used MarsBaR (http://marsbar.sourceforge.net) to create four spherical regions-of-interest (ROIs with 10mm radius) for each coordinate (Figure 1). Subsequently, measures for regional functional connectivity, metabolism, and grey matter volume were extracted from these cores for each patient.
Outcome measures

Degree centrality as surrogate for functional connectivity: Degree centrality of functional connectivity of a given region reflects the sum of all functional connectivity weights, which are connected to the region (32). We performed calculation of voxel-wise DC by canonical procedures as implemented in the REST toolkit (http://www.restfmri.net) (33). Specifically, for each subject, a whole brain DC map was obtained by calculating for each voxel i the sum of Fisher r-to-z normalized Pearson’s correlation coefficients $z_{ij}$ for all other voxels j of the brain. Subsequently, the voxel-wise DC values and the averaged DC values were extracted from each of the four core regions (RAng, RFI, LT, IFG) for each subject.

FDG-metabolism as surrogate for regional metabolism: Preprocessed FDG-PET images were scaled by normalization of whole-brain FDG uptake values to cerebellar vermis FDG uptake (34, 35) and were spatially smoothed using a Gaussian kernel full-width at half-maximum of 12 mm. Afterwards, from four core ROIs, we extracted voxel-wise FDG-metabolism values from the normalized FDG map of each subject. To be consistent with DC, we extracted the voxel-wise and the averaged FDG-uptake values.

Voxel-based morphometry as surrogate for grey matter volumes: To detect grey matter volume alterations within the four network cores, we followed a VBM protocol described in a previous study (29, 36). Briefly, we used the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm.html) to analyze grey matter volume. T1-weighted images were corrected for bias-field inhomogeneity, registered using linear (12-parameter affine) and non-linear transformations, and tissue-classified into grey matter, white matter, and cerebro-spinal fluid within the same generative model. Then, the resulting grey matter images were modulated to account for volume changes that result from the normalization process. We considered non-linear volume changes to control head size differences. Afterwards, our images were smoothed with a Gaussian kernel of 8mm (FWHM). To be consistent with DC and MET, we extracted the voxel-wise and averaged VBM values from core ROIs.
Multi-modal outcome measure: Voxel-wise multi-modal outcome measures were created by concatenating uni-modal voxel-wise measures, respectively, into corresponding vectors \(<DC, MET, VBM>_{vx}\). Voxel-wise multi-modal outcome vectors were of main interest in the study, since they preserve maximal imaging information.

Classification of individual patients
Support Vector Machine: Canonical SVM was used to classify individual patients based on their multi-modal voxel-wise outcome measures. The basic idea of SVM procedures is to construct a separating hyperplane between the training instances (outcome measures-of-interest) of two classes (i.e., two groups of patients such as patients with AD vs. others) (detail in the supplemental data) (37).

Validation of classification: Leave-one-out cross-validation was applied to validate SVM-based classification, i.e. for each round of training, one subject was removed from the two classes and used for testing while the remaining data was used for training (resulting in 40 rounds of validation). Across rounds of validation, classification accuracy is then the percentage of cases that were assigned correctly to the clinical diagnosis (18, 19, 38). The validity of classification was evaluated by following measures: accuracy, sensitivity, and specificity.

Control analyses
Non-voxel-wise multi-modal values: To control for the impact of multi-modality and voxel-wise account, correspondent averaged and/or uni-modal outcome vectors were defined. Specifically, to control findings for information loss due to averaging, \(<DC, MET, VBM>_{av}\) was defined and used for SVM-based classification. In addition, further correspondent uni-modal voxel-wise/averaged outcome vectors (e.g. \(<DC>_{vx}\) or \(<DC>_{av}\)) were used to control information loss due to ignoring multi-modal aspects of neurodegeneration-induced brain changes.

Classification analysis based a core region not derived from the NDH: In order to
evaluate group separating power of NDH-based regions versus non NDH-based regions, we extracted the voxel-wise uni-modal and multi-modal values from another ROI not derived from the NDH (i.e. the right primary motor cortex with coordinates (12, -16, 74) (39), then we applied SVM to compare the classification results from this ROI with the above-mentioned core regions.

Statistical comparison between multi-modal voxel-wise and non multi-modal/voxel-wise values: In order to evaluate group-separating power of multi-modal voxel-wise vs. ‘other’ approaches, we used the McNemar’s test to calculate the statistical significance between voxel-wise multi-modal <DC, MET, VBM>vx values and ‘other’ values (such as uni-modal averaged <DC>vx or <MET>vx or <VBM>vx) (40).
Results

For each neurodegenerative disease and corresponding network core, SVM together with leave-one-out cross validation was applied to voxel-wise multi-modal outcome measures \(<DC, MET, VBM>_{vx}\) in order to separate patients of the given disease from those of other syndromes (Table 2). Classification accuracies were 77.5% for AD vs. others, 82.5% for bvFTD vs. others, 97.5% for SD vs. others, 87.5% for PNFA vs. others.

To evaluate the use of multi-modal versus uni-modal voxel-wise outcome measures, we studied classification results based on uni-modal voxel-wise \(<DC>_{vx}, <MET>_{vx}, \text{ and } <VBM>_{vx}\) (Table 2). Results were as follows: for \(<DC>_{vx}\), 70% for AD vs. others, 70% for bvFTD vs. others, 77.5% for SD vs. others, 87.5% for PNFA vs. others; for \(<MET>_{vx}\), 72.5% for AD vs. others, 60% for bvFTD vs. others, 97.5% for SD vs. others, 85% for PNFA vs. others; for \(<VBM>_{vx}\), 32.5% for AD vs. others, 72.5% for bvFTD vs. others, 92.5% for SD vs. others, 82.5% for PNFA vs. others. Statistical comparisons revealed that the voxel-wise multi-modal classification results were superior to uni-modal approaches in separating individual patients. In particular, voxel-wise multi-modal \(<DC, MET, VBM>_{vx}\) accuracies were significantly different compared to \(<DC>_{vx}\) or \(<MET>_{vx}\) or \(<VBM>_{vx}\) for both AD and bvFTD groups, compared to \(<DC>_{vx}\) or \(<VBM>_{vx}\) for SD group, and compared to \(<MET>_{vx}\) or \(<VBM>_{vx}\) for PNFA group (p<0.05) (Table 2).

To evaluate the use of averaged versus voxel-wise multi-modal outcome measures, we assessed classification results based on averaged multi-modal \(<DC, MET, VBM>_{av}\). The accuracy results based on the averaged values were 72.5% for AD vs. others, 72.5% for bvFTD vs. others, 90% for SD vs. others, and 87.5% for PNFA vs. others, which were significantly lower than accuracies for corresponding voxel-wise values (p < 0.05), except of PNFA. In PNFA, averaged approach demonstrated already high classification accuracy. These results showed that averaged multi-modal outcomes performed worse than voxel-wise measures in separating individual patients.
To evaluate the impact of NDH-based versus non NDH-based ROIs for separating individual patients, group-separating power of a ROI outside NDH-based networks of interest was investigated. Classification results based on the voxel-wise multi-modal $\langle$DC, MET, VBM$\rangle_{v}$ values from a ROI in the primary motor cortex were 45% for AD vs. others, 60% for bvFTD vs. others, 90% for SD vs. others, 87.5% for PNFA vs. others, which were significantly lower ($p < 0.001$) than accuracies for corresponding NDH-based ROIs, except of PNFA.
Discussion
To test whether multi-modal imaging based on the brain network degeneration hypothesis might be useful to separate individual patients with different neurogenerative syndromes, we assessed patients with AD, bvFTD, SD, and PNFA in a hybrid PET/MR scanner. We defined the multi-modal voxel-wise outcome measure $<\text{DC, MET, VBM}>_{\text{vx}}$, which reflects regional degree centrality of functional connectivity, metabolism of regional activity, and voxel-based morphometry of grey matter volume. Based on core regions of four intrinsic brain networks, which are specific for patients’ syndromes, $<\text{DC, MET, VBM}>_{\text{vx}}$ classified individual patients accurately for their diagnostic category. These preliminary results demonstrate that combining advanced multi-modal neuroimaging with distinct network-based degeneration patterns separates individual patients of different neurodegenerative syndromes.

We found that $<\text{DC, MET, VBM}>_{\text{vx}}$ separated individual patients with AD, bvFTD, SD, or PNFA, respectively, with classification accuracy ranging from 77.5 to 97.5% (Table 2). $<\text{DC, MET, VBM}>_{\text{vx}}$ was defined as a concatenated vector based on three uni-modal outcome measures (e.g. $<\text{DC}>_{\text{vx}}$) (Figure 1). Uni-modal outcome measures, in turn, were derived from standard procedures of uni-modal imaging data analysis. Critically, $<\text{DC, MET, VBM}>_{\text{vx}}$ was restricted to regions, which were derived from disease specific intrinsic networks due to NDH \(4, 6\). To be independent from the current sample and circular analysis, exact coordinates of core regions were derived from a previous study \(4\). Recent findings provided overwhelming evidence that distinct intrinsic brain networks are primarily affected by different neurodegenerative syndromes, respectively \(4, 5, 7\). More specifically, several findings suggest that critical proteins of neurodegeneration such as tau spread in a prion-like trans-synaptic way along brain networks \(12, 13, 15\). Our finding of network core-based classification of individual patients with different neurodegenerative syndromes supports such network degeneration hypothesis; but beyond regional information, one should note that used imaging-based information of these cores is not specific to any of neurodegenerative
disorders, especially those with similar underlying pathologies like bvFTD, PNFA and SD.

Classification accuracies: Classification accuracies for different syndromes range from 77.5 to 97.5% (Table 2). These accuracies are comparable with or superior to those of similar studies. For example, a previous study applied VBM and diffusion tensor imaging (DTI) to separate FTLD subtypes (i.e. bvFTD, SD, and PNFA) from healthy controls. The authors revealed that DTI measurement, particularly radial diffusivity, provided better accuracies (67.6-81.4%) compared to grey matter atrophy (45.7-65.7%) or white matter atrophy (47.4-59.2%) (41). Moreover, Dukart and colleagues demonstrated classification accuracy of 60.0% using structural MRI, 80.0% using FDG-PET, and 94.3% using combined FDG-PET and structural MRI to separate AD from FTLD patients (18). This study supports our result that multi-modal imaging is superior to classify individual patients with different neurodegenerative syndromes. However, a recent study demonstrated that combination of rs-fMRI, DTI, and anatomical MRI did not significantly improve classification accuracy compared to the uni-modal measurements (27). Discrepancy between our results and these results might be due to different imaging modalities and their whole-brain versus our NDH approach. In addition, Tang and colleagues applied automated image-based classification procedure to separate patients with different neurodegenerative disorders using FDG-PET and spatial covariance analysis and achieved 84% sensitivity, 97% specificity for idiopathic Parkinson’s disease, 88% sensitivity and 94% specificity for progressive supranuclear palsy, and 85% sensitivity and 96% specificity for multiple system atrophy. This approach worked well with uni-modal imaging and does not require a priori knowledge of cores from NDH (42).

Multi-modal versus uni-modal outcome measures: In general, classification accuracies based on multi-modal outcomes <DC, MET, VBM>_vx were higher than those based on uni-modal measures such as <DC>_vx (Table 2). Uni-modal values separated syndromes with different success. For example <DC>_vx separated each disease with more than
70% accuracy, while $<\text{MET}>_v^x$ separated AD, SD, and PNFA but not bvFTD. The results were not robust for $<\text{VBM}>_v^x$, probably because our patients were in the mild to moderate stage of diseases. Together with successful multi-modal disease classification, this means that although uni-modal outcomes are partly different across syndromes, multi-modal values boost this difference. This finding suggests that pathological changes of specific syndromes are differentially reflected by different aspects of changes (i.e. changes in regional functional connectivity, activity, and brain structure), which are detected by different views into the brain. Therefore, our finding suggests that multi-modal and regionally specific imaging markers have a higher potential to serve as successful biomarkers for neurodegenerative syndromes. It’s worthy to note that for PNFA versus others, $<\text{DC}>_v^x$ accuracy equals that of multi-modal approach (87.5%). Similarly, for SD versus others $<\text{MET}>_v^x$ accuracy equals that of multi-modal approach (97.5%). These results may not be generalizable due to the small sample size of these groups but further studies with larger samples should focus on this issue i.e., for specific disorders such as PNFA and SD, specific imaging modality may provide comparable accuracy to that of the multi-modal approach.

**Voxel-wise versus averaged outcome measures:** Results indicate further that voxel-wise outcome measure has a better performance for classification than regional averaged measures. This finding suggests that within core regions, gradients of brain measures provide valuable information to separate syndromes. This point highlights the value of voxel-wise outcome measures, which are often ignored when using averaging procedures.

**Classification on a core region not derived from the NDH:** The classification results based on voxel-wise multi-modal $<\text{DC, MET, VBM}>_v^x$ from the motor core were worse than four cores derived from the NDH, particularly in AD, bvFTD, and SD groups. These findings support our hypothesis based on NDH and highlight the role of network abnormalities in pathophysiology of neurodegenerative diseases.
**Concatenated multi-modal outcome measures versus integrated measures:** It is noteworthy that we used simple concatenation to build multi-modal outcome measures. Concatenation preserves voxel-wise and multi-modal information but does not integrate measures to reflect physiologically relevant relationships across values. For example one might suggest that aberrant DC is systematically linked with aberrant local metabolism (30), and integrative values might reflect such link (e.g. spatial correlation between DC and MET) and can be used for classification (9). Future research is necessary to develop integrated measures of different aspects of activity, which are pathophysiologically relevant and valid for disease classification.

**Limitations and strength:** The current study has several limitations. First, the sample size of this study is small particularly in the FTLD subgroups, which limits the power of our findings. However, the prevalence of FTLD patients particularly of SD and PNFA is low so that it is difficult to recruit a large patient sample in a mono-centric study. Second, our findings are not validated for several aspects, which range from diagnostic validation to methodological-analytic issues. For example, validity of results depends critically on the validity of diagnosis of neurodegenerative syndromes (43), which should be optimally based on neuropathological findings; or, though leave-one-out cross validation of classification results was performed, validation of findings in an independent sample of patients might be helpful. Third, classification results might be biased, since clinical diagnostic procedures involved qualitative inspection of FDG-PET and structural MRI data. Forth, as mentioned above, our multi-modal outcome measure is only for regional, but not mechanistic-physiological aspects specific for different neurodegenerative syndromes. Fifths, applying this regional approach based on the NDH is not feasible for other neurodegenerative variants when prior knowledge of specific cores is unavailable. Taken theses points together, our study fulfills criteria of a preliminary study, which searches for initial evidence that combining network degeneration hypothesis and multi-modal imaging is helpful for individual patient separation in different neurodegenerative syndromes. On the other, hand our study has some strengths: first, the idea of combining the NDH and multi-modal imaging is simple.
Second, the NDH, which has been strongly confirmed by a huge amount of different studies, is applicable for different neurodegenerative syndromes. Third, to our best knowledge, this is the first study on FTLD patients using the simultaneous PET/MR measurement. Finally, applied analytical methods are well elaborated and widely used and available. Given the high intra-individual variability of neural functions, the simultaneous PET and MRI measurement in a single examination provides unique opportunities to study the relationship between different parameters in the same condition (29-31). However, separate MRI and PET imaging could be used also to assess metabolism, atrophy and connectivity in neurodegenerative syndromes successfully. In addition, FDG-PET imaging can be somehow substituted by blood flow marker such as arterial spin labeling (44, 45), which allows this technique to be applied to MRI-based studies when PET imaging is not available.

Conclusion
We provide preliminary evidence that multi-modal imaging and network neurodegeneration hypothesis together have the potential to yield pathophysiology-related imaging biomarkers for neurodegenerative syndromes.
Conflict of interest disclosures:
This work was supported by German Federal Ministry of Education and Research (BMBF 01ER0803 to C.S.), German research foundation (DFG) grants (Nr. DR 445/4-1 and DR 445/5-2 to A.D. and SFB 824 to M.S.), the Kommission für Klinische Forschung of the Klinikum Rechts der Isar der Technischen Universität München (KKF 8765162 to C.S), the BMBF (Federal Ministry of Education and Research, Germany): Competence Net Neurodegenerative Dementias (project: FTLD Consortium to J.D-S), and the German Academic Exchange service (DAAD) for financial support of M.T. The authors report no other disclosures relevant to the manuscript.

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References:


Figure 1. Study Flowchart. The main core region of each network was created based on previous study (4). Subsequently, the voxel wise values and the averaged values of three modalities were extracted from each core for all subjects. Then, support vector machine was applied to classify each patient. DC (degree centrality); MET (glucose metabolism); VBM (voxel-based morphometry); 18-fluorodeoxy-glucose positron emission tomography (FDG-PET); sMRI (structural magnetic resonance imaging); rs-fMRI (resting-state functional magnetic resonance imaging); SVM (support vector machine).
Table 1. Demographic and clinical data of patients

<table>
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<tr>
<th></th>
<th>AD (n=20)</th>
<th>bvFTD (n=11)</th>
<th>SD (n=4)</th>
<th>PNFA (n=5)</th>
<th>p-value</th>
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<td><strong>Age</strong></td>
<td>72.2 (8.7)</td>
<td>61.0 (9.6)</td>
<td>65.7 (6.0)</td>
<td>68.0 (7.9)</td>
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<td><strong>Gender (male)</strong></td>
<td>13</td>
<td>9</td>
<td>2</td>
<td>1</td>
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<td><strong>Duration of symptom (y)</strong></td>
<td>4.92 (1.9)</td>
<td>6.91 (4.5)</td>
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<td>3.60 (1.5)</td>
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<td><strong>MMSE</strong></td>
<td>22.03 (4.61)</td>
<td>23.73 (7.0)</td>
<td>18.75 (12.8)</td>
<td>19.00 (5.92)</td>
<td>0.062</td>
</tr>
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</table>

Group comparisons by ANOVA, except of gender with Kruskal-Wallis test. Abbreviations: AD, Alzheimer’s disease; SD, semantic dementia; PNFA, progressive non-fluent aphasia; bvFTD, behavioral variant frontotemporal dementia; MMSE, Mini–mental state examination. *p-value indicate the statistically significant difference between four groups using analysis of variance (ANOVA).
Table 2. Classification based on voxel-wise uni-modal and multi-modal outcome measures

<table>
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<tr>
<th>Measurements</th>
<th>Validity</th>
<th>AD vs. others (AD core)</th>
<th>bvFTD vs. others (bvFTD core)</th>
<th>SD vs. others (SD core)</th>
<th>PNFA vs. others (PNFA core)</th>
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<td>Acc (%)</td>
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<td>70</td>
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<td>&lt;DC&gt;vx</td>
<td>sens (%)</td>
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<td>spec (%)</td>
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<tr>
<td>&lt;DC, MET, VBM&gt;vx</td>
<td>sens (%)</td>
<td>80</td>
<td>54.5</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>spec (%)</td>
<td>75</td>
<td>93.1</td>
<td>97.2</td>
<td>100</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer’s disease; SD, semantic dementia; PNFA, progressive non-fluent aphasia; bvFTD, behavioral variant frontotemporal dementia; DC, degree centrality as proxy for regional functional connectivity; MET, glucose metabolism as proxy for regional activity; VBM, voxel-based morphometry as proxy for regional grey matter volume; vx, voxel-wise; Acc, accuracy; sens, sensitivity; spec, specificity. ‘Uni vs. multi’ and corresponding *p-value indicate the statistically significant difference between uni-modal (<DC>vx or <MET>vx or <VBM>vx) vs. multi-modal <DC, MET, VBM>vx values.
Based on the network degeneration hypothesis: separating individual patients with different neurodegenerative syndromes in a preliminary hybrid PET/MR study

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