Differential neurocognitive network perturbation in amnestic and aphasic Alzheimer disease

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Abstract

Objective

To determine if Alzheimer disease (AD) is associated with aphasic rather than amnestic dementias in certain circumstances related in part to perturbations in different networks.

Methods

Three groups were investigated: 14 participants suspected of having the neuropathology of AD based on clinically diagnosed amnestic dementia of the Alzheimer type (DAT), 26 individuals with primary progressive aphasia (PPA) with either a positive ¹⁸F-florbetapir amyloid PET scan or confirmed AD at autopsy, and 26 neurologically intact controls. The groups were compared using rs-fMRI. Seeds included the left hemisphere inferior frontal gyrus (IFG) for the language network, the left hippocampus for the episodic memory network, and the left posterior cingulate for the default mode network (DMN).

Results

Greater connectivity perturbations were found from the hippocampus for the DAT group and from the IFG for the PPA group. Furthermore, connectivity alterations in the PPA group were more asymmetric and favored the language-dominant left hemisphere. Loss of connectivity from the DMN seed was of a similar magnitude in the PPA and DAT groups.

Conclusions

Despite the presumptive common underlying neuropathology of amyloid plaques and neurofibrillary tangles, the 2 groups displayed 2 different patterns of network perturbation, each concordant with the clinical presentation and the anatomy of neurodegeneration.

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Glossary

A β = β -amyloid; **AD** = Alzheimer disease; **BOLD** = blood oxygenation level–dependent; **DAT** = dementia of the Alzheimer type; **DMN** = default mode network; **EPI** = echoplanar imaging; **IFG** = inferior frontal gyrus; **MNI** = Montreal Neurological Institute; **NC** = normal controls; **PCC** = posterior cingulate/precuneus; **PPA** = primary progressive aphasia; **rs-fMRI** = resting-state fMRI; **SUVr** = standard uptake value ratio.

In typical sporadic late-onset Alzheimer disease (AD), the core amnesic deficit is believed to arise in part due to an accumulation of pathology and atrophy of the medial temporal cortex, an episodic memory network hub. One atypical phenotype of AD, primary progressive aphasia (PPA), is characterized by language impairment with predominant accumulation of neuropathology and atrophy in the left hemisphere perisylvian language network.^{1,2} Patients with PPA-AD have the same characteristic neurofibrillary tangles and β -amyloid (A β) plaques as those with amnesic AD (dementia of the Alzheimer type [DAT]), albeit with a different spatial distribution.²

Selective vulnerability for the language network in PPA-AD and of the medial temporal memory network in DAT-AD has been well-characterized by atrophy and FDG PET hypometabolism.³ However, less is known about how the disruption of large-scale distributed networks that support cognition differ by AD phenotype. This study used resting-state fMRI (rs-fMRI) to examine network-level differences between aphasic vs amnesic AD phenotypes in 3 networks: the language network, episodic memory network, and default mode network (DMN). We hypothesized differences would be clinically concordant, with reduced connectivity of the language network in PPA, reduced connectivity of the episodic memory network in DAT, and no DMN connectivity differences between PPA and DAT because the DMN has no known domain-specific functional affiliation.

Methods

Participants

Twenty-seven individuals with a root diagnosis of PPA enrolled in Northwestern's PPA research program were included based on availability of (1) a T1-weighted structural and rs-fMRI scan, (2) positive ¹⁸F-florbetapir amyloid PET, and/or (3) AD at autopsy. Fifteen individuals with a clinical diagnosis of DAT and 26 normal controls (NC) of a similar age and education with identical MRI scans were included as comparison groups. NC participants were screened prior to enrollment for major medical conditions. The PPA and DAT participants were diagnosed by a neurologist based on clinical judgement and neuropsychological testing using previously described criteria.^{4,5} Briefly, the PPA diagnosis was based on identification of an isolated and progressive language disorder consistent neurodegenerative etiology. T2 fluid-attenuated inversion recovery scans were used to rule out the presence of vascular lesions.

Standard protocol approvals, registrations, and patient consents

Northwestern's institutional review board approved the study. Informed consent was obtained from each participant.

MRI and resting-state blood oxygenation level–dependent (BOLD) fMRI acquisition and analysis

Magnetic resonance scanning for all participants was performed on Northwestern's 3T Siemens (Munich, Germany) TIM Trio. A 1 mm³ T1-weighted magnetization-prepared rapid gradient echo and 10-minute echoplanar imaging (EPI) (3.0 × 1.7 × 1.7 mm³, repetition time 2.5 seconds, echo time 20 ms) were acquired. FreeSurfer was used for reconstruction and surface-wise rs-fMRI analysis. Preprocessing included rigid alignment for motion, slice-timing correction, and bandpass filtering (0.01–0.1 Hz). Motion-damaged brain volumes were censored based on a 0.3-mm frame displacement.⁶

Three dilated spherical surface seeds were chosen based on the areas of highest confidence in the network assignment by Ji et al.⁷ using the Glasser et al.⁸ parcels: left inferior frontal gyrus (IFG) (Montreal Neurological Institute [MNI] 305 –50, 22, 16) for the language network; left hippocampus (MNI 305 –25, –15, –20) for the episodic memory network; left posterior cingulate/precuneus (PCC) (MNI 305 –6, –50, 28) for the DMN. These fsaverage seeds were spherically warped to participant's native surface and projected into EPI volume space based on the surface-defined cortical ribbon and FreeSurfer's boundary-based registration from EPI to T1. BOLD contrast effect seed-to-vertex maps were calculated regressing the top 3 principal components of motion, CSF, and white matter.

Statistics

Differences in demographics and neuropsychological performance between groups were assessed with analysis of variance, 2-tailed independent 2-sample *t* tests, or χ^2 . For the seed-to-vertex analysis, a pseudo mixed effects analysis was performed using a weighted least squares random effects model, taking first level subject contrast effect variance to the group level.⁹ Cluster-wise corrections for multiple comparisons used Metropolis-Hastings Markov chain Monte Carlo simulations at a cluster-forming threshold of *p* < 0.01. The vertex-wise corrected statistical test results are displayed as clusters on FreeSurfer's template brain.

PET processing and analysis

Amyloid PET processing followed the current ¹⁸F-florbetapir standard.¹⁰ Briefly, statistical parametric mapping was used to

Table Demographic and clinical features of primary progressive aphasia (PPA), dementia of the Alzheimer type (DAT), and normal control (NC) groups

	PPA	DAT	NC	ANOVA <i>p</i> Value
No.	26	14	26	NA
Age, y	67.7 ± 7.1	71.7 ± 10.5	67.5 ± 7.1	0.154
% Male	53.8	42.9	50.0	NA
Education, y	16.3 ± 2.3	16.3 ± 3.3	15.7 ± 2.1	0.691
Symptom duration, y	5.4 ± 2.5	6.1 ± 2.6	Not applicable	NA
PPA subtype	PPA-L: 10, PPA-G: 11, PPA-U: 5	Not applicable	Not applicable	NA
MMSE, %				
All	65.1 ± 23.3	73.6 ± 12.1	99.6 ± 6.8	<0.001 ^{b,c}
PPA-L	61.3 ± 29.4			
PPA-G	72.4 ± 19.9			
PPA-U	56.7 ± 13.1			
WAB-AQ, %				
All	77.1 ± 15.4	NA	NA	NA
PPA-L	78.6 ± 13.5			
PPA-G	76.9 ± 29.2			
PPA-U	74.5 ± 11.1			
WAB-Rep, %				
All	59.9 ± 21.6	NA	99.1 ± 2.1	NA ^b
PPA-L	57.0 ± 22.9			
PPA-G	63.9 ± 21.6			
PPA-U	57.0 ± 22.1			
BNT, %				
All	52.4 ± 25.7	72.1 ± 27.2	96.7 ± 3.9	<0.001 ^{a,c}
PPA-L	59.5 ± 25.6			
PPA-G	55.8 ± 25.3			
PPA-U	30.7 ± 17.7			
PPVT, %				
All	87.2 ± 17.6	NA	98.6 ± 2.0	NA ^b
PPA-L	88.9 ± 11.4			
PPA-G	91.4 ± 11.3			
PPA-U	71.5 ± 35.4			
NAT-NAVS, %				
All	58.4 ± 22.2	NA	98.6 ± 3.4	NA ^b
PPA-L	73.9 ± 18.1			

Table Demographic and clinical features of primary progressive aphasia (PPA), dementia of the Alzheimer type (DAT), and normal control (NC) groups (*continued*)

	PPA	DAT	NC	ANOVA <i>p</i> Value
PPA-G	50.3 ± 22.0			
PPA-U	54.4 ± 18.9			

Abbreviations: ANOVA = analysis of variance; BNT = Boston Naming Test; G = agrammatic; L = logopenic; MMSE = Mini-Mental State Examination; NA = not available; NAT-NAVS = 15 noncanonical items from the Northwestern Anagram Test and 15 noncanonical items from the Northwestern Assessment of Verbs and Sentences used to measure grammatical sentence production; PPVT = Peabody Picture Vocabulary Test; U = unclassifiable; WAB-AQ = Western Aphasia Battery aphasia quotient; WAB-Rep = Western Aphasia Battery repetition subtest.⁵

Age, education, symptom duration, MMSE, WAB-AQ, WAB-Rep, BNT, PPVT, and NAT-NAVS are provided as means (±SD). Sex (male), MMSE, WAB-AQ, BNT, PPVT, and NAT-NAVS are provided as a percentage out of 100.

^a Two-tailed independent sample *t* test significantly different (*p* < 0.05) between all PPA and DAT.

^b Two-tailed independent sample *t* test significantly different (*p* < 0.05) between all PPA and NC.

^c Two-tailed independent sample *t* test significantly different (*p* < 0.05) between DAT and NC.

calculate the standard uptake value ratio (SUVR) with a florbetapir PET template and 6 bilateral regions: anterior and posterior cingulate, precuneus, medial orbital frontal, lateral temporal, and superior parietal.¹⁰ A conservative mean cerebral-to-cerebellar SUVR ≥ 1.17 threshold was used for amyloid positivity.¹⁰

Data availability

Anonymized data are available through our collaborative request process (brain.northwestern.edu).

Results

Of the 27 participants with PPA, suspicion or confirmation of AD was determined as follows: 12 received AD neuropathologic diagnosis at autopsy (of these, 5 also had a positive amyloid PET scan), and 15 were amyloid-positive on PET. Five participants with DAT came to autopsy showing high AD neuropathologic change. None of the autopsied cases had comorbid frontotemporal lobar degeneration pathology, which is consistent with previous reports.¹¹ One participant with PPA and 1 participant with DAT were excluded due to excessive motion,⁶ leaving 26 participants with PPA, 14 participants with DAT, and 26 NC for analysis.

There were no significant demographic differences (table; *p* > 0.05). Participants with PPA and participants with DAT did not differ in symptom duration or Mini-Mental State Examination score (*p* > 0.05). Consistent with their prominent aphasia, the PPA group was significantly more impaired than the DAT group on the Boston Naming Test (*p* = 0.021).

Participants with PPA had reduced connectivity compared to participants with DAT from left IFG seed to left angular gyrus, *f*.

Figure 1 Resting-state connectivity differences between primary progressive aphasia with suspected underlying Alzheimer disease (PPA) compared to dementia of the Alzheimer type (DAT)

rontal, and bilateral parietal lobule, while participants with DAT had reduced connectivity to occipital cortex and fusiform gyrus (figure 1A). From the left hippocampus seed, the PPA group had reduced connectivity relative to the DAT group for posterior parts of the middle and inferior temporal gyrus (figure 1B). The DAT group had more widespread reduced connectivity compared to participants with PPA across bilateral frontal and medial cortex.

The PPA and DAT groups showed no between-group differences for the left PCC DMN seed (figure 1C). This leaves at least 2 possibilities: both groups are not different from normal or both groups have similarly altered functional connectivity. To examine this, each group was compared to 26 NC and independently showed reduced connectivity for the left PCC seed (figure 2), supporting the notion that an altered DMN is common to both the aphasic and amnesic AD phenotypes.

Discussion

This study compared functional connectivity impairments in the aphasic vs amnesic variants of AD. The IFG node of the

left hemisphere language network displayed greater reduction of connectivity in the PPA vs DAT group. In contrast, the hippocampal node of the episodic memory network showed a more widespread pattern of reduced connectivity in the DAT compared to the PPA group. The amnesic and aphasic variants shared a common pattern and magnitude of reduced connectivity within the core DMN. The differential topography of network dysfunction provides further support for the contention that the clinical heterogeneity of dementia reflects the anatomy of functional perturbations rather than the molecular nature of the underlying neuropathology.^{1,12}

Two prior studies have examined functional connectivity differences between typical amnesic vs aphasic phenotypes of AD defined by amyloid PET.^{13,14} Results were consistent with our lack of difference in the DMN and showed mixed findings for the language network. Lehmann and colleagues¹³ found no differences in connectivity between aphasic vs amnesic AD in the language network, executive control network, visual network, or DMN. Whitwell et al.¹⁴ examined within-network coherence and found clinically concordant differences between AD phenotypes. Neither study examined the hippocampal node of the memory network.

Figure 2 Resting-state connectivity differences from the default mode network between primary progressive aphasia with suspected underlying Alzheimer disease (PPA) and dementia of the Alzheimer type (DAT) groups compared to normal controls (NC)

A limitation of the present study is the partial reliance on amyloid PET (53% of the participants) to identify AD status for participants with PPA. An important future direction will be studies of functional networks based on autopsy-proven cohorts.

Despite the fact that both aphasic and amnesic groups presumably have similar cellular neuropathology characterized by beta-amyloid and hyperphosphorylated tau,² they showed different physiologic network vulnerabilities. This report demonstrates the potential utility of using rs-fMRI to characterize the physiologic basis of clinical heterogeneity in neurodegenerative diseases.

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Disclosure

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Name	Location	Role	Contribution
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Jaiashre Sridhar, MS	Northwestern University, Chicago, IL	Author	Analyzed the data
Benjamin Rader, MPH	Northwestern University, Chicago, IL	Author	Major role in the acquisition of data

Continued

Appendix *(continued)*

Name	Location	Role	Contribution
Christina Coventry, MS, RN	Northwestern University, Chicago, IL	Author	Major role in the acquisition of data
Todd Parrish, PhD	Northwestern University, Chicago, IL	Author	Acquisition of MRI data, oversaw analysis of the data
M.-Marsel Mesulam, MD	Northwestern University, Chicago, IL	Author	Designed and conceptualized study, interpreted the data, revised the manuscript for intellectual content
Emily Rogalski, PhD	Northwestern University, Chicago, IL	Author	Designed and conceptualized study, interpreted the data, revised the manuscript for intellectual content

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