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The neuropsychological profiles and semantic-critical regions of right semantic dementia

Keliang Chen[a,1], Junhua Ding[b,1], Biying Lin[a], Lin Huang[a], Le Tang[a], Yanchao Bi[b], Zaizhu Han[b], Yingru Lv[c,*], Qihao Guo[a,**]

[a] Department of Neurology, Huashan Hospital, Fudan University, Shanghai, China
[b] State Key Laboratory of Cognitive Neuroscience and Learning, IDG/McGovern Institute for Brain Research, Beijing Normal University, Beijing, China
[c] Department of Radiology, Huashan Hospital, Fudan University, Shanghai, China

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ABSTRACT

Introduction: Previous literature has revealed that the anterior temporal lobe (ATL) is the semantic hub of left-sided or mixed semantic dementia (SD), whilst the semantic hub of right-sided SD has not been examined.
Methods: Seventeen patients with right-sided SD, 18 patients with left-sided SD and 20 normal controls (NC) underwent neuropsychological assessments and magnetic resonance imaging scans. We investigated the relationship between the degree of cerebral atrophy in the whole brain and the severity of semantic deficits in left and right-sided SD samples, respectively.
Results: We found the semantic deficits of right-sided SD patients were related to bilateral fusiform gyri and left temporal pole, whilst the left fusiform gyrus correlated with the semantic performance of left-sided SD patients. Moreover, all the findings couldn't be accounted for by total gray matter volume (GMV) or general cognitive degradation of patients.
Discussion: These results provide novel evidence for the current semantic theory, that the important regions for semantic processing include both anterior and posterior temporal lobes.

1. Introduction

Semantic dementia (SD) is a variant of progressive primary aphasia which is characterized by the specific semantic loss and preserved abilities of other cognitive functions (Gorno-Tempini et al., 2011; Hodges and Patterson, 2007). Its typical neuroanatomical feature is severe brain atrophy of the anterior temporal lobes (ATL) in both hemispheres (Gorno-Tempini et al., 2004a; Mummery et al., 2000).

According to the predominant atrophy hemisphere, this disorder can be split into two sub-types: left and right-sided SD. Their difference not only exists in the atrophy pattern, but also in the neuropsychological performance. Left-sided SD patients exhibit more naming and comprehension changes, whereas right-sided SD individuals suffer from more behavioral and face recognition problems (Brambati et al., 2009; Josephs et al., 2009; Seeley et al., 2005; Thompson et al., 2003).

Nevertheless, compared with left-sided SD, patients with right-sided SD are relatively rare. A study of a large series of consecutive SD patients found that only 25% cases were predominantly right-sided (Hodges et al., 2010). Therefore, sample size is a common limitation for research investigating right-sided SD. Until now, most research are still case studies (Brambati et al., 2009; Gorno-Tempini et al., 2004b; Joubert et al., 2004; Seeley et al., 2005; Snowden et al., 2012) and investigations with small samples (Kamminga et al., 2015; Kumfor et al., 2016). Only a few studies recruited big samples of right-sided SD (Binney et al., 2016; Chan et al., 2009; Hodges et al., 2010; Snowden et al., 2017). For example, Chan et al. (2009) collected 20 right-sided SD patients and compared their imaging and neuropsychological data with left-sided SD patients. Although these studies are excellent, further work is needed to use comprehensive assessments and voxel-based brain analyses to gain a better understanding of right-sided SD patients. Moreover, severity-matched groups and mild cases would be also required.

In fact, SD is thought to be direct evidence for the hub-plus-spoke model, which emphasizes the vital role of the ATL in semantic processing (Patterson et al., 2007; Ralph et al., 2017). Considerable studies have explored the semantic hub in SD individuals (Ding et al., 2016;

* Correspondence to: Y. Lv, Department of Radiology, Huashan Hospital, Fudan University, 12 Wulumuqi Zhong Road, Shanghai 200040, China.
** Correspondence to: Q. Guo, Department of Neurology and Institute of Neurology, Huashan Hospital; Fudan University, 12 Wulumuqi Zhong Road, Shanghai 200040, China.
E-mail addresses: xxzlyr@163.com (Y. Lv), dr.guoqihao@126.com (Q. Guo).
[1] These authors contributed equally to the manuscript.

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Mion et al., 2010). Using strict regressions, they have demonstrated that the fusiform gyrus underpinned SD's semantic deficits. It's important to note that these studies only used left-sided or mixed SD cohorts, which might miss the chance to identify other areas. For example, floor and ceiling effects would occur in the left temporal pole and right fusiform gyrus, respectively. Indeed, right-sided SD patients also suffer from severe semantic deficits. Thus, investigating these patients would resolve the above issue and contribute to the understanding of semantic theory. To our knowledge, the semantic hub of right-sided SD has not been systematically examined.

In our study, we applied comprehensive neuropsychological assessments and voxel-wised imaging scans in 17 cases of mild right-sided SD and 18 cases of mild left-sided SD with comparable severity. Then we explored the neuropsychological deterioration, atrophy pattern and semantic-related areas of these two groups. We assumed that (1) both groups would present with severe semantic deficits; (2) left-sided SD group would present with more severe language problems than right-sided SD group; (3) in right-sided SD sample, the semantic-related regions would include other regions such as the temporal pole beyond the fusiform gyrus. In summary, by using a big sample of right-sided SD patients, our study identifies their comprehensive characteristics and provides new evidence for the semantic model.

2. Method

2.1. Subjects

Thirty-five SD patients were identified from the memory disturbance clinic of neurology department at Huashan hospital, Shanghai. The inclusion criteria included: reaching the current diagnostic criteria of SD (Gorno-Tempini et al., 2011), mild severity (MMSE > 18), > 6 years of education and completing neuropsychological assessments and MRI scans. Moreover, we measured the severity of white-matter hyperintensity through the Fazekas Scale (Fazekas et al., 1987) using T2 images. All subjects' periventricular hyperintensity (PVH) scores and deep white matter hyperintensity (DWMH) scores were ≤1. Thus, no subjects were excluded for the white-matter hyperintensity.

Twenty normal controls (NC) were recruited from the community, whose age, gender and education were matched with patients. All subjects were right-handed (measured by Edinburgh Handedness Inventory; Oldfield, 1971), native Chinese speakers with normal or corrected audition and vision and no psychiatric disease. Informed consent was obtained from all individual participants.

2.2. Neuropsychological tests

All subjects underwent routine clinical assessments (Guo and Hong, 2013) including domains of general cognitive function (MMSE & Memory and Executive Screening), episodic memory (Auditory Verbal Learning Test & Rey-Osterrich Complex Figure Test: long-delayed recalling), language (Similarity test, Boston naming test & Animal Verbal Fluency Test), attention (Symbol Digit Modalities Test), working memory (Digital Span Test), executive function (Trail Making Test & Stroop Color-Word Test), visuospatial skills (Rey-Osterrich Complex Figure Test: copy & Point Size Judgment Test), social cognitive function (Reading the Mind in the Eyes Test) and calculation (Exact Calculation, Magnitude Comparison & Proximity Judgment; see Table 1).

In addition, a comprehensive battery was used to examine semantic and non-semantic functions (Chen et al., 2017; Ding et al., 2016), including picture naming, facial verification, sound naming, naming to definition, picture associative matching, word associative matching, word-picture verification, word reading, repetition and picture description (see Table 1 and Supplementary material for details).

2.3. Image acquisition

Subjects were scanned in a 3 T MAGNETOM Verio MRI scanner. MPRAGE T1 weighted images were obtained with the following parameters: sagittal orientation, repetition time = 2300 ms, echo time = 2.98 ms, flip angle = 9°, matrix size = 240 × 240,field of view = 240 × 256 mm, slice number = 192, slice thickness = 1 mm, voxel size = 1 × 1 × 1 mm^3.

2.4. Image preprocessing

T1-weighted images were first resampled to 1.5 × 1.5 × 1.5 mm^3 and segmented into gray matter, white matter and cerebrospinal fluid using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/). Next, images were normalized into the Montreal neurological institute (MNI) space. Then, gray matter volume (GMV) images were generated via affine transformation and non-linear warping, and smoothed using an 8-mm full-width at half-maximum Gaussian kernel. One patient was excluded due to the poor image quality.

2.5. Classification of patients

We first divided SD patients into left and right-sided groups according to the atrophy degree of bilateral ATLs qualitatively and then verified our classification results with the laterality index, which was evaluated by the formula: (Right ATL GMV- Left ATL GMV)/(Right ATL GMV + Left ATL GMV). The ATL was defined by the regions of temporal poles in the Automated Anatomical Labeling (AAL) Atlas (Tzourio-Mazoyer et al., 2002). A positive index value indicates a patient suffers from left-sided SD, and vice versa. Specifically, one patient was classified as left-sided SD by visual inspection due to bad quality of her T1-weighted image.

2.6. Statistical analyses of demographic and neuropsychological variables

We used SPSS19.0 (IBM Corp., Armonk, NY) to carry out these analyses. One-way analyses of variance were employed to reveal the differences among left, right-sided SD and NC groups. Then, we adopted post-hoc comparisons with the least significant difference (LSD) method. Specifically, gender was compared using a Chi-square test.

To measure the semantic performance of patients, principle component analysis (PCA) was conducted across all the battery tasks in left and right-sided SD groups respectively. We only extracted the factors whose eigenvalues were > 1, rotated them using the varimax method and calculated factor scores with the regression model. The factor score with high loadings on semantic tasks was considered as the semantic measure for further analyses.

2.7. Statistical analyses of imaging variables

All the analyses were performed using Resting-State fMRI Data Analysis (REST) (Song et al., 2011) and corrected with the Gaussian random field (GRF) theory (voxel $p < 0.001$ and cluster $p < 0.05$) for multiple comparisons.

First, to identify the atrophy patterns of left and right-sided SD, the GMV images were compared using two-sample *t*-tests between each of SD groups and NC.

Next, to determine the critical regions of semantic processing in left and right-sided SD patients, we correlated the GMV images with the semantic PCA scores controlling age, gender and education in these two groups, respectively. Furthermore, total GMV and MMSE scores were used as nuisance covariates to eliminate their potential bias. In order to explore the influence of floor and ceiling effects on our data, the mean volumes of significant clusters in right and left-sided SD groups were further compared among three groups using one-way analyses of variance.