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Quantitative Meta-Analysis of Gray Matter Abnormalities in Semantic Dementia

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Abstract. Cumulative evidence of gray matter abnormalities in semantic dementia (SD) has been reported using voxel-based morphometry (VBM). However, these studies have not been reviewed quantitatively. To estimate gray matter changes in SD quantitatively, we systematically searched whole-brain VBM studies comparing SD patients with healthy controls in the PubMed, ISI Web of Science, and EMABSE databases from January 1990 to August 2011. Coordinates with significant differences between the gray matter volumes of SD patients and healthy controls were extracted from clusters. Meta-analysis was performed using anatomic likelihood estimation. Seven studies, with 68 SD patients and 167 healthy controls, were included. Gray matter volume reductions were found in bilateral fusiform and inferior temporal gyri, extending to the medial portion of the temporal lobes (including amygdala and parahippocampal gyri), left temporal pole, middle temporal gyrus, and caudate. No significant increase in gray matter volume was found. Our findings provide strong evidence of atrophy in bilateral temporal lobes with predominate impairment on the left side, parahippocampal gyrus/amygdala, and left caudate, representing the pathophysiology of SD.

Keywords: Frontotemporal lobar degeneration, magnetic resonance imaging, meta-analysis, semantic dementia

INTRODUCTION

Semantic dementia (SD), a variant of frontotemporal lobar degeneration (FTLD), is characterized by the progressive deterioration of semantic knowledge and progressive aphasia [1]. The impairment pattern in SD presents a typical multimodal semantic impairment and profound anomia with relative preservation of syntactic and phonological processes, day-to-day memory, and visuospatial skills [2, 3]. However, behavioral disturbances of frontotemporal dementia, such as personality and eating habit changes, loss of empathy, and compulsions, eventually develop in the later course of the disease [1, 4, 5].

Over recent decades, the brain changes that mediate the clinical syndrome were identified by structural neuroimaging studies [6–8]. Most of these studies use the region of interest (ROI) approach, which indicated that SD is associated with anatomical damage to the temporal lobe with an anteroposterior gradient and the most significant change occurring in the anterior part of the temporal lobe [9–11]. However, ROI studies are limited because only a few studies have examined gray matter anomalies outside the temporal regions [10, 12].

A recently developed whole-brain voxel-based technique, called voxel-based morphometry (VBM), is a semi-automated, time-efficient, operator-independent, and unbiased analytical technique [13], which allows voxel-wise comparisons of the local density or volumes of gray matter (GM) and white matter between groups without having to specify *a priori* ROIs [13, 14]. From a whole-brain perspective, VBM studies on SD have confirmed the changes in the temporal lobes, which are consistent with the results identified by functional neuroimaging methods [6, 8]. These studies have also accumulated pieces of evidence on changes occurring outside the temporal lobes, which have enhanced our

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understanding of the neuropathology of SD. However, the findings of these studies have been controversial. For instance, automated VBM or manual volumetry performed on SD patients demonstrated significant atrophy of the hippocampus [8, 12], whereas some other studies did not [15, 16]. Some studies also tried to find GM abnormalities in the frontal lobes but failed, whereas atrophy of frontal lobes was identified in other studies but in different regions [8, 16, 17]. However, the sample sizes of these VBM studies on GM volume (GMV) changes in SD are often small, resulting in insufficient statistical power. Therefore, a quantitative meta-analysis of the VBM literature is necessary to reveal whole-brain GM changes in SD.

The anatomic likelihood estimation (ALE) method is a powerful voxel-based meta-analytic technique originally designed for functional neuroimaging studies [18]. ALE is also appropriate for anatomical image datasets, such as those in VBM [19–21] and diffusion tensor imaging studies [22]. This work aims to timely review systematically and voxel-wisely meta-analyze the VBM studies using the revised ALE method [22] to obtain robust whole-brain GM changes in SD. This analysis is expected to reveal the abnormalities in a distributed network of frontal, temporal, and limbic regions in SD.

MATERIALS AND METHODS

Inclusion of studies

A systematic search of the PubMed, ISI Web of Science, and EMBASE databases from January 1998 to August 2011 was conducted. The keywords used were (“semantic dementia”) and (“voxel*”, “voxel-wise”, “voxel-based”, “VBM”, “morphometry”). The references of the relevant articles were also searched for additional studies.

Selection of studies and extraction of data

A study was considered for inclusion if it 1) reported a VBM (GMV or GM density comparison between SD patients and healthy control (HC) subjects); 2) reported whole-brain results of changes in standard Talairach or Montreal Neurological Institute (MNI) stereotactic spatial coordinates; 3) used significance thresholds corrected for multiple comparisons or uncorrected with spatial extent thresholds; and 4) was peer-reviewed and published in English. When the same author name, similar characteristics of participants, and data appeared in two or more publications, the study with the most complete data description was selected to avoid repetitive data. For similar studies, which have met the aforementioned inclusion criteria but had overlapping data, the study with the largest sample size was selected.

A study was excluded if 1) the whole-brain results of changes in stereotactic coordinates were not obtained even after corresponding with the authors by phone or e-mail; 2) its data overlapped with those of another article; 3) some results were uncorrected and the spatial extent threshold was not reported; or 4) no HC group was used. The method used in the current study was based on the Meta-analysis of Observational Studies in Epidemiology guidelines for meta-analyses of observational studies [23]. The coordinates in each study were independently extracted by two neurologists (namely, Jing Yang and PingLei Pan) based on the ALE method [24, 25].

ALE meta-analysis of VBM studies

Voxel-based meta-analysis was performed on selected studies using ALE software [25] (Ginger ALE 2.0.4, http://www.brainmap.org/) to compare the VBM changes between the SD patients and HC subjects. A standardized atlas (MNI or Talairach spaces) was identified for each study and used to convert the coordinates. The coordinates reported in the MNI spaces in the selected studies were converted into Talairach coordinates using the Lancaster transform, icbm2tal [25], as implemented in Ginger ALE 2.0.4. The coordinates reported in the Talairach space in the selected studies which had been transformed into Talairach spaces using Brett transformation, were converted back to MNI space and subsequently converted into Talairach spaces using icbm2tal [25] based on the Lancaster formula in Ginger ALE 2.0.4 (http://brainmap.org/ale/index.html).

Stereotactic loci were modeled as the center of a probability distribution and summed across studies to identify the most consistently reported voxels as showing significant differences between groups. The full width at half maximum (FWHM) was set according to a quantitative uncertainty model described in a previous study [25]. A total of 5,000 permutations were performed using FWHM, which was calculated using the number of subjects in each experiment. The threshold was set at $p < 0.05$ for statistical significance and clusters of suprathreshold voxels exceeding 200 mm^3. The ALE maps were overlaid onto a high-resolution brain template Colin1.1.nii in the Talairach space

(http://www.brainmap.org/ale) for visualization using Mango (http://ric.uthscsa.edu/mango/).

RESULTS

Included studies and sample characteristics

The search strategy identified 127 studies. Among which, seven VBM studies [8, 15–17, 26–28] reporting eight SD–HC comparisons (one study included two SD groups as shown in Table 2) met the inclusion criteria. These studies compared the whole-brain differences of 68 SD patients with 167 HCs. A flow diagram of the identification and attrition of studies is provided in Table 1. The VBM studies and demographic characteristics of the participants are shown in Table 2. In each study, the diagnosis of SD was based on the published criteria [2], and no significant difference was found in terms of the ages and genders of the SD and HC groups.

Ten clusters were identified in the ALE meta-analyses under false discovery rate $p < 0.05$ and voxels >200. As illustrated in Fig. 1 and Table 3, GMV decreases were mainly found in the anterior temporal lobes, which consist of the left temporal pole (BA 38) and middle temporal gyrus, bilateral inferior temporal (BA 20) and fusiform gyri (BA 20), and the parahippocampal gyrus/amygdala. Moreover, a GMV decrease was also identified in the left caudate. No GMV increase was found in the brain regions of SD patients.

The effect of the statistical threshold chosen for the generation of ALE maps was examined. The use of a more conservative threshold ($p < 0.01$) revealed similar results, except that cluster volumes were generally smaller and hence required the consideration of clusters under 200 mm^3.

Table 1
Searching strategies

Number of studies	Description of the criterion
127	Original searching using keywords
124	Published in English and about human subjects
89	Titles and abstracts screened for SD
72	About voxel-based morphometry on gray matter
19	Full articles screened for patients with semantic dementia versus healthy controls
10	Report whole-brain results of changes in stereotactic coordinates
7	Exclude studies with overlapped sample or with insufficient data

DISCUSSION

This study pooled VBM studies for the meta-analysis of GMV differences between SD patients and HCs. The meta-analysis found that SD patients had asymmetric and broader GMV reductions in the bilateral parahippocampal gyrus/amygdala and left caudate as well as in the bilateral temporal lobes. The finding provides strong evidence that broader GM atrophy is involved in SD, although temporal lobe atrophy plays a key role in the mediation of semantic deficit in SD.

In this study, the bilateral inferior temporal lobes, including fusiform and inferior temporal gyri, are the

Table 2
Characteristics of included studies and participants in the meta-analysis

No. study	Number of subjects (female)	Mean age	Average MMSE	Scanner (T)	Thickness (mm)	FWHM (mm)	Number of foci
1. Desgranges, 2007 [8]	SD:10(NA)	65.7 (8.6)	24.2 (3.08)	1.5	1.5	12	6
	HC:17(NA)	65.8 (7.4)					
2. Grossman, 2004 [15]	SD:8(NA)	65.5 (13.0)	23.8 (4.6)	1.5	1.3	12	4
	HC:12(NA)	68.5 (9.4)					
3. Libon, 2009 [13]	SD:10(NA)	66.10 (10.77)	25.10 (3.75)	3/1.5	1.0/1.3	4	7
	HC:43(NA)	NA					
4. Mummery, 2000 [18]	SD:6(5)	60.5	NA	2	NA	12	17
	HC:14(9)	62					
5. Pereira, 2009 [32]	SD:8(4)	62.9 (6.40)	21.0 (5.86)	1.5	NA	8	2
	HC:25(11)	63.8 (7.20)					
6. Brambati, 2009 [19]	SD(LTLV):13(4)	62.0 (6.3)	22.0 (6.9)	1.5	1.5	12	15
	SD(RTLV):6(3)	62.5 (5.8)	21.2 (7.0)				15
	HC:25(16)	64.8 (6.9)					
7. Ash, 2009 [33]	SD:7(NA)	66.8 (7.3)	22.5 (8.2)	1.5/3	NA	8	3
	HC:31(NA)	Matched					

Key: HC, healthy controls; MMSE, Mini-Mental State Examination; SD, patients with semantic dementia; FWHM, full width at half maximum; NA, not available; LTLV, left temporal lobe variant of semantic dementia; RTLV, right temporal lobe variant of semantic dementia.

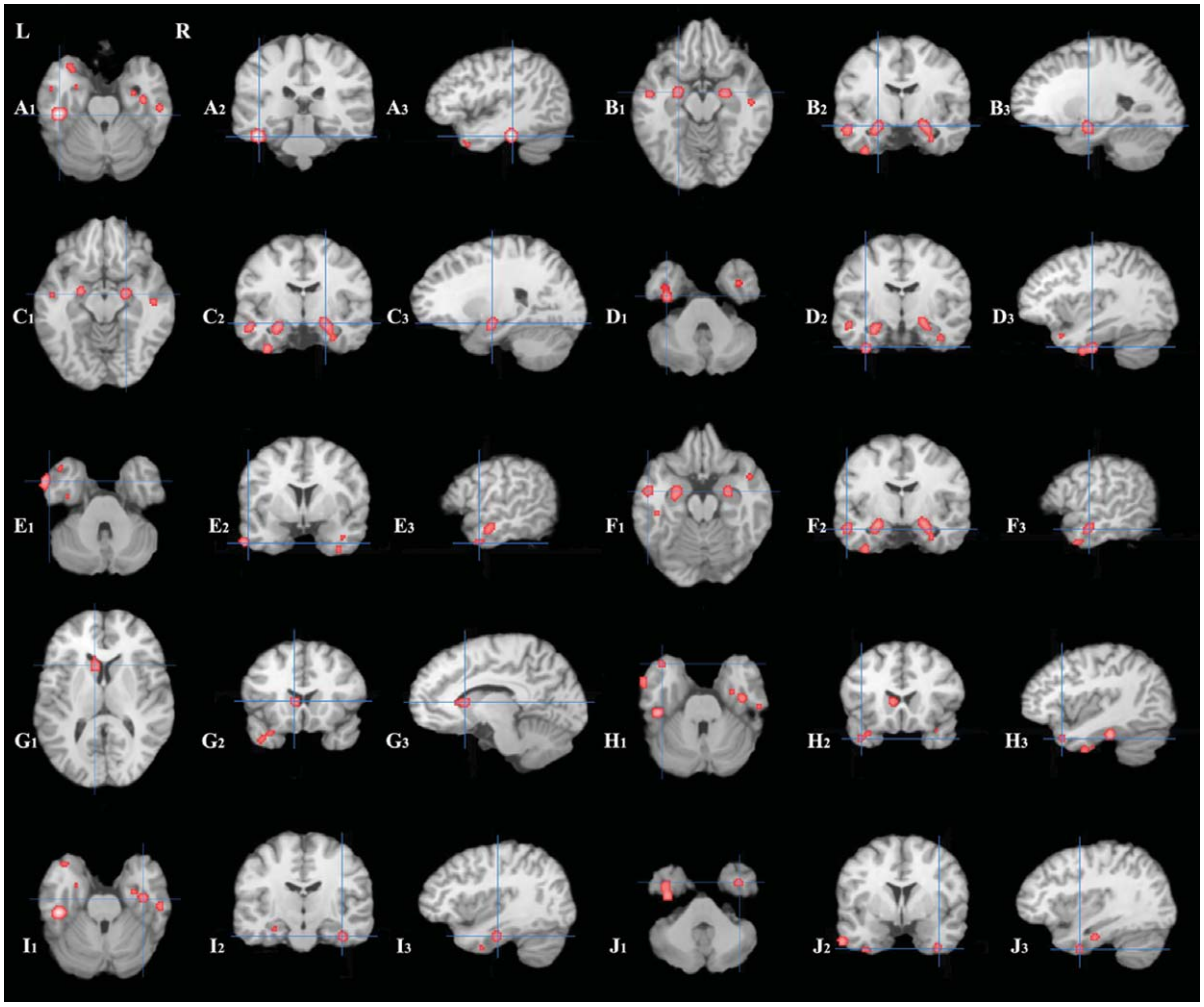

Fig. 1. Axial, coronal, and sagittal sections for GMV reductions in SD patients compared with healthy controls. The images labeled A to J correspond to the results listed in Table 3.

Table 3
GMV reduction in SD patients via anatomic likelihood estimation meta-analysis ($p < 0.05$)

Cluster	Volume (mm^3)	Peak ALE value (10^{-2})	Talairach coordinates X	Y	Z	Location	# of studies contributed to the cluster
A	1106	1.88	–42.57	–31.02	–23.81	Left fusiform gyrus (BA 20).	1, 2, 4, 6.
B	1048	1.18	–23.95	–10.52	–17.24	Left Parahippocampal Gyrus/Amygdala	1, 2, 4, 6, 7
C	1008	1.11	23.81	–11.04	–15.69	Right amygdala (BA20)	1, 4, 6
D	792	1.21	–33.96	–10.06	–37.22	Left parahippocampal/amygdale, and inferior temporal gyrus (BA 20).	1, 3, 4, 5, 6
E	576	0.98	–50.65	–9.96	–17.79	Left middle temporal gyrus (BA 21)	1, 4, 6
F	512	1.12	–7.06	14.08	7.26	Left middle temporal gyrus (BA 21)	1, 3, 6
G	408	0.88	–34.6	13.58	–25.65	Left caudate	1, 4, 6
H	352	1.05	38.4	–17.07	–26.33	Left temporal pole (BA38)	1, 2, 3, 4, 6, 7
I	344	1.20	–54.55	–2.2	–30.24	Right fusiform (BA20)	1, 4, 6
J	200	0.92	35.12	–2.18	–37.61	Right inferior temporal gyrus (BA 20)	1, 3, 4, 6, 7

Key: SD, patients with semantic dementia; HC, healthy controls; MMSE, Mini-Mental State Examination; FWHM, full width at half maximum; NA, not available; LTLV, left temporal lobe variant of semantic dementia; RTLV, right temporal lobe variant of semantic dementia.

key regions of GMV reduction. This result is also supported by previous functional imaging studies and pathological studies on SD [6, 8, 10, 29]. In addition, postmortem studies revealed that fusiform and inferior temporal gyri suffer from neuronal loss across all histopathological subtypes of SD [29]. These areas are involved in language and semantic processing [10, 30] and face and object recognition [31]. Therefore, this structural impairment contributes to the symptoms and pathogenesis of SD.

The bilateral temporal poles have been suggested as one of the three-part neural network that supports semantic cognition, which consists of the left prefrontal cortex, temporoparietal junction, and bilateral temporal poles [32]. A significant slowing down on semantic tasks was observed when rTMS over temporal poles was used in neurologically intact participants, indicating that temporal poles are critically important in the representation and activation of semantic memory [32]. Furthermore, the naming performance of patients with neurodegenerative diseases, such as Alzheimer's disease and FTLD, was found to be related to the metabolite levels in the left temporal lobe [33].

GMV reduction in the bilateral parahippocampal gyrus/amygdala and left caudate was identified in the current meta-analysis, and this finding was also supported by some functional imaging studies and pathological studies [6–8, 29]. These regions were suggested to play a role in the control of appetitive behavior in a study that identified the increased neural response of healthy volunteers to food pictures [34]. Therefore, atrophy in these structures contributes to the occurrence of feeding behavior impairment in SD patients. Bilateral parahippocampal gyrus/amygdala impairment also contributes to the behavior deficits observed in SD because these structures also belong to a distributed network for emotional behavioral control [35–38]. No significant GMV reduction in parietal, occipital, and hippocampal complex regions was identified in SD, indicating that visuospatial [17, 39] and normal day-to-day memory functions [17, 40] are fairly intact in SD.

SD has left (LTLV) and right (RTLV) temporal lobe atrophy predominant variants according to the asymmetrical temporal atrophy found via neuroimaging methods. These two phenotypes present not only different atrophy patterns but also different clinical symptoms. LTLV is characterized by word-finding difficulties and impaired comprehension, whereas personality changes dominate RTLV [3, 17, 41]. This study indicates that SD had asymmetric impairment in both temporal lobes with severe GM atrophy in the left side than that in the right side, confirming the asymmetrical hemispheric involvement common in SD, with patients suffering greater left than right atrophy. This finding is supported by the report that LTLV is roughly three times more prevalent than the RTLV [17, 42]. However, the result of asymmetrical involvement should be taken with caution. On the one hand, as some early RTLV cases present predominant behavioral abnormalities with relatively spared language abilities, the diagnosis of SD is not easily made without the careful neuropsychological and imaging examinations [23, 46]. In these cases, RTLV may be underdiagnosed. On the other hand, the overlap of clinical symptoms and atrophy progression of controlateral hemisphere occur in both phenotypes with disease progression [19, 49]. Therefore, the side of onset and stage of disease would affect the result of our study. However, because the included studies did not classify the patients into LTLV and RTLV groups, except one [17], we could not perform separate meta-analyses on LTLV or RTLV. The separate analysis of these two phenotypes is an interesting scientific study to determine the different atrophy patterns in SD.

Contrary to our expectations, the current meta-analysis did not reveal changes in frontal lobes, which have been reported to cause impairment in many studies [8, 16, 43, 44]. This finding has several plausible explanations. First, three among seven included studies identified changes in the frontal lobes but in different regions [16, 26, 27]. Second, SD patients with frontal lobe atrophy develop executive dysfunction and behavioral symptoms similar to the later stage of behavior variant frontotemporal dementia. However, the patients included in the current meta-analysis were in the early stage of the disease according to their Mini-Mental Status Examination scores, although hypometabolism was observed in one study [8].

Thus, clinical variables, such as the stage of illness, disease duration, age, and symptom dimensions, may affect the changes in the brain structures of SD patients. However, the low number of included studies did not allow us to control these factors. Therefore, further studies using a larger homogenous sample sizes are needed to explore the influence of these factors.

Our meta-analysis has several methodology limitations. First, voxel-based meta-analyses are based on coordinates from published studies instead of raw data. Thus, the results are less accurate [45]. Second, the publication bias is unavoidable since we did not review studies published in languages other than English. Third, the methodological differences of VBM studies, such as different preprocessing protocols (traditional or

optimized), smoothing kernels, and statistical threshold methods, could not be ruled out entirely.

In summary, our meta-analysis of whole-brain VBM studies on SD identified the GMV reduction in bilateral temporal lobes with predominant impairment on the left side, parahippocampal gyrus/amygdala, and left caudate. A long-term and larger sample of clinical homogeneous SD patients is necessary to identify clearly the changes related to the illness and to highlight its pathological mechanism.

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Authors' disclosures available online (http://www.j-alz.com/disclosures/view.php?id=1330).

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