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Self-appraisal in behavioural variant frontotemporal degeneration

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Abstract

Objective—Previous work investigating deficits in self-appraisal in behavioural-variant frontotemporal degeneration (bvFTD) has focused on a single domain: social/behavioural processes. We examined whether a domain-specific versus multi-domain model best explains degraded self-appraisal in bvFTD.

Methods—49 patients with bvFTD and 73 patients with Alzheimer's disease (AD) were administered quantitative assessments of episodic memory, naming and grammatical comprehension. Self-appraisal of cognitive test performance was assessed by asking patients to rate their performance immediately after completing each neuropsychological test. A discrepancy score was created to reflect the difference between patient performance on neuropsychological tests and self-appraisal of their test performance. Self-appraisal for each neuropsychological measure was related to grey matter (GM) density in each group using voxel-based morphometry.

Results—bvFTD patients were poor at evaluating their own performance on all cognitive tests, with no significant correlations between self-appraisal and actual performance. By contrast, poor self-appraisal in AD was restricted to episodic memory performance. Poor self-appraisal on each task in bvFTD and AD was related to reduced GM density in several ventral and rostral medial prefrontal regions. Crucially, poor self-appraisal for all domains in bvFTD was related to a specific area of reduced GM density in the subgenual cingulate (BA 25).

Conclusion—Poor self-appraisal in bvFTD affects multiple domains, and this multi-domain impairment pattern is associated with frontal disease in the subgenual cingulate.

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INTRODUCTION

Self-appraisal refers to impaired awareness of one's own abilities. The ability to appraise our own performance is a unique component of daily human functioning that allows us to recognise our own limitations. Poor self-appraisal has been observed in patients with neurological disease for a wide array of cognitive and behavioural domains including sensory, perceptual, motor and social functioning.¹ Despite several studies examining self-appraisal deficits, the precise nature and neural basis remains unclear.²

Poor self-appraisal may be *domain-specific*, that is, restricted to a specific area of functioning such as neglect of left hemi-space that can accompany a right hemisphere stroke. Poor self-appraisal has been described in Alzheimer's disease (AD), where impaired self-appraisal involves memory impairment.^{3,4} Several studies report poor insight regarding behaviour and social comportment in behavioural-variant frontotemporal degeneration (bvFTD).⁵⁻⁸ Degraded self-appraisal may extend beyond a single domain to involve a *multi-domain* pattern that includes multiple areas of functioning. For example, patients with a semantic variant of primary progressive aphasia, an aphasic subtype of FTD, have demonstrated reduced insight for both their language-related and behavioural symptoms.⁹ Because poor self-appraisal is such an important diagnostic feature of bvFTD^{10,11} and has such profound consequences for day-to-day functioning, the present study was the first to assess the specificity of a self-appraisal deficit across multiple domains and in a comparative manner in bvFTD and AD.

The neural basis of self-appraisal in patients with neurodegenerative disease is not well understood. Few studies have evaluated the anatomical basis of impaired self-appraisal in these conditions. Medial prefrontal cortex (PFC) in the right frontal lobe appears to play a crucial role in self-appraisal.¹²⁻¹⁵ This area is important for social cognitive processing, and, in particular, knowledge about the self,¹⁶ and this may confound assessments of the neuroanatomy of self-appraisal focusing on social content. Moreover, the precise area within medial PFC that is critical for self-appraisal remains to be specified. The present study was the first to assess the neural basis for impaired self-appraisal objectively and comparatively in multiple areas of cognition in bvFTD and AD. We hypothesised that only bvFTD would demonstrate a self-appraisal deficit in multiple cognitive domains, and that this multi-domain deficit would be associated with changes in ventral medial PFC.

METHODS

Patients

One hundred and twenty-two subjects participated in this research. All patients were evaluated and recruited by an experienced cognitive neurologist from the Department of Neurology, University of Pennsylvania. bvFTD and AD patients were classified based on published criteria.^{11,17} At least two trained reviewers of a consensus committee confirmed the presence of specific diagnostic criteria and also assigned patients to AD or a specific FTD phenotype based on an independent review of the semi-structured history obtained from patients and their families, a detailed neurological examination, and a comprehensive mental status evaluation. Inter-rater reliability for clinical diagnosis was 85% agreement. When there was disagreement between reviewers, the case was discussed by the entire committee to arrive at a consensus diagnosis, and agreement on the remaining 15% was obtained at follow-up assessment. This sample of mild to moderately demented patients included: bvFTD (n=49; MMSE (mean $\pm$ SE) 23.6 $\pm$ 0.9; range 4–30), who presented with progressive social and personality difficulties, often with alterations of executive functioning; and patients with mild-to-moderate AD (n=73; MMSE (mean $\pm$ SE) 20.6 $\pm$ 0.7; range 9–28), who had episodic memory deficits as well as difficulty in language, executive,

and visual perceptual-spatial domains. All patients participated in an informed consent procedure approved by the University of Pennsylvania Institutional Review Board.

The initial clinical diagnosis of a neurodegenerative disease was consistent with the results of serum and cerebrospinal fluid studies of infection, inflammation and neoplasia (when available). Structural imaging studies (MRI or CT) were available on all subjects to establish an initial clinical diagnosis, and if functional neuroimaging studies (SPECT or PET) were available, these results were also taken into account. However, imaging studies were not available to the consensus committee to minimise selection bias in clinical-imaging correlation studies such as this. Some of these patients were taking a fixed dosage of a cholinesterase inhibitor (eg, donepezil, rivastigmine or galantamine) or memantine. Some of these patients may also have been medicated with a low dosage of a non-sedating antidepressant (eg, serotonin-specific reuptake inhibitors such as sertraline) or an atypical neuroleptic agent (eg, quetiapine), as indicated clinically, but none of the patients demonstrated any evidence of sedation suggesting over-medication. Exclusion criteria included the presence of other neurological conditions such as stroke, closed head trauma or hydrocephalus (as determined by imaging studies reviewed by a neurologist), primary psychiatric disorders such as depression or psychosis, or a systemic illness that can interfere with cognitive functioning. Table 1 summarises the demographic features of these patients. Analysis of variance (ANOVA) indicated no differences in education or disease duration from symptom onset. AD patients were older than bvFTD patients ($t(120)=4.52$, $p<0.001$).

Neuropsychological protocol

We focused on three distinct domains of cognitive functioning. Not all participants performed all tasks due to a variety of reasons (eg, scheduling conflict, technical difficulty) and table 1 indicates the number of people who performed each task. ANOVAs, t-tests and correlations were performed to assess cognitive performance and relate this to self-appraisal. The measures included:

- ▶ *Boston Naming Test (BNT)*: Visual confrontation naming was assessed with a 30-item version of the BNT.¹⁸ The stimuli were equally divided into high-frequency, mid-frequency and low-frequency items. Patients were given as much time as they needed to respond. The dependent variable was the total number of correct responses.
- ▶ *Test of Receptive Grammar (TROG)*: The TROG¹⁹ is a sentence–picture matching task measuring grammatical comprehension. Patients were shown four pictures and asked to choose the picture that best matches the sentence. Both inflectional morphology (eg, pluralisation, gender) and long-distance syntactic relations (eg, passive voice) were assessed.
- ▶ *Rey Complex Figure Immediate Free Recall*: Immediately after figure copy, patients performed a visuospatial interference task for one minute; patients were then asked to draw the figure from memory.

Patient's self-appraisal of neuropsychological test performance

Immediately following each task, subjects were asked to rate how well they performed. Ratings were indicated by making a mark along a 50 mm line ranging from very poor performance to very high performance. The location of the mark was measured and multiplied by two to provide a quantitative score ranging from 0 (very low) to 100 (very high). Participants were trained in the use of this scale prior to the study, and none of the patients had any difficulty performing this task.

Self-appraisal discrepancy scores

Discrepancy scores were generated for each subject to reflect the difference between patient performance on each task and their self-appraisal. To obtain this score, we used the patient self-appraisal of test performance (as described above) and subtracted the score they obtained on the corresponding test. In order to adjust for absolute level of performance on each task, we divided the raw difference by the patient score on the test (eg, good insight associated with a small discrepancy score: self-appraisal rating on BNT (100) minus patient score on BNT (29/30=96) divided by patient score (96)).

Structural imaging procedure and analysis

Volumetric MRI images were available for a subset of patients with bvFTD (n=37) and AD (n=17). The subgroups of patients for whom MRI images were available exhibited the same patterns of behavioural performance as the larger groups composed of all patients. A cohort of 30 healthy seniors (mean age=64.4 years (SD=10.3); mean education=15.24 (SD=1.8)) matched for age, education and years gender (all $p>0.05$) was used as a reference group to assess grey matter (GM) density. High-resolution T1-weighted three-dimensional spoiled gradient echo images were acquired with repetition time=1620msec, echo time=3msec, slice thickness=1.0 mm, flip angle=15°, matrix=192×256, and in-plane resolution=0.9×0.9 mm. All images were preprocessed using PipeDream (<https://sourceforge.net/projects/neuropipedream/>) and Advanced Normalisation Tools (ANTS, <http://www.picsl.upenn.edu/ANTS/>) to perform the most stable and reliable multivariate normalisation and structure-specific processing currently available.²⁰⁻²² PipeDream deforms each individual dataset into a standard local template space in a canonical stereotactic coordinate system. Core processing involves mapping T1 structural MRI to a population-specific, unbiased average-shape and average-appearance image derived from a representative local population consisting of 25 healthy seniors and 25 patients with FTD.²³ This superior method for registration and normalisation avoids the need to use identical participants in the local template and allows us to compare variable anatomy from distinct populations (healthy subjects and patients).²⁴ To normalise individual subjects' MRI to standardised template space we used a diffeomorphic registration method that is defined as being smooth and topology preserving and additionally symmetric so that it is not biased towards the reference space for computing deformation maps. We then used SPM5 to smooth GM density images using a 4 mm FWHM Gaussian kernel and to compare GM density in bvFTD and AD to healthy seniors using a two-sample t-test with a voxel level threshold of $p<0.005$ (false discovery rate (FDR)-corrected) and a 400 adjacent voxel extent.

In the second analysis, we used the regression module of SPM5 to relate GM density in the AD and bvFTD cohorts directly to the self-appraisal discrepancy scores in a whole-brain analysis. This involved variable numbers of patients since some patients did not perform all behavioural tasks. We used the findings of the GM density analysis to mask the regressions. In this manner, we were able to restrict our interpretation of the regression analysis to those brain regions known to be significantly abnormal and highly likely to have disease. The statistical threshold for the regression analyses was set at $p<0.05$ (FDR-corrected for both voxel level and cluster level analyses), and we accepted only clusters comprised of 15 or more adjacent voxels. We report regressions for tasks where patients had poor self-appraisal. This includes BNT, TROG and Rey Recall in bvFTD and only Rey Recall in AD (see below). We examined the intersection of clusters identified by regressions with these tasks using the MarsBar Toolbox.²⁵

RESULTS

Neuropsychological results

Table 1 summarises neuropsychological performance. Between-group comparisons found that AD patients score lower than bvFTD patients on all three neuropsychological tests: BNT ($t(120)=2.87$, $p<0.005$); TROG ($t(67)=2.01$, $p<0.023$); Rey Recall ($t(105)=4.79$, $p<0.001$). Co-varying for age had no effect on this pattern of performance.

Neuropsychological self-appraisal results

ANOVAs for patients' self-appraisal of their neuropsychological performance are summarised in table 1. Self-appraisal was higher for bvFTD than AD patients on BNT ($t(120)=4.17$, $p<0.001$) and Rey Recall test performance ($t(62)=3.59$, $p<0.001$). There was no difference for TROG self-appraisal.

Pearson correlations between actual test performance and patients' self-appraisal of their own test performance were calculated (table 2). After Bonferroni correction for multiple comparisons, the bvFTD group produced no significant correlations between test performance and self-appraisal. By contrast, the AD group showed correlations between test performance and self-appraisal for BNT ($r=0.541$, $p<0.001$) and TROG ($r=0.585$, $p<0.001$), but not Rey recall ($r=0.070$, $p<0.670$).

Self-appraisal of cognitive functioning was then assessed with Fisher r to z transformations. These are summarised in table 2. For the bvFTD group, the Fisher r to z statistic failed to demonstrate significant associations between test performance and measures of self-appraisal for all three neuropsychological tests, suggesting *multi-domain* self-appraisal deficits for all measures. By contrast, for the AD group, the Fisher r to z statistic demonstrated poor self-appraisal only when patients were asked to appraise their own performance of their recall of the Rey complex figure. AD patients displayed appropriate self-appraisal with respect to their performance on the BNT and TROG ($p<0.001$, both tests).

Imaging analyses

Figure 1 illustrates the imaging results. Mid-sagittal views illustrate reduced GM density in panel A, and supplement table E-1 summarises the location of peak voxels in these whole-brain contrasts. Panel A (green) shows reduced GM density in bvFTD compared to controls in medial PFC, including ventral and rostral areas. Panel A (red) shows that reduced GM density in AD was present in medial PFC, although with less ventral and rostral involvement. AD also showed reduced GM density in medial parietal/temporal/occipital regions.

The results of the regression analysis relating self-appraisal discrepancy scores to reduced GM density are summarised in table 3. In bvFTD, self-appraisal limitations for BNT, TROG and Rey Figure Recall were each related to various regions in ventral and rostral medial PFC (figure 1, panel B, green). Similar anatomic associations were also evident in the AD group for their poor self-appraisal on the Rey Recall measure (figure 1, panel B, red). Crucially, the regression analysis demonstrated a specific area of GM related to self-appraisal for all tasks only in bvFTD involving the subgenual cingulate (BA 25).

To evaluate if the subgenual region is specific to a multi-domain self-appraisal impairment in bvFTD, we examined the relationship between GM density and self-appraisal discrepancy scores for Rey Recall. We selected the Rey Recall since this is the only test in which bvFTD and AD patients exhibited poor self-appraisal. We evaluated mean GM density in regions of

interest defined by the three subgenual clusters that were observed in the bvFTD group. In bvFTD, all three of these regions showed a significant negative association with self-appraisal scores ($r(12)=-0.634$, $p=0.010$; $r(12)=-0.466$, $p=0.054$; $r(12)=-0.599$, $p=0.015$). In AD, we found no significant correlations between self-appraisal and GM density ($r(15)=-0.101$, $p=0.350$; $r(15)=-0.096$, $p=0.357$; $r(15)=-0.113$, $p=0.333$). This demonstrated the lack of association in the multi-domain subgenual region in AD, and the specificity of a multi-domain self-appraisal deficit for bvFTD due to subgenual disease.

DISCUSSION

This study investigated self-appraisal of patients' own deficits in several cognitive domains in bvFTD and AD. We found that bvFTD patients show significant deficits in self-appraisal across multiple cognitive domains, suggesting a fundamental impairment in self-evaluation and self-monitoring. This was evident in all domains of cognitive functioning that we examined, suggesting a broad, *multi-domain* impairment in self-appraisal. We observed impaired self-appraisal only for episodic memory in the AD group, suggesting a *domain-specific* impairment for these patients. We found that deficits in self-appraisal for each task are related to several ventral and rostral medial PFC regions in both bvFTD and AD. Crucially, bvFTD patients had a unique association of impaired self-appraisal for all tasks with the subgenual cingulate, emphasising the critical role of this area for a multi-domain impairment of self-appraisal.

Several methods may be used to assess self-appraisal.²²⁶ The most common method compares similar questionnaires administered to patients about themselves and to their caregivers about the patients. However, this strategy has statistical limitations,²⁷ and caregiving burden or level of distress may bias a caregiver's ratings of the patient's impaired self-awareness.⁴ Another approach is for a clinician to judge the patient's awareness and insight based on a history from a caregiver and a patient interview.² Since the clinician typically has limited exposure to the patient's behaviour beyond a brief examination in a context relatively unfamiliar to the patient, it is difficult to evaluate impairment or self-appraisal in a fine-grained manner. The method employed for the present study evaluates patients' self-appraisal of performance on objective, quantitative neuropsychological tests. This was in order to minimise biases such as caregiver stress, while neuropsychological testing allowed us to have an objective measurement of performance. Moreover, we could quantify self-appraisal about specific behaviours in a manner that is not confounded by factors such as the familiarity of the environment, and we could apply this technique equally to diverse domains of behaviour. Finally, we assessed self-appraisal of cognitive functioning to minimise the risk of confounding self-appraisal with social knowledge that may be impaired in bvFTD.

It has been claimed that social functioning alone is the one valid domain for assessing self-appraisal.⁴ However, social awareness itself is quite complex and may be compromised for a variety of reasons.² For example, diminished self-appraisal in bvFTD may be most evident for social situations that are modulated by limited interpretation of negative feedback,⁶ and impaired theory of mind may contribute to limited social awareness.²⁸ However, the findings of the present study emphasise that diminished self-appraisal in bvFTD is amodal, is equally prominent in multiple domains of performance, and is not restricted to social cognition.⁸ Moreover, diminished self-appraisal across multiple cognitive domains cannot be easily attributed to demographic features such as longer disease duration or dementia severity, since patients with AD had impaired self-appraisal for episodic memory but preserved self-appraisal for naming and sentence processing regardless of disease duration or dementia severity. Future work should assess the role of disease duration in self-appraisal empirically in bvFTD.

While bvFTD patients showed broad-based diminution of self-appraisal, the AD group in the present study demonstrated reduced self-appraisal only in one domain of impairment: episodic memory. This is consistent with other work suggesting that AD patients have particular difficulty evaluating their own episodic memory.^{26,29} Poor self-appraisal in AD may also include activities of daily living, instrumental activities of daily living, and mood and behavioural symptoms,^{30,31} although these observations may have been confounded by the episodic memory component of these tasks. We minimised this confound by probing self-appraisal immediately following task performance. Our observation of reduced self-appraisal involving memory but not naming or sentence comprehension thus is more consistent with a narrower, *modality-specific* impairment in AD, and correlated self-appraisal for memory and comprehension diminishes the likelihood that memory for performance interferes with self-appraisal using our technique. Additional work is needed to evaluate the scope of impaired self-appraisal in AD.

Atrophy in ventral and rostral medial PFC was associated with poor self-appraisal scores. These regions were consistently implicated across the AD and bvFTD patients with poor self-appraisal, suggesting the importance of the medial frontal lobe for self-appraisal. This is consistent with prior imaging studies in neurodegenerative disease that highlight the importance of the frontal lobes, specifically ventral medial PFC.^{61,532} For example, ventral medial PFC has been associated with interpreting the value of feedback from the environment.³³ A similar evaluation process may be implicated in evaluating oneself. Some work has associated ventral medial frontal regions with interpreting negative feedback in functional neuroimaging studies of healthy adults and brain-behaviour assessments in bvFTD.⁶ Previous studies also suggest a role for the dorsal anterior cingulate cortex (ACC) in social cognition.¹⁶³⁴ Prior research demonstrated the ACC is involved in conflict monitoring and awareness of errors,³⁴⁻³⁶ and conflict theory suggests that errors are a type of conflict that are monitored by the same process for conflict detection.³⁷ We found atrophy in dorsal ACC in both AD and bvFTD, but we failed to find a relationship between this area and reduced self-appraisal.

The present study highlighted a specific region of ventral medial PFC that is compromised only in bvFTD patients who had a multi-domain deficit in self-appraisal. This subgenual region of the cingulate has projections to other medial PFC regions via the cingulum and centres important for interpreting the value of feedback in ventral medial PFC.³⁸ Although we found that the subgenual region was important only for the bvFTD subjects, a recent study also found that this area was important for self-appraisal accuracy on memory tasks in AD subjects.³⁸ However, Ries and colleagues examined only one domain (ie, memory) and having a range of cognitive domains would be essential in determining the extent of impaired self-appraisal in AD. Furthermore, this study utilised caregivers' ratings on a questionnaire to determine the patients' self-appraisal accuracy which can be confounded. We hypothesise that this subgenual area plays a crucial integrative role in a large-scale neural network for self-appraisal, including processes involved in the evaluation of self and others, and damage to this area results in a multi-domain deficit in self-appraisal that we observed in bvFTD.

This study has several limitations. We assessed primarily memory and language domains, and having a broader range of cognitive tests including behavioural, executive and visuospatial measures would be helpful in determining the full extent of impaired self-appraisal. Furthermore, it has been suggested that self-appraisal is most validly measured in domains involving patients' everyday activities,⁴ and future work should address this by assessing self-appraisal in carefully controlled day-to-day domains of functioning that depend on several specific cognitive and social demands. Also, we do not have neuropathological confirmation of the diagnoses of these patients. With these caveats in

mind, we conclude that a multi-domain deficit in self-appraisal is a characteristic of bvFTD, and these patients appear to be particularly compromised in their self-appraisal due to disease in the subgenual portion of medial PFC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Significant grey matter atrophy in patient cohorts, and regressions relating self-appraisal discrepancy scores to atrophy. (A) Anatomic distribution of significant grey matter atrophy in patients with behavioural variant frontotemporal degeneration (green) at $x=6$ and Alzheimer's disease (red) at $x=4$. (B) Significant regressions relating self-appraisal scores to cortical atrophy in behavioural variant frontotemporal degeneration (green) and Alzheimer's disease (red) at $y=42$ (left panel) and $y=19$ (right panel). Rostral medial (purple arrow); ventral medial (yellow arrow), subgenual cingulate (blue arrow).

Table 1
Mean (SD) and range of demographic characteristics, neuropsychological test performance and self-appraisal ratings in patient cohorts*

	AD	bvFTD
Demographic information		
Age (years)	71.55 (8.57), range 47–87	63.69 (9.49), range 36–82
Education (years)	15.46 (2.95), range 11–22	15.57 (3.21), range 8–22
Disease duration (months)	64.76 (38.46), range 24–144	75.75 (40.38), range 12–168
Neuropsychological test performance		
Boston naming test (max=30)	17.22 (7.96) (n=73), range 1–30	21.57 (8.55) (n=49), range 0–30
TROG (max=24)	20.05 (4.55) (n=44), range 7–24	22.00 (2.39) (n=25), range 16–24
Rey recall (max=36)	6.04 (6.75) (n=65), range 0–30	13.21 (8.68) (n=42), range 0–31
Patient self-appraisal of their neuropsychological test performance [†]		
Boston naming test	67.13 (22.54), range 0–100	82.89 (16.84), range 25–100
TROG	87.50 (19.62), range 25–100	94.13 (12.87), range 50–100
Rey recall	37.44 (28.31), range 0–100	63.101 (23.33), range 25–100

TROG, Test of Receptive Grammar.

* AD, Alzheimer's disease; bvFTD, behavioural variant frontotemporal degeneration. Not all patients performed all measures due to a variety of limitations, including intercurrent illness, scheduling conflict and technical difficulty.

[†] Self-appraisal rating scale range =0–100.

Table 2
Relationship between neuropsychological performance and self-appraisal of performance*

	AD	bvFTD
Fisher r to z transformation: actual test performance versus patient's appraisal of their test performance		
BNT score/BNT self-appraisal	r=0.541	r=0.375
	z=3.06	z=0.394
	p<0.001	p>0.05, NS
TROG score/TROG self-appraisal	r=0.585	r=0.120
	z=3.47	z=0.121
	p<0.001	p>0.05, NS
Rey recall score/Rey recall self-appraisal	r=0.120	r=-0.145
	z=0.121	z=0.146
	p>0.05, NS	p>0.05, NS

BNT, Boston Naming Test; TROG, Test of Receptive Grammar.

* AD, Alzheimer's disease; bvFTD, behavioural variant frontotemporal degeneration.

Table 3
Anatomic locus of peak voxel in clusters relating selfappraisal discrepancy scores to grey matter atrophy in patient cohorts*

Peak voxels where grey matter is correlated with self-appraisal score				
Location (Brodmann area)	Cluster coordinates [†]			Cluster size (voxels)
	X	Y	Z	
AD (Rey recall)				
R frontal (10)	30	43	18	389
R frontal (32)	11	43	2	423
R frontal (32)	20	15	42	197
R frontal (11)	−14	35	−20	113
bvFTD (areas of overlap for Rey recall, TROG and BNT)				
L frontal (11)	−1	32	−22	733
L frontal (25) [‡]	−5	16	−12	87
R frontal (32)	4	41	11	222
R frontal (25) [‡]	3	19	−12	59
R frontal (10)	14	47	12	17
R frontal (11)	4	53	−22	17
R frontal (32)	11	42	13	15
R frontal (25) [‡]	2	14	−12	7

BNT, Boston Naming Test; TROG, Test of Receptive Grammar.

* AD, Alzheimer's disease; bvFTD, behavioural variant frontotemporal degeneration; L, left; R, right.

[†] Peak locus of these clusters are derived from MNI space converted to Talairach space using MNI2TAL.

[‡] Regions used in self-appraisal discrepancy score analyses.