# Neuropsychological, Behavioral, and Anatomical Evolution in Right Temporal Variant Frontotemporal Dementia: A Longitudinal Single Case Analysis

## Introduction

Frontotemporal dementia (FTD) comprises a group of clinical syndromes characterized by progressive impairment of behavior and/or language. These syndromes include a behavioral variant (bvFTD), the nonfluent variant of primary progressive aphasia (NFV-PPA), and the semantic or temporal variant (tvFTD). FTD subtypes have been the subject of a growing body of research, which has revealed a distinct clinical, neuroanatomical, and pathological profile for each syndrome. A majority of patients with the temporal variant feature left greater than right temporal lobe atrophy, referred to previously as the left temporal lobe variant (LTLV); they present as the classic semantic variant of primary progressive aphasia (SV-PPA) with progressive loss of word and object knowledge. Patients with more prominent right temporal involvement (RTLV) are less prevalent and typically present with behavioral symptoms, personality change, and loss of person-specific knowledge (Edwards-Lee et al., 1997; Gainotti et al., 2003; Joubert et al., 2006; Miller et al., 1993; Seeley et al., 2005; Thompson et al., 2003; Tyrrell et al., 1990).

The left temporal lobe has been widely implicated in semantic processing in a number of studies addressing SV-PPA (e.g., Hodges et al., 1992; Mummery et al., 2000). The role of the right temporal lobe has been less thoroughly examined, however there is increasing evidence for its role in empathy and emotion processing (Rankin et al. 2005; 2006; Rosen et al. 2002); abstract conceptual social knowledge (Zahn et al., 2009) and social functioning (Liu et al, 2004); configurational processing of faces and monuments; multimodal semantic knowledge for persons (Joubert et al., 2003; 2006; Snowden et al. 2004) and food (Gorno-Tempini et al., 2004b); as well as taste recognition (Small et al., 1997) and eating behavior (Uher et al., 2005).

Only a handful of studies have examined the clinical and anatomical evolution of FTD syndromes (e.g., Brambati et al., 2007; 2009; Gorno-Tempini et al., 2004a; Janssen et al., 2005; Seeley et al., 2005; Whitwell et al., 2004). In tvFTD, neuroimaging findings suggest spreading disease from one anterior temporal lobe to the other, with bilateral amygdala (mostly ipsilateral) involvement, as well as later atrophy of frontal, insular and inferoposterior temporal cortices (Brambati 2007; Seeley et al., 2005). The clinical picture typically reflects the topography of cortical atrophy. In RTLV, behavioral deficits outweigh semantic deficits early on; in LTLV, the opposite pattern is observed. As atrophy spreads from one temporal lobe to the other, the syndrome not seen predominantly at presentation becomes more apparent (Seeley et al., 2005). Regardless of laterality (RTLV vs. LTLV), these cases often reveal a common pathological profile, characterized by TDP-43 positive, tau-negative inclusions (Davies et al., 2005; Grossman et al., 2007; Hodges et al., 2004; 2010).

Few studies to date have examined the progression of behavior and anatomical damage in patients who later came to autopsy. In this study, we examine longitudinal neuropsychological, behavioral, and anatomical data for a patient, JT, who presented with the RTLV of FTD. This patient was previously described in a case report examining her cognitive and behavioral profile approximately three years after symptom onset (Gorno-Tempini et al., 2004b). Here we explore the progression of the disease, from both a behavioral and a neuroanatomical perspective, by reviewing data from three evaluations spanning three years. We also provide information regarding neuropathological diagnosis and distribution of pathology at autopsy.

## Methods

JT was evaluated clinically on three occasions, each separated by approximately one year (Time 1 took place approximately 3 years after symptom onset). Neurological, neuropsychological (Table 1), and neuropsychiatric evaluations were conducted. Language functions were assessed using the *Western Aphasia Battery* (Kertesz et al., 1982), as well as tests examining semantic and syntactic skills, reading, and motor speech ability. Behavioral and personality changes were characterized using a survey of behavioral disorders, as well as several questionnaires (administered at Times 1 and 2 only) examining social and personality changes, each of which was completed by JT's daughter.

High-resolution 3D structural MR images were obtained within four months of each clinical assessment. Images were segmented into grey matter, white matter, and cerebrospinal fluid and first normalized to standard space using the unified segmentation procedure in SPM5 (Ashburner & Friston, 2005) with subsequent registration using the DARTEL toolbox (Ashburner, 2007). Modulated, smoothed gray matter images were derived from each of the patient's three MRI scans as well as for 32 age-matched healthy female controls. In order to examine regional gray matter atrophy over time, gray matter volume in each of JT's scans was compared to that in the control group using t-tests.

## Results

JT's symptoms began at age 62 with prominent behavioral and personality changes and multimodal semantic loss for foods and people (Gorno-Tempini et al., 2004b). Caregiver questionnaires revealed that her personality shifted from being dominant and extraverted to submissive and introverted; her level of empathy was reduced and she became increasingly cold-hearted, neurotic, and arrogant. The inventory of behavioral disorders revealed early agitation and disinhibition, along with aberrant motor behavior and eating and sleep disorders (Time 1). In addition to these behaviors, irritability and apathy were noted at Time 2; delusions, anxiety and euphoria were observed at Time 3.

As the disease progressed, JT's semantic impairment became more pronounced. Results from language assessments (Table 2) revealed prominent naming difficulty and poor performance on semantic association tasks (Time 1), with later development of single-word comprehension deficits and surface dyslexia (apparent at Time 2 and more prominent at Time 3). Syntactic comprehension was spared until the final assessment, at which point severe lexical deficits rendered sentence comprehension impossible. By contrast, non-semantic aspects of language, such as fluency and repetition, were largely spared until later in the disease.

Voxel-based morphometry (VBM; Figure 1) revealed spreading asymmetric atrophy (right greater than left) over a three-year period, with early involvement of the right amygdala and hippocampus, parahippocampal and fusiform gyri, and temporal pole and less prominent atrophy in the left amygdala and parahippocampal gyrus. With disease progression, atrophy spread to additional right, then left cortical regions, including posterior and inferolateral temporal cortex and the insula. Frontal lobe involvement was relatively mild.

JT died and underwent brain autopsy 4 years, 8 months after her Time 3 evaluation. The pattern of gross atrophy mirrored that identified with MRI. Microscopically, microvacuolation, astrogliosis, and neuronal loss were seen in anterior inferior temporal, subgenual cingulate, insular, and entorhinal cortices, as well as in ventral striatum, with conspicuous sparing of the hippocampus. Immunohistochemical analyses revealed ubiquitin and TDP-43 immunoreactive

neuronal inclusions, primarily taking the form of long dystrophic neurites in superficial greater than deep layers of affected cortices, although abundant round, circumscribed neuronal cytoplasmic inclusions were seen in striatum and dentate gyrus. The morphology and distribution of TDP-43 inclusions was consistent with FTLD-TDP, Type 1 (Sampathu et al., 2006).

**Conclusion**

JT showed an evolution of clinical symptoms from initial deficits in behavior, personality, and mild semantic loss specific to foods and people, evolving to a pronounced, multi-modal semantic impairment. This clinical pattern was reflective of the underlying distribution of atrophy and histopathology, which increasingly involved the left anterior temporal lobe in addition to the right. Thus, early behavioral and personality deficits corresponded to involvement of right temporal structures, whereas the development of a language profile consistent with SV-PPA corresponded to atrophy spreading into left temporal structures.

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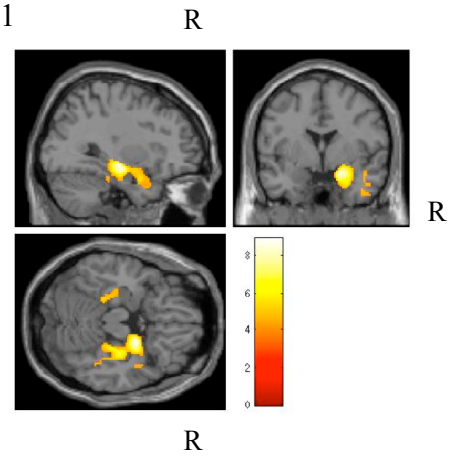
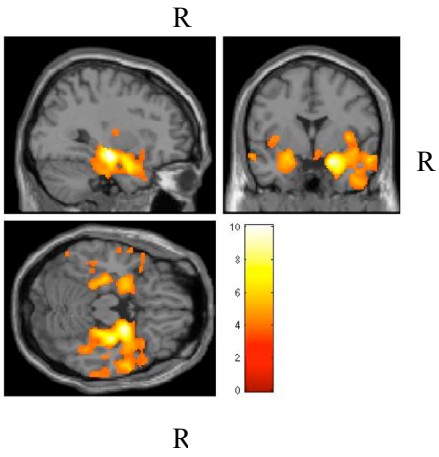
**Figure 1. Results of voxel-based morphometry analyses at three time points (JT vs. 32 normal controls; p<.01, FDR correction. Color bar indicates t-values.)**

Time 1




Time 2




Time 3

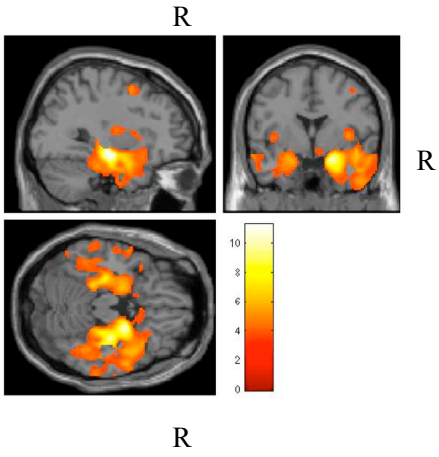


**Table 1. Demographic and Neuropsychological Data**

| | Possible | 2002 | 2003 | 2004 |
|---|---|---|---|---|
| Age | -- | 65 | 66 | 67 |
| Education | -- | 15 | 15 | 15 |
| MMSE | 30 | 24* | 12* | 7* |
| Modified Rey Copy | 17 | 16 | 13* | 11* |
| VOSP Number Location | 10 | 6* | 9 | NC |
| Rey Figure Recall (10 minute delay) | 17 | 5* | 0* | NC |
| Rey Figure Recognition | 1 | 1 | 0* | 0* |
| Backward digit span | 7 | 6 | 6 | 2* |
| WMS III Visual Reproductions I (scaled score) | 19 | 6 | 4* | NC |
| WMS III Visual Reproductions II (scaled score) | 19 | 4* | 4* | NC |
| CVLT 30 sec. Free Recall | 9 | 1* | 2* | NC |
| CVLT 10 min. Free Recall | 9 | 0* | 0* | NC |
| CVLT 10 min. Recognition | 9 | 0* | 0* | NC |
| Calculations (multiplication, subtraction, addition) | 5 | 5 | 2* | 2* |
| WMS III Digit Span (scaled score) | 19 | 17 | 16 | NC |
| WMS III Spatial Span (scaled score) | 19 | 16 | 13 | NC |
| Benton Facial Recognition Test | 54 | 42 | NC | NC |
| Experimental Famous Face Battery (Gorno-Tempini et al., 2004b): | | | | |
| • Famous Face Naming | 20 | 0* | NC | NC |
| • Famous Face Recognition | 20 | 14* | NC | NC |
| • Face Recognition (short version) | 6 | 6 | 4 | 2 |
| • Famous Face Semantic Association | 20 | 5* | NC | NC |
| • Famous Name-to-Face Matching | 20 | 6* | NC | NC |

* indicates impaired performance
NC = not collected
MMSE = Mini Mental State Examination
VOSP = Visual Object and Space Perception Battery
WMS III = Wechsler Memory Scale III
CVLT = California Verbal Learning Test
Note: only a subset of tests could be administered in 2004, due to the severity of the patient's language impairment

**Table 2. Language Assessment Results**

| | Possible | 2002 | 2003 | 2004 |
|---|---|---|---|---|
| WAB Fluency | 10 | 9 | 9 | 9 |
| WAB Information Content | 10 | 9 | 8 | 6 |
| WAB Repetition | 100 | 100 | 98 | 97 |
| WAB Auditory Word Recognition | 60 | 58 | 50 | 28 |
| Pyramids and Palm Trees (words) | 52 | 43* | 27* | NC |
| Pyramids and Palm Trees (pictures) | 52 | 27* | 22* | NC |
| Boston Naming Test | 60 | 6* | 3* | NC |
| WAB Sequential Commands | 80 | 80 | 78 | 2 |
| CYCLE (Sentence Comprehension) Subtests: | | | | |
| • Cycle 2,3 (declaratives, possession) | 10 | 10 | 9 | 5* |
| • Cycle 4 (active & passive voice; double embedding) | 15 | 14 | 15 | 6* |
| • Cycle 5,7 (passive voice, subject relatives) | 10 | 10 | 10 | 5* |
| • Cycle 8 (object clefting; object relative clauses) | 10 | 10 | 10 | NC |
| • Cycle 9 (object relatives; relative pronouns) | 10 | 9 | 7* | 1* |
| PALPA Reading Regular Words | 30 | 30 | 30 | 14* |
| PALPA Reading Exception Words | 30 | 27* | 20* | 6* |
| Motor Speech Evaluation (Wertz et al., 1984) | -- | WNL | WNL | WNL |

* indicates impaired performance for tests with norms available; no norms available for WAB subtests
NC = not collected
WAB = Western Aphasia Battery
CYCLE = Curtiss-Yamada Comprehensive Language Evaluation- Receptive
PALPA = Psycholinguistic Assessment of Language Processing in Aphasia
WNL = within normal limits
Note: only a subset of tests could be administered in 2004, due to the severity of the patient's language impairment