SPECIAL SECTION

COGNITIVE AND BEHAVIORAL PROFILE IN A CASE OF RIGHT ANTERIOR TEMPORAL LOBE NEURODEGENERATION

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Abstract

Semantic dementia (SD) is a clinical variant of frontotemporal lobar degeneration (FTLD) characterized by progressive deterioration of semantic memory with relative sparing of other cognitive functions. It is associated with mainly left anterior temporal atrophy, and is also referred to as "left-temporal lobe variant" of FTLD. Recently, patients with mainly right-sided atrophy, or "right-temporal lobe variant"(RTLV), have been described. While some authors have reported that the initial and most significant deficit in these right-sided cases is a difficulty in recognizing famous people, others have observed that major behavioral abnormalities are the presenting symptoms. Here we report a detailed neuropsychological, language, behavioral and neuroimaging assessment of JT, a case of right temporal lobe variant of FTLD. JT showed early and prominent behavioral changes accompanied by a severe impairment in recognizing foods by their look, flavor or name. Later she also developed a difficulty in recognizing familiar people and objects. Standardized caregiver questionnaires of JT's pre- and post-morbid personality and interpersonal functioning showed that she went from being a flexible, dominant, extraverted, person to showing rigid, submissive and introverted behaviors. Her levels of neuroticism significantly increased, while her scores on agreeableness and cognitive and emotional empathy dropped. Voxel-based morphometry (VBM) showed most significant atrophy in the right amygdala/anterior hippocampal complex and collateral sulcus, extending to the right insula. We discuss the atypical cognitive and behavioral features of this case of RTLV of FTLD and stress the importance of behavioral changes and atypical semantic deficits for early diagnosis.

Key words: temporal lobe, semantic dementia, FTD, right-temporal lobe variant of FTD

Introduction

Semantic dementia (SD) is a clinical syndrome characterized by a progressive loss of conceptual knowledge. Patients typically present in the presenium with difficulty in recalling and understanding words, and later show impairment in recognizing objects (Lambon Ralph et al., 1998, 1999; Hodges et al., 1992). Surface dyslexia is also part of the SD clinical picture, as patients have greater difficulty reading words with irregular pronunciations (such as "yacht") compared to regularly spelled words (such as "context"). Within the language domain, speech, phonological and syntactic processing are usually spared. Spatial abilities, non-verbal reasoning and day-to-day episodic memory also remain relatively intact, while episodic memory is often impaired on formal testing (see Hodges and Miller, 2001). Current clinical research criteria list SD as one of the possible clinical presentations of frontotemporal lobar degeneration (FTLD) (Neary et al., 1998). Neuroimaging findings in SD indicate that the anterior temporal lobe is the site of most prominent atrophy and/or hypometabolism, providing a powerful model for studying this brain region rarely hit by other neurological diseases (Mummery et al., 2000; Galton et al., 2001; Chan et al., 2001; Rosen et al., 2002a). Voxel-based Morphometry studies (VBM) and region of interest analysis on MRI scans have shown that the hippocampal/amygdala structures and the infero-lateral temporal neocortex are both significantly atrophied in SD (Chan et al., 2001; Rosen et al., 2002a, 2002b). It has also been shown that the ventro-medial frontal lobe and the insula are involved (Rosen et al., 2002a). The finding that orbitofrontal cortex and amygdala are damaged in SD is consistent with reports that personality changes, disturbances in social behavior, and abnormalities in emotional processing can be part of the clinical syndrome.

Most reported cases of semantic dementia have shown mainly left anterior temporal lobe atrophy. Thus, the classic clinical picture of SD with prominent semantic memory deficits has also been labeled as the "left temporal lobe variant"(LTLV) of FTLD (Edwards-Lee et al., 1997). Less evidence is available regarding the clinical presentation of cases with "right-temporal lobe variant" (RTLV) of FTLD. Only a few reports of RTLV cases have concentrated on describing early difficulties in processing information regarding familiar people, either as progressive disturbance in recognizing familiar faces, or as a more generalized semantic deficit for person-specific information (Gainotti et al., 2003; Barbarotto et al., 1995; Gentileschi et al., 1999; Tyrrell et al., 1990; Evans et al., 1995). In these cases, the presence of behavioral changes was sometimes mentioned, but its significance and the time of first manifestation was not reported (Gainotti et al., 2003). Furthermore, behavioral and neuropsychiatric features were not formally tested and quantified. On the other hand, other authors described the personality and behavioral changes that occur early in RTLV (Edwards-Lee et al., 1997; Perry et al., 2001; Miller et al., 1993; Rankin et al., 2003). For Instance, Perry and colleagues (2001) reported that blunted affect, decreased empathy, deficits in emotional processing and expression, and abnormal social interactions were the main features of RTLV. Since personality becomes a stable trait in early adulthood and remains constant throughout old age, with only gradual fluctuation during maturation, significant changes in personality can be a useful tool in detecting early symptoms of neurological disease (Rankin et al., 2003; Mychack et al., 2001).

Here we describe the case of a 67 year-old, right-handed woman, JT, who presented with changes in personality and social behavior, and a semantic memory impairment initially noticed only for food items and familiar people. Other aspects of language, such as syntactic processing remained completely intact. VBM showed that JT's medial right anterior temporal lobe was significantly atrophied when compared with 35 age-matched female controls. We present a detailed assessment of JT's cognitive and behavioral changes. We emphasize that personality changes and atypical semantic memory deficits can be early symptoms in RTLV.

Methods

Case Report

JT is a right-handed 67-year old woman who first came to our attention at the UCSF Memory and Aging Center in May of 2002. JT's symptoms became evident to her family during an episode in 1999 when, at a restaurant, she was not able to recognize the look and the taste of apple butter, a food traditionally eaten in her family. JT's reaction was inappropriate and unusual for her, as she became very angry and frustrated with the waiter. At about the same time, JT's family noticed a major change in her personality. She was described formerly as a very strong, reserved and independent person. In keeping with family attitudes, she would always show her best side to the world and never complained or showed emotional distress. For example, she did not share her grief over the loss of her husband. She was a very social and extroverted person, involved in the lives of family and friends. Her daughter described her as a "loner inside a very friendly person". JT loved to travel and shared her knowledge about the world in her work as a successful travel agent for thirty years. In contrast with this pre-morbid personality, during hospitalization following a car accident in early 2000, JT was irritable and demanding, and complained continuously about being left alone, despite frequent visits from her daughter. She had become self-centered and unconcerned about other people's feelings and needs for example she made her daughter feel guilty for not moving into the medical facility, despite knowing the daughter's family and work responsibilities. During the following year, JT's clinical picture rapidly progressed. She became so self-centered that, on one occasion, while her daughter was crying about a personal incident, the patient continued to complain about her own difficulties and failing to acknowledge her daughter's distress. Her semantic difficulties extended from food items to recognizing familiar people and later to words and common objects. She complained particularly of not remembering the names of countries and cities that she had visited multiple times. JT developed a compulsion for drinking wine, but since she could not recall its flavor, her caregiver was able to trick her by filling the wine bottle with grape juice. JT's deficit in recognizing food items was not limited to the visual modality, and tasting foods or being presented with their names did not help her. Similarly, hearing the voices or the proper names of familiar people did not improve her ability to recognize them. Even though her calculation abilities seemed to be spared (she successfully played games involving numbers), in 2001 JT had to stop controlling her own finances because she could no longer understand words written on documents. JT's eating behavior also changed dramatically, and she showed a marked preference for sweets and for condiments that she would sometimes consume as food. For example, she liked to eat butter and, left alone, she would eat a whole pack. In 2001, she started trying to eat non-food items, such as flowers. Her taste in clothes also dramatically changed. She went from wearing sober, neutrally colored clothes, to eccentric, brightly colored items in unusual combinations, such as bright purple with bright orange. It was common for her to choose a single color, such as turquoise, and wear that color from head to toe without regard for whether she combined clashing shades of that color. JT never showed frank signs of social or sexual disinhibition; however, her daughter reports that she would inappropriately discuss details of her medical problems during social and family gatherings. While insightful to her semantic memory deficits, she was not aware of her behavioral changes.

JT spent much of her time doing puzzles and successfully gambling on computer games. She also became increasingly attracted to toys and objects that would appeal to young children. Her mood declined, which she related to her forced retirement. JT's visuo-spatial functions and episodic memory seemed relatively spared, and she never had episodes of spatial or temporal disorientation.

When first seen in May 2002, JT's general neurological examination was normal. Her speech and language output were remarkably fluent and grammatically correct. She was oriented in time and place and was able to carry out a conversation using high-frequency words. When confronted with a word she did not recognize she would typically say "See, I do not know what that means. This is my problem". JT's MRI scan showed anterior temporal atrophy more marked on the right. During the same visit, she was diagnosed as having SD based on the Neary criteria for FTLD. Results of blood tests were normal and apolipoprotein E genotype was 3/3.

All the data reported in this study were collected between May and July 2002. Since then, as of March 2003, JT has become very irritable and has begun to show outbursts of verbal aggressiveness towards her caregiver, even in public places. Her compulsive behaviors have worsened. She picks at her fingers and scratches herself to the point of causing skin lesions. Her mood and behavioral symptoms had initially responded to therapy with SSRIs, but after about six months became less controllable. Her semantic memory functions have also deteriorated further. For instance, it is no longer necessary for her caregiver to fill a wine bottle with juice because she no longer recognizes the wine bottle itself. She has trouble recognizing even close family members from their faces, names or voices (except for her own children). During her last visit to the clinic in March 2003, she was not able to recognize the examiner, by face or voice, yet she was able to remember that a doctor from a country she loves very much had visited her at her home the previous month.

Cognitive and Behavioral Assessment

General Neuropsychological and Functional Evaluation: The patient underwent a complete neuropsychological and functional evaluation. To provide comparable normative data for the tests without published norms, the same battery was administered to ten age-matched normal control subjects. General intellectual function was assessed using the Mini-Mental State Examination (Folstein et al., 1975). Assessment of visuospatial abilities included copying a modified version of the Rey-Osterreith figure, 8 items from the Beery Visuo-Motor Integration battery (each copy rated on a 2-point scale) (Beery, 1997), the WAIS-III Block Design Test (Wechsler, 1997a) and the Number Location test from the Visual Object Space Perception Battery (Warrington and James, 1991). Nonverbal episodic memory was measured by asking the patient to freely recall the modified version of the Rey-Osterreith complex figure after a 10-minute delay, as well as the Visual Reproduction and Faces tests from the Wechsler Memory Scale-Third Edition (Wechsler, 1997b). Verbal memory was measured using the California Verbal Learning Test-Mental Status Version (CVLT-MS) (Delis et al., 2000a, 2000b). A variety of measures were used to assess executive functioning: Digit Span and Spatial Span tests from the WMS-III; subtests from the Delis-Kaplan Executive Functions System (Delis et al., 2001) including three California Trails subtests, four trials of the California Stroop (Color Time, Word Time, Interference Time, and Set-Shifting with Interference Time) and the Tower of California test of cognitive flexibility and nonverbal reasoning. Also, the 64-card version of the Wisconsin Card Sorting Test (Heaton, 1993) was administered. Ability to perform 5 arithmetic calculations was also assessed. Praxis was evaluated by asking subjects to perform 7 buccofacial, transitive limb, and intransitive limb praxis tasks, each of which was rated on a 2-point scale.

At the time of clinical assessment, the patient underwent a functional assessment that included a structured caregiver interview based on the Washington University, St. Louis (WUSTL) worksheets for calculation of the Clinical Dementia Rating Scale (CDR) (Morris, 1993).

Speech and Language Assessment: Speech and language production: Articulation was tested using the Motor Speech Evaluation (Wertz et al., 1984) (MSE). The MSE elicits speech samples with such tasks as vowel prolongation, repetition of syllables, words and phrases; oral reading; and picture description. The examiner determines the presence or absence of dysarthria and apraxia of speech as well as a severity rating (1-7) for each. Spontaneous speech and syntactic production were evaluated using the spontaneous speech section (including answering questions and describing the picnic scene) from the Western Aphasia Battery (Kertesz, 1980) (WAB). The repetition subtest of the WAB was used to assess word and sentence repetition skills.

Lexical retrieval and semantic memory: Confrontation naming was evaluated using the 60 item version of the Boston Naming Test (BNT), with an experimental recognition component added at the end of the test. Patients were shown the drawings of the non-named items and given three alternatives in a verbally presented forced-choice word recognition paradigm. A second naming test of 64 line drawings taken from the Snodgrass and Vanderwart corpus was administered, and included 32 living and 32 non-living objects. To test verbal and visual semantic abilities, both the three-picture and three-word version of the "Pyramid and Palm Trees" test were administered (Howard and Patterson, 1992). The "Auditory Word Recognition" subtest of the WAB and the Information test of the WAIS-III were also performed.

Syntactic comprehension: Sentence and syntactic comprehension abilities were tested using the "Sequential Command" subtest of the WAB and, more extensively, by selected subtests of the

Curtiss-Yamada Comprehensive Language Evaluation-Receptive (Curtiss and Yamada, 1988) (CYCLE-R). Eleven subtests of the CYCLE-R were administered, containing five sentences each, for a total of 55 sentences. All subtests require that the patient listen to a sentence presented verbally and select the line drawing that matches the meaning of the sentence from an array of three or four line drawings. The subtests span a range of sentence types comprising different levels of morphosyntactic complexity, from simple constructions, such as simple declaratives and possession (CYCLE level 2 and 3), more elaborated structures (active voice, agentless and agentive passive voice, double embedding: CYCLE level 4, 5, 6) and the most complex structures (object clefting, subject relative clauses, negative passives, object relative clauses and object relative clauses with relativized object: CYCLE level 7, 8, 9). The numbers denominating the levels correspond to the age at which children normally learn to comprehend the considered type of sentence.

Reading skills: Single word reading was tested by the "Regularity and Reading" subtest of the Psycholinguistic Assessments of Language Processing in Aphasia (Kay et al., 1992) (PALPA). Reading of a passage was also administered as part of the MSE.

Face processing and recognition of emotional faces: JT's ability to match unfamiliar faces was tested using the Benton Facial Recognition Test (Benton and Van Allen, 1968).

Famous face processing and person-specific semantic information was tested using an experimental battery of tests comprising four different tasks: 1) Famous face confrontation naming. When a face was not named, the proper name was given and subjects were asked to provide information regarding the person; 2) Famous face recognition, in which the subject has to point to the familiar face in an array of four (three unfamiliar distractors); 3) Famous face semantic association test, in which subjects need to associate two famous faces for profession in an array of four (one famous and one unfamiliar distractor); 4) Famous proper-name to face matching, in which subjects were asked to match a verbally presented proper name with the corresponding face in an array of four (two famous and two unfamiliar distractors). All tests comprised 20 items. The famous faces were chosen from a pool that was shown to 15 normal controls (mean age: 58). Only faces that were correctly named by at least 14 subjects in this group were used for the experimental tasks. JT's performance in the famous face tests was compared to five age-matched controls (three females and two males).

Recognition of facial expression was evaluated using the Florida Affect Battery (FAB), which consists of multiple subtests for the assessment of the understanding of facial and vocal expressions of emotion (Bowers et al., 1992). For this analysis, only the data on facial expressions were used. In each of the facial affect subtests, photographs of faces (all female), depicting one of five expressions: happiness, sadness, anger or fear, or no emotion (neutral), are presented. The administered emotion tasks included discrimination, naming, selection, and matching of facial expressions**.**

Gustatory Functions and Semantic Memory for Food Items: Primary taste functions were tested using a solution discrimination test. Seven control subjects (mean age 49.4;) and JT were first presented with a sugar solution (20% sucrose) in a paper cup and asked to taste it and describe the taste. Irrespective of their response, all participants were informed that the solution was sugar water. Then two more solutions were presented, one with a higher concentration of sugar (27% sucrose) and one with a lower concentration of sugar (11% sucrose). Subjects were then asked to rank the three solution based on sweetness. This procedure was repeated for three sour solutions (5.9%, 11.1%, and 15.8% lime juice) and three salty solutions (0.69%, 1.37%, and 2.04% NaCl).

JT's semantic and naming abilities for different flavors were also tested using a selection of individually flavored candies as stimuli (jelly beans, Jelly Belly Company). Jelly beans are small chewy candies, which come in many colors and flavors, but all share a consistent size, shape and texture. Five control subjects (mean age 48.4) and JT were sequentially presented with twelve jelly beans and asked to taste each one. The order of presentation was: Peanut butter, cherry, coconut, sizzling cinnamon, licorice, banana, jalapeño pepper, lime, cappuccino, sardine, green apple and buttered popcorn (butter). After each jelly bean presentation subjects were asked to: 1) spontaneously name its flavor; 2) select a picture from an array of five 4×6 inch color photographs of food items that best matched the flavor and 3) select a word from an array of five food names that best matched the flavor (JT only). To test knowledge about the same items without involving the gustatory modality, subjects were asked to: 1) Name the food item in the twelve photographs; 2) Match the food item in each photograph with the correct name out of a choice of five written names; and 3) Match the written name of each food item with its appropriate photograph when given a choice of five photographs Control subjects were able to name all of the items in the photographs successfully and were thus not given the last two tasks.

Behavioral and Personality Assessment: Data from the neuropsychiatric inventory (NPI) were analyzed (Cummings, 1997). The NPI is a caregiver-based survey that evaluates the presence of twelve major behavioral disorders. The major categories of behavior assessed include delusions, hallucinations, aggression/agitation, depression, anxiety, elation/euphoria, apathy, disinhibition, irritability/lability, aberrant motor behavior, sleep-disturbances, and eating disorders. This instrument has previously demonstrated differences in the patterns of behavioral abnormalities between FTD and AD (Levy et al., 1996).

The patient and ten controls also underwent evaluation of change in their social and personality functioning using other-report questionnaires. The Interpersonal Adjectives Scale (IAS) (Wiggins and Coutu, 1995) is a self- or other-report questionnaire designed to measure the interpersonal aspects of personality (Wiggins et al., 1988) (See Figure 1). The underlying theory posits that all social interactions, and by extension individual personality styles, can be mapped along two orthogonal axes: power/dominance, and love/affiliation. The IAS yields an efficient, valid, and theoretically sound evaluation of the two orthogonal personality constructs (dominance and affiliation), and provides information about how these two primary axes work together to create an overall "personality." Also, the IAS provides information about changes in the profile compared to a large normative sample.

The NEO-Five Factor Inventory (NEO-FFI) (Costa and McCrae, 1992) was also used to measure personality change in the patient. It was chosen to complement the IAS by providing additional information about some of the patient's fundamental, non-social personality traits. The NEO-FFI is based on the Five Factor Theory of personality, and measures five orthogonal personality constructs (openness, conscientiousness, extraversion, agreeableness, and neuroticism).

The third questionnaire used to measure personality and social change was the Interpersonal Reactivity Index (IRI) (Davis, 1983). This measure was designed to assess both cognitive and emotional components of empathy. It was chosen because previous studies had shown a significant loss of empathy in patients with damage to the non-dominant temporal lobe (Rankin et al., 2003; Perry et al., 2001). Its 28 items include two 7-item subscales measuring cognitive empathy: Perspective Taking (PT: the tendency to spontaneously imagine the cognitive perspective of another person), and Fantasy (FS: the tendency to project oneself into the place of fictional characters in books and movies); as well as two 7-item subscales measuring emotional empathy: Empathic Concern (EC: the other-centered emotional response resulting from the perception of another's emotional state), and Personal Distress (PD: the self-centered emotional response involving fear or distress that results from witnessing another's stressful circumstances or negative emotional state). The PD subscale reflects a primitive form of empathy that interferes with effective perspective taking; thus it tends to drop as the other scales rise and is negatively related to measures of overall social functioning. Higher scores on the PT, FS, and EC scales are associated with a more highly developed capacity for empathy.

Because of the patient's cognitive deficits, and because many dementia patients tend to lose the capacity for accurate self-assessment, the patient's social and personality functioning was obtained from a first-degree relative, the daughter. A retrospective evaluation of the patient's premorbid behavior was used as a baseline. The patient's daughter, as well as first-degree relatives of the controls, were asked to fill out two personality questionnaires, one describing the subject's current characteristics, and the other describing how they were before the onset of their disease (or before retirement in the case of the normal controls). Personality assessment by first degree relatives of dementia patients has been demonstrated to have very good inter-rater reliability (Strauss et al., 1993; Heinik et al., 1999) and informant ratings using the IAS in particular have excellent internal and temporal reliability (Kurtz et al., 1999). IAS questionnaires were scored using the IAS computer scoring program (Wiggins and Coutu, 1995; Wiggins, 1995) which generates T-scores by comparing patient scores to the normative sample data set collected by the IAS developers (Wiggins and Coutu, 1995; Wiggins, 1995). NEO-FFI percentile scores were calculated using the published norms for women, in Appendix B of the NEO manual (Costa and McCrae, 1992). IRI percentile scores were calculated by comparing the patient's scores to the scores of the 10 normal control subjects. Change scores were calculated by comparing current and retrospective informant ratings.

Anatomical Analysis using Voxel-based Morphometry

MRI Scanning: MRI scans were obtained on a 1.5-T Magnetom VISION system (Siemens Inc., Iselin, N.J.) equipped with a standard quadrature head coil. Structural MRI sequences included a volumetric magnetization prepared rapid gradient echo MRI (MPRAGE, TR/TE/TI = 10/4/300 ms) to obtain T1-weighted images of the entire brain, 15^o flip angle, coronal orientation perpendicular to the double spin echo sequence, 1.0 x 1.0 mm^2 in-plane resolution and 1.5 mm slab thickness. These images were used for the VBM analysis.

Voxel-based Morphometry: Voxel-based Morphometry (VBM) allows the detection of regional brain atrophy by voxel-wise comparison of MRI grey matter volumes on MRI scans (Ashburner and Friston, 2000; Good et al., 2002). The technique comprises an image pre-processing step (spatial normalization, segmentation, modulation and smoothing) followed by statistical analysis. Both stages were implemented in the SPM99 software package (www.fil.ion.ucl.ac.uk/spm) using standard procedures, including an ad-hoc age-matched template (Ashburner and Friston, 2000; Good et al., 2002). The technique can be applied to compare single subjects versus groups, as long as a sufficient smoothing kernel has been applied (Salmond et al., 2002). In this study, normalized, segmented and modulated gray matter images were spatially smoothed with a 12 mm FWHM isotropic Gaussian kernel. JT's scan was compared to 35 age-matched female controls (mean age 67). Age and total intracranial volume were entered into the design matrix as nuisance variables. We accepted a level of significance of $p < 0.05$ corrected for multiple comparisons but, because of the risk of false negatives in single subject analysis, we also report effects at $p < 0.001$ uncorrected.

Results

Cognitive and Behavioral Assessment

The patient's scores were typically converted to standard scores using published normative data.

Neuropsychological and Functional Evaluation: JT's performance in all tests of visuospatial functioning (see Table I for details), was average with the exception of the VOSP number location. Her poor performance on this test appeared to be due to her inadequate comprehension of the rules of the test. She also performed in the normal range on a facial discrimination task (Benton Facial Recognition Test; see below). JT showed low-average or impaired performance in both verbal and non-verbal memory tests. She performed in the

TABLE I

JT Demographic, Functional and General Neuropsychological Data compared to Published Normative Data, or to Age-matched Normal Control Subjects

	JT		
DEMOGRAPHICS AND FUNCTIONAL DATA:			
	Score	%ile	Rating
Age	66	–	–
Education	15	–	–
Geriatric Depression Scale	19	< 1	Impaired
MMSE (max = 30)	24	< 1	Impaired
CDR	0.5	–	–
NEUROPSYCHOLOGICAL DATA:			
Visuospatial Functions:			
Modified Rey-O Copy (max = 17)	16	67	Average*
WAIS-III Block Design (SS)	10	50	Average
Beery 8-Item Test (max = 16)	13	21	Average*
VOSP Number Location	6	< 1	Impaired
Visual Memory:			
Modified Rey-O Delay (max = 17)	5	1	Impaired*
WMS-III Faces I (Scaled Score)	9	37	Average
WMS-III Visual Reproductions			
VR I (Scaled Score)	6	9	Low Average
VR II (Scaled Score)	4	2	Impaired
Verbal Memory:			
CVLT-MS (max = 9)			
30" Free Recall	1	< 1	Impaired
10' Free Recall	0	< 1	Impaired
10' Recognition	0	< 1	Impaired
Executive Functions:			
WMS-III Digit Span (Scaled Score)	17	99	Very Superior
WMS-III Spatial Span (SS)	16	98	Very Superior
Wisconsin Card Sorting Test			
% Errors	22	70	Average
% Perseverative Errors	6	95	Superior
% Non-Perseverative Errors	16	25	Average
% Conceptual Responses	73	73	Average
D-KEFS Design Fluency			
5 Dots	15	99	Very Superior
Empty Dots Only	11	75	High Average
Switching	9	84	High Average
D-KEFS Trails			
Number Time	33	83	High Average
Letter Time	26	93	Superior
Number-Letter Sequencing Time	53	92	Superior
D-KEFS Tower of California (SS)	16	98	Very Superior
D-KEFS Stroop			
Color Time	34	43	Average
Word Time	21	79	High Average
Interference Time	53	71	Average
Set-Shifting Time	52	91	Superior

*Standard score computed in reference to the 10 normal control subjects.

high average to very superior range on tests of verbal and non-verbal executive functioning.

Speech and Language Assessment: JT's speech assessment showed no signs of dysarthria or apraxia of speech. On the fluency component of the WAB, JT lost one point due to anomic and recognition errors that she replaced with filler words, such as "thing" (See Table II). However, language production was remarkably preserved with production of grammatically correct, complex sentences. Repetition was impaired, while single word comprehension, tested with the WAB "word recognition" subtest, was perfect. JT was significantly impaired in both the word and picture version Pyramids and Palm Trees test, with greater difficulty in the picture task. JT was also markedly impaired in the sixty-four item naming task, showing a greater deficit for living items. She was able to name only two out of 60 items in the Boston Naming Test, with correct recognition of 25% of the non-named items. Despite the severe naming deficit, JT's comprehension of syntactic structures was above average and her reading abilities were preserved, even for exception words. Her semantic memory impairment resulted in an impaired score in the WAIS-III Information subtest. JT performed in the low average range on a test of phonemic fluency (FAS: 30 words, 13th%ile), but category fluency was severely impaired (Animals: 3 words/min, < 1st percentile), consistent with her semantic loss.

Face Processing and Recognition of Emotional Faces: Consistent with the neuropsychological results, JT showed average performance on the Benton Facial Recognition Test. She was, however, severely impaired in all tasks that involved famous faces and proper names. She was completely unable to name any famous face and showed significant difficulty in matching faces for profession and in matching a famous proper name to a face. She was also impaired in choosing whether a face looked familiar, but to a lesser degree. JT's impairment did not seem to be confined to the visual modality because, when presented with the proper name corresponding to each of the twenty unnamed famous faces, she was able to provide defining information for only four, and fourteen did not even sound familiar to her.

On the FAB, JT showed significant impairment in recognizing facial expressions depicting negative emotions, while she demonstrated perfect performance for faces expressing happiness.

Gustatory Functions and Semantic Memory for Food Items: JT was able to discriminate the sugary, salty, and sour solutions but failed to name them and reported that she had never experienced these tastes before. However, she was able to successfully rank the three concentration levels for

TABLE II

JT Demographic Language, Facial Processing, Person-specific Semantics and Facial Expression Recognition Data compared to Published Normative Data or to Age-matched Normal Control Subjects

Language data		Score	%le	Rating
Speech and WAB Spech fluency (max = 10)		9	NA	NA
WAB repetition (max = 100)		80	< 1	Impaired*
WAB word recognition (max = 60)		60	NA	Very Superior
Pyramids and Palm Trees:	Words (max = 52)	43	< 1	Impaired
	Pictures (max = 52)	27	< 1	Impaired
Sixty-Four Item Naming Test:	Total (max = 64)	10	< 1	Impaired*
	Living (max = 32)	2	< 1	Impaired*
	Manmade (max = 32)	8	< 1	Impaired*
Boston Naming Test:	Total named correct (max = 60)	6	< 1	Impaired
	Recognized items (% of non named)	25	–	–
WAB sequential commands (max = 80)		80	NA	Very superior
CYCLE (syntactic task):	Total (max = 55)	53	79	High Average*
	Cycle 2,3 (max = 10)	10	–	–
	Cycle 4 (max = 15)	14	–	–
	Cycle 5,7 (max = 10)	10	–	–
	Cycle 8 (max = 10)	10	77	High Average*
	Cycle 9 (max = 10)	9	50	Average*
PALPA reading words:	Regular (max = 30)	30	100	Very Superior
	Exception (max = 30)	30	100	Very Superior
Category Fluency: Animal		3	< 1	Impaired
Phonemic Fluency: FAS		30	13	Low Average
WAIS-III Information (Scaled Score)		2	< 1	Impaired
<u>Face Processing and Person-Specific Semantics:</u>				
Benton Face Recognition Test (max = 54)		42	20	Average
Famous Face Naming (max = 20)		0	< 1	Impaired
Famous Face Recognition (max = 20)		14	< 1	Impaired
Famous Face Association (max = 20)		5	< 1	Impaired
Famous Proper Name to face matching (max = 20)		6	< 1	Impaired
Florida Affect Battery (% correct)				
	Happiness	100	–	Very Superior
	Fear	75	< 1	Impaired
	Sadness	50	< 1	Impaired
	Anger	58	< 1	Impaired

*Standard score computed in reference to the 10 normal control subjects.

TABLE III
Patient Personality Scores before and after Onset of Illness

Measure	Before illness			Current		
	Raw Score	% ile	Rating	Raw Score	% ile	Rating
IAS						
PA – Assured/Dominant	51	94	*Extremely High*	24	2	*Extremely Low*
BC – Arrogant/Calculating	15	21	Low Average	28	76	High Average
DE – Cold-Hearted	26	97	*Extremely High*	26	97	*Extremely High*
FG – Aloof/Introverted	18	31	Average	31	88	High Average
HI – Unassured/Submissive	29	46	Average	40	84	High Average
JK – Unassuming/Ingenuous	42	62	Average	32	18	Low Average
LM – Warm/Agreeable	52	46	Average	32	< 1	*Extremely Low*
NO – Gregarious/Extraverted	45	34	Average	31	< 1	*Extremely Low*
Vector Length	0.4	8	Very Flexible	3.0	> 99	*Extremely Rigid*
NEO-FFI						
Openness	16	3	*Extremely Low*	8	< 1	*Extremely Low*
Conscientiousness	48	99	Extremely High	41	85	High Average
Extraversion	35	88	High Average	17	3	*Extremely Low*
Agreeableness	41	94	Very High	36	68	Average
Neuroticism	6	97	Extremely Low	41	1	*Extremely High*
IRI						
Fantasy	19	63	Average	17	27	Average
Perspective Taking	22	39	Average	8	1	*Extremely Low*
Empathic Concern	32	87	High Average	17	< 1	*Extremely Low*
Personal Distress	12	67	Average	23	90	High Average

each. Controls made no errors on ranking sweet and sour solutions but one subject confused the lowest two concentrations of salty solutions. Therefore, JT demonstrated normal primary taste functions, as she was able to correctly discriminate the solutions and their different concentrations.

The jelly bean taste recognition and semantic memory test showed that control subjects were able to name the flavor of more than half of the jelly beans with no prompting (7.7; sd 2.0) while JT failed to spontaneously name any of the flavors. When given five photographs and asked to pick the one that most closely matched the jelly bean's flavor, control subjects were nearly perfect (11; sd 0.9), while JT successfully matched seven out of 12 jelly beans. JT's score was well above chance (2.4) but she was still severely impaired on this task (Z score = – 4.5; < 0.1%). JT performed worse when five written words were given and she was asked to match the word to the jelly bean flavor (4). Furthermore, JT was unable to name any of the items in the photographs and was able to recognize only four of the written names of the food items. When JT was presented with a word and five photographs, she was able to match six out of twelve of the words to their appropriate photographs control performance was perfect.

Measures of Personality and Interpersonal Functioning: Consistent with JT's clinical history, the NPI revealed agitation, depression, disinhibition, aberrant motor behavior, sleep problems and an eating disorder.

On every quantitative measure of her personality functioning, the patient demonstrated significant changes from pre-morbid to post-morbid state that were far beyond what was seen in the normal control group (See Table III). On the IAS personality scale, the patient's pre-morbid scores the 97th percentile for Cold behaviors, and the 94th percentile for Assured/Dominant behaviors. Otherwise, her scores generally was average her overall personality style was unusually healthy due to its flexibility (as measured by the Vector Length scale). This scale measures the degree to which the individual is capable of exhibiting all facets of personality according to what is appropriate for the particular social situation at hand. The patient's premorbid scores indicate that she was capable of a wide and well-balanced variety of behaviors, suggesting that she typically behaved in a socially adept manner. This flexibility showed a dramatic shift, as evinced by her post-morbid vector length score of greater than the 99th percentile compared to healthy female control subjects. This suggests that she became rigid in her approach to interpersonal interactions, using the same stereotyped and often inappropriate behaviors regardless of situational demands. This rigid personality style included a number of features that differed significantly from how she had behaved premorbidly, including pathologically low (< 3rd percentile) levels of Assured/Dominant, Warm/Agreeable, and Gregarious/Extraverted behaviors. She went from low average to high average in her tendency to demonstrate Arrogant/Calculating behaviors, and her tendency towards Aloof/Introverted and Unassured/Submissive behaviors increased. Notably, she remained in the 97th percentile for her tendency to exhibit Cold-Hearted behaviors, which had not changed significantly from their extremely high premorbid levels. The ten normal control subjects, by contrast, showed a range of less than 10 percentile points of change on any of their scores between the two time points tested, suggesting that the patient's personality change is unlikely due to normal aging (See Figure 1).

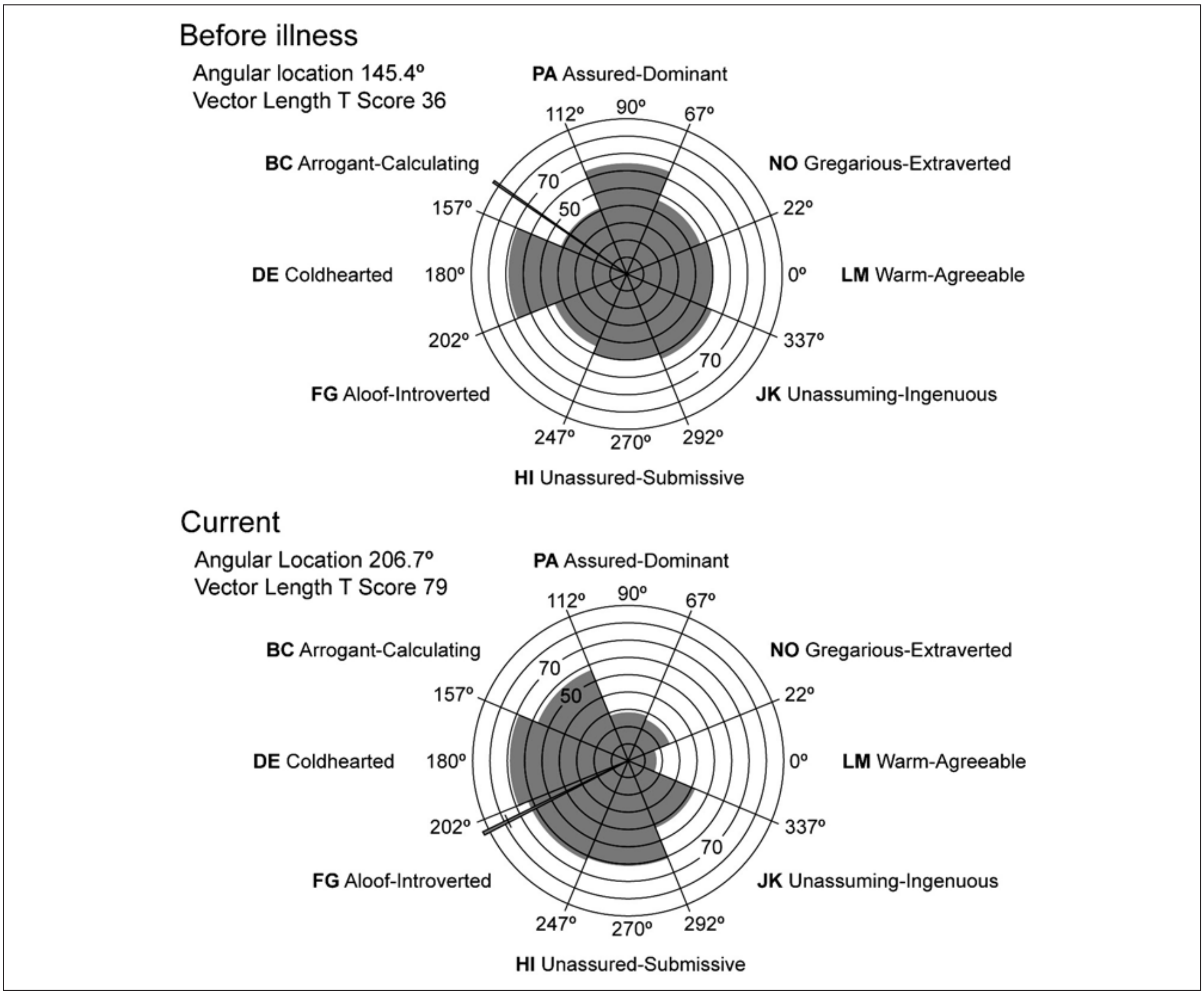

Fig. 1 – *Premorbid and current ratings of the patient's scores on the Interpersonal Adjectives Scales (IAS), adapted from the IAS scoring program report.*

The NEO-FFI showed the greatest changes in the patient's behavior occurred in the domains of Neuroticism, which increased to extremely high levels from having been extremely low premorbidly, and Extraversion, which went from high average to extremely low. Both her level of Agreeableness and her level of Conscientiousness dropped significantly from pre-morbid to post-morbid assessments. Notably, her extremely low (3rd percentile) level of Openness remained extremely low after the onset of the disease. The changes to the Conscientiousness, Extraversion, Agreeableness, and Neuroticism scores over time were of a much greater magnitude than was seen in the normal control group (see Figure 2A).

On the IRI, the patient again showed significant changes on a number of subscales. In the area of cognitive empathy, the greatest change was a 38 percentile drop in Perspective Taking, down to the extremely low level (1st percentile). Her level of Fantasy dropped slightly, but remained within the average range. Her ability to express emotional empathy also changed significantly, as demonstrated by her loss of Empathic Concern for others (which dropped to below the 1st percentile from a high average morbid level). Her level of Personal Distress pre-morbid increased, suggesting that she was reverting back to a more primitive form of emotional empathy, perhaps as a correlate to the loss of her ability to perform cognitive Perspective Taking. As with the other measures, changes in normal controls were extremely small compared to those in the patient (See Figure 2B).

Anatomical Analysis using Voxel-based Morphometry

JT's VBM results showed a remarkably focal pattern of atrophy, confined to the right anterior temporal lobe (See Figure 3). At time of scanning (three years from the first clinical symptoms) JT's gray matter volumes were significantly decreased only in the medial portion of the anterior temporal lobe, in the amygdala/hippocampal structures

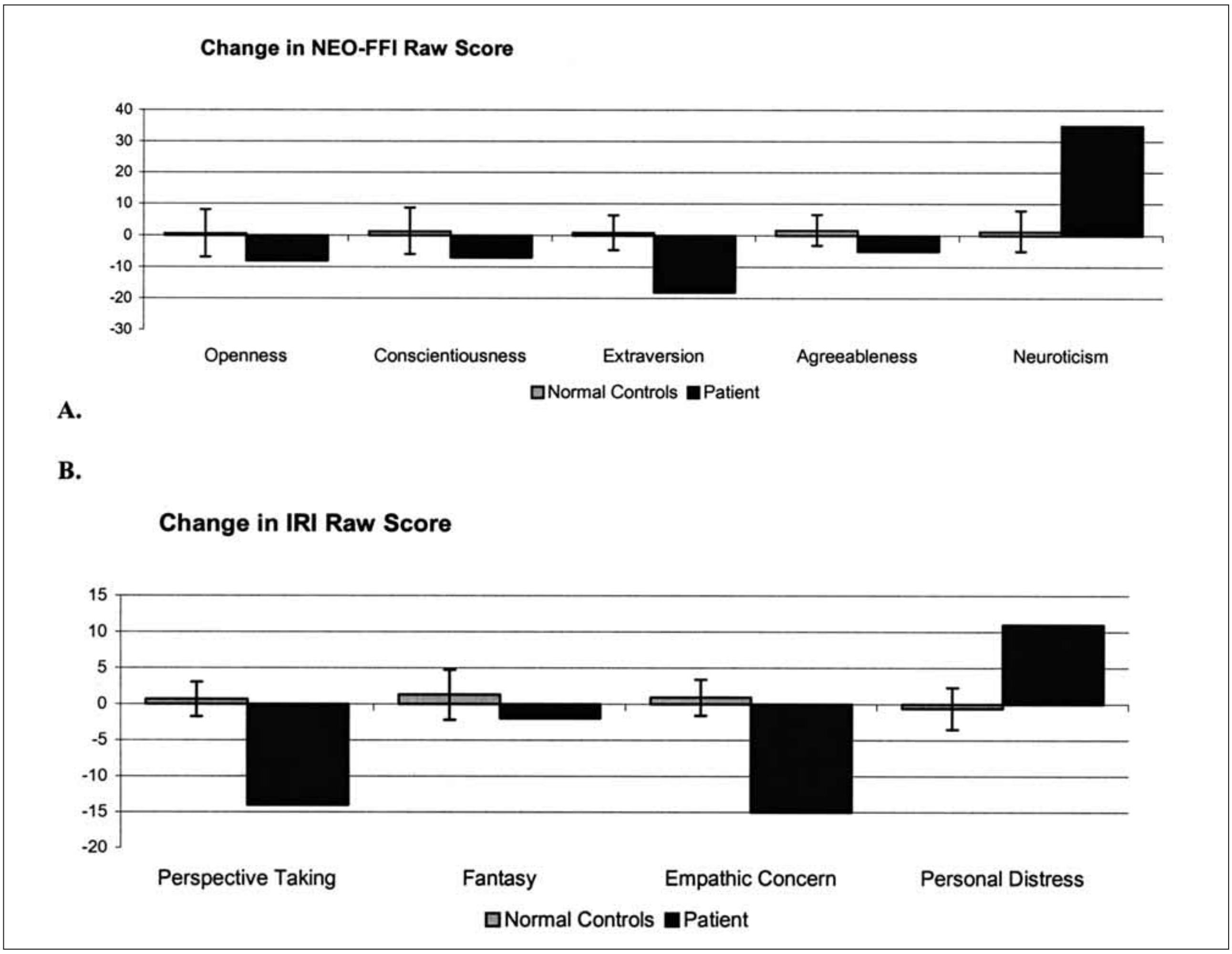

Fig. 2 – *Ratings of the patient's current functioning are contrasted with ratings of the patient before she became ill. Ratings of 10 normal control subjects' current functioning are contrasted with retrospective ratings describing "how they were before retirement", or if not retired, "5 years ago."* ***A)****: The magnitude of change in the patient's scores on the NEO-Five Factor Inventory, a measure of the Big Five Factors of personality.* ***B)****: The magnitude of change in the patient's scores on the Interpersonal Reactivity Index (IRI), a measure of cognitive and emotional empathy.*

extending inferiorly into the temporal pole and posteriorly along the collateral sulcus and the anterior fusiform gyrus. When the threshold of the analysis was lowered to a level of significance of $p < 0.001$ uncorrected for multiple comparisons, small regions of atrophy in the corresponding left anterior temporal sites and in the right posterior insula also appeared. More lateral regions in the temporal lobe and the frontal lobes did not show significant gray matter loss.

Discussion

We studied the cognitive, behavioral and anatomical features of JT, a case of right temporal lobe variant (RTLV) of FTLD. This case provides valuable insight into both the clinical presentation of RTLV and the functions of the right temporal lobe. JT's clinical presentation was mainly characterized by: 1) a semantic deficit that was particularly severe for food items and familiar people; and 2) early marked behavioral and personality changes.

To our knowledge, this is the first described case of SD presenting with a multimodal visual, gustatory and verbal semantic deficit in recognizing food items. Our case also showed changes in eating behaviors typical of SD in general (Ikeda et al., 2002), and a tendency to orally examine all objects repeatedly and indiscriminately, as originally described in primates with bilateral anterior temporal lobe ablation (Kluver and Bucy, 1939). The combination of a marked deficit in flavor and food recognition, hyperoral behavior and changed eating habits created a particularly dramatic picture in JT, who, if not controlled, would eat floral table decorations and large quantities of butter, oil and jam by themselves. Converging animal and human physiological studies have identified the insula as the primary cortical gustatory area (Small et al., 1999; Frey and Petrides, 1999) and the right anterior temporal lobe (Small et al., 1997), amygdala and orbitofrontal

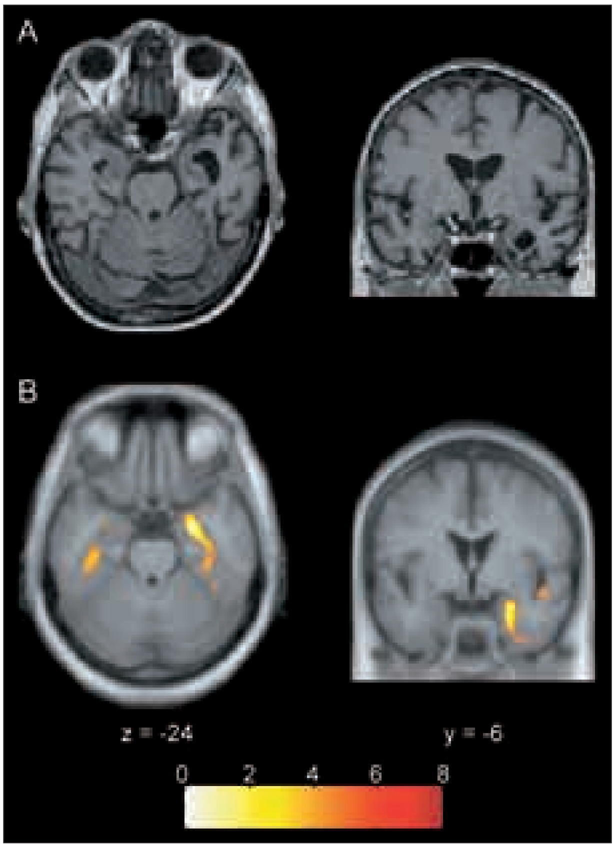

Fig. 3 – *A) Axial and coronal sections of JT's original T1 weighted MRI scan.* ***B)*** *Areas of significant atrophy in JT versus 35 age-matched female healthy controls. The figures was obtained within the SPM99 program using a statistical threshold of p < 0.001 uncorrected for multiple comparisons. Regions of significant gray matter loss are superimposed on an axial and coronal sections of the mean image of the scans used to obtain the template image. Both in A) and B) scans are displayed in neurological convention (right is right).*

cortex (O'Doherty et al., 2001) as areas involved in processing taste quality and pleasantness. Consistent with these findings, VBM showed greater atrophy in the right temporal pole, amygdala and insula in JT.

JT complained of a difficulty in recognizing familiar people, which appeared a few months after the food-related and personality changes. Her deficit was not limited to the visual domain (prosopagnosia) but also included proper names. Of the few reported cases of RTLV, deficits limited to both familiar faces (Gentileschi et al., 1999; Tyrrell et al., 1990), and multimodal person-specific semantics (Kitchener and Hodges, 1999), have been described. Gainotti and colleagues (2003) have recently described a case of RTLV that presented with a more complex deficit in recognizing familiar people. Furthermore, Mendez and Ghajarnia (2001) described a case showing prosopagnosia and olfactory agnosia.

Lesion studies and functional imaging data converge in indicating that the fusiform gyrus is the primary site of face perception (De Renzi et al., 1994; Gorno-Tempini et al., 1998; Kanwisher et al., 1997). Converging evidence indicates that multimodal person-specific semantic information is processed in the antero-lateral temporal lobe. However, the issue of hemispheric lateralization of both of these functions is still debated (Hodges and Graham, 1998; Gorno-Tempini et al., 1998; Gorno-Tempini and Price, 2001; Leveroni et al., 2000). In JT, VBM showed the most significant atrophy in the right temporal pole and the right collateral sulcus/anterior fusiform region, indicating a possible role of these regions, not only in face-perception, but also in higher recognition processes. When the level of significance of the analysis was lowered to an uncorrected level, the left anterior fusiform gyrus was also atrophied. Surprisingly, more lateral neocortical regions in the anterior temporal lobe were not involved.

At the time of testing, JT's semantic deficit was no longer limited to food items and familiar people but involved other categories of objects. JT showed a significant generalized naming deficit that was particularly severe for living items. Despite the severe semantic deficit, other aspects of her cognitive functions, such as frontal-executive skills, comprehension of complex syntactic structures and reading regular and irregular words, were remarkably spared. While episodic memory for everyday events seemed to be spared, JT performed poorly on formal tests of verbal and non-verbal memory. This finding has previously been reported and is consistent with the anatomical involvement of the anterior hippocampus in SD (Rosen et al., 2002a).

The second major feature of JT's clinical presentation was the early change in personality and social behavior. We quantified this change

TABLE IV

Results of the Voxel-based Morphometry Study comparing JT with 35 Healthy Control Subjects

Area (BA)	x	y	z	Z score
Right amygdala/anterior hippocampus	26	– 3	– 27	5.8*
	32	– 14	– 21	4.9*
R collateral sulcus/fusiform gyrus (20/37)	35	– 18	– 19	4.9*
	37	– 28	– 16	4.8*
R temporal pole (20)	35	– 5	– 44	5.1*
Right posterior insula/superior temporal gyrus	48	7	– 16	4.2**
Left amygdala/anterior hippocampus	– 24	– 4	– 20	3.7**
Left collateral sulcus/fusiform gyrus	– 35	– 24	– 16	4.6**

*$p < 0.05$ corrected for multiple comparisons
**$p < 0.001$ uncorrected for multiple comparisons

using psychometrically validated assessment tools, specifically designed to measure personality and empathic functioning. We used an other-report method to circumvent problems caused by the patient's potential comprehension deficits and lack of insight. Because personality and social behavior are highly variable among healthy individuals, we performed a retrospective evaluation of the patient's premorbid behavior to use as a baseline. We only considered personality changes, rather than the presence or absence of specific traits, as signs of disease. For example, at the time of examination JT showed low levels of openness (NEO-FFI) and high levels of cold behaviors (IAS). Previous research has suggested that these qualities often develop in temporal variant FTLD patients (Rankin et al., 2003, 2004; Perry et al., 2001). However, analysis of JT's premorbid functioning showed that she had always been an emotionally reserved and private individual, making this particular scale score less relevant because no change could be measured.

Though the patient's level of emotional distance and reserve seemed unchanged from premorbid levels, there was evidence for loss of warmth. The NEO showed that she had retained the ability to act according to social expectations at times, but the IAS suggested that this was no longer accompanied by interpersonal warmth and kindness (< 1st percentile). This may be a result of damage to brain areas in the right temporal lobe that are important for interpretation of facial expression and voice prosody, such as the right amygdala (Rosen et al., 2002b; Morris et al., 1996). Consistent with previous findings, JT's test results showed mild impairment in the recognition of facial expressions, specifically for negative but not positive emotions (Rosen et al., 2002b). It is likely that these abnormalities in emotional comprehension and expression contribute significantly to the behavioral abnormalities characteristic of FTLD.

The implications of this alteration in facial emotion perception were also borne out in JT's empathy testing. Studies of empathy in FTLD using the IRI suggest that temporal variant patients show a definitive loss of emotional response to another's distress (Rankin et al., 2004). This pattern was suggested by JT's clinical history and was confirmed by her test scores. While she once displayed an average to high average level of both cognitive and emotional empathy, her ability to take the perspective of others and her empathic concern for others were both extremely low at the time of the assessment (< 1st percentile). On the other hand, the "fantasy" component of empathy (the ability to project oneself into fictional or hypothetical future situations), which is theoretically another aspect of cognitive empathy, did not appear to have changed significantly in JT's case.

A number of other personality traits and social skills also changed early in JT's disease process. Overall, she developed a stereotyped, rigid manner of interacting with others that limited her social repertoire and made it more likely that she will behave inappropriately in interpersonal situations. This finding is typical in FTLD but not Alzheimer's disease patients (Rankin et al., 2003). Consistent with previous research on FTLD (Rankin et al., 2003), JT also almost entirely stopped exhibiting extraverted behaviors according to both the NEO and the IAS, though her premorbid level of extraversion was in the average to high average range. Previous finding that temporal lobe FTLD patients tend to retain much of their social dominance was not borne out in this case. JT dropped from having an extremely high level of social dominance (94th percentile) to having extremely low dominance (2nd percentile). She also became significantly more likely to be demanding and even calculating in her social interactions, and was less unassuming and ingenuous, a shift which has previously been observed to differentiate temporal from frontal variant FTD patients (Rankin et al., 2004).

Finally, JT demonstrated dramatically increased levels of neuroticism on the NEO questionnaire, along with high levels of personal distress on the IRI. These increases seem to be a nonspecific finding in dementia patient groups who have been studied with this instruments. Patients with Alzheimer's disease as well as both frontal and temporal variant FTLD have shown a similar pattern (Rankin et al., 2004; Welleford et al., 1995).

In summary, evidence from JT's case demonstrates that atypical semantic deficits and behavioral changes can be the earliest and most destructive symptoms in RTLV. The use of standardized, quantitative measures of personality and behavioral changes holds great potential to improve the early differential diagnosis of RTLV, and to increase our knowledge of the functions of the right anterior temporal lobe.

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