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Clinical characterization of bvFTD due to FUS neuropathology

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Abstract

In 2009, inclusions containing the fused in sarcoma (FUS) protein were identified as a third major molecular class of pathology underlying the behavioral variant frontotemporal dementia (bvFTD) syndrome. Due to the low prevalence of FUS pathology, few clinical descriptions have been published and none provides information about specific social-emotional deficits despite evidence for severe behavioral manifestations in this disorder. We evaluated a patient with bvFTD due to FUS pathology using a comprehensive battery of cognitive and social-emotional tests. A structural MRI scan and genetic tests for tau, progranulin, and FUS mutations were also performed. The patient showed preserved general cognitive functioning and superior working memory, but severe deficits in emotion attribution, sensitivity to punishment, and the capacity for interpersonal warmth and empathy. The gray matter atrophy pattern corresponded to this focal deficit profile, with preservation of dorsolateral fronto-parietal regions associated with executive functioning but severe damage to right worse than left frontoinsula, temporal pole, subgenual anterior cingulate, medial orbitofrontal cortex, amygdala, and caudate. This patient demonstrates the striking focality associated with FUS neuropathology in patients with bvFTD.

Keywords

behavioral variant frontotemporal dementia; FTL-D-FUS; social emotional testing; voxel-based morphometry; FUS neuropathology

INTRODUCTION

Patients with the behavioral variant of frontotemporal dementia (bvFTD) develop abnormal social and emotional behavior early in the disease, often before manifesting cognitive deficits. Attempts to delineate a precise profile of the bvFTD syndrome have been hampered by the heterogeneity of its underlying pathology. Until recently, bvFTD was thought to arise from either of two distinct neuropathological processes initially affecting the same neural networks, with approximately half showing frontotemporal lobar degeneration (FTLD) with tau-immunoreactive inclusions (FTLD-tau) and the other half showing inclusions containing the transactive response DNA-binding protein of 43 kDa (TDP-43, FTLD-TDP) (Mackenzie, Neumann et al. 2009). A small minority of patients continued to show neuronal inclusions immunoreactive only for ubiquitin, and most of these individuals presented with severe behavioral symptoms and an early age of onset in the absence of a family history (Josephs, Lin et al. 2008; Mackenzie, Foti et al. 2008; Roeber, Mackenzie et al. 2008;

Seelaar, Klijnsma et al. 2009). This clinicopathological entity was referred to as atypical FTLT with ubiquitinated inclusions (aFTLD-U); in 2009, these inclusions were found to harbor fused in sarcoma (FUS) protein (Neumann, Rademakers et al. 2009). Follow-up studies suggest that the aFTLD-U subtype of FTLT-FUS accounts for 5–10% of patients with bvFTD (Seelaar, Klijnsma et al. 2009; Urwin, Josephs et al. 2010).

The link between FUS and FTLT arose following the discovery that mutations in the fused in sarcoma/translocated in liposarcoma gene (FUS/TLS) accounts for about 4% of familial cases of amyotrophic lateral sclerosis type 6 (Kwiatkowski, Bosco et al. 2009; Vance, Rogelj et al. 2009). Neuropathological studies of those with FUS/TLS mutations showed FUS-immunoreactive neuronal cytoplasmic inclusions. Shortly thereafter, a series of reports demonstrated that aFTLD-U (Neumann, Rademakers et al. 2009), neuronal intermediate filament inclusion disease (NIFID) (Neumann, Roeber et al. 2009), and basophilic inclusion body disease (BIBD) (Munoz, Neumann et al. 2009), were united by FUS-immunoreactive pathology, giving rise to the new FTLT major molecular class, FTLT-FUS. FTLT-FUS occurs almost always in the absence of a FUS gene mutation (Cairns and Ghoshal). FUS mutations appear to be rare among patients with FTLT spectrum disorders (Van Langenhove, van der Zee et al.), however, and the impact of FUS mutations on the development of FUS neuropathology is not yet well understood.

All three FTLT major molecular classes cause the bvFTD syndrome, which features altered social conduct, loss of insight, disinhibition, and diminished emotional responsiveness and empathy (McKhann, Albert et al. 2001). Since FTLT-FUS was recently discovered and remains the least prevalent FTLT pathology, the clinical syndrome of bvFTD due to FTLT-FUS has not yet been well-characterized. In this report, we describe Mr. X, a bvFTD patient with prominent social and behavioral impairments but preserved executive, language, and visuospatial functioning. Autopsy revealed ventral frontal, insular, temporal, amygdalar, and striatal degeneration due to the aFTLD-U subtype of FTLT-FUS. Here we provide a complete profile of this patient, including comprehensive social/emotional testing, neuroimaging, and neuropathological analysis, seeking to elucidate the key features of this clinico-pathological entity.

CLINICAL HISTORY

Mr. X was a right-handed man who presented with progressive behavioral changes. Prior to symptom onset, he was a charming husband, father, friend, and coworker, described as warm, gregarious, sensitive and generous. He worked first as an editor and later as a manager at a software company.

At age 37, Mr. X began reading books about death and dying to his 3-year-old daughter. He then read books about neurological diseases and played computer solitaire frequently. A year later, a former partner stopped paying child support, but he did not pursue the matter, which his wife thought was an uncharacteristic reaction. At age 40, Mr. X developed repetitive behaviors. He counted white cars during road trips and played an “alphabet game” with license plates. The same year, Mr. X was laid off for reasons reportedly unrelated to his job performance, but he seemed unbothered and did not seek new employment.

By age 42, he developed increasing apathy with bizarre, ritualistic behaviors. He was unhelpful during his family’s move to a new home. He developed a urination routine at bedtime consisting four trips to the bathroom before turning off the lights. His hygiene declined, and his hair and beard grew long. He wore his daughter’s hair clips in his beard and combed his mustache over his mouth. Mr. X asked his wife for help with lane changes, turn signals, and directions while driving. By the next year, he had become more reserved and less engaged in hobbies and social activities.

Several situations occurring when he was age 44 years suggested that Mr. X's emotional responsiveness had become even more diminished. His son ran away from home, and Mr. X grew depressed and withdrawn but took no steps to address the situation. When the September 11th, 2001 attacks occurred, the patient's wife noted that he was surprisingly unmoved. Mr. X started to tell repetitive, conversationally intrusive jokes and puns, and frequently rearranged letters of people's names to make plays on words.

During the next year, Mr. X's judgment continued to decline. He taunted his young teenage nephew harshly. He led his 8-year-old daughter into a river with a swift current using a broom handle. Although she was visibly struggling, he appeared unconcerned, and other adults had to intervene. Later that year, Mr. X was laid off from work after a series of demotions. Despite being offered his "dream job" by a former boss, he did not pursue it.

By age 46, Mr. X became more impulsive and socially disinhibited and developed repetitive motor behaviors and hyperorality. He ran red lights when driving. On one occasion, he caused a car accident but drove away, requiring the police to pursue him home. He became interested in singing and enjoyed changing lyrics to make them silly or satirical, often in a sexually charged manner. Much of his humor concerned flatulence. He engaged in repetitive storytelling, joking, and questioning without seeming aware that he had told the same story within the hour. He had repetitive finger tapping, hand and leg rubbing, and counted his steps while pacing. He preferred sweets, including sugary cereals and popsicles, and lost interest in his favorite foods. He stuffed gumballs in his mouth and nose and ate frozen peas.

By age 49, he developed a profound loss of disgust reflected by several occasions where he placed his daughter's toys in the toilet. Attention to bodily pain was inconsistent; he had poorly localized nonspecific pains, but was dismissive of severe cuts in his feet. Impulsiveness continued and other compulsive behaviors emerged. He began spending money irresponsibly on the internet. He drank water compulsively and felt compelled to fill water glasses to a precise level. He had minor difficulties picking up small items and turning book pages, but his gait and balance remained stable. He took short walks alone, often invading his neighbors' privacy.

The following year, Mr. X developed new rituals. He opened the refrigerator hundreds of times per day and stuffed tissues into his nose until he sneezed, creating piles of tissues that littered the floor. His craving for sweets declined, and he preferred crunchy foods. Restlessness was replaced by apathy and inertia. He developed urinary incontinence and was indifferent to accidents. He had episodes of agitation during which he would bang on windows and doors; risperidone improved these symptoms.

Throughout his illness, Mr. X maintained good memory for remote events; he occasionally asked repetitive questions and had rare difficulty recognizing acquaintances' names and faces. There were no word-finding or comprehension difficulties. By age 50, Mr. X moved into a supervised living setting. He continued to display prominent behavioral disinhibition, mild parkinsonism, and no signs of motor neuron disease. He became more passive until his death from aspiration pneumonia at the age of 51.

Mr. X's father was diagnosed with Parkinson's disease at age 78; he died at age 80, and no autopsy was performed. His mother, who had a history of depression and alcoholism, died from ovarian cancer at 58. His sister was reported to have a "poor memory" all her life. His son has depression and a postural tremor.

EXAMINATION

Mr. X's first evaluation at our center occurred at age 47, ten years after his initial symptoms. He interrupted the exam frequently to tell jokes or walk into the hall. He asked examiners their age and marital status, and imitated drum playing on their heads. He told the examiner she had "a big pimple" on her nose and casually removed his pants while she was out of the room. He made puns and sang songs about flatulence.

Mr. X was alert and generally cooperative. He was poorly groomed. Although he eloquently described his behaviors and their impact on his family, he showed little emotion during his description. He repetitively clasped his hands and tapped his fingers. His spontaneous speech was fluent without paraphrastic errors, dysarthria, hypophonia, or paucity of content. He named, repeated, and followed commands without difficulty. Cranial nerve exam was unremarkable. He had a high frequency postural tremor. There was normal muscle bulk, tone, and power. Sensory exam was intact. Reflexes were brisk throughout, with no spread or primitive reflexes, and plantar responses were flexor bilaterally. There was no dysmetria or difficulty with rapid simple movements. Gait examination revealed normal posture and stride length, with mildly diminished bilateral arm swing and normal turning. Retropulsive instability was absent.

On examination the following year, Mr. X's speech was hypophonic. He had a compulsion for shaking others' hands. He followed 2 step-commands and could not perform the Luria sequence. There was a reduced blink rate and hypomimia. Initiation of saccadic eye movements was slightly delayed. Cogwheel rigidity and a mild postural tremor were present in the upper extremities. Gait was mildly stooped with reduced stride length and arm swing.

NEUROPSYCHOLOGICAL BATTERY

Cognitive Testing

A neuropsychologist administered a standardized battery of tests (Table 1). Performance on verbal and visuospatial memory tasks was below average, but he lacked evidence of frank encoding deficits and was oriented to time and place. His performance in all other domains ranged from average to superior. Two notably exceptional domains included excellent visuospatial skills and semantic knowledge. Frontal lobe functions revealed a mixed picture: while he scored in the superior range for attention, working memory, information processing speed, and within the average range for set shifting (Trailmaking) and cognitive control (Stroop), his generation of novel verbal and visuospatial material ranged from average to low average.

The following year, Mr. X's performance diminished substantially across all domains, and many test scores fell in the impaired range. Semantic comprehension, visuospatial functioning, attention and working memory remained intact, while memory and executive functioning declined. While his cognitive abilities had clearly declined, his low scores were also due in part to poor cooperation with testing.

Socio-Emotional Examination

Mr. X underwent a detailed battery of tests designed to objectively measure emotional, social, and personality functioning. (see Supplementary Materials for procedural details) (Narvid, Gorno-Tempini et al. 2009).

Emotion Comprehension Tasks (Comprehensive Affective Testing System, CATS; The Awareness of Social Inference Test-Emotion Evaluation Test, TASIT EET)—(CATS) Mr. X scored perfectly in tests of emotional voice prosody

discrimination and naming (CATS-Emotion Prosody and Name Prosody). After struggling with a few items on the facial affect task (CATS-Affect Matching), he refused to continue. Mr. X was significantly impaired in identifying emotions (8/14) seen in more realistic scenarios, missing items involving both positive and negative emotions (TASIT-EET).

Social Cue Detection Tasks (TASIT Social Inference-Minimal, SI-M)—Mr. X correctly answered most yes-no questions about characters' thoughts, feelings, words, and actions after watching sincere and sarcastic communications on video (SI-M: Sincere: 17/20, Simple Sarcasm: 17/20), demonstrating intact comprehension of paralinguistic facial and vocal cues conveying sarcasm. By contrast, he performed in the low normal range when required to recognize sarcastic, paradoxical intentions based on speech content with few paralinguistic cues (Paradoxical Sarcasm: 15/20).

Knowledge of Social Rules (Social Norms Questionnaire, SNQ)—Mr. X correctly identified 21/22 inappropriate social behaviors (e.g., "Is it appropriate to tell a coworker you don't like their hairstyle?" [NO]).

Pseudo-Economic Decision-making (Iowa Gambling Task, IGT; Ultimatum/Dictator Game)—In decision-making games, Mr. X chose risky (high reward, high punishment) choices with increasing frequency (ratio of advantageous/risky decks: Trials 1–20: 16/4; Trials 21–40: 20/0; Trials 41–60: 1/19). In the Ultimatum game, he shrewdly made a fair monetary offer when he knew his confederate could punish him for being unfair (kept 5/offered 5 quarters). In the dictator condition, however, he made a highly unfair offer when told his confederate could not punish him for being unfair (kept 9/offered 1 quarter), reflecting an abnormal indifference to offending the confederate.

Cognitive Theory of Mind Task (UCSF Cog ToM)—This task requires intact working memory and abstract reasoning to identify multiple individuals' perspectives, but does not require inferences about emotions. Mr. X performed perfectly on control, first order, and second order cognitive ToM questions (12/12 each) demonstrating that he could correctly identify others' knowledge state in a non-emotional context based on environmental cues.

Complex/Emotional Theory of Mind Tasks (Castelli Triangles, Awkward Moments Test, AMT)—When shown videos of pairs of triangles moving in ways that people normally anthropomorphize as if they were social interactions, Mr. X made concrete, inaccurate descriptions of the triangles' movements and did not ascribe emotional or social meaning to their behavior, scoring in the impaired range (Intentionality: 7/20; Appropriateness; 2/12; Length; 12/16). He commented that it was strange that the examiners were asking what a triangle felt, which suggests that he never became aware of the higher social intentions being portrayed.

When asked about the basic narrative of videos depicting social interactions, he performed well (Multiple Choice: 11/12). However, his spontaneous responses were concrete and he initially failed to imagine characters' thoughts or intentions. His responses improved with prompting, and he could sometimes imagine what a character thought or felt (first order ToM). However, he did not make second-order ToM inferences about what one character thought another character knew, even with maximal prompting, resulting in an impaired overall score (Intention Score: 7/24).

Informant Reports of Real-life Social Behavior—Mr. X's spouse completed questionnaires describing his personality, empathy and social behavior.

Personality: Mr. X's premorbid personality was warm and agreeable, with 1 SD above average levels of extraversion (T=60) and ingenuousness (T=62), average levels of warmth (T=55), dominance (T=46), and submissiveness (T=44), and 1.5 SD below average levels of coldness (T=37), introversion (T=35), and arrogance (T=36). His self-report describing his current personality matched his wife's retrospective account (Figure 1). His wife's description of his current personality was highly divergent from her retrospective account with 2.5 SD higher than average levels of coldness (T=75), 1 SD above average levels of arrogance (T=62), introversion (T=57), and submissiveness (T=58), average levels of dominance (T=46), extraversion (T=51), and ingenuousness (T=46), and negligible levels of Warmth (T=0).

Empathy: Mr. X became much less likely to take others' perspectives (IRI-PT: Before 23/28; Current 0/28), or project himself into the lives of fictional characters in movies or books (IRI-FS: Before 24/28, Current 3/28). He showed much less empathic concern for others (IRI-EC: Before 27/28, Current 2/28), and demonstrated more self-centered emotional reactivity (IRI-PD: Before 12/28, Current 22/28).

Social Cue Awareness (Revised Self-Monitoring Scale, RSMS): According to his wife, Mr. X's ability to sense how others perceived of his behavior was very poor (RSMS-EX: 7/36, <1st %ile), and he had lost awareness of the need present himself appropriately in social settings (RSMS-SP: 17/42, <1st %ile).

In sum, Mr. X performed well on traditional neuropsychological testing, even on most measures of frontal lobe function, despite incapacitating behavioral impairment. Social-emotional examination revealed intact discrimination of emotions and sarcasm based on paralinguistic cues, but impaired detection of emotions in realistic scenarios. Although knowledge of social rules was intact, he did not spontaneously apply these rules in daily life. Furthermore, he was indifferent to punishment when high rewards were at stake. While his capacity for complex cognitive theory of mind was intact, he was unable to attribute social and emotional meaning to social interactions. His personality drastically changed from warm and agreeable to cold and introverted, with a much lower level of empathic concern and impaired sensitivity to social cues.

NEUROIMAGING

A voxel-based morphometry (VBM) analysis compared Mr. X's T1-weighted structural MRI scan at initial evaluation with 15 healthy control males matched for age and education (mean age 50.5, range 39-57) (see Table 2, Figure 2, and Supplementary Materials for methods). Compared to controls, Mr. X showed right worse than left volume loss in the anterior temporal lobe, amygdala, anterior hippocampus, anterior insula, and pre- and subgenual anterior cingulate cortex. Bilateral anterior striatal atrophy was particularly prominent in the head of the caudate, worse on the right.

GENETIC TESTING

No mutation was identified in *MAPT*, *GRN*, or *FUS*. He was heterozygous for the extended *MAPTH1-H2* inversion polymorphism. Apolipoprotein E genotype was E3/E3. Genetics methods are detailed in the Supplementary Materials.

NEUROPATHOLOGY

Gross examination revealed moderate ventriculomegaly with mild substantia nigra pigment loss. There was severe bilateral striatal and right amygdala atrophy. The cortical ribbon was

thinned, most prominently in regions identified on the VBM analysis. Ventral rootlets of the spinal cord were normal.

Hematoxylin and eosin (H & E) staining showed mild arteriosclerosis in inferior frontal gyrus (pars opercularis) but no microinfarcts or other disease-specific abnormalities. Nonspecific cortical and subcortical microvacuolation and astrogliosis were prominent within atrophied regions, in some cases accompanied by moderate to severe neuronal loss (see Supplementary Table 1). There was severe loss of hippocampal neurons in CA1 and subiculum (hippocampal sclerosis). Ubiquitin immunohistochemistry revealed large numbers of neuronal cytoplasmic inclusions (NCIs) in dentate gyrus granule cells and left ventromedial frontal cortex. Moderate to small numbers of NCIs were found in middle temporal gyrus, substantia nigra, periaqueductal gray, and right ventromedial frontal cortex (although severe neuron loss in this region may have precluded identification of NCIs). Moderate to small numbers of ring- or halo-shaped or “vermiform” neuronal nuclear inclusions were found in dentate gyrus granule cells and left ventral medial frontal cortex. No glial cytoplasmic inclusions were identified. Small numbers of dystrophic neurites were found in CA1/subiculum. Additional immunohistochemical analyses demonstrated that the ubiquitinated inclusions were immunoreactive for FUS (Figure 3) but not for hyperphosphorylated tau (CP-13 antibody), TDP-43, alpha-synuclein, and alpha-internexin. Silver stains and amyloid-beta immunohistochemistry revealed no neuritic or diffuse plaques or neurofibrillary pathology (see Supplementary Materials for neuropathological details).

DISCUSSION

This report comprehensively describes a patient with bvFTD due to underlying FTL-D-FUS. Similar to previous reports (Mackenzie, Foti et al. 2008; Roeber, Mackenzie et al. 2008; Neumann, Rademakers et al. 2009; Seelaar, Klijnsma et al. 2009; Rohrer, Lashley et al. 2010; Urwin, Josephs et al. 2010), Mr. X had a severe behavioral syndrome, and a paucity of motor symptoms until late in the illness. Complementing a recent survey across patients with FTL-D-FUS diagnosed at major dementia referral centers (Urwin, Josephs et al. 2010), the present paper provides an in-depth and multidisciplinary characterization of a single patient.

Despite Mr. X's incapacitating behavioral impairment, scores on traditional neuropsychological testing fell within normal limits for most cognitive domains. Although his cognitive profile included relative weaknesses in verbal and visual memory and verbal fluency, his executive functioning ranged from average to very superior (>99th percentile), consistent with the preservation of dorsolateral frontoparietal structures that mediate executive functioning. Conversely, novel social-emotional tests illustrated deficits reflecting his real-world behavior. Consistent with findings in two small series (Josephs, Whitwell et al. 2010; Rohrer, Lashley et al. 2010), VBM showed focal atrophy in medial frontal anterior insula, bilateral anterior and medial temporal cortex, amygdala, and caudate.

Clinicoanatomical correlations

Mr. X's substantial impairments in social and emotional functioning included (1) inability to imagine and name others' emotions, (2) difficulty weighing the potential punishment value of an action against its potential reward, often expressed as social dysdecorum, and (3) severely decreased expression of warmth and empathy.

Imaging Emotions—Even when emotional cues were exaggerated across multiple modalities (facial expression, voice prosody, upper body posture and gesticulations) in realistic vignettes, Mr. X could not identify emotions correctly. While he could detect

differences in auditory paralinguistic cues, suggesting that some aspects of signal detection and attention were intact, he could not integrate this information within its social-emotional context. The severe atrophy to Mr. X's right temporal pole, a region associated with empathy and knowledge of abstract social concepts may have contributed to this deficit (Rankin, Gorno-Tempini et al. 2006; Zahn, Moll et al. 2009).

Similarly, he performed cognitive theory of mind tasks perfectly, suggesting that attention, memory, and executive functions required for these tasks were intact; however, when a task required him to spontaneously imagine another's emotion or mental state, he was unable to do so. This discrepancy could be observed in Mr. X's ability to accurately describe the impact of his symptoms on his family yet demonstrate no self-consciousness, regret, or concern about his family's experience. Previous reports suggest that patients with bvFTD typically demonstrate impairment in both cognitive and emotional theory of mind (Gregory, Lough et al. 2002). Mr. X's selective impairment on advanced theory of mind tasks, however, suggests a focal deficit in inferring emotional and mental states despite preserved memory and executive functioning. Studies of advanced theory of mind in healthy developing children and adolescents (Blakemore 2008), normal adults (Kringelbach and Rolls 2004), and patients with lesions (Martin-Rodriguez and Leon-Carrion) converge to implicate the medial aspects of the frontal lobe in this capacity, particularly the anterior cingulate and rostromedial frontal cortex. Our VBM analysis of Mr. X's initial MRI found substantial damage to these medial aspects of the frontal lobe, with relative sparing of dorsolateral frontal areas, consistent with the proposed link between medial frontal regions and emotional aspects of theory of mind.

Emotional Reward and Punishment—While Mr. X retained sensitivity to reward, demonstrating capacity to pursue financial and even some social rewards, he was insensitive to subtle and even overt punishment cues. For instance, in the ultimatum/dictator game, he strategized to keep as many quarters as possible for himself and did not care whether he offended his study partner. In the computerized gambling paradigm, the financial reward and punishment cues were objective and quantifiable, in contrast to the more subtle social cues in the dictator game. Nevertheless, Mr. X chose disadvantageous decks of cards associated with greater monetary rewards, and never altered his choices despite unambiguous monetary punishment cues. This lack of sensitivity to punishment is reflected in elements of his history, e.g. failing to help his drowning daughter. Punishment insensitivity may also have manifested as socially inappropriate questioning and tendency to tell intrusive jokes and puns, during which he often received negative social feedback from others. These socially disinhibited behaviors could have represented pursuit of reward, but they were clearly carried out with little consideration of social punishment (i.e., others' disapproval, offense, or hurt feelings).

Studies examining the anatomical substrates of positive and negative reinforcement suggest a medial to lateral gradient in the orbitofrontal cortex (OFC) (Kringelbach and Rolls 2004; Rankin, Liu et al. 2007; Sollberger, Stanley et al. 2009). Functional imaging and lesion studies suggest that the medial OFC is involved in evaluating reward value, while lateral OFC primarily evaluates reinforcers that have a valence related to punishment (Kringelbach and Rolls 2004). Positive reinforcement activates medial orbitofrontal cortex subregions, the cortical endpoint of a frontal-subcortical network of reward processing structures including the caudate, nucleus accumbens, thalamus, and periaqueductal gray (Ridderinkhof, van den Wildenberg et al. 2004). Disinhibition has been associated with ventromedial prefrontal cortex damage in bvFTD patients (Rosen, Allison et al. 2005). Our patient exhibited profound atrophy in both medial (reward) and lateral (punishment) aspects of the ventral OFC, and in subcortical structures of the reward network, including the head of the caudate and other basomedial frontal subcortical areas. Despite this widespread damage, it is

possible that phylogenetically older thalamic and brainstem structures remained intact, allowing him to retain some primitive reward responsiveness (to food or sexual cues) even as more cortically-mediated, learned associations for abstract (social and monetary) punishment cues degraded.

Expressive warmth—Mr. X's ability to express himself in a warm, empathic manner changed dramatically. While many patients with neurodegenerative disease experience changes in the ability to correctly perceive social signals, the majority retain a fundamental capacity to experience and express emotional connection with others. Conversely, patients with bvFTD lose this capacity for expressive warmth early in their disease, leading others to describe them as cold, disinterested, or unfeeling [23]. When this loss of warmth occurs in conjunction with normal levels of assertiveness or dominance, the resulting interpersonal style could be best characterized as aggressive, intrusive, and actively insensitive (Sollberger, Stanley et al. 2009), consistent with KJ's clinical picture. Studies of the neuroanatomical substrates of warm, empathic behavior implicate right worse than left ventral frontal, frontoinsula, and medial and anterior temporal structures (Rankin, Gorno-Tempini et al. 2006; Sollberger, Stanley et al. 2009), all of which were focally damaged in Mr. X.

Compulsive Motor Behavior—In addition to Mr. X's social-emotional dysfunction, he also exhibited persistent, diverse stereotyped motor behaviors, ranging from simple clapping and foot tapping to complex compulsive motor routines, including his compulsions to repeatedly take off and put on his shoes or to leave the room in the midst of conversations or tasks. He also displayed environmental dependency, drumming on examiners' heads and opening his refrigerator repetitively, reflecting an inability to suppress automatic responses to his environment. Studies have linked simple motor stereotyped behaviors or tics with the striatum (Cortez, Charntikov et al.; Edwards, Dale et al. 2004) and more complex compulsive routines to the dorsal anterior cingulate cortex (Rosen, Allison et al. 2005); both striatum and regions of the dorsal anterior cingulate were atrophied in Mr. X. Josephs and colleagues showed that at a group level, patients exhibiting complex motor stereotypes showed greater caudate and putamen atrophy relative to cortical volume loss when compared to patients without stereotypes (Josephs, Whitwell et al. 2008). Mr. X had severe caudate atrophy, with relative sparing of dorsolateral frontal and posterior temporal and parietal cortex, consistent with a report of three patients with FTLT-FUS who showed disproportionate caudate atrophy relative to patients with FTLT-tau or TDP-43 pathology (Josephs, Whitwell et al. 2010).

Emotional/Executive Dissociation—Mr. X's cognitive and behavioral profile was unusual for a patient with bvFTD in that he had many preserved functions on social-emotional testing despite profound real-life behavioral deficits. For example, Mr. X's ability to perform primary social perception tasks, such as discriminating and naming emotional voice prosody, was normal. He correctly used paralinguistic (primarily auditory) cues to discriminate sarcastic from sincere speech. These aspects of social perception are associated with inferior and lateral temporal regions (Belin 2006; Ethofer, Anders et al. 2006; Rankin, Gorno-Tempini et al. 2006; Wildgruber, Ackermann et al. 2006; Sollberger, Stanley et al. 2009; Torralva, Roca et al. 2009), which were comparatively preserved in Mr. X at his first assessment. Mr. X's refusal to perform the static facial affect tasks might have masked a latent deficit in visual aspects of emotion perception, but this remains uncertain. Overall, Mr. X's pattern of deficits reflect the focal anatomic pattern associated with the earliest phase of the bvFTD syndrome, described by Seeley and colleagues (Seeley, Crawford et al. 2009). This "salience network" is comprised of anterior insula, dorsal and ventral ACC,

amygdala, striatum, and brainstem structures, and functions to rapidly alert the organism to homeostatically relevant information.

Unlike most patients with moderate to advanced neurodegenerative disease, however, Mr. X retained aspects of social cognition that require executive functioning. Personality tests revealed that his social dominance, a trait associated primarily with dorsolateral frontal cortex (Rankin, Kramer et al. 2003; Sollberger, Stanley et al. 2009), was unchanged. Preserved social executive functions were consistent with sparing of dorsolateral frontoparietal cortex, as seen on neuroimaging. In contrast, many patients with bvFTD presenting with tau and TDP-43 pathology, and with familial forms of these diseases, demonstrate more substantial executive dysfunction by the time of initial presentation (Rabinovici, Rascovsky et al. 2008; Wittenberg, Possin et al. 2008).

In summary, this patient presenting with bvFTD due to underlying FTLD-FUS demonstrated a focal pattern of socio-emotional deficits at initial presentation, including impairment in emotion attribution, sensitivity to punishment cues, and the capacity to express emotional warmth and empathy. This pattern stood in stark contrast to his normal, often superior executive functioning and retained social dominance and assertiveness. In keeping with his focal clinical deficit profile, initial neuroimaging showed circumscribed atrophy of the right greater than left frontoinsula, anterior temporal lobe, medial frontal cortex, amygdala, and caudate, areas known to be involved in socio-emotional functioning. Additional studies are needed to determine whether focal socio-emotional network dysfunction with preservation of executive-control systems will prove to be a consistent and predictive feature of underlying FTLD-FUS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Interpersonal Adjectives Scales (IAS): (a) Chart shows 8 personality traits tested organized according to axes denoting the degree of power and affiliation associated with each trait, (b) Mr. X's pre-morbid personality is predominantly agreeable, gregarious and ingenuous with average levels of dominance, (c) Mr. X's personality during the illness reflects a shift to cold-hearted, aloof, and arrogant with unchanged levels of dominance.

Figure 2.

Voxel-based morphometry analysis (SPM5) of the patient's 1.5T T1-weighted structural MRI scan, compared to 15 male age-matched controls. Due to the reduced power afforded by this single-subject analysis, the threshold has been set at a low, uncorrected level (t-value threshold > 2.5) to better match the degree of atrophy shown on his raw structural MRI scan (also shown).

Figure 3.

Neuropathology. (A–C) Hematoxylin and eosin staining revealed nonspecific signs of neurodegenerative, including microvacuolation and gliosis. These changes were moderate in right medial orbitofrontal cortex (A) and severe in right uncus (B) and CA1/subiculum (C), where they were accompanied by profound neuronal loss (hippocampal sclerosis). Immunohistochemical stains revealed neuronal cytoplasmic and nuclear inclusions that were positive for ubiquitin (D) and FUS (F) but negative for TDP-43 (E). The neuronal nuclear inclusions adopted a “veriform” shape characteristic of FTLD-FUS inclusions. Scale bars represent 100 μ m in A–C, 20 μ m in D and E, 20 μ m in F (upper panel), and 10 μ m in F (lower panels).

Table 1

Summary of standard neuropsychological, functional, and neuropsychiatric measures for Mr. J, both at initial presentation and one year later. All scores represented as raw scores (percentile), with bold/italic text indicating that the patient performed at a clinically impaired level.

AGE AT TESTING	47	48
MMSE (max=30)	30	21
CDR Total	1.0	3.0
CDR: Sum of Boxes	5.5	15.0
Language:		
PPVT-R Word Comprehension (max=16)	16	16
CYCLE Sentence Comprehension (max=10)	10	10
Pyramids & Palm Trees -- pictures (max=52)	51	39 (<1st %ile)
WAIS-III Information (max=28)	19 (64th %ile)	20 (64th %ile)
Boston Naming Test (max=15)	15 (90th %ile)	12 (5th %ile)
FAS Verbal Fluency (# words)	35 (36th %ile)	8 (<1st %ile)
Animals/min	16 (14th %ile)	4 (<1st %ile)
Visuospatial Function:		
Modified Rey-O Copy (max=17)	17	16
Cube Copy (max=2)	2	1
VOSP Number Location (max=10)	10	10
WAIS-III Block Design (max=68)	61 (>99th %ile)	33 (36th %ile)
Episodic Memory:		
Modified Rey-O Delay (max=17); recog	7; yes	0; no
<i>Wechsler Memory Scale - III</i>		
Visual Reproductions I (max=104)	85 (50th %ile)	30 (<1st %ile)
Visual Reproductions II (max=104)	10 (5th %ile)	0 (<1st %ile)
<i>California Verbal Learning Test-MS (max=9)</i>		
4-trial total correct	6,8,7,8 (50th %ile)	0,0,6,5 (2nd %ile)
30" free recall	6 (16th %ile)	3 (2nd %ile)
10' free recall	2 (7th %ile)	0 (2nd %ile)
10' recognition hits	7 (16th %ile)	7 (16th %ile)
10' recognition false positives	3 (16th %ile)	11 (<1st %ile)
Simple Attention/Working Memory:		
Span of digits forward (max=9)	9 (96th %ile)	8 (85th %ile)
Span of digits backward (max=8)	7 (94th %ile)	5 (56th %ile)
Digit Span (max=30)	26 (>99th %ile)	22 (91st %ile)
Spatial Span (max=32)	17 (74th %ile)	17 (74th %ile)
Executive function:		
Abstraction total (max=6)	5	3
Calculation (max=5)	5	3

<i>Delis-Kaplan Executive Function System</i>		
CA Trails Switching (# secs)	66 (64th %ile)	155 (<1st %ile)
CA Stroop Inhibition (# secs)	56 (50th %ile)	100 (<1st %ile)
Design Fluency Filled Dots (# designs)	5 (9th %ile)	5 (9th %ile)

SPM5 voxel-based morphometry results for gray matter volume, comparing structural MRI scans of patient to 15 age-matched healthy control males with VBM-compatible structural T1-weighted MRI scans. To compensate for the lack of power resulting from this small, uncorrected results are presented; no areas survived FWE correction for multiple comparisons.

Table 2

Anatomic regions	x	y	z	T-score	p-value
R caudate head	14	18	6	7.64	0.000
L caudate head	-10	18	2	5.88	0.000
R hippocampus/amygdala	24	-6	-22	6.87	0.000
L hippocampus/amygdala	-14	-10	-18	4.45	0.000
L amygdala	-20	2	-18	4.27	0.001
L parahippocampal gyrus	-8	2	-18	4.01	0.001
R superior temporal pole	34	22	-28	5.61	0.000
R inferior temporal pole	44	10	-48	5.45	0.000
R insula	40	4	-2	3.98	0.001