



Neural correlates of reduced awareness in instrumental activities of daily living in frontotemporal dementia



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ABSTRACT

A decline in instrumental activities of daily living has been described as the earliest functional deficit in patients with neurodegenerative disease. It embraces specific competencies such as: “*recalling the date and telephone calls, orienting to new places, remembering the location of objects at home, understanding conversation and the plot of a movie, keeping belongings in order, doing mental calculations and handling money, remembering appointments and shopping lists and performing clerical work*”. Since changes in instrumental daily living activities are one of the descriptors of behavioural-variant frontotemporal dementia, we decided to investigate the neural correlates of a reduced awareness in this specific domain in twenty-three consecutive behavioural-variant frontotemporal dementia patients. Gray matter volume changes associated with a reduced awareness for the instrumental domain, assessed using a validated caregiver-patient discrepancy questionnaire, were examined. Interestingly, we found disabilities in instrumental daily living activities and a reduced awareness of these to be related to medial prefrontal cortex atrophy, where the mid-cingulate cortices, dorsal anterior insula and cuneus play an important role. Importantly, if the executive system does not function correctly, the comparator mechanism of action self-monitoring does not detect mismatches between the current and previous performance states stored in the personal database, and produces a reduced awareness for the instrumental domain.

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Abbreviations: ACE-R, Addenbrooke's Cognitive Examination – Revised version; AD, Alzheimer's Disease; ADL, Activity of Daily Living; AQD, Awareness of Deficit Questionnaire - Dementia scale; AQD_iADL, Instrumental Activity of Daily living domain in AQD; bv-FTD, behavioural variant of Frontotemporal Dementia; CDR, Clinical Dementia Rating scale; CMRglc, Cerebral Metabolic Rate of Glucose Consumption; CPM-36, Coloured Progressive Matrices; CSF, Cerebrospinal Fluid; CT, Computed Tomography; DIS-S, Dishinhibition Scale; FDG-PET, fluorodeoxyglucose - positron emission tomography; FTD, Frontotemporal Dementia; FTLD, Frontotemporal Lobar Deterioration; GM, Grey Matter; HDR-S, Hamilton Depression Rating Scale; IADL, Instrumental Activity of Daily Living; MA, Attentional Matrices; MAS, Mania Scale; MBq, Megabecquerel; MCI, Mild Cognitive Impairment; MMSE, Mini-Mental State Examination; MNI, Montreal Neurological Institute; MRI, Magnetic Resonance Imaging; MRV, Markov Random Field; PVE, Partial Volume Estimation; ROC, Receiver-Operating Characteristic; ROI, Region of Interest; SANLM, Spatially Adaptive NonLocal Means; SN, Saliency Network; SSS, Single Scatter Simulation; TIV, Total Intracranial Volume; TMT, Trail Making Test; TT, Token Test; WCST, Wisconsin Card Sorting Test; WM, White Matter.

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1. Introduction

The cognitive changes associated with degenerative diseases, such as behavioural-variant frontotemporal dementia (bv-FTD), lead to a progressive decline in the patient's ability to perform activities of daily living (ADL). In particular, Mioshi et al. (2007) analyzed which aspects of ADL are most affected in bv-FTD patients. A unique pattern of deficits for basic ADL emerged in terms of: initiation; planning and execution. The authors concluded that bv-FTD has a devastating effect on ADL. More recently, and in line with these findings, Lima-Silva et al. (2015), showed that bv-FTD patients obtained lower scores for initiation and planning/organisation through a direct and indirect assessment of ADL. They underlined that functional changes in bv-FTD seem to be better documented by indirect measures completed by caregivers. The neural correlates of self-awareness for ADL were recently examined in several neurodegenerative diseases (Shany-Ur et al., 2014), by calculating the discrepancy between self- and informant ratings using the patient competency rating scale, an instrument validated in studies with traumatic injury patients (Prigatano and Altman, 1990). Patients

with bv-FTD overestimated their functioning in comparison to their informant ratings. The MRI neuroanatomic correlates of self-awareness for ADL corresponded with atrophy in widespread right frontal regions (the orbital inferior and superior frontal gyri, medial orbitofrontal cortex, dorsal middle and superior frontal gyri) and in the anterior insula, putamen, thalamus, temporal lobe regions and the pons.

While ADL include basic self-maintenance skills such as bathing, getting dressed or eating, instrumental activities of daily living (IADL) consist of more complex activities such as using public transportation, managing finances, or shopping and reflect the ability to live independently in the community. IADL require a greater complexity of neuropsychological organisation and higher processing capacity than ADL functions, and are more likely to be sensitive to the early effects of cognitive decline (Pérès et al., 2008). Indeed, a comprehensive review underlined a special role played by executive functions in the decline in IADL abilities in healthy older adults and Mild Cognitive Impairment subjects (Royall et al., 2007). To date, no studies have examined the decline in IADL abilities in bv-FTD.

Diminished ability to perceive one's own impairments is common in FTD patients, among whom impaired self-awareness occurs early in their illness and is included as one of five core diagnostic features in the Neary criteria (Neary et al., 1998). The clinical characterization of FTD patients as having extensive loss of self-awareness, self-monitoring and self-knowledge (Eslinger et al., 2005), linked to metacognitive dysfunctions, associated with medial prefrontal pathophysiology has been supported by studies using "patient vs. informant discrepancy" approaches.

Migliorelli et al. (1995), using the caregiver-patient discrepancy strategy, developed the *Anosognosia Questionnaire-Dementia (AQ-D)*, a valid and practical instrument to rate a reduction in awareness of illness in neurodegenerative diseases, such as Alzheimer's Disease (AD). Although validated for AD, most of the items in this scale actually analyze patients' current level of impairment in basic and instrumental ADL, behavioural and mood changes. Indeed, a factor analysis of the AQ-D produced the factors of unawareness for deficits on basic ADL, instrumental ADL, depression, and disinhibition (Starkstein et al., 2006). Importantly, one of these factors, identified in terms of impaired awareness in instrumental activities of daily living (AQD_iADL), was designated as factor 1 by the authors (see paragraph 2.3 for more details). It accounted for most of the variance and rated as the earliest functional deficit in patients with cognitive impairment. Since changes in daily living activities are one of the descriptors in bv-FTD independently of cognitive dysfunction (Mioshi et al., 2007), we decided to consider it in our analyses.

The aims of the current study are to: (1) Explore the relationship between the structural brain changes correlated with IADL; (2) Study awareness in instrumental activities of daily living (AQD_iADL) according to the AQ-D scale based on the associated cerebral structural change; (3) Propose a link between the neuroanatomical changes and a reduction in the awareness of IADL possibly associated with the medial prefrontal cortex, investigating these aspects for the first time in a highly selected dataset of bvFTD patients.

2. Materials and methods

2.1. Participants

Sixty-seven consecutive subjects (29 males, 38 females, mean age \pm SD = 69.37 ± 7.04 yrs), complaining of cognitive impairment, were admitted as in-patients to the Neurological Unit of the Department of Neuroscience of the University of Torino (Italy) and investigated according to a standardized protocol. All the patients underwent an extensive clinical, neuropsychological, neuroradiological and neurogenetic examination. According to the criteria of Rascovsky et al. (2011), 15 patients (9 males, 6 females, mean age \pm SD = 68.13 ± 9.49 yrs) fulfilled the criteria for *probable* behavioural variant frontotemporal dementia (bvFTD) while 8 patients (4 males, 4 females, mean age \pm SD = 69.63

± 7.44 yrs) fulfilled the criteria for *possible* bvFTD. All 23 of these patients (13 males, 10 females, mean age \pm SD = 68.65 ± 8.68 yrs) were included in the present study.

A group of healthy subjects, with an MMSE score of > 25 (Folstein et al., 1975), served as controls for PET (9 males, 6 females, mean age \pm SD = 64.3 ± 7.7 yrs) and MRI analyses (7 males, 8 females, mean age \pm SD = 62.0 ± 4.4 yrs). Controls had normal neurological and psychiatric evaluations and a negative history of neurological disorders.

Written informed consent was obtained from all participants and the study was approved by the Hospital Ethics Committee.

2.2. Neuropsychological assessment

All subjects underwent an extensive neuropsychological battery. Screening tools for the assessment of overall cognitive functions were administered: the Mini-Mental State Examination (MMSE: Folstein et al., 1975) and the Addenbrooke's Cognitive Examination – Revised version (ACE-R: Mioshi et al., 2006). Specific cognitive domains were assessed with the use of different scales: selective attention with Attentional Matrices (MA: Spinnler and Tognoni, 1987), divided attention and cognitive shifting with the Trial Making Test (TMT: Spinnler and Tognoni, 1987; Reitan and Wolfson, 1994), episodic memory with the Recall of a Short Story test (Babcock: Spinnler and Tognoni, 1987), reasoning in the visual modality with Coloured Progressive Matrices (CPM-36: Spinnler and Tognoni, 1987), language comprehension with the Token Test (TT: De Renzi and Vignolo, 1962; Spinnler and Tognoni, 1987), executive functions were analysed with the Wisconsin Card Sorting Test (WCST: Berg, 1948).

Patients were also assessed using neuropsychiatric rating scales of mood changes: apathy and depression with the HDR-S (Hamilton, 1960), disinhibition and hypomania with the Disinhibition Scale and the Mania Scale (DIS-S: Starkstein et al., 2004; MAS: Bech et al., 1978, respectively).

2.3. Functional assessment and awareness of disease assessment

We verified the subjects' level of autonomy in daily living in terms of basic and instrumental activities (ADL: Katz et al., 1963; IADL: Lawton and Brody, 1969). The ADL scale is considered the most appropriate tool for assessing functional status as a measurement of the subject's ability to perform activities of daily living independently. The ADL ranks adequacy of performance in the six functions of bathing, dressing, toileting, transferring, continence, and feeding. Patients are scored yes/no for independence in each of the six functions. A score of 6 indicates full function, 4 indicates moderate impairment, and 2 or less indicates severe functional impairment (Katz et al., 1963). The IADL is an appropriate instrument for assessing independent living skills that are considered more complex than the basic activities of daily living as measured by the ADL scale. The IADL scale is most useful for identifying how a person is functioning at the present time, and for detecting improvements or deterioration over time. There are eight domains of function measured with the Lawton IADL scale. Subjects are scored on eight areas of function (using the telephone, shopping, preparing food, housekeeping, doing laundry, using transportation, handling medications, and handling finances). Subjects are scored according to their highest level of functioning in that category. A summary score ranges from 0 (low function, dependent) to 8 (high function, independent). The lower the score the higher the level of dependence.

Awareness of disease was analyzed by means of a domain-specific assessment as proposed by Barrett et al. (2005), using the AQ-D scale (Migliorelli et al., 1995). Before performing the neuropsychological assessment, all patients were tested with the AQ-D scale. The AQ-D was used with the aim of differentiating between aware and unaware patients. It is an instrument of proven reliability and validity for rating the severity of unawareness of deficits in people with dementia (Starkstein et al., 2006; Migliorelli et al., 1995). The questionnaire

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