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

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Martina Amanzio[1a, 2b, *]

martina.amanzio@unito.it

Federico D'Agata[3c]

Sara Palermo[4d]

Elisa Rubino[5e]

Milena Zucca[5e]

Antonello Galati[6f]

Lorenzo Pinessi[5e]

Giancarlo Castellano[6f]

Innocenzo Rainero[2b, 5e]

[1a]Department of Psychology, University of Turin, Via Verdi 10, 10123 Turin, Italy

[2b]Centro Interdipartimentale di Studi Avanzati in Neuroscienze, National Institute of Turin (NIT), Regione Gonzole 10, 10043 Orbassano, Italy

[3c]Neuroradiology, Department of Neuroscience, Neuroradiology, Via Cherasco 15, 10126, Turin, Italy

[4d]Neurology II, Department of Neuroscience, Neurology II, Via Cherasco 15, 10126 Turin, Italy

[5e]Neurology I and Alzheimer Evaluation Unit, Department of Neuroscience, Via Cherasco 15, 10126 Turin, Italy

[6f]Nuclear Medicine, AOU Cittá della Salute e della Scienza, C.so Bramante 88, 10126, Turin, Italy

*Corresponding author at: Department of Psychology, University of Turin, Via Verdi 10, 10123 Turin, Italy.

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 cuneous 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.

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, Dishinibition 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, Salience Network; SSS, Single Scatter Simulation; TIV, Total Intracranical Volume; TMT, Trail Making Test; TT, Token Test; WCST, Wisconsin Card Sorting Test; WM, White Matter

Keywords: behavioural variant frontotemporal dementia; instrumental activities of daily living; awareness of deficit questionnaire - dementia scale; magnetic resonance imaging; voxel-based morphometry

~~1.~~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.~~2 Materials and methods

~~2.1.~~2.1 Participants

Sixty-seven consecutive subjects (29 males, 38 females, mean age ± 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 ± 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 ± SD = 69.63 ± 7.44 yrs) fulfilled the criteria for *possible* bvFTD. All 23 of these patients (13 males, 10 females, mean age ± 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 ± SD = 64.3 ± 7.7 yrs) and MRI analyses (7 males, 8 females, mean age ± 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.~~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.~~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, Eslinger, Ballentine, and Heilman (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 consists of 30 questions divided into two sections, a cognitive and a behavioural part. The cognitive part assesses cognitive functioning and performance in basic and instrumental activities of daily living; on the other hand, the behavioural part assesses changes in mood and behaviour. The same questions were put to the patient (Form A) and to the patient's caregiver (Form B) each blinded with respect to the other. Each question carried a score ranging from 0 (never) to 3 (always); the minimum and maximum total scores obtainable for each form varied from 0 to 90 respectively. The cognitive and behavioural sections contained 22 and 8 questions, respectively, thus the scores could range from 0 to 66 and from 0 to 24.

The final score was obtained from the difference between Form B and Form A. Higher positive scores indicate a reduced awareness of deficits, thus caregivers rated the patients as more impaired than would appear from the patients' own self-evaluations. In detail, patients with a score of 32 or more were classified as being unaware, whereas those with a score of less than 14 were classified as being aware of their deficits (Migliorelli et al., 1995).

Since this method is based on a subtractive index of perception by caregivers and patients, the exclusion of any bias in the caregivers' judgments is crucial (Amanzio et al., 2011). Indeed, the caregivers (with an MMSE score of > 25) had normal neurological and psychiatric evaluations and a negative history of neurological disorders.

Finally, we followed the classification of Starkstein et al. (2006) who used principal component analysis to subdivide the Awareness of Deficit Questionnaire - Dementia scale (AQ-D: Migliorelli et al., 1995) into four domains taking into consideration the factors loading on each item. We decided to analyze in more detail one of these factors concerning impaired awareness in instrumental activities of daily living (AQD_iADL), and designated as factor 1 by the authors. Factor 1 embraces 12 items: "recalling the date, orienting to new places, recalling telephone calls, remembering the location of objects at home, understanding conversation, understanding the plot of a movie, keeping belongings in order, handling money, doing mental calculations, remembering shopping lists, remembering appointments, and performing clerical work". Thus it accounted for most of the variance and also rated as the earliest functional deficit in patients with cognitive impairment.

~~2.4.~~2.4 Genetic investigation and cerebrospinal fluid investigation

All the bvFTD patients were screened, according to standardized methods, for mutations in the progranulin (*PGRN*) and (*MAPT*) genes. Furthermore, patients were genotyped for the APOE alleles and for expansions in the C9orf72 gene.

A cerebrospinal fluid (CSF) examination was performed in all the bvFTD patients thus excluding any comorbidity. In addition to the standard examination, the CSF concentrations of beta-amyloid (1–42 abeta), total Tau (t-Tau) and 181-phospho-Tau (p-Tau) were

determined using ELISA kits (Innogenrtic, Ghent, Belgium. See supplemental material Table S1).

~~2.5.~~2.5 Procedures

The neuropsychological assessment was performed in three experimental sessions, held on separate days, and each lasting about one-hour, with a view to preventing fatigue and lack of adherence to the tasks.

Patients underwent the neuroimaging assessment before being subjected to lumbar puncture for cerebrospinal fluid tests.

~~2.6.~~2.6 Neuroimaging assessment

~~2.6.1.~~2.6.1 *PET scan and analysis*

The PET study was performed at the Nuclear Medicine Department of "Città della Salute e della Scienza" Hospital in Turin, Italy. Methods for PET were similar to Baudino et al. (2012). In a quiet waiting room participants, lying in a supine position, were asked to refrain from moving and instructed "to keep their eyes closed, to not engage in any structured mental activity (i.e. counting, rehearsing), and to avoid falling asleep". They were then blindfolded and ear plugged and received intravenously about 4.5-5.5 MBq kg^{-1} of 2-deoxy-2-[18F]fluoro-D-glucose. About 30 minutes later the PET/CT scan was performed by a Philips Gemini scanner (Philips Medical System, Cleveland, Ohio USA). The brain scan acquisition time was 20 minutes. Reconstructed brain images had a dimension of 128 x 128 x 90 voxels (2 x 2 x 2 mm^3). After the planned whole body [18F]FDG-PET/CT examination was performed, the coronal, sagittal and transverse data sets were reconstructed using a 3D iterative technique (row action maximum likelihood algorithm, RAMLA-3D) and corrected with single scatter simulation (SSS).

[18F]FDG-PET brain images were preprocessed and voxel-based statistical analyses were performed using SPM8 (www.fil.ion.ucl.ac.uk/spm) running on the MATLAB 7.5 platform. All images were non-linearly spatially normalized into the Montreal Neurological Institute (MNI) space and smoothed with an isotropic Gaussian kernel of 12 mm Full Width Half Maximum. Confounding effects of global activity differences were removed by normalizing the count of each voxel to the mean count of a standardized pontine region of interest (ROI), in order to avoid a biased normalization (Brown et al., 2014). The ROI was a rectangular multislice region (x/x'=−8/8, y/y'=−32/-24, z/z'=−44/-34; MNI space) sampling 144 voxels on the central pontine region and manually drawn on the PET SPM template using the MRIcro application (http://www.sph.sc.edu/comd/rorden/mricro.html). Both ROI coordinates and dimensions were chosen to avoid low-count background voxel sampling and to minimize the random noise effect. A previous careful visual inspection of the pons was conducted on each spatially normalized but non-smoothed brain scan in order to detect metabolic changes which could alter the ROI measure. The same ROI was then employed on each spatial normalized and smoothed brain image and the pons mean voxel values (Y_p) sampled. Using the image calculation tool of SPM, the scaled voxel values (Y') of each brain were set at $Y' = (Y/Y_p)$ where Y was the non-scaled ("raw") voxel value. Only voxel values greater than 80% of the Cerebral Metabolic Rate of Glucose Consumption (CMRglc) were included in the analysis.

~~2.6.2.~~2.6.2 *MRI scan and VBM analysis*

MRI was performed at the Department of Neuroscience, AOU of "Città della Salute e della Scienza" Hospital in Turin, Italy. The structural MRI scans of all participants were acquired on a 1.5 T MRI (Achieva, Philips). T1-Weighted 3D Turbo Field-Echo sequences (matrix = 256 x 256; voxel size 1 x 1 x 1 mm^3; number of slices: 190; TR: 7 ms; TE: 3 ms; TFE shots = 89) were obtained with full brain coverage and isotropic voxels, equivalent to an MPRAGE (Magnetic Prepared Rapid Acquisition Gradient Echo). Acquisition time was approximately 5 minutes.

We performed VBM using the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm.html) and SPM8 (Wellcome Trust Centre for Neuroimaging) running on the MATLAB 7.5 platform.

The VBM analysis comprised the following steps: T1 images were normalized to an MNI template space and segmented into gray matter (GM), white matter (WM) and CSF, the images were inspected for a quality check, and finally image data were smoothed with an isotropic Gaussian kernel of 8 mm Full Width Half Maximum.

The VBM8 toolbox is an extension of the New Segment Toolbox in SPM8. The segmentation approach is based on an adaptive Maximum A Posterior (MAP) technique and does not need a priori information about tissue probabilities (Rajapakse et al., 1997). Additionally, the segmentation approach uses a Partial Volume Estimation (PVE) with a simplified mixed model of at most two tissue types (Tohka et al., 2004). Furthermore, we applied two denoising methods. The first method is a spatially adaptive non-local means (SANLM) denoising filter (Manjón et al., 2010). This filter removes noise while preserving edges and is implemented as a preprocessing step. The second method is a classical Markov Random Field (MRF) approach, which incorporates spatial prior information of adjacent voxels into the segmentation estimation (Rajapakse et al., 1997). Another important extension to the SPM8 segmentation is the integration of the Dartel normalisation (Ashburner, 2007) into the toolbox, with a high-dimensional spatial normalisation with an existing Dartel template in MNI space (http://www.braindevelopment.org).

We computed the total GM, WM and CSF with the same toolkit; Total Intracranial Volume (TIV) was estimated as GM + WM + CSF.

~~2.7.~~2.7 Statistical Analysis

We used an independent two-tailed two-sample t-test (equal or not equal variance assumed based on a Levene's test) to compare means of demographic scores of controls and patients for neuroimaging data.

Between groups CMRglc and GM comparison analyses were performed using a two independent-samples t-test between cases and controls with age and sex as confounding factors for CMRglc and age and TIV for GM (Barnes et al., 2010).

The smoothed GM images were entered into a statistical analysis in multiple regression models with a covariate of non-interest (previously chosen) and one variable of interest: IADL and AQD_iADL, respectively. The models were estimated with SPM8 (no global normalization and no grand mean scaling).

All SPM results were thresholded at $p < .005$ corrected for multiple comparisons, with an extent threshold cluster extent (Ke) of 50 voxels (150 for VBM). All the small clusters were filtered with a p Family-Wise Error (FWE) corrected greater than .05 (in brief Ke > FWEc). The cluster threshold was directly estimated by SPM8. Statistical inferences were performed by applying the Random Field Theory.

MRIcron software (www.mccauslandcenter.sc.edu/mricro/mricron) was used, with the AAL (Automated Anatomical Labelling) and the Brodmann areas (BA) templates, to obtain anatomical localization of significant cluster peaks. The results were reported in the MNI coordinates system. The result maps are reported in the figures in accordance with neurological convention (left is left). Explorative univariate linear regression analysis was carried out to study the relationship between IADL and AQD_iADL (as independent variables) and changes in GM in the insula and cingulate cortex, respectively. The results are reported as scatter-plots (see the supplemental material).

SPSS 13.0 was used for all other statistical analyses, $p < .05$ was considered as significant.

~~3.~~3 Results

~~3.1.~~3.1 Genetic investigation, CSF examination and neuropsychological assessment

Genetic testing did not reveal any changes in the patients. The cerebrospinal fluid examination did not suggest any comorbidities or diagnosis of Alzheimer's disease. The neuropsychological assessment reflected the diagnoses made by the clinical exams. The demographic and clinical-neuropsychological data related to the patient population are summarized in Table 1.

Table 1 Demographic characteristics of the experimental sample and clinical-neuropsychological synopsis. Where possible, maximum scores for each test are shown in square brackets. Wherever there is a normative value, the cut-off scores are given in the statistical normal direction; the values refer to the normative data for healthy controls matched according to age and education. Maximum scores for the tests are shown in square brackets.

alt-text: Table 1

	Mean ± SD	Cut –off
Demographic and clinical data		
Gender (M/F)	13/10	
Age (years)	68.65 ± 8.68	
Schooling (years)	8.96 ± 3.64	
Early cognitive symptoms complaints (months)	42.36 ± 36.60	
Neuropsychological and neuropsychiatric assessment		
Mini-Mental State Examination [30]	23.50 ± 3.00	≥ 23.8
Addenbrooke's Cognitive Examination – Revised version [100]	67.91 ± 13.18	≥ 82
Attentional Matrices [60]	32.76 ± 8.00	≥ 30
Trial Making Test A [500]	84.61 ± 50.95	< 94
Trial Making Test B [500]	254.78 ± 162.35	< 283
Trial Making Test B-A	158.87 ± 115.75	< 187
Babcock [16]	6.26 ± 3.53	≥ 4.75
Coloured Progressive Matrices-36 [36]	22.78 ± 6.67	≥ 18.96

Token Test [36]	28.86 ± 4.57	≥ 26.5
Wisconsin Card Sorting Test categories	1.00 ± 1.00	≥ 37.1
Wisconsin Card Sorting Test % errors	46.17 ± 15.00	
Wisconsin Card Sorting Test % perseverative errors	31.12 ± 15.40	≤ 42.7
Hamilton Depression Rating Scale [67]	12.65 ± 9.52	≤ 7
Disinhibition Scale [96]	12.74 ± 8.35	≤ 16.9
Mania Scale [44]	3.48 ± 4.54	≤ 15
Functional assessment and awareness of disease assessment		
ADL [6]	5.61 ± 0.84	≥ 4
IADL [8]	6.30 ± 1.49	≥ 6
AQD_iADL [16]	5.96 ± 8.62	≤ 4

Legend: M = male; F = female; AQD_iADL = Awareness of Deficit Questionnaire - Dementia scale for instrumental activity domain; ADL = Activity of Daily Living Scale; IADL = Instrumental Activity of Daily Living Scale.

~~3.2.~~3.2 Neuroimaging assessment

The demographic characteristics of patients and control subjects obtained during neuroimaging acquisition are summarized in Table 2. Patients and controls subjected to the CMRglc analysis did not differ in terms of age and sex. A significant difference between patients and controls for VBM analysis was found for age. Importantly, as reported in the method section, we adjusted the analyses for age as a confounding variable.

Table 2 Synopsis of the demographic data of patients and controls subjected to the neuroimaging assessment. T-test results show no significant difference among groups.

alt-text: Table 2

Data	FTLD	Controls PET	p	Controls MRI	p
Number of Subjects	23	18	-	15	-
Age in years (Mean ± SD)	68.6 ± 8.7	64.3 ± 7.7	.296	62.0 ± 4.4	.004
Gender [M/F]	13/10	9/6	.551	7/8	.741

Legend: mean ± standard deviation, p for two independent sample t-test or Fisher's exact test.

Importantly, due to a lack of cooperation on behalf of some patients, or to technical problems (i.e.: request to exit, movements in the scanner), PET data were not acquired for 5 patients and MRI data were not acquired for 6 patients.

~~3.2.1.~~3.2.1 *Group comparison*

Patients had lower values for regional CMRglc (see Fig. S1 and Table S2 in the supplemental material) and GM (see Fig. S2 and Table S3 in the supplemental material), compared to controls, mainly in the temporal cortex with some clusters in the occipital, parietal and orbitofrontal cortices. Perfusion and brain atrophy of these areas reflect the diagnostic criteria by Rascovsky et al. (2011).

~~3.2.2.~~3.2.2 *Correlations with IADL, AQD_iADL*

Regional GM correlated with IADL in the left insula (see Fig. 1 and Table 3).

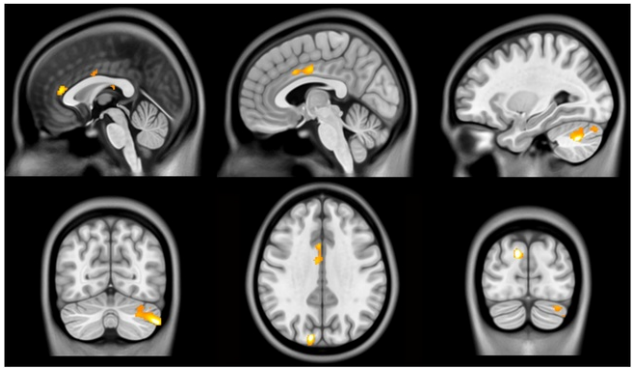

Fig. 1 Correlation of regional GM volume with IADL (p < .005), cluster extent > 50, Ke > FWEc. Neurological convention (left is left). L = left, R = right.

alt-text: Fig. 1

Table 3 Gray matter correlation with the Instrumental Activity of Daily Living scale (Lawton and Brody, 1969).

alt-text: Table 3

Region	BA	Ke	x	y	z	p
L Insula	48	1378	− 45	− 9	1	< 0.001

Legend: L = left, R = right, BA = Brodmann Area, Ke = voxel cluster extension, xyz in mm. Represented clusters are p < .005 and Ke > FWEc.

Regional GM correlated with AQD_iADL in the cuneus, anterior and middle cingulate cortex (ACC, MCC) and posterior cerebellum (see Fig. 2 and Table 4).

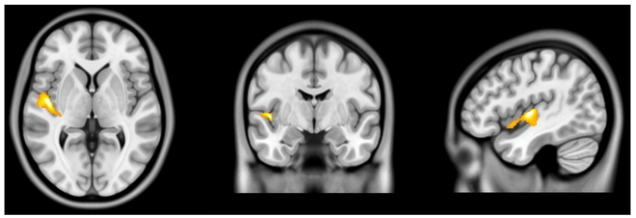

Fig. 2 Correlation of regional GM volume in FTLD with AQD-iADL (p < .005), cluster extent > 150, Ke > FWEc. Neurological convention (left is left). L = left, R = right.

alt-text: Fig. 2

Table 4 Gray matter correlation with the Awareness of Deficit Questionnaire - Dementia scale Factor 1 (AQD_iADL) concerning awareness for the ability in the Instrumental Activity of Daily Living.

alt-text: Table 4

Regions	BA	Ke	x	y	z	p
R Cerebellum crus 1	-	2463	30	− 63	− 38	< 0.001
L Cuneus	19	445	− 12	− 86	32	< 0.001
R Anterior Cingulate cortex	24	408	2	35	14	< 0.001
L Cerebellum III	-	366	− 11	− 30	− 14	< 0.001
L Middle Cingulate cortex	23	356	− 5	− 4	38	0.001

Legend: L = left, R = right, BA = Brodmann Area, Ke = voxel cluster extension, xyz in mm. Represented clusters are p < .005 and Ke > FWEc.

A positive correlation between IADL and insula volume was found, indicating greater GM in more independent patients. There was a negative correlation between AQD-IADL and cingulate volume, indicating less GM in patients with lower awareness (see the supplemental material).

4.4 Discussion

The current study demonstrates, for the first time, the structural changes related to IADL and awareness for the instrumental domain (according to the AQ-D scale factor 1: AQD_iADL) in bv-FTD patients. Specifically, neuroanatomical changes and a reduction in IADL were found in the left insula. On the other hand, the structural neuroanatomical basis of a reduced awareness in IADL was associated with gray matter reduction in the anterior and middle cingulate cortices, cuneus, anterior and posterior cerebellum. The results that emerged from this study are very interesting, since there is a lack of studies analyzing IADL and reduced awareness in bv-FTD patients of deficits in IADL. The current findings are also important in order to elucidate the interrelationship among the associated cerebral structural changes and to provide clinically useful neurodegenerative disease biomarkers. Patients with functional limitations in their daily living and reduced awareness may represent an important target population for tailoring specific interventions with important clinical implications, in terms of adherence to treatments and prognosis.

In formulating a theoretically informative and clinically useful model of a reduction of IADL and awareness of this in bvFTD patients, it is important to consider both the independent functioning of each brain region and how regions may interact with each other as key components of one or more distributed networks, while acknowledging that this process of reverse inference is necessarily speculative.

Interestingly, the relationship we found between functional limitations in daily living, reduced awareness of these and gray matter reduction, refers to regions involved in loading executive-monitoring onto the processing of task-relevant information in order to avoid interference by goal-irrelevant stimuli. In particular, the dorsal cingulate, dorsal anterior insula cortices and cuneous are some of the regions that have been identified as major nodes of the task-positive network, a macroscale network typically first recognised as anticorrelated with the default mode network, that appears to subserve self-referential processing, particularly during wakeful rest (Fox et al., 2005). These areas may be considered as a “hub” that connects systems involved in action monitoring, representation of the affective qualities of sensory events and interoceptive signals, where the anterior and middle cingulate cortices play important roles (Dosenbach et al., 2006). Indeed, action monitoring is particularly important in situations that require higher processing capacity such as those related to the IADL. It requires a representation of expected values of different actions, as well as the continuous monitoring of outcomes in terms of updating. Monitoring such occurrences is necessary to provide feedback as to when strategic processes must be more strongly engaged to adapt ongoing behaviour.

Diminished ability to perceive one's own impairments is common in FTD patients, where impaired self-awareness occurs early in their illness (Neary et al., 1998). Self-awareness relies on comparing knowledge of current abilities with past abilities; it may be inaccurate when such knowledge is affected by monitoring deficits in self-referential processes, as in the case of bvFTD patients (Bastin et al., 2012), with the ventromedial and frontopolar cortex regions appearing to be particularly important for self-awareness of social, emotional, cognitive and disease domains. Studies using patient vs. informant discrepancy approaches have supported 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 prefrontal pathophysiology. Metacognitive processing contributes to the self-regulation of behaviour through the central executive functions. This includes how effectively and accurately an individual is able to use self-knowledge and self-monitoring abilities to guide cognition and behaviour in social and non-social contexts (Fernandez-Duque et al., 2000). Metacognitive impairments may be important contributing factors to social behavioural impairments of poor self-monitoring, disinhibition, erratic judgement, and declining adjustment to progressive deficits in FTD patients (O'Keeffe et al., 2007).

We found, for the first time in the literature on bv-FTD patients, specific structural changes to be associated with an inability to report unsuccessful experiences in IADL through the AQ-D. In particular, our results showed patients to have less GM than controls in the anterior cingulate cortex (BA 24). Interestingly, in our previous article concerning impaired awareness of deficits in Alzheimer’s Disease and the role of everyday executive dysfunction, the factors retained from the factor analysis, in terms of self-monitoring, inhibition, set-shifting, and mood orientation changes, appeared to be important skills for awareness of IADL [AQD_iADL] (Amanzio et al., 2013). Consistent with this, AD patients with impaired self-awareness showed reduced activation in the MCC compared to subjects aware of their deficits (Amanzio et al., 2011).

In the present study, we hypothesized that a reduced awareness of limitations in IADL may arise as a result of disruption of the comparator mechanisms responsible for action monitoring. If the executive system does not function correctly, due to structural changes found in the ACC, the comparator mechanism of action self-monitoring (neutrally inscribed in the MCC), does not detect mismatches between the actual and the previous state of performance on IADL, and produces a reduced awareness for the instrumental domain. We observed this phenomenon as an inability to report unsuccessful experiences in patients’ everyday living activities through the AQ-D.

4.1.4.1 Conclusions

We found reduced awareness for deficits in IADL related to medial PFC atrophy and in line with specific findings reported in the literature suggesting a role of the monitoring network in self-awareness-disabilities (O'Keeffe et al., 2007; Amanzio et al., 2011). Bv-FTD patients experience problems in daily life functioning where they may risk harming themselves or others because they cannot judge situations adequately. Grossman (2002) underlined how these clinical disorders may contribute significantly to their progressive adaptive behavioural difficulties in home, vocational and social settings, leading to disability and the need for supervisory care (Gregory & Hodges, 1996; Grossman, 2002).

Our data suggest that monitoring reduced awareness of IADL deficits, using a joint approach that combines clinical scales (such as IADL and AQD_iADL) and VBM-based-biomarkers, in the early course of bv-FTD could represent an important diagnostic aspect.

Conflict of interest declaration

Relevant conflicts of interest/financial disclosures: There is nothing to report as far as any of the authors are concerned.

Description of authors' roles

- Martina Amanzio: The study is based on a conception by M.A. who wrote the first draft of the paper and participated in the review and critique processes. She also organized the study and participated in the statistical analyses (execution and organization, review and critique).
- Federico D'Agata: He participated in writing the paper, MRI acquisition and in the statistical analyses.
- Sara Palermo: She performed the neuropsychological assessment (execution and organization), participated in the statistical analyses, participated in writing the paper and created the info-graphic.
- Elisa Rubino: She performed the neurological assessment (execution) and she took part in the organization of the study and in the diagnostic phase (organization and diagnosis).
- Milena Zucca: She performed the neuropsychological assessment (execution).
- Antonello Galati: He participated in PET acquisition and in the statistical analyses.
- Lorenzo Pinessi: He reviewed the manuscript.
- Giancarlo Castellano: He participated in PET acquisition and in the statistical analyses.
- Innocenzo Rainero: He supervised the neurological assessment. He took part in the organization of the study and participated in writing the paper (organization, review and critique).

Uncited references

~~Albert et al., 2011~~

~~American Psychiatric Association, 2013~~

~~Boutoleau-Bretonnière et al., 2008~~

~~Brambati et al., 2007~~

~~Broe et al., 2003~~

~~Budson and Solomon, 2012~~

~~Dubois et al., 2014~~

~~Good et al., 2001~~

~~Hénon et al., 1998~~

~~Hughes et al., 1982~~

~~Jefferson et al., 2006~~

~~Jekel et al., 2015~~

~~Kanwisher and Yovel, 2006~~

~~Marshall et al., 2014~~

~~Mathias and Lucas, 2009~~

~~Palermo et al., 2015~~

~~Petersen and Negash, 2008~~

~~Ritchie et al., 2001~~

~~Roy et al., 2012~~

~~Schroeter et al., 2008~~

~~Seeley et al., 2008~~

~~Shen et al., 2012~~

~~Sturm et al., 2006~~

~~Sturm et al., 2008~~

~~Walter et al., 2001~~

~~Wicklund et al., 2007~~

~~Winblad et al., 2004~~

~~Yoshida et al., 2012~~

~~Zhou et al., 2010~~

~~Appendix A.~~Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.exger.2016.08.008.

References

Albert M.S., DeKosky S.T., Dickson D., Dubois B., Feldman H.H., Fox N.C., Gamst A., Holtzman D.M., Jagust W.J., Petersen R.C., Snyder P.J., Carrillo M.C., Thies B. and Phelps C.H., The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease, *Alzheimers Dement.* **7**, 2011, 270–279.

Amanzio M., Torta D.M.E., Sacco K., Cauda F., D'Agata F., Duca S., Leotta D., Palermo S. and Geminiani G.C., Unawareness of deficits in Alzheimer's disease: role of the cingulate cortex, *Brain* **134**, 2011, 1061–1076.

American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders, 5th ed., 2013, APA; Washington, DC.

Ashburner J., A fast diffeomorphic image registration algorithm, *NeuroImage* **38**, 2007, 95–113.

Barnes J., Ridgway G.R., Bartlett J., Henley S.M., Lehmann M., Hobbs N., Clarkson M.J., MacManus D.G., Ourselin S. and Fox N.C., Head size, age and gender adjustment in MRI studies: a necessary nuisance?, *NeuroImage* **53**, 2010, 1244–1255.

Bastin C., Feyers D., Souchay C., Guillaume B., Pepin J.L., Lemaire C., Degueldre C., Collette F. and Salmon E., Frontal and posterior cingulate metabolic impairment in the behavioral variant of frontotemporal dementia with impaired autonoetic consciousness, *Hum. Brain Mapp.* **33**, 2012, 1268–1278.

Baudino B., D'agata F., Caroppo P., Castellano G., Cauda S., Manfredi M., Geda E., Castelli L., Mortara P., Orsi L., Cauda F., Sacco K., Ardito R.B., Pinessi L., Geminiani G., Torta R. and Bisi G., The chemotherapy long-term effect on cognitive functions and brain metabolism in lymphoma patients, *Q. J. Nucl. Med. Mol. Imaging* **56**, 2012, 559–568.

Bech P., Rafaelsen O.J., Kramp P. and Bolwig T.G., The mania rating scale: scale construction and inter-observer agreement, *Neuropharmacology* **17**, 1978, 430–431.

Berg E.A., A simple objective technique for measuring flexibility in thinking, *J. Gen. Psychol.* **39**, 1948, 15–22.

Boutoleau-Bretonnière C., Vercelletto M., Volteau C., Renou P. and Lamy E., Zarit burden inventory and activities of daily living in the behavioral variant of frontotemporal dementia, *Dement. Geriatr. Cogn. Disord.* **25**, 2008, 272–277.

Brambati S.M., Renda N.C., Rankin K.P., Rosen H.J., Seeley W.W., Ashburner J., Weiner M.W., Miller B.L. and Gorno-Tempini M.L., A tensor based morphometry study of longitudinal gray matter contraction in FTD, *NeuroImage* **35**, 2007, 998–1003.

Broe M., Hodges J.R., Schofield E., Shepherd C.E., Kril J.J. and Halliday G.M., Staging disease severity in pathologically confirmed cases of frontotemporal dementia, *Neurology* **60**, 2003, 1005–1011.

Brown R.K., Bohnen N.I., Wong K.K., Minoshima S. and Frey K.A., Brain PET in suspected dementia: patterns of altered FDG metabolism, *Radiographics* **34**, 2014, 684–701.

Budson A.E. and Solomon P.R., New diagnostic criteria for Alzheimer's disease and mild cognitive impairment for the practical neurologist, *Pract. Neurol.* **12**, 2012, 88–96.

De Renzi E. and Vignolo L.A., The token test: A sensitive test to detect receptive disturbances in aphasics, *Brain* **85**, 1962, 665–678.

Dosenbach N.U., Visscher K.M., Palmer E.D., Miezin F.M., Wenger K.K., Kang H.C., Burgund E.D., Grimes A.L., Schlaggar B.L. and Petersen S.E., A core system for the implementation of task sets, *Neuron* **50**, 2006, 799–812.

Dubois B., Feldman H.H., Jacova C., Hampel H., Molinuevo J.L., Blennow K., DeKosky S.T., Gauthier S., Selkoe D., Bateman R., Cappa S., Crutch S., Engelborghs S., Frisoni G.B., Fox N.C., Galasko D., Habert M.O., Jicha G.A., Nordberg A., Pasquie F., Rabinovici G., Robert P., Rowe C., Salloway S., Sarazin M., Epelbaum S., de Souza L.C., Vellas B., Visser P.J., Schneider L., Stern Y., Scheltens P. and Cummings J.L., Advancing research diagnostic criteria for Alzheimer's disease: the IWG 2 criteria, *Lancet Neurol.* **13**, 2014, 614–629.

Eslinger P.J., Dennis K., Moore P., Antani S., Hauck R. and Grossman M., Metacognitive deficits in frontotemporal dementia, *J. Neurol. Neurosurg. Psychiatry* **76**, 2005, 1630–1635.

Folstein M.F., Folstein S.E. and McHugh P.R., "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician, *J. Psychiatr. Res.* **12**, 1975, 189–198.

Fox M.D., Snyder A.Z., Vincent J.L., Corbetta M., Van Essen D.C. and Raichle M.E., The human brain is intrinsically organized into dynamic, anticorrelated functional networks, *Proc. Natl. Acad. Sci. U. S. A.* **102**, 2005, 9673–9678.

Good C.D., Johnsrude I.S., Ashburner J., Henson R.N., Friston K.J. and Frackowiak R.S., A voxel-based morphometric study of ageing in 465 normal adult human brains, *NeuroImage* **14**, 2001, 21–36.

Grossman M., Frontotemporal dementia: a review, *J. Int. Neuropsychol. Soc.* **8**, 2002, 566–583.

Hamilton M., A rating scale for depression, *J. Neurol. Neurosurg. Psychiatry* **23**, 1960, 56–62.

Hénon H., Pasquier F., Durieu I., Pruvo J.P. and Leys D., Medial temporal lobe atrophy in stroke patients: relation to pre-existing dementia, *J. Neurol. Neurosurg. Psychiatry* **65**, 1998, 641–647.

Hughes C.P., Berg L., Danziger W.L., Coben L.A. and Martin R.L., A new clinical scale for the staging of dementia, *Br. J. Psychiatry* **140**, 1982, 566–572.

Jefferson A.L., Paul R.H., Ozonoff A. and Cohen R.A., Evaluating elements of executive functioning as predictors of instrumental activities of daily living (IADLs), *Arch. Clin. Neuropsychol.* **21**, 2006, 311–320.

Jekel K., Damian M., Wattmo C., Hausner L., Bullock R., Connelly P.J., Dubois B., Eriksdotter M., Ewers M., Graessel E., Kramberger M.G., Law E., Mecocci P., Molinuevo J.L., Nygård L., Olde-Rikkert M.G., Orgogozo J.M., Pasquier F., Peres K., Salmon E., Sikkes S.A., Sobow T., Spiegel R., Tsolaki M., Winblad B. and Frölich L., Mild cognitive impairment and deficits in instrumental activities of daily living: a systematic review, *Alzheimers Res. Ther.* **7**, 2015, 17.

Kanwisher N. and Yovel G., The fusiform face area: a cortical region specialized for the perception of faces, *Philos. Trans. R. Soc. Lond. Ser. B Biol. Sci.* **361**, 2006, 2109–2128.

Katz S., Ford A.B., Moskowitz R.W., Jackson B.A. and Jaffe M.W., Studies of illness in the aged. the index of adl: a standardized measure of biological and psychosocial function, *JAMA* **185**, 1963, 914–919.

Lawton M.P. and Brody E.M., Assessment of older people: self-maintaining and instrumental activities of daily living, *Gerontologist* **9**, 1969, 179–186.

Lima-Silva T.B., Bahia V.S., Carvalho V.A., Guimarães H.C., Caramelli P., Balthazar M.L., Damasceno B., Bottino C.M., Brucki S.M., Nitrini R. and Yassuda M.S., Direct and indirect assessments of activities of daily living in behavioral variant frontotemporal dementia and Alzheimer disease, *J. Geriatr. Psychiatry Neurol.* **28**, 2015, 19–26.

Manjón J.V., Coupé P., Martí-Bonmatí L., Collins D.L. and Robles M., Adaptive non-local means denoising of MR images with spatially varying noise levels, *J. Magn. Reson. Imaging* **31**, 2010, 192–203.

Marshall G.A., Lorius N., Locascio J.J., Hyman B.T., Rentz D.M., Johnson K.A. and Sperling R.A., Regional cortical thinning and cerebrospinal biomarkers predict worsening daily functioning across the Alzheimer's disease spectrum, *J. Alzheimers Dis.* **41**, 2014, 719–728.

Mathias J.L. and Lucas L.K., Cognitive predictors of unsafe driving in older drivers: a meta-analysis, *Int. Psychogeriatr.* **21**, 2009, 637–653.

Migliorelli R., Tesón A., Sabe L., Petracca G., Petracchi M., Leiguarda R. and Starkstein S.E., Anosognosia in Alzheimer's disease: a study of associated factors, *J. Neuropsychiatr. Clin. Neurosci.* **7**, 1995, 338–344.

Mioshi E., Dawson K., Mitchell J., Arnold R. and Hodges J.R., The Addenbrooke's Cognitive Examination Revised (ACE-R): a brief cognitive test battery for dementia screening, *Int. J. Geriatr. Psychiatry* **21**, 2006, 1078–1085.

Mioshi E., Kipps C.M., Dawson K., Mitchell J., Graham A. and Hodges J.R., Activities of daily living in frontotemporal dementia and Alzheimer disease, *Neurology* **68**, 2007, 2077–2084.

Neary D., Snowden J.S., Gustafson L., Passant U., Stuss D., Black S., Freedman M., Kertesz A., Robert P.H., Albert M., Boone K., Miller B.L., Cummings J. and Benson D.F., Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria, *Neurology* **51**, 1998, 1546–1554.

O'Keeffe F.M., Murray B., Coen R.F., Dockree P.M., Bellgrove M.A., Garavan H., Lynch T. and Robertson I.H., Loss of insight in frontotemporal dementia, corticobasal degeneration and progressive supranuclear palsy, *Brain* **130**, 2007, 753–764.

Palermo S., Benedetti F., Costa T. and Amanzio M., Pain anticipation: an activation likelihood estimation meta-analysis of brain imaging studies, *Hum. Brain Mapp.* **36**, 2015, 1648–1661.

Pérès K., Helmer C., Amieva H., Orgogozo J.M., Rouch I., Dartigues J.F. and Barberger-Gateau P., Natural history of decline in instrumental activities of daily living performance over the 10 years preceding the clinical diagnosis of dementia: a prospective population-based study, *J. Am. Geriatr. Soc.* **56**, 2008, 37–44.

Petersen R.C. and Negash S., Mild cognitive impairment: an overview, *CNS Spectr.* **13**, 2008, 45–53.

Prigatano G.P. and Altman I.M., Impaired awareness of behavioral limitations after traumatic brain injury, *Arch. Phys. Med. Rehabil.* **71**, 1990, 1058–1064.

Rajapakse J.C., Giedd J.N. and Rapoport J.L., Statistical approach to segmentation of single-channel cerebral MR images, *IEEE Trans. Med. Imaging* **16**, 1997, 176–186.

Rascovsky K., Hodges J.R., Knopman D., Mendez M.F., Kramer J.H., Neuhaus J., van Swieten J.C., Seelaar H., Dopper E.G., Onyike C.U., Hillis A.E., Josephs K.A., Boeve B.F., Kertesz A., Seeley W.W., Rankin K.P., Johnson J.K., Gorno-Tempini M.L. Rosen H., Prioleau-Latham C.E., Lee A., Kipps C.M., Lillo P., Piguet O., Rohrer J.D., Rossor M.N., Warren J.D., Fox N.C., Galasko D., Salmon D.P., Black S.E., Mesulam M., Weintraub S., Dickerson B.C., Diehl-Schmid J., Pasquier F., Deramecourt V., Lebert F., Pijnenburg Y., Chow T.W., Manes F., Grafman J., Cappa S.F., Freedman M., Grossman M. and Miller B.L., Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia, *Brain* **134**, 2011 2456–2477.

Reitan R.M. and Wolfson D., A selective and critical review of neuropsychological deficits and the frontal lobes, *Neuropsychol. Rev.* **4**, 1994, 161–198.

Ritchie K., Artero S. and Touchon J., Classification criteria for mild cognitive impairment: a population-based validation study, *Neurology* **56**, 2001, 37–42.

Roy M., Shohamy D. and Wager T.D., Ventromedial prefrontal-subcortical systems and the generation of affective meaning, *Trends Cogn. Sci.* **16**, 2012, 147–156.

Royall D.R., Lauterbach E.C., Kaufer D., Malloy P., Coburn K.L., Black ~~K.J~~K.J. and Association, C.o.R.o.t.A.N., The cognitive correlates of functional status: a review from the Committee on Research of the American Neuropsychiatric Association, *J. Neuropsychiatr. Clin. Neurosci.* **19**, 2007, 249–265.

Schroeter M.L., Raczka K., Neumann J. and von Cramon D.Y., Neural networks in frontotemporal dementia--a meta-analysis, *Neurobiol. Aging* **29**, 2008, 418–426.

Seeley W.W., Crawford R., Rascovsky K., Kramer J.H., Weiner M., Miller B.L. and Gorno-Tempini M.L., Frontal paralimbic network atrophy in very mild behavioral variant frontotemporal dementia, *Arch. Neurol.* **65**, 2008, 249–255.

Shany-Ur T., Lin N., Rosen H.J., Sollberger M., Miller B.L. and Rankin K.P., Self-awareness in neurodegenerative disease relies on neural structures mediating reward-driven attention, *Brain* **137**, 2014, 2368–2381.

Shen X., Liu H., Hu Z., Hu H. and Shi P., The relationship between cerebral glucose metabolism and age: report of a large brain PET data set, *PLoS One* **7**, 2012, e51517.

Spinnler H. and Tognoni G., standardizzazione italiana e taratura di test neuropsicologici, *Ital. J. Neurol. Sci.* **6**, 1987.

Starkstein S.E., Garau M.L. and Cao A., Prevalence and clinical correlates of disinhibition in dementia, *Cogn. Behav. Neurol.* **17**, 2004, 139–147.

Starkstein S.E., Jorge R., Mizrahi R. and Robinson R.G., A diagnostic formulation for anosognosia in Alzheimer's disease, *J. Neurol. Neurosurg. Psychiatry* **77**, 2006, 719–725.

Sturm V.E., Rosen H.J., Allison S., Miller B.L. and Levenson R.W., Self-conscious emotion deficits in frontotemporal lobar degeneration, *Brain* **129**, 2006, 2508–2516.

Sturm V.E., Ascher E.A., Miller B.L. and Levenson R.W., Diminished self-conscious emotional responding in frontotemporal lobar degeneration patients, *Emotion* **8**, 2008, 861–869.

Tohka J., Zijdenbos A. and Evans A., Fast and robust parameter estimation for statistical partial volume models in brain MRI, *NeuroImage* **23**, 2004, 84–97.

Walter L.C., Brand R.J., Counsell S.R., Palmer R.M., Landefeld C.S., Fortinsky R.H. and Covinsky K.E., Development and validation of a prognostic index for 1-year mortality in older adults after hospitalization, *JAMA* **285**, 2001, 2987–2994.

Wicklund A.H., Johnson N., Rademaker A., Weitner B.B. and Weintraub S., Profiles of decline in activities of daily living in non-Alzheimer dementia, *Alzheimer Dis. Assoc. Disord.* **21**, 2007, 8–13.

Winblad B., Palmer K., Kivipelto M., Jelic V., Fratiglioni L., Wahlund L.O., Nordberg A., Bäckman L., Albert M., Almkvist O., Arai H., Basun H., Blennow K., de Leon M., DeCarli C., Erkinjuntti T., Giacobini E., Graff C., Hardy J., Jack C., Jorm A., Ritchie K., van Duijn C., Visser P. and Petersen R.C., Mild cognitive impairment--beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment, *J. Intern. Med.* **256**, 2004, 240–246.

Yoshida D., Shimada H., Makizako H., Doi T., Ito K., Kato T., Shimokata H., Washimi Y., Endo H. and Suzuki T., The relationship between atrophy of the medial temporal area and daily activities in older adults with mild cognitive impairment, *Aging Clin. Exp. Res.* **24**, 2012, 423–429.

Zhou J., Greicius M.D., Gennatas E.D., Growdon M.E., Jang J.Y., Rabinovici G.D., Kramer J.H., Weiner M., Miller B.L. and Seeley W.W., Divergent network connectivity changes in behavioural variant frontotemporal dementia and Alzheimer's disease, *Brain* **133**, 2010, 1352–1367.

~~Appendix A.~~ Appendix A. Supplementary data

Multimedia Component 1

Supplementary material

alt-text: Image 1

Highlights

- IADLs may be prematurely damaged in frontotemporal dementia
- Gray matter volume changes related to reduced awareness for deficits in IADLs were examined
- Medial PFC atrophy was implied, suggesting a disruption of the monitoring salience network
- The monitoring network play an important role in self-awareness-disabilities
- Unawareness for IADLs deficits should be monitored using VBM-biomarkers

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Queries and Answers

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Answer: Amanzio M, Vase L, Leotta D, Miceli R, Palermo S, Geminiani G. Impaired awareness of deficits in Alzheimer's disease: the role of everyday executive dysfunction. J Int Neuropsychol Soc. 2013 Jan;19(1):63-72

Query:

Citation "Gregory & Hodges, 1996" has not been found in the reference list. Please supply full details for this reference.

Answer: Gregory CA, Hodges JR. Clinical features of frontal lobe dementia in comparison to Alzheimer's disease. J Neural Transm Suppl. 1996;47:103-23.

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