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Authors

Shany-Ur, Tal
Lin, Nancy
Rosen, Howard J
et al.

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Self-awareness in neurodegenerative disease relies on neural structures mediating reward-driven attention

Tal Shany-Ur,[1,2] Nancy Lin,[1] Howard J. Rosen,[1] Marc Sollberger,[1,3] Bruce L. Miller[1] and Katherine P. Rankin[1]

1 Memory and Aging Center, Department of Neurology, University of California, San Francisco, USA
2 The National Institute for the Rehabilitation of the Brain Injured, Tel Aviv, Israel
3 Department of Neurology, University Hospital Basel, Basel, Switzerland

Correspondence to: Katherine P. Rankin,
Memory and Aging Center,
Department of Neurology,
University of California, San Francisco,
675 Nelson Rising Lane, Suite 190,
San Francisco, CA 94158, USA
E-mail: krankin@memory.ucsf.edu

Accurate self-awareness is essential for adapting one's tasks and goals to one's actual abilities. Patients with neurodegenerative diseases, particularly those with right frontal involvement, often present with poor self-awareness of their functional limitations that may exacerbate their already jeopardized decision-making and behaviour. We studied the structural neuroanatomical basis for impaired self-awareness among patients with neurodegenerative disease and healthy older adults. One hundred and twenty-four participants (78 patients with neurodegenerative diseases including Alzheimer's disease, behavioural variant frontotemporal dementia, right-temporal frontotemporal dementia, semantic variant and non-fluent variant primary progressive aphasia, and 46 healthy controls) described themselves on the Patient Competency Rating Scale, rating observable functioning across four domains (daily living activities, cognitive, emotional control, interpersonal). All participants underwent structural magnetic resonance imaging. Informants also described subjects' functioning on the same scale. Self-awareness was measured by comparing self and informant ratings. Group differences in discrepancy scores were analysed using general linear models, controlling for age, sex and disease severity. Compared with controls, patients with behavioural variant frontotemporal dementia overestimated their functioning in all domains, patients with Alzheimer's disease overestimated cognitive and emotional functioning, patients with right-temporal frontotemporal dementia overestimated interpersonal functioning, and patients with non-fluent aphasia overestimated emotional and interpersonal functioning. Patients with semantic variant aphasia did not overestimate functioning on any domain. To examine the neuroanatomic correlates of impaired self-awareness, discrepancy scores were correlated with brain volume using voxel-based morphometry. To identify the unique neural correlates of overlooking versus exaggerating deficits, overestimation and underestimation scores were analysed separately, controlling for age, sex, total intracranial volume and extent of actual functional decline. Atrophy related to overestimating one's functioning included bilateral, right greater than left frontal and subcortical regions, including dorsal superior and middle frontal gyri, lateral and medial orbitofrontal gyri, right anterior insula, putamen, thalamus, and caudate, and midbrain and pons. Thus, our patients' tendency to under-represent their functional decline was related to degeneration of domain-general dorsal frontal regions involved in attention, as well as orbitofrontal and subcortical regions likely involved in assigning a reward value to self-related processing and maintaining accurate self-knowledge. The anatomic correlates of underestimation (right rostral anterior cingulate cortex, uncorrected significance level) were distinct from overestimation and had a substantially smaller effect size. This suggests that

underestimation or 'tarnishing' may be influenced by non-structural neurobiological and sociocultural factors, and should not be considered to be on a continuum with overestimation or 'polishing' of functional capacity, which appears to be more directly mediated by neural circuit dysfunction.

Introduction

Neurodegenerative diseases cause progressive, characteristic patterns of decline in various functional domains. The affected domains vary across diseases, and patients may present with a decline in activities of everyday living, motor, cognitive, social-interpersonal or emotional abilities, depending on the regions of atrophy. While many neurological conditions impact some aspects of functioning, patients with different diseases have varying ability to recognize their impairments (Prigatano, 2009; Zamboni and Wilcock, 2011). Lack of self-awareness for neurological impairments such as cortical blindness (Anton, 1898) and hemiplegia has historically been termed 'anosognosia' (Babinski, 1914), a term later used to describe lack of awareness for other more subtle neurological impairments such as cognitive and behavioural deficits (McGlynn and Schacter, 1989). The term 'impaired self-awareness' refers to the inability to accurately estimate one's functional capacity (Prigatano, 2009).

Accurate self-awareness is essential for optimal everyday functioning, as it allows choosing activities that suit one's abilities and limitations (Johnson et al., 2002; Rosen et al., 2010), thus preventing possibly harming self and others. Higher congruence between one's actual abilities and one's self-estimation increases the chance of successful goal-directed, self-regulated behaviour (Schmitz et al., 2006). However, patients with impaired self-awareness may not adapt their behaviour to current limitations, possibly resulting in hazardous behaviour in circumstances where, for instance, they can no longer drive or manage finances. Impaired self-awareness can also negatively impact patient care and rehabilitation, as it may cause resistance to treatment and rehabilitation efforts (Sherer et al., 1998; Aalten et al., 2005; Rosen, 2011; Zamboni and Wilcock, 2011).

Numerous models have been proposed to explain the cognitive processes underlying impaired self-awareness in individuals with neuropsychological deficits. Some have emphasized the involvement of domain-specific processes, such as perception of sensory input, episodic memory, verbal abilities, or executive control mechanisms. Other models suggest the involvement of additional, domain-general mechanisms, such as a conscious-awareness system and comparator mechanisms (McGlynn and Schacter, 1989; Schacter, 1990; Agnew and Morris, 1998). According to these influential models, impaired self-awareness may result from domain-specific dysfunctions of perceptual or episodic memory abilities, preventing 'registration' of one's decreased functioning into one's long-term memory. Additionally, impaired self-awareness may reflect domain-general failures, either due to generally diminished consciousness, or due to failure or disconnection of attentional mechanisms responsible for comparing recently registered self-related information with previous self-knowledge (Agnew and Morris, 1998). Recent models additionally point out the role of motivational and emotional factors (Rosen, 2011).

The neuroanatomical basis for self-awareness has been examined by various study paradigms, and direct investigation of brain-behaviour correlations sheds some light on the various neuropsychological models. Lesion studies demonstrated that impaired awareness for motor deficits is more related to right hemisphere injuries (Babinski, 1914; Belyi, 1987; Schmitz et al., 2006). Correspondingly, there is more anosognosia for hemiplegia after right Wada test-induced inactivation (Adair et al., 1995). In right lesion patients, anosognosia for hemiplegia and neglect is related to dorsal premotor and primary motor cortices, dorsolateral prefrontal cortex (PFC), and the insula (Berti et al., 2005). Imaging studies involving patients accordingly demonstrated the importance of frontal lobes in self-awareness. Inaccurate self-appraisal in traumatic injury patients is related to reduced medial PFC glucose metabolism (Fontaine et al., 1999), and unawareness of symptoms in schizophrenic patients is related to bilateral dorsolateral PFC atrophy (Flashman et al., 2001). Self-evaluation accuracy is related to anterior dorsolateral PFC activation, particularly on the right, in traumatic injury patients as well as healthy participants (Schmitz et al., 2006). Functional neuroimaging studies with healthy participants correspondingly demonstrate increased right dorsolateral PFC activation during self-referential appraisal tasks (Fossati et al., 2003; Schmitz et al., 2004). Other studies propose that self-referential processing depends on activation of bilateral cortical midline structures (Johnson et al., 2002; Northoff et al., 2006; Schmitz and Johnson, 2007). Neuroimaging studies also emphasize the role of the anterior insula in self-awareness (Berti et al., 2005; Schmitz and Johnson, 2007; Craig, 2009).

Impaired self-awareness is a common, though not homogenous phenomenon among patients with neurodegenerative diseases. Patients with different diseases may exhibit impaired self-awareness at different time points in the disease course, show distinct patterns of preserved and impaired awareness for different deficits, and exhibit divergent degree of impaired self-awareness. Patients with behavioural variant frontotemporal dementia (FTD) characteristically show early, severe lack of awareness of their behavioural and personality decline, and sometimes their cognitive deficits. Patients with Alzheimer's disease often lack self-awareness of their cognitive decline early, but deficient emotional

self-awareness develops later (Neary *et al.*, 1998; Eslinger *et al.*, 2005; Mendez and Shapira, 2005; Rankin *et al.*, 2005; Williamson *et al.*, 2010; Rosen, 2011). Patients with primary progressive aphasia (PPA) typically have more accurate insight than Alzheimer's and behavioural variant FTD patients (Banks and Weintraub, 2008). However, though patients with semantic variant PPA have relatively accurate awareness of their language impairment they sometimes show modestly impaired self-awareness of their social-behavioural changes that progresses to a severe deficit later on (Eslinger *et al.*, 2005).

In patients with neurodegenerative disease, several studies have suggested that impaired self-awareness is related to right prefrontal hypometabolism or atrophy, specifically in ventromedial or orbitofrontal regions, though the precise anatomical basis for this phenomenon is still unclear (Rosen, 2011; Zamboni and Wilcock, 2011). Patients with FTD with right frontal hypoperfusion experience more changes in their self-perceptions (Miller *et al.*, 2001; Mendez and Shapira, 2005), and anosognosia for memory loss in patients with Alzheimer's disease is correlated with right dorsolateral PFC hypoperfusion (Reed *et al.*, 1993). Some studies have also reported the involvement of atrophy in left orbitofrontal (Salmon *et al.*, 2006; Shibata *et al.*, 2008), and temporal and parietal regions (Ries *et al.*, 2007; Zamboni *et al.*, 2010).

Self-awareness is commonly measured by comparing the patient's self-rating of functioning with a more accurate gold standard, such as an informant's rating. The Patient Competency Rating Scale (PCRS) was specifically designed for this purpose (Prigatano, 1986). Originally designed for measuring insight loss in patients with traumatic brain injury, the PCRS assesses the patient's abilities across four domains: activities of daily living, cognitive, emotional, and interpersonal abilities. The questionnaire is administered to the patient and to a knowledgeable informant, assuming the informant's assessment is more accurate. The discrepancy between patient- and informant ratings indicates the patient's self-awareness level. Importantly, impaired self-awareness may be manifested by either positive or negative discrepancy scores. Positive discrepancy scores indicate that patients overestimate their functioning, overlooking deficits obvious to others. Negative discrepancy scores indicate that patients underestimate their functioning, exaggerating deficits that are less obvious to others. As they reflect different psychological tendencies, overestimating and underestimating one's functioning may have divergent neurological causes.

Our first study goal was to characterize self-awareness for competency across multiple functional domains in a large, well-powered sample of patients with neurodegenerative disease and healthy older adults. We hypothesized that patients with behavioural variant FTD would demonstrate impaired self-awareness for their functioning across all domains, and that patients with Alzheimer's disease would show milder deficits in self-awareness, but that these deficits will occur only in domains for which they have sustained a loss of function, i.e. cognitive and activity of daily living abilities.

Our second goal was to identify the structural neuroanatomical correlates of impaired self-awareness of functioning among older participants with and without neurodegenerative diseases. We believed that the tendency to overestimate functioning would be neurologically distinct from the tendency to underestimate functioning, and that overestimation would be much more common in patients. We further hypothesized that overestimation (overlooking deficits), would correlate with atrophy in regions involved in caring about, attending to and accurately evaluating ones' own competency, including bilateral right, more than left prefrontal and subcortical regions (Rosen, 2011; Zamboni and Wilcock, 2011). We further hypothesized that underestimation (exaggerating deficits) would correlate with regions related to error monitoring, negative self-appraisal, and depression, such as the anterior cingulate.

Materials and methods

Participants

One hundred and twenty-four subjects participated in the study, including 46 healthy older control subjects and 78 patients diagnosed with one of five neurodegenerative diseases: 35 patients met NINDS-ADRDA criteria for Alzheimer's disease (McKhann *et al.*, 1984), 21 were diagnosed with behavioural variant FTD (Neary *et al.*, 1998), seven had a right-temporal variant FTD (Josephs *et al.*, 2009), eight were diagnosed with semantic variant PPA, and seven were diagnosed with non-fluent variant PPA (Gorno-Tempini *et al.*, 2011). Behavioural variant and right-temporal FTD were represented as separate groups because right-temporal FTD patients, while behaviourally disordered, have relative sparing of many frontal structures (Whitwell *et al.*, 2009), which we hypothesized might be relevant to self-awareness. Each study participant had an informant who was a family member or long-term friend who completed a questionnaire about the participant, so that 124 informants additionally participated.

Patients' diagnoses were determined by a team of neurologists, neuropsychologists and nurses, following thorough neurological, behavioural, neuropsychological and neuroimaging assessments. We excluded patients with severe language comprehension impairment or those with behavioural deficits such as severe perseverative responses that clearly affected validity of their testing. Control subjects were recruited through recruitment talks and local advertisements, and had to have an unremarkable neurological exam and MRI scan, and no functional or cognitive deficits. Patients were recruited to the research programme through our memory clinic or referrals from external clinics. The study was approved by the Committee on Human Research at the University of California San Francisco and all participants consented to participate. Demographic characteristics are presented in Table 1.

Self-awareness accuracy: PCRS self-ratings versus informant-ratings

PCRS (Prigatano, 1986) includes 30 items encompassing functioning across four domains: activities of daily living (e.g. washing dishes), cognitive functioning (e.g. remembering names of familiar people), social interpersonal functioning (e.g. participating in group activities) and emotional regulation (e.g. accepting criticism from others). Participants and their informants rated how much of a problem the participant has with each function, on a scale of 1 (can't do) to 5 (can do with ease), with higher scores reflecting better capacity. Self-awareness was determined by calculating the discrepancy between

Table 1 Demographic characteristics of study groups (n = 124)

Mean (SD)	AD (n = 35)	bvFTD (n = 21)	rtFTD (n = 7)	svPPA (n = 8)	nfvPPA (n = 7)	NC (n = 46)	F-value	P-value
Age	64.8 (8.6)*	59.7 (7.2)*	61.9 (6.9)	57.9 (6.6)*	66 (9.2)	69.9 (7.1)	7.41	<0.001
Sex (M/F)	17/18	12/9	3/4	4/4	4/3	19/27	$\chi^2 = 1.8$	ns
MMSE	23.4 (3.8)*	24.9 (3.6)*	27 (1.2)	21.8 (8.2)*	24.9 (6)*	29.4 (0.8)	15.11	<0.001
CDR	0.7 (0.2)*	1.3 (0.8)*	0.6 (0.2)*	0.8 (0.6)*	0.6 (0.4)*	0 (0)	36.9	<0.001
Education	15.8 (2.4)*	15.2 (3)*	16.3 (3.2)	17.1 (2.3)	17 (3.4)	17.5 (2.3)	3.02	0.013
Overestimators[a]	28	17	6	3	6	17		
Underestimators[b]	18	10	4	7	4	46		

AD = Alzheimer's disease; bvFTD = behavioural variant FTD; CDR = Clinical Dementia Rating; NC = healthy older controls; nfvPPA = non-fluent variant primary progressive aphasia (PPA); rtFTD = right temporal FTD; svPPA = semantic variant PPA; ns = not significant.
*Group mean is significantly different from control subjects mean ($P < 0.05$) using Dunnett's *post hoc t*-tests.
[a]Number of patients in the 'overestimators' data set, including neutral and overestimating patients, but not underestimators.
[b]Number of patients in the 'underestimators' data set, including neutral and underestimating patients, but not overestimators.

self- and informant ratings on each subdomain, and on the overall score, calculated by summing all subdomain scores. Positive discrepancy scores reflected overestimation and negative scores reflected underestimation of functioning. The PCRS has been validated in studies with traumatic injury patients, showing high test–retest reliability coefficients of both patients and caregivers (Prigatano *et al.*, 1990).

Behavioural data analysis

All dependent measures (including standardized discrepancy scores, described below) underwent regression diagnostics to check for the heteroscedasticity and multicollinearity of residuals, and we confirmed the use of parametric statistics was appropriate. Group differences on potentially confounding covariates were analysed using a general linear model (SAS proc glm) (Table 1).

Group differences in self-awareness (discrepancy scores) were analysed using SAS proc glm controlling for age, sex, and Mini-Mental State Examination (MMSE) score (used as a proxy for disease severity to equalize this clinical factor across patients). The least-square mean of each diagnostic group was compared to that of the control subjects using Dunnett-Hsu *post hoc* tests.

Voxel-based morphometry

The structural T_1-weighted images were preprocessed by segmenting them into grey matter, white matter, and CSF images, normalizing to Montreal Neurological Institute (MNI) space using the segmentation procedure, and warping each image to a template using the Diffeomorphic Anatomical Registration through Exponentiated Lie algebra (DARTEL) toolbox in SPM5 (Ashburner, 2007). The grey and white matter smoothed images were then combined using the voxel lesion-symptom mapping (VLSM) toolbox running on MATLAB (http://www.neuroling.arizona.edu/resources.html; vlsm version 2.42). The online Supplementary material includes detailed information about MRI images acquisition and preprocessing.

Main effects analyses

The neuroanatomical correlates of impaired self-awareness were determined by correlating PCRS self-informant discrepancy scores voxelwise with the combined grey and white matter smoothed images, using voxel-based morphometry (Bates *et al.*, 2003). We used the VLSM toolbox running on MATLAB (http://www.neuroling.arizona.edu/resources.html; vlsm version 2.42). We analysed overall discrepancy as well as the subdomains discrepancy scores. To avoid the possible effect of extreme values on the brain-behaviour correlations analysis, discrepancy scores were converted to z-scores based on the mean and standard deviation (SD) of all participants. Extreme outlier data points were transformed to a z-score of +3 or −3 SD to avoid false correlations. To identify their unique neuroanatomical correlates, we created separate data sets for overestimation and underestimation. The 'overestimators' data set included participants with a z-score >0.5 SD below the mean discrepancy score. The 'underestimators' data set included participants with a z-score <0.5 SD above the mean discrepancy score. This ensured that the analysis of overestimation included neutral and overestimating participants, but not extreme underestimators, and that the analysis of underestimation included neutral and underestimating participants, but not extreme overestimators. Table 1 portrays the number of participants in each data set.

Statistical maps were masked with the template used for image preprocessing. Regionally specific differences in volumes at each voxel were assessed using general linear models, and the significance of each effect was determined using the theory of Gaussian fields (SPM5 defaults). Age, sex, total intracranial volume and scan type (1.5 T, 3 T or 4 T) were entered as covariates into each design matrix. We controlled for MMSE score, as a proxy for disease severity. However, as a conservative error check, in order to ensure that the brain regions related to impaired self-awareness do not simply reflect regions related to the impaired functional abilities, we performed a second set of analyses controlling for the extent of actual functional decline, as reported by informants on the PCRS, instead of MMSE score. Actual decline was determined by transforming informant ratings of the patients' functioning into z-scores, using the mean and SD of the control subject informant ratings data set. Since the resulting z-scores were not normally distributed (patients showed moderate to severe functional decline while control subjects showed minimal decline), they were parameterized into the following nominal variables: 1 (z-score > −1.5); 2 (−3 < z-score < −1.5); 3 (z-scores ⩽ −3). A 1000-permutation analysis was used to identify the study-specific T-threshold at $P < 0.05$ to correct for family-wise error (FWE) (Hayasaka and Nichols, 2004).

In the primary main effect analysis, of the neural correlates of PCRS overall discrepancy score, we conducted two additional

error checks to rule out the possibility of co-atrophy errors, as described in the Supplementary material. The rationale for conducting these analyses has been described previously (Rankin *et al.*, 2009).

Results

Behavioural results: PCRS self-ratings versus informant ratings

Self-ratings, informant ratings and self-informant discrepancy scores are presented in Table 2. Patients with behavioural variant FTD significantly overestimated their overall functional competency compared with control subjects that showed minimal discrepancy ($P < 0.001$). No other diagnostic group was significantly impaired on self-awareness for overall functioning. Analysis of self-informant discrepancy in each subdomain revealed that patients with behavioural variant FTD significantly overestimated their competency for activities of daily living ($P = 0.005$), cognitive functioning ($P < 0.001$), interpersonal functioning ($P < 0.001$), and emotion regulation ($P = 0.016$) (an outlier patient who was an extreme underestimator on the emotional domain was removed from this analysis). Patients with right-temporal FTD significantly overestimated their interpersonal functioning ($P < 0.001$), but were accurate in other domains. Patients with Alzheimer's disease significantly overestimated their cognitive functioning ($P = 0.041$) and emotion

regulation ($P = 0.018$). Patients with non-fluent variant PPA significantly overestimated their emotion regulation ($P < 0.001$) and interpersonal functioning ($P = 0.032$). Patients with semantic variant PPA did not overestimate functioning in any domain.

Voxel-based morphometry

The neural correlates of overestimating overall functional competency

The analysis of the neural correlates of PCRS overall discrepancy score, using the 'overestimators' data set, yielded similar results when controlling for disease severity or conducting a more conservative analysis controlling for extent of actual functional decline (Fig. 1 and Table 3). The tendency to overestimate one's overall functioning corresponded with atrophy in bilateral, right greater than left frontal and subcortical regions, including dorsal parts of the superior and middle frontal gyri, lateral and medial orbitofrontal gyri, orbital parts of the inferior and superior frontal gyri, right anterior insula, putamen, thalamus, and caudate, and pons and midbrain.

In a shared effects analysis we controlled for group membership to identify regions of atrophy significantly related to impaired self-awareness that appear in more than one diagnostic group, thus more likely represent a generalizable brain-behaviour relationship, rather than an artefact resulting from the correlated atrophy pattern within one group. The results (Table 3) supported the main effect analysis results. Regions that survived

Table 2 Self-ratings, informant-ratings and self-informant discrepancy scores of functional competency

Mean (SD)	AD	bvFTD	nfvPPA	rtFTD	svPPA	NC	F	P
Overall competency (maximum = 150)								
Self	124.4 (11.6)*	117.1 (18.1)*	128.3 (7.1)	120.9 (18.5)*	116.1 (11.7)*	137.3(8.3)	7.33	<0.001
Informant	112.5 (16.2)*	93.2 (21.7)*	116.3 (10)*	110.1 (20.8)*	119.6 (17.8)*	143.7 (6.3)	25.58	<0.001
Self-informant	11.9 (17.1)	23.4 (24.8)*	12 (13)	10.7 (16.2)	−3.5 (14.7)	−6.4 (8.7)	8.25	<0.001
Capacity for ADLs (maximum = 40)								
Self	34.6 (3.9)*	31.2 (6.9)*	37.1 (3)	35.6 (4.4)*	36.1 (2.9)	38.8 (1.9)	11.30	<0.001
Informant	31.7 (5.9)*	24.5 (8.9)*	37.1 (2.4)	33.7 (6.2)*	35.8 (4)	39.4 (1.1)	20.45	<0.001
Self-informant	2.9 (5.6)	6.7 (8.5)*	0 (4.1)	1.9 (6.3)	0.4 (3.4)	−0.6 (1.6)	4.44	0.001
Cognitive functioning (maximum = 40)								
Self	31.6 (3.9)*	31.3 (5.6)*	35.1 (2.2)	31.4 (5.1)*	30 (4.7)*	36.8 (2.1)	8.29	<0.001
Informant	26.7 (6)*	23.8 (6.1)*	32.9 (2.7)	30.1 (8.8)*	30.3 (6.2)*	38.4 (2.3)	19.88	<0.001
Self-informant	4.9 (6.7)*	7.7(7.9)*	2.3 (4)	1.3 (5.4)	−0.3 (5.8)	−1.5 (2.8)	6.54	<0.001
Emotional regulation (maximum = 35)								
Self	28.9 (3.2)	26.9 (4.8)*	29.6 (2.4)	25.9 (6.1)*	24.4 (2.9)*	30.1 (3.3)	3.87	0.003
Informant	26.6 (3.9)*	24.4 (4.6)*	23.9 (3)*	25 (3.7)*	26.5 (5.1)*	32.5 (2.7)	11.26	<0.001
Self-informant	2.4 (4.5)*	2.6 (5.8)*	5.7 (3.9)*	0.9 (3.8)	−2.1 (4)	−2.4 (3.8)	5.23	<0.001
Interpersonal functioning (maximum = 35)								
Self	29.3 (3.6)	27.9 (4)*	26.4 (2.4)*	28 (4.8)	25.8 (3.9)*	31.6 (2.9)	3.83	0.003
Informant	27.5 (4)*	20.4 (6.4)*	22.4 (4.4)*	21.3 (5.7)*	27.1 (4.2)	33.5 (1.8)	26.4	<0.001
Self-informant	1.8 (3.9)	7.6 (6.8)*	4 (4.6)*	6.7 (5.2)*	−1.4 (5)	−1.9 (2.7)	13.49	<0.001

Group effects on scores were analysed using SAS proc glm controlling for age, sex and MMSE score.
*Group least-square mean significantly different from healthy control subjects least-square mean ($P < 0.05$), with Dunnett-Hsu *post hoc* tests.
AD = Alzheimer's disease; ADL = activity of daily living; bvFTD = behavioural variant FTD; CDR = Clinical Dementia Rating; NC = healthy older controls; nfvPPA = non-fluent variant PPA; rtFTD = right temporal FTD; svPPA = semantic variant PPA.
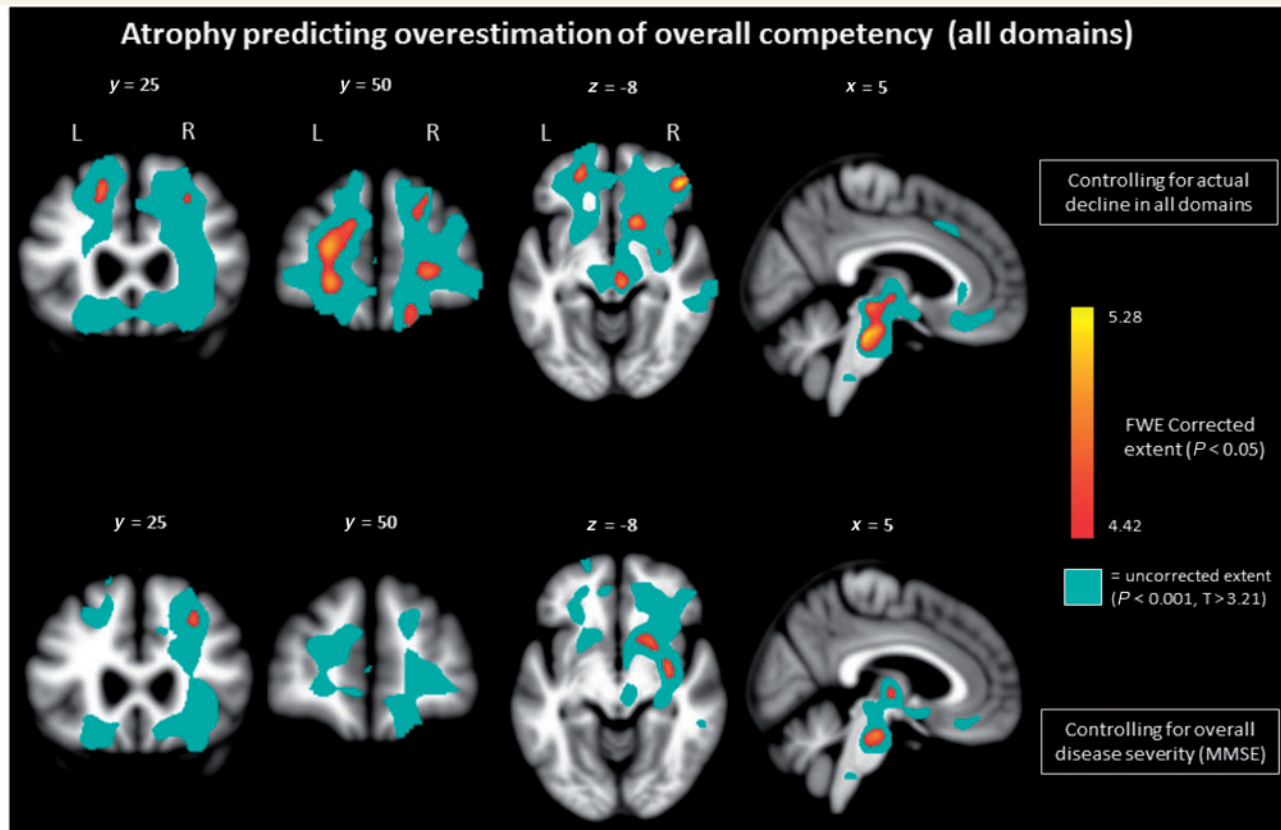
Figure 1 T-score maps showing regions where atrophy predicted overestimating self-functioning (measured by positive discrepancy scores between self and informant ratings on PCRS overall score), controlling for age, sex, total intracranial volume, scan type, and extent of actual functional decline (*top* row) or overall diseases severity (*bottom* row).

the FWE-corrected critical T threshold (T = 4.44) included right orbital inferior frontal gyrus, middle frontal gyrus, caudate head, and putamen, left superior frontal gyrus, and the pons. These results must be considered in light of the main effect results, because this method may improperly exclude regions legitimately related to awareness score that are only atrophic in one group.

Because voxel-based morphometry is a univariate approach that is unable to identify the relative contributions of various peak regions to the variable of interest, and we expected that a co-atrophy artefact could appear due to similarities in progression patterns within patient groups, we performed an additional multiple variable analysis to determine the unique contribution of each region found in the main effects analysis in the context of other significant regions. We extracted voxel intensities at each peak coordinate and entered them together as predictors of self-awareness in a linear regression analysis using SAS proc reg. Voxel probability values, taken from subjects in the 'overestimators' data set, were modelled together using a backwards stepwise regression forcing standard confounds to remain in the model (sex, age, total intracranial volume, MMSE), with discrepancy score as the dependent variable. The final model explained 57% of the variance (F = 12.84, P < 0.001) and

included right middle frontal gyrus, right putamen, and the pons (P < 0.05).

The neural correlates of overestimating functional competency in subdomains

Overestimating competency for activities of daily living corresponded with atrophy in widespread right frontal regions [orbital inferior and superior frontal gyri, medial orbitofrontal cortex (OFC), dorsal middle and superior frontal gyri], anterior insula, putamen, thalamus, medial and lateral temporal lobe regions, and the pons (all regions survived FWE correction). Overestimating cognitive functioning corresponded with atrophy in bilateral superior and middle frontal gyri, and right inferior frontal and cingulate gyri, insula, caudate, and middle temporal gyrus (right middle frontal and middle temporal gyri survived correction). Overestimating emotional control corresponded with atrophy in bilateral OFC and anterior insula, and right superior frontal gyrus, anterior cingulate cortex and caudate (bilateral OFC and insula and right superior frontal gyrus survived correction). Overestimating interpersonal abilities corresponded with atrophy in right OFC, anterior insula, putamen, and fusiform gyrus (the latter two survived correction). The results are presented in Fig. 2 and Table 4 (Supplementary Table 1 presents the uncorrected results).

Table 3 The neural correlates of self-awareness: regions where atrophy predicted overestimating overall functional competency (corrected results and corrected-level cluster sizes)

Brain region	Volume (mm³)	Peak MNI coordinates			Max T
		x	y	z	(P_FWE < 0.05)
Right IFG, orbital part*,#	3576	46	42	−8	5.21
Right SFG	a	22	55	2	4.65
Right insula, anterior	a	32	30	4	4.74
Right medial orbital gyrus	384	16	48	−18	4.70
Right MFG*,#	328	28	22	42	4.80
Right MFG	288	24	52	34	4.67
Right putamen*,#	808	16	16	−8	4.94
Right gyrus rectus	a	17	16	−13	4.59
Right putamen*,#	184	32	0	−4	4.64
Right caudate	a	14	16	−9	4.81
Pons*,#	4064	2	−26	−24	5.18
Midbrain	a	7	−24	−6	4.95
Right thalamus#	a	5	−12	1	4.69
Left MFG*	2488	−22	48	12	5.05
Left medial orbital gyrus	a	−23	52	−6	4.86
Left SFG*,#	1144	−16	30	46	5.28
Left putamen	40	−22	12	−2	4.49

Regions where atrophy was significantly related to higher discrepancy between self-other ratings of overall functional competency (among overestimators), controlling for actual overall functional decline, age, sex, total intracranial volume, and scan type.
ᵃPart of the larger cluster given in the above row, having the same volume.
*Significant regions controlling additionally for diagnostic group (P_FWE < 0.05).
#Significant regions controlling for disease severity (MMSE score) instead of actual functional decline (P_FWE < 0.05).
IFG = inferior frontal gyrus; MFG = middle frontal gyrus; SFG = superior frontal gyrus.

The neural correlates of underestimating overall functional competency

The analysis of the neural correlates of PCRS overall discrepancy score, using the 'underestimators' data set, controlling for overall disease severity and all other confounds, indicated that the tendency to underestimate one's overall functioning corresponded with atrophy in right greater than left rostral anterior cingulate (Supplementary Fig. 1). However, this result did not survive correction for multiple comparisons (T = 4.43, P < 0.001, uncorrected; FWE-corrected critical threshold across the whole brain was T = 4.59; corrected P = 0.06). The analysis pointed to involvement of the same regions when controlling for actual functional decline, but again this result did not survive correction.

Discussion

When asked to rate their competency across four functional domains: daily living activities, cognitive abilities, emotional control, and interpersonal functioning, most patients with neurodegenerative diseases overestimated their functioning compared with how their informants rated them, whereas some patients and most healthy older participants showed accurate estimation, or slight underestimation. Atrophy specifically related to overestimating

one's overall functioning included a network of right greater than left frontal and subcortical regions: dorsal parts of the superior and middle frontal gyri, lateral and medial orbitofrontal gyri; right anterior insula, putamen, thalamus, and caudate, and the midbrain and pons in the brainstem.

Domain general and domain specific aspects of self-awareness

Current theories about self-awareness suggest it may require both domain-general and domain-specific processes, which has implications for understanding its underlying neural mechanisms. Self-awareness is often divergent across domains, and has been shown to be impaired for some functional domains and preserved in other domains in patients with neurodegenerative (Rosen, 2011) and neuropsychiatric disorders (Gilleen et al., 2011). When we analysed specific subdomains of function, distinct but overlapping neuroanatomical patterns emerged. Overestimating activities of daily living corresponded with atrophy in right frontal regions, insula, thalamus, putamen and caudate, medial and lateral temporal regions, and the pons. Overestimating cognitive functioning corresponded with atrophy in right middle frontal and middle temporal gyri, regions associated with perspective-taking and personal semantic information (Sturm et al., 2013a). Overestimating emotional control corresponded with atrophy in
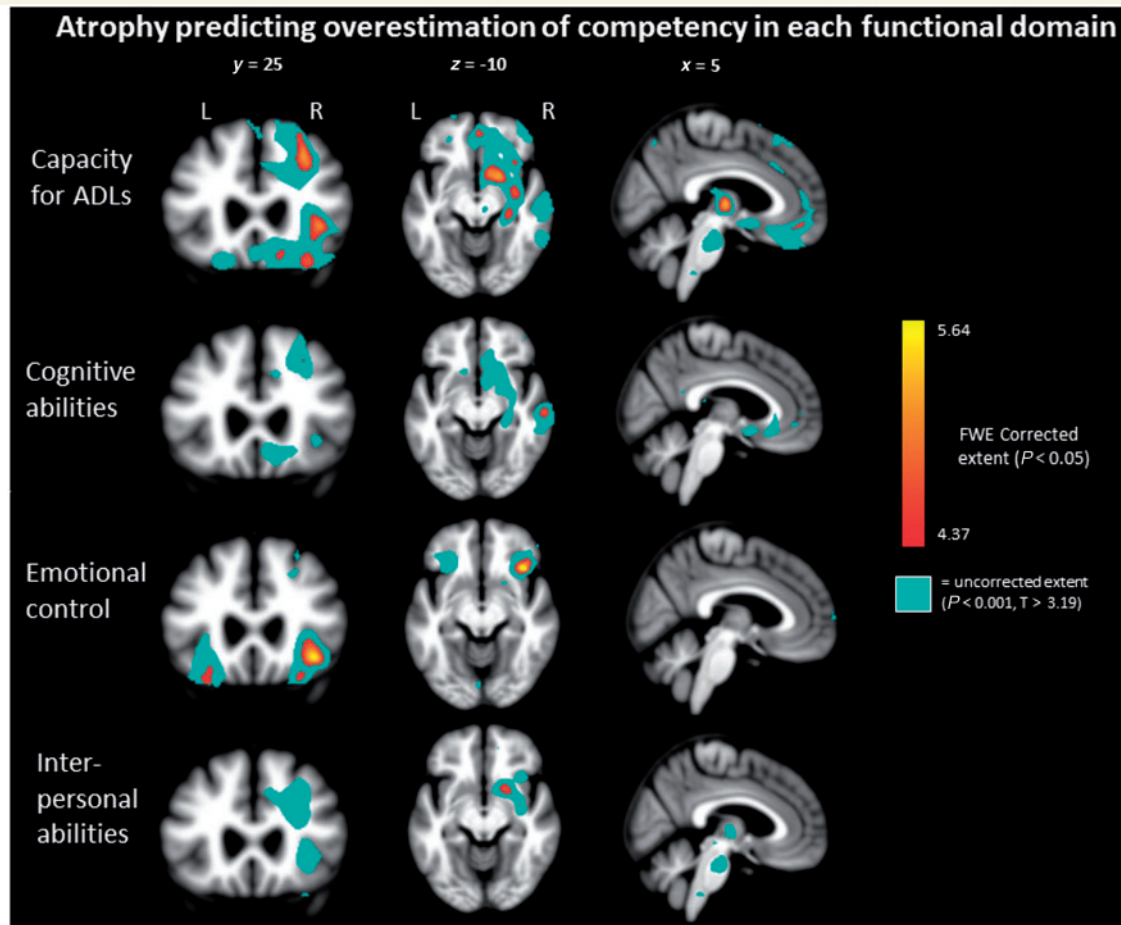
Figure 2 T-score maps showing regions where atrophy predicted overestimating self-functioning (measured by positive discrepancy scores between self and informant ratings) on each PCRS subscale, controlling for age, sex, total intracranial volume, scan type, and overall diseases severity (MMSE). ADL = activity of daily living.

right superior frontal gyrus and anterior insula, and bilateral OFC, regions associated with evaluation of emotional salience (Seeley *et al.*, 2007). Overestimating interpersonal abilities corresponded with atrophy in the right putamen and fusiform gyrus (and inferior frontal gyrus and anterior insula at an uncorrected threshold), regions involved in salience processing and person perception (Kanwisher and Yovel, 2006).

Our analyses within functional subdomains did show some modality-specific anatomic correlates, supporting the hypothesis that there are domain-specific processes involved in self-awareness. However, modality-independent regions, known to mediate attention and reward-related processing, consistently appeared across subdomains, suggesting that these regions play a superordinate role in performing domain-general processing leading to accurate self-awareness. Thus, our findings support a model in which impaired self-awareness reflects a combination of domain-specific dysfunctions in perceptual, semantic or mnemonic abilities alongside domain-general failures of motivational-emotional, attentional, and/or executive mechanisms (Agnew and Morris, 1998; Rosen, 2011).

Sustained task control, attention and memory in self-awareness

Atrophy in right dorsolateral PFC regions, including dorsal superior and middle frontal gyri, was consistently related to impaired self-awareness in our analyses. This region has been implicated in self-referential appraisal (Fossati *et al.*, 2003; Schmitz *et al.*, 2004), and task control mechanisms, and is proposed as part of a frontoparietal network involved in top–down attention processes, including selecting and monitoring one's behaviour based on one's goals (Corbetta and Shulman, 2002). Dosenbach and colleagues (2007) isolated a subcomponent of this larger network that is involved in sustained task control, including aligning one's current behaviour with long-term goals. This 'cingulo-opercular network' includes dorsal anterior cingulate/medial superior frontal cortex, anterior insula/frontal operculum, and anterior PFC, a network overlapping with regions we found to be related to impaired awareness. Thus, self-monitoring processes appear to be partly subserved by neural networks that allow sustained attention that is directed to long-term goals. Accurate

Table 4 The neural correlates of self-awareness: regions where atrophy predicted overestimating competency in each subdomain (corrected results and corrected-level cluster sizes)

Domain and brain region	Volume (mm³)	Peak MNI coordinates			Max T
		x	y	z	($P_{FWE} < 0.05$)
Awareness for ADLs					
Right MFG	1784	28	28	44	5.27
Right SFG	a	27	29	51	4.88
Right SFG, orbital part	1096	14	34	−22	4.85
Right insula, anterior	1632	40	24	−2	5.20
Right IFG, orbital part	a	30	22	−20	4.84
Right orbital gyrus, medial	352	2	50	−10	4.77
Right thalamus	616	6	−12	6	5.32
Right putamen*	4432	22	10	−8	5.24
Right caudate	a	14	13	−11	5.04
Right amygdala	a	20	6	−17	4.80
Right olfactory	a	18	10	−14	5.03
Right insula, posterior	a	42	5	5	4.70
Right parahippocampus	816	32	−22	−16	4.76
Right hippocampus	a	31	−21	−13	4.66
Right middle occipital gyrus	464	38	−86	10	4.93
Right inferior temporal gyrus	72	62	−50	−8	4.52
Pons	144	0	−22	−24	4.49
Awareness for cognitive abilities					
Right middle temporal gyrus*	40	62	−20	−10	4.76
Right MFG#	248	24	52	30	5.02
Awareness for emotional control					
Right IFG, orbital part*	2480	38	24	−10	5.64
Right insula, anterior	a	40	20	−2	4.74
Right SFG	72	18	66	22	4.63
Left insula, anterior	304	−30	26	−26	4.65
Left IFG, orbital part	a	−25	28	−16	4.44
Awareness for interpersonal abilities					
Right putamen*	696	24	10	−4	5.03
Right fusiform gyrus*	16	28	−12	−40	4.63

Regions where atrophy was significantly related to higher discrepancy between self-other ratings of functional competency in each subdomain (among overestimators), controlling for overall disease severity (MMSE), age, sex, total intracranial volume, and scan type.
aPart of the larger cluster given in the above row, having the same volume.
*Significant regions, controlling for actual functional decline instead of MMSE ($P_{FWE} < 0.05$).
#Significant result ($P_{FWE} < 0.05$) when controlling for actual functional decline but not when controlling for MMSE.
ADLs = activities of daily living; IFG = inferior frontal gyrus; MFG = middle frontal gyrus; SFG = superior frontal gyrus.

self-awareness is a reasonable target as a long-term social goal, because for healthy functioning one must maintain accurate maps between one's limitations and larger environmental demands.

Our finding that impaired self-awareness is related to medial PFC atrophy is consistent with literature suggesting a role not only of attentional networks, but also the ruminative, self-reflective memory-based 'default mode network' in maintaining self-focus; i.e. the task control network performs the attentional function, while the default mode network provides the self-related content. Accurate self-awareness relies on self-referential processes such as encoding and retrieving self-relevant information, processes involving the medial PFC (Johnson et al., 2002; Northoff et al., 2006; Schmitz and Johnson, 2007). Studies have shown significantly more medial PFC activity during thinking about personality, mental states and physical traits of oneself compared with others (Jenkins and Mitchell, 2011), and a dorsal medial

PFC-cortical-subcortical system may underlie self-reflection, self-evaluation and top–down retrieval of this information (Schmitz and Johnson, 2007).

Self-awareness is likely linked with autobiographical memory, which is comprised of episodic memory for self-relevant events and semantic knowledge about the self (Conway and Pleydell-Pearce, 2000), and mediated by these same anterior default mode network structures. According to some views, there is a specific self-relevant, personal semantic memory system that is constantly updated and constructed by the same memory systems subserving construction of other types of declarative knowledge, sharing overlapping processes with both semantic and episodic memory (Renoult et al., 2012). Because accurate self-awareness relies on comparing knowledge of current abilities with past abilities, it may be inaccurate when such knowledge is affected by memory deficits, as in the case of Alzheimer's disease (Mograbi et al., 2009).

Reward and self-awareness

Impaired self-awareness in our study was also consistently related to atrophy in bilateral orbitofrontal regions, particularly ventromedial, including the medial orbital gyri, suggesting these may be part of a core network supporting domain-general awareness. These regions were previously implicated in studies of impaired self-awareness in neurodegenerative diseases, even in studies investigating diverse objects of self-awareness such as movement, emotion, and cognition (Salmon *et al.*, 2006; Shibata *et al.*, 2008; Hornberger *et al.*, 2014). Interestingly, self-awareness of abnormal movements is more impaired in patients with Huntington's disease than those with Parkinson's disease, a difference attributed to the greater pathology of orbitofrontal-limbic regions in Huntington's disease (Sitek *et al.*, 2011).

The ventromedial and ventrolateral OFC are represented in two distinct networks involved in different aspects of processing the personal salience of information. A circuit involving the lateral OFC termed the 'emotional salience network' (Seeley *et al.*, 2007), seems to support guiding one's behaviour towards self-related goals in current specific situations. However, the medial OFC subserves representations that appear to be stable over time, affecting long term goal-related behaviour by continuously directing one's attention towards stimuli that are expected to yield future rewards (Rothkirch *et al.*, 2012).

The ventromedial OFC is particularly involved in evaluating valences, representing and updating the personalized subjective reward value placed on objects, information, and goals (O'Doherty, 2004; Rolls, 2004). Impaired awareness for cognitive symptoms in Alzheimer's disease was previously correlated with decreased metabolic activity in the ventromedial OFC, suggesting that dysfunction in this region prevents patients from updating the 'qualitative value' of their current abilities (Salmon *et al.*, 2006). Ventral medial PFC, especially on the right, has been linked with behavioural variant FTD patients' failure to care about accurate self-appraisal (Mendez and Shapira, 2011).

Our findings additionally indicated that impaired self-awareness was related to striatal atrophy, especially the dorsal striatum. Like the OFC, the striatum is highly involved in reward processing (Delgado, 2007), and activity in the nucleus accumbens increases based on the stimuli's self-relatedness and relevance (Phan *et al.*, 2004). This link between reward and self-relevance is part of a self-reinforcing loop; for instance, choosing one stimulus over another, increases the perceived value of the chosen stimulus and this self-preference modification is accompanied by caudate nucleus activity (Sharot *et al.*, 2009).

Our results support the hypothesis that degeneration in orbitofrontal and striatal structures subserving reward evaluation and self-relatedness processing may decrease the degree to which the self is associated with reward. Atrophy in these structures may reduce the reward value of maintaining adequate levels of self-focus to yield an accurate self-concept, leading to impaired self-awareness. Accurate self-evaluation thus might be considered a personal goal that one has to find rewarding and 'care' about to engage in it.

Subcortical contributions to reward-mediated attention

Overestimation of functioning was related to several subcortical structures including the putamen, thalamus, caudate, pons and midbrain. Together, these regions may be involved in linking between reward processing and attention, guiding one's attention to rewarding information. This corresponds with recent findings that activity in a network comprising the midbrain, caudate, thalamus, and anterior midcingulate cortex reflects the degree of interaction between reward and difficulty, with greater recruitment of this network during demanding tasks that are rewarding. This circuit likely mediates the dopaminergic system so that attentional resources are allocated towards targets with greater expected personal value (Krebs *et al.*, 2012), and is also involved in mediating general arousal during cognition, a function particularly dependent on the locus coeruleus (Sara and Bouret, 2012). Thus, this circuit may enhance the ability to attend to oneself when the self or self-processing is considered rewarding.

The links between cortical midline structures and subcortical structures may also subserve transforming lower-level, interoceptive bodily sensations and representations of self into higher-level self-referential mental representations (Northoff *et al.*, 2006). Atrophy in this system may impair the ability to update one's representations about current physical state and capacities. Our results suggest that selective damage to specific parts of this subcortical network may be sufficient to cause inaccurate self-awareness in our patients.

Separate neural mechanisms for 'tarnishing'

Most healthy adults in our study slightly underestimated their functioning, supporting previous results (Rankin *et al.*, 2005). Our analysis of the structural correlates of underestimating one's functioning demonstrated correspondence with right rostral anterior cingulate atrophy, though this result did not survive multiple comparisons correction. The effect size in our sample may have been small, and because few patients 'tarnished', this structural correlation may have primarily been the result of the underestimation tendency among healthy subjects, in whom less variability in brain volume is expected. Notwithstanding its small effect size, this finding corresponds with studies showing that negative self-evaluation is related to insufficient anterior cingulate activation, probably due to decreased inhibition of negative self-related emotional content (Sperduti *et al.*, 2013). Interestingly, reduced grey matter concentration in right anterior cingulate gyrus is related to attention biases towards negative stimuli (Leung *et al.*, 2009). Also, reduced pregenual anterior cingulate volume is related to decreased self-conscious emotional reactivity (Sturm *et al.*, 2013*b*). We found that volume loss in this area may create an increased tendency to 'tarnish', which could be viewed as a paradoxical result, or it may in fact reflect dysfunction of the overall circuit underlying emotional reactivity, in which anterior cingulate volume loss could release negative emotionality.

The tendency to underestimate or 'tarnish' one's functioning is likely multifactorial and influenced by socio-cultural factors, because downplaying one's positive attributes is often rewarded in social settings, and considered in many cultures to be required to meet social norms for diplomacy and humility. Furthermore, underestimating one's capacities is associated with depressed mood (Sperduti *et al.*, 2013), thus non-structural, biochemical factors may also play a role in this tendency. Further investigation of these multiple factors is warranted. Notably, better awareness in dementia often predicts mild depression and anxiety, possibly reflecting a negative psychological reaction to one's declining capacities, thus patients with relatively preserved awareness may benefit from psychological interventions in order to manage their affective symptoms (Aalten *et al.*, 2005).

Clinical relevance to neurodegenerative diseases

Patients with behavioural variant FTD significantly overestimated their overall functional competency, and their competency within each functional subdomain. While no other diagnostic group showed impaired self-awareness for overall functioning, analysis of self-awareness across domains revealed that patients with Alzheimer's disease overestimated their cognitive and emotion regulation capacities, patients with right-temporal FTD overestimated their interpersonal functioning, patients with non-fluent variant PPA overestimated their emotion regulation and interpersonal functioning, while patients with semantic variant PPA did not overestimate functioning on any domain.

Most studies exploring the neural correlates of impaired awareness in dementia point to involvement of right hemispheric, particularly frontal and temporo-parietal regions (Zamboni and Wilcock, 2011). While some studies point to medial-orbital involvement (Shibata *et al.*, 2008; Rosen *et al.*, 2010; Hornberger *et al.*, 2014), others point to dorsolateral PFC involvement (Reed *et al.*, 1993). As highlighted by a recent review, studies measuring awareness for cognitive test-performance report more frontal involvement, whereas studies measuring awareness for personality and behavioural changes pointed to lateral temporal-parietal involvement (Zamboni and Wilcock, 2011).

Frontal lobe dysfunction has been implicated in impaired awareness in behavioural variant FTD (Miller *et al.*, 2001), other FTD-spectrum disorders (O'Keeffe *et al.*, 2007), and Alzheimer's disease (Reed *et al.*, 1993). Our finding that patients with behavioural variant FTD had the most comprehensive awareness deficit supports previous reports of the ubiquitous awareness deficit among this clinical group (Eslinger *et al.*, 2005; Mendez and Shapira, 2005; Rankin *et al.*, 2005; Rosen *et al.*, 2010), supporting the role of frontal lobe dysfunction in this phenomenon. Indeed, impaired metacognitive awareness is predicted by frontal executive neuropsychological measures (O'Keeffe *et al.*, 2007; Rosen *et al.*, 2010). Patients with FTD lack awareness of error-making during task performance, and the degree of this impairment is predicted by the extent of attention deficits (O'Keeffe *et al.*, 2007) and by right lateral and bilateral OFC atrophy (Possin *et al.*, 2009, 2012). Unlike other patients that may attend to

their own errors and translate this information into a more precise self-concept of their declining cognitive abilities, patients with behavioural variant FTD are inattentive to their errors, and may not process the implications of this information for their self-representation (Rosen, 2011).

FTD patients with predominantly right temporal atrophy are often characterized by personality changes and inappropriate behaviours (Josephs *et al.*, 2009). This group showed a selective impairment in awareness for interpersonal abilities, the functional domain where they show the most profound decline. Impaired awareness for behavioural deficits has been previously associated with right temporal atrophy (Zamboni and Wilcock, 2011; Sollberger *et al.*, 2014). A proposed mechanism for this finding was that impaired empathy and understanding of others' minds, frequently associated with right temporal atrophy, affects the ability to understand others' reactions to one's inappropriate behaviour, and to update one's self-knowledge accordingly (Zamboni *et al.*, 2010). Poor metacognitive awareness has been directly related to impaired empathy (O'Keeffe *et al.*, 2007). It was also proposed that impaired awareness for social deficits results from impaired updating of autobiographical information, stored as semantic knowledge about the self, located in the temporal lobes (Ruby *et al.*, 2007). Indeed, failure to update self-relevant knowledge due to memory deficits is a proposed mechanism for impaired self-awareness in patients with Alzheimer's disease as well (Mograbi *et al.*, 2009).

Though patients with non-fluent PPA are generally considered to have fairly preserved social and emotional functioning and insight, our results with this small non-fluent PPA group suggest they may overestimate their interpersonal and emotion regulation capacities. This may have occurred because of the mechanism by which we measured self-awareness. Though we have used caregiver reports as the 'gold standard' for the patient's actual functioning, it is possible that patients with non-fluent PPA actually experience themselves as being unchanged in their emotional and interpersonal relatedness, but because they can no longer communicate those capacities in the same way to their caregivers, they were rated as having a decline in these domains. Alternatively, these patients' left dorsolateral PFC atrophy may have negatively impacted the neural mechanism underlying socio-emotional regulation. Other studies have suggested that patients with non-fluent PPA have impaired awareness for behavioural aspects of their functioning (Eslinger *et al.*, 2005). Further investigation of the mechanisms of this phenomenon in warranted.

Notwithstanding the cognitive mechanisms suggested above, i.e. impaired attention, error monitoring, perspective taking and memory, it has also been argued that patients with behavioural variant FTD exhibit loss of concern about objects of awareness including the self, or 'anosodiaphoria' (Mendez and Shapira, 2011). Our results suggest that the degree to which self-related processing is rewarding likely influences the degree of self-attention, the level of arousal around self-related processes, and the level of accuracy of self-related processing. This is consistent with the view that behavioural variant FTD patients' unawareness of self may be in part due to anosodiaphoria combined with other direct mechanisms.

Limitations

The method we used to assess self-awareness has some known limitations. When measuring awareness by calculating self-inform-ant discrepancy, the caregiver's estimation may be affected by subjective factors. However, previous studies have demonstrated fairly high reliability coefficients of caregivers' responses on the PCRS (Prigatano et al., 1990). Additionally, though such question-naires were designed and validated as informant measures to examine impaired awareness in patients with neurodegenerative disease, they lack direct measurement of performance (Rosen, 2011). Future investigations combining other modalities could reveal additional important relationships. Self-ratings could be impacted by cognitive deficits, mainly in the memory and verbal domains and/or behavioural deficits. To overcome this possibility we excluded participants with severe verbal comprehension def-icits and those who evidenced response biases that would suggest invalid responding.

The voxel-based morphometry method used for studying the structural correlations of self-awareness also has some limitations. First, we included a heterogeneous population of participants. This is common in studies exploring structural behavioural correlations, as variability in behaviour and in grey matter atrophy patterns increases the variance and thus the power in correlation analyses, and the inclusion of patients with damage to the widest possible array of cortical regions allows closer approximation of a 'whole brain analysis' of behavioural correlates (Rankin et al., 2009). Other limitations to the voxel-based morphometry method include spatial normalization of structural images, questionable ability to generalize results that are based on an atrophy model, and poten-tial for bias due to inclusion of clusters of patients with similar atrophy patterns (co-atrophy effects). To overcome these issues, we ran an additional analysis controlling for diagnostic group and identified regions where atrophy was related to impaired self-awareness in more than one group. This confirmed that our main results likely represent a generalizable brain-behaviour rela-tionship. Although we did not have the power to examine distinct patterns within disease groups to predict the degree to which the anatomic aetiology of impaired awareness symptoms differs across syndromes, this would be an ideal target for future studies. Another methodological limitation was that we used scans obtained from different scanners. However, the impact of mixing structural imaging data obtained from different hardware has been directly studied in the context of voxel-based morphometry in patients with neurodegenerative disease, and it does not seem to have a substantial impact on accuracy of the results if scanner type is explicitly included as a nuisance covariate in the analysis, which we did (Kloppel et al., 2008; Abdulkadir et al., 2011).

Our findings both converge and diverge from previous voxel-based morphometry studies in patients with neurodegenerative disease that have demonstrated involvement of specific prefrontal regions in self-awareness (Rosen et al., 2010; Hornberger et al., 2014). Compared with previous studies, in the current study we had a substantially larger sample size, and used a psychometrically validated instrument for measuring self-awareness that has previ-ously been confirmed useful in anosgnostic patients. Notably, we separated the voxel-based morphometry analysis of overestimators

and underestimators, hypothesizing that these reflect different im-pairments and thus divergent underlying neural correlates. Consequently, we were able to detect a broader network involving additional cortical and subcortical regions, which enabled us to link these anatomical regions with further component processes under-lying self-awareness.

Conclusion

Impaired self-awareness, particularly the tendency to overestimate one's functioning, overlooking functional decline, was related to degeneration of dorsal frontal regions implicated in attending to and reflecting upon one's behaviour in order to align it with one's long-term goals, as well as orbitofrontal and subcortical regions involved in associating adequate levels of self-focus with personal reward. Atrophy related to underestimating one's functioning included right rostral anterior cingulate cortex. Although this result did not survive multiple comparisons correction, it fits with studies showing that negative self-evaluation is related to insuffi-cient anterior cingulate activation, leading to impaired inhibition of negative self-related emotional content.

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Supplementary material

Supplementary material is available at *Brain* online.

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